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Three typed copies of the article and one copy in a 3.5" high density floppy diskette processed in Wordperfect 6.0 or MS Word 6.0 should be submitted to the Editor. The text should be type-written in double space on one side of the paper not larger than ISO A4 with a 5 cm margin and paper should be numbered consecutively. The first page of the type script should bear the names of the author(s) and the name and address of the laboratory or institution where the work has been carried out, in addition to the title of the paper. The full address of the principal author to whom proofs will be sent should be given as footnote, as should any permanent change of address and/or appointment. A short (running) title of not more than 45 characters should be given. Please write as concisely as possible. Amendments should be made in the texts and not in the margins. All submitted manuscripts are reviewed by the editors and rejected manuscripts will not be returned. Ethical aspects will be considered in the assessment of the paper.

**Arrangement :**

Papers should be divided into: (a) Title page (b) Summary (c) Introduction (d) Materials and methods (e) Results (f) Discussion (g) Acknowledgement (h) Reference (i) Tables (j) Figures and Captions. The summary should not exceed 250 words and should state concisely what was done, the main findings and how the work was interpreted.

**Style :**

Abbreviations and symbols must be standard and SI units should be used throughout. Whenever possible drugs should be given their approved generic name. Acronyms should be used sparingly. Statistical analysis must explain the methods used. Reference should follow the Vancouver format. In the text they should appear as numbers starting at 1. At the end of the paper they should be listed (double spaced) in numerical order corresponding to the orders of citation in the text. All authors should be quoted for papers with upto six authors, for papers with more than six authors the first six only should be quoted followed by et al.

Abbreviations for titles of medical periodicals should conform to those used in the latest edition of Index Medicus. The first and last page numbers for each reference should be provided. Abstracts and letter must be identified as such. Authors must check references against original sources for accuracy. Examples of reference are given below:

**Articles in Journals :**

1. Paganini Hill A, Chao A, Ross Rk, Henderson BE. Aspirin use and chronic disease : a cohort study of the elderly. BMJ 1989; 299: 1247-50.
2. Parkin DM, Clayton D, Blook RJ, Massyer E, Fried HP, Iranov E, et al. Childhood Leukaemia in Europe after Chernobyl : 5 years follow-up. Br J Cancer 1996; 73 : 1006-12.

**Chapter in a Book :**

1. Phyllyps SJ, Whisnant JP. Hypertension and Stroke. In : Lurgh JH, Brennes BM, editors. Hypertension : Pathophysiology, diagnosis and management. 2nd ed. New York : Raven Press; 1995. p. 465-78.

Tables should be as few as possible and should present only essential data. Each table should be type-written on separate sheets, have a title or caption with Roman numbers. All photographs, graphs, diagrams should be referred to as figures and should be numbered consecutively in the text in Arabic numericals. The legends for illustrations should be typed on separate sheets. Photographs and photomicrographs should be unmounted glossy prints. Photomicrographs should have internal scale markers, include in the legend the original magnification and the stain used. Line diagrams and graphs should be on separate sheets drawn with black Indian ink on white paper. A photocopy of all illustrations should be submitted.

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Manuscripts and other communication for the editors should be addressed to Prof. M N Alam, The Editor, Bangladesh Journal of Medicine and Professor of Medicine, Bangabandhu Sheikh Mujib Medical University, Shahbagh, Dhaka, Bangladesh.

## ORIGINAL ARTICLES

# A STUDY OF BIOAVAILABILITY OF OMEPRAZOLE IN BANGLADESHI HEALTHY POPULATION

CHANCHAL KUMAR GHOSH[1], PROJESH KUMAR ROY[1], SM ISHAQUE[1], A.S.M.A RAIHAN[1], SITESH CHANDRA BACHAR[2], MAHMUD HASAN[1]

**Abstract:**

*Helicobacter pylori infection is a major cause of peptic ulcer disease. So eradication of H. pylori is the mainstay of treatment of peptic ulcer disease. Eradication rates of H. pylori in most of the western country is very high. But in Bangladesh H. pylori eradication rate is very low. Antibiotic resistance and re-infection is a cause for low eradication rate. But further studies are needed to find out other possible factor/factors. Most studies in Bangladesh was conducted with omeprazole in capsule form. So systemic availability of omeprazole capsule and plasma concentration (and AUC) cab be studied which may be a responsible factor. This study is designed to find out the bioavailability of omeprazole capsule in healthy Bangladeshi population and to compare this to that of other population in the world. Twelve healthy volunteers were recruited for the study. The subjects were divided into two groups ; Six of them were randomly selected in each. One group received 40mg omeprazole intact capsule of one trade and other group received 40mg omeprazole intact capsule of another trade once daily for consecutive 8 days at 8.00 hours on each day. On the first and eight days of dosing, 10ml of blood sample was collected from each subject at 0.0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0 and 6.0 hours after dosing. Blood samples was centrifuged at 2500 r.p.m for 15 minutes and plasma was stored at -20$^0$C. Omeprazole concentration in plasma was determined using a reveres phase high performance liquid chromatography (HPLC).*

*From the concentration, the area under the curve (AUC) of omeprazole was determined for each subject by the* trapezoidal rule*. From the result it was observed that the plasma concentration of omeprazole was increased up to 6 hours in both Trade-A and Trade-B in day-1 and day-8. Thus the AUC of omeprazole was also increased. But most of the studies in western population showed that the maximum plasma concentration was within 0.5 to 2.0 hours. So the increasing pattern of plasma concentration and AUC of omeprazole in this study showed a difference from that of western studies. In this study all the subjects exhibited increased plasma concentration and AUC which may be due to the genetic variation of omeperazole metabolism as an Asian which may be due to slow or "poor metabolizers" (PMs), of the study population, who are deficient in CYP2C19. It is revealed that the plasma concentration and AUCs of both the products after single and repeated doses of omeperazole capsule were higher in comparison to other studies in western population.*

**Introduction**

Peptic ulcer disease is common in Bangladesh. The prevalence of duodenal ulcer and gastric ulcer was estimated to be 11.98% and 3.58% respectively[1]. Helicobacter pylori infection is now accepted as a major cause of peptic ulcer disease. H. pylori is widely prevalent in Bangladesh, with 60% of children being infected by the age of 3 months and 80% being infected by the age of 3 years[2]. In adult, about 92% have been found to be sero-positive for H. pylori antibody[3]. So eradication of H. Pylori is the mainstay of treatment of peptic ulcer disease. There are several FDA-approved treatment regimens for H. Pylori eradication. All contain a Proton Pump inhibitor and 2/3 antibiotics, like amoxycillin, clarithromycin, metronidazole, tertracycline etc for 1 to 2 weeks. To be considered useful, a therapeutic regimen should have an efficacy of > 80% in clinical trials[4]. Eradiation rates of H. Pylori in most of the western country is very high, usually > 80%. But most studies in developing countries shown that eradication rate is much lower than those obtained in Western countries.[5, 6, 7, 8]. Several trials for H. Pylori eradication under taken in Bangladesh also showed a low eradication rate with different H. Pylori eradication regimens [9, 10, 11, 12] . In most of the

1. Department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University, Dhaka;
2. Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhaka, Dhaka-1000.

studies, the eradication rate was between 30-64% [10, 11, 12]. Ulcer healing rate was also lower than those of other studies conducted in the different countries of the world [13, 14, 15].

Antibiotic resistance (Amoxycillin/Metronidazole) & re-infection is a cause for low eradication rate of H. Pylori in Bangladesh. Poor compliance and lack of patient adherence is also a cause of low eradication rate. But further studies are needed to find out the factor or factors responsible for the low eradication rate in Bangladeshi patients. Most studies in Bangladesh was conducted with omeprazole (PPI). Proton pump inhibitors are bactericidal to H. pylori in vitro[5]. In vivo they reduce intragastric acidity so much that the organism can not find enough acid to survive its own endogenous production of $NH_4OH$ from urea[5]. The antisecretory effect of omeprazole is directly proportional to the AUC. It is not dependent on the plasma concentration at any given time. The omeprazole AUC reflects the product of the concentration of omeprazole in plasma and the time it is available in the systemic circulation and, therefore, available to the parietal cells. So systemic availability of omeprazole capsule and plasma concentration (and AUC) can be studied which may be a responsible factor. There are several studies in the world showing the pharmacokinetics and bioavailability of omeprazole after single and repeated oral administration [16, 17, 18, 19, 20]. But there is no study available in Bangladesh showing the concentration and bioavailability of omeprazole.

This study is designed to find out the concentration of omeprazole in plasma and the time it is available in the systemic circulation (AUC) after single and repeated doses of 40 mg omeprazole capsule in healthy Bangladeshi population and to compare this to that of other population in the world.

**Materials and Methods**

This study was conducted in the department of Gastroenterology, Bangabandhu Sheikh Mujib Medical Unviersity, Shahbag, Dhaka. Plasma concentration of omeprazole was assayed in the quality control laboratory of Novartis (Bangaldesh) limited, Tongi, Gazipur, Bangladesh. The study was conducted from January 2006 to April 2007.

Twelve healthy volunteers (male) were recruited for the study. Their mean (±SD) age was 24.0(±3.055) years, their mean (±SD) weight 56.67 (±6.69) Kg and their mean (±SD) height was 163.94 (±2.614) cm. Each subject gave informed consent to participate in the study, which was approved by the ethical review committee of the department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University, Dhaka. Twelve subjects were randomly divided in two groups, six in each. One group (six subject) received 40 mg omeprazole intact capsule of one trade (Trade A) and other group received 40 mg omeprazole intact capsule of another trade (Trade B) once daily for consecutive 8 days. Both of these product were of Bangladeshi Pharmaceuticals Company. All twelve subjects received 40 mg omeprazole capsule at 08.00 hours on each day, 30 minutes before the first food of the day and an overnight fast under supervision. Subjects receiving either omeprazole or any other proton pump inhibitor in the preceding month, significant past history of disease that may alter omeprazole bioavailability like chronic liver disease, chronic renal failure, gastric surgery etc, subjects having a history of substance abuse, subjects having gastrointestinal disorders which might impair drug absorption were excluded from the study. There were no drop-outs.

On the first and eight days of dosing, subjects had serial blood sampling for plasma drug levels. An intravenous cannula was inserted into an fore arm vein and 10 ml blood samples were withdrawn at 0.0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0 and 6.0 hours after dosing for plasma omeprazole levels on day 1 and day 8. Subjects were observed during these times in gastroenterology unit, BSMMU. Subjects had a standard breakfast 30 minutes after dosing and had nothing further by month until the blood samples were drawn on that day. Blood samples were collected into tubes containing heparin sodium and centrifuged at 2500 r.p.m. for 15 minutes. Plasma was decanted and samples were stored at -20° C until being shipped in batches to the quality control laboratory of Novartis (Bangladesh) Limited for analysis.

Omeprazole concentration in plasma was determined using a reverse phase high performance liquid chromatography (HPLC), column: cosmosil C18, 5 $\mu m, 250 \times 4.6$ mm at flow rate 1ml/min, injection volume l00ml using 1ml of mobile phase containing acetonitrile 33% (V/V) and phosphate buffer (0.2M potassium dihydrogen phosphate and 0.2M sodium hydroxide with water) pH 8.0 67% (V/V).

From the concentration, the area under the curve (AUC) of omeprazole was determined for each subject by the *trapezoidal rule* following the formula[21]

$$[AUC]_{t_{n-1}}^{t_n} = \frac{C_{n-1} + C_n}{2} \; t_n - t_{n-1}$$

where [AUC] = area under the curve, $t_n$ = time of observation of omeprazole concentration $C_n$, and

= time of prior observation of omeprazole concentration corresponding to $C_{n-1}$ .

**Results**

The bioavailability of omeperazole in Bangladeshi healthy populations with two preparations manufactured by two different Bangladeshi pharmaceuticals was studied. The products were identified as Trade-A and Trade-B, each contains omeperazole 40mg in capsule form. Twelve healthy subjects were participated in the study. The subjects were divided into two groups; six of them were randomly selected in each. All subjects completed their dosing schedules of omeperazole. No adverse events were reported during dosing with the drug. Each of them participated in the study according to the protocol.

Blood samples for plasma omeperazole concentration were taken at 0.0 hour before starting the dose and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0 and 6.0 hours after dosing on day -1 and day-8. Ten ml of blood sample was collected from each subject in respective time and the plasma was separated.

The concentration of omeperazole in the plasma for Trade-A and Trade-B on day-1 (Table-1) and day-8 (Table-2) was determined using High Performance Liquid Chromatography (HPLC).

**Table-I**

*The concentration (ng/ml) of omeperazole in individual subject after 1st dose on day-1 of Trade–A and Trade–B in different time.*

| Subject | Time (hours) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0.0 | 0.5 | 1.0 | 1.5 | 2.0 | 2.5 | 3.0 | 6.0 |
| | Concentration (ng/ml) of Trade-A | | | | | | | |
| 1 | 0.0 | 241.4 | 963.8 | 1533.2 | 1730.0 | 2560.4 | 2749.1 | 3233.3 |
| 2 | 0.0 | 238.3 | 967.0 | 1500.3 | 1759.7 | 2563.6 | 2717.4 | 3198.2 |
| 3 | 0.0 | 241.5 | 934.7 | 1519.6 | 1729.5 | 2549.4 | 2701.3 | 3196.5 |
| 4 | 0.0 | 238.0 | 956.2 | 1551.5 | 1728.6 | 2545.1 | 2709.8 | 3193.8 |
| 5 | 0.0 | 245.4 | 970.0 | 1583.1 | 1760.2 | 2543.1 | 2740.4 | 3154.6 |
| 6 | 0.0 | 248.5 | 989.4 | 1717.1 | 1855.7 | 2615.5 | 2799.1 | 3197.9 |
| | Concentration (ng/ml) of Trade-B | | | | | | | |
| 1 | 0.0 | 246.5 | 1034.2 | 1684.0 | 1830.8 | 2571.3 | 2844.2 | 3204.2 |
| 2 | 0.0 | 242.2 | 988.8 | 1660.2 | 1849.7 | 2612.0 | 2864.6 | 3165.2 |
| 3 | 0.0 | 248.8 | 992.3 | 1697.5 | 1894.4 | 2643.8 | 2887.8 | 3179.0 |
| 4 | 0.0 | 251.8 | 1030.5 | 1627.4 | 1857.4 | 2738.6 | 3056.3 | 3196.9 |
| 5 | 0.0 | 244.6 | 1064.9 | 1660.7 | 1887.6 | 2770.3 | 3119.0 | 3204.2 |
| 6 | 0.0 | 248.9 | 2042.0 | 1704.2 | 1893.2 | 2834.2 | 3160.4 | 3204.3 |

$t_{n-1}$

**Table-II**

*The plasma concentration (ng/ml) of omeperazole in individual subject after 8th dose on day-8 of Trade–A and Trade-B in different time.*

| Subject | Time (hours) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0.0 | 0.5 | 1.0 | 1.5 | 2.0 | 2.5 | 3.0 | 6.0 |
| Plasma Concentration (ng/ml) of Trade-A | | | | | | | | |
| 1 | 1395.5 | 1564.7 | 1626.7 | 1753.8 | 1882.4 | 2064.2 | 2143.5 | 2575.7 |
| 2 | 1367.2 | 1561.5 | 1610.9 | 1636.2 | 1883.7 | 2041.8 | 2147.3 | 2574.7 |
| 3 | 1399.2 | 1567.1 | 1609.0 | 1726.5 | 1883.7 | 2105.2 | 2182.1 | 2579.9 |
| 4 | 1462.5 | 1599.6 | 1607.0 | 1760.2 | 1905.5 | 2169.0 | 2200.8 | 2578.3 |
| 5 | 1410.2 | 1569.0 | 1621.7 | 1878.6 | 1979.1 | 2201.9 | 2232.9 | 2612.2 |
| 6 | 1536.7 | 1590.6 | 1660.2 | 1906.1 | 2011.4 | 2231.7 | 2295.8 | 2640.8 |
| Plasma Concentration (ng/ml) of Trade-B | | | | | | | | |
| 1 | 1569.1 | 1596.5 | 1659.8 | 1938.7 | 2010.2 | 2254.8 | 2318.2 | 2675.9 |
| 2 | 1535.4 | 1567.2 | 1684.0 | 1979.1 | 2041.8 | 2295.6 | 2330.8 | 2709.8 |
| 3 | 1569.0 | 1589.0 | 1717.6 | 2010.9 | 2064.8 | 2265.5 | 2360.4 | 2738.6 |
| 4 | 1535.2 | 1622.3 | 1760.2 | 2065.3 | 2119.7 | 2388.6 | 2521.6 | 2834.2 |
| 5 | 1514.4 | 1660.1 | 1779.8 | 2107.0 | 2170.0 | 2455.9 | 2539.6 | 2833.5 |
| 6 | 1451.5 | 1785.7 | 1865.9 | 2190.9 | 2223.2 | 2482.6 | 2571.3 | 2824.1 |

From the concentration, the area under the curve (AUC) of omeperazole was determined.

The AUC of the individual subject in respective time intervals for Trade-A and Trade –B on day-1 was represented in Table – 3, on day-8 in Table-4.

The mean AUCs of omeprazole on day-1 after the 1st dose of Trade-A between the time intervals 0.0 — 0.5, 0.5 — 1.0, 1.0 — 1.5, 1.5 — 2.0, 2.0 — 2.5, 2.5 — 3.0, and 3.0 — 6.0 hours were 60.55 ± 0.935, 301.43 ± 4.716, 632.75 ± 21.147, 832.02 ± 28.413, 1080.99 ± 16.950, 1326.93 ± 12.720, 8898.02 ± 62.320 ng hr/ml respectively, and the mean AUCs of omeprazole on day-1 after 1st dose of Trade-B between the same time intervals were 61.79 ± 0.780, 359.82 ± 95.450, 716.11 ± 98.830, 885.29 ± 10.530, 1142.47 ± 27.600, 1420.94 ± 54.89, 9271.53 ± 205 ng-hr/rnl respectively.

The mean AUCs of omeprazole on day-8 after the 8th dose of Trade-A between the time intervals 0.0 — 0.5, 0.5 — 1.0, 1.0 — 1.5, 1.5 —2.0, 2.0 — 2.5, 2.5 — 3.0, and 3.0 — 6.0 hours were 750.99 ± 17.14, 799.44 ± 6.51, 854.04 ± 21.55, 929.50 ± 30.67, 1014.99 ± 29.65, 1083.98 and 7191.0 ± 114.65 ng-hr/ml respectively and the mean AUCs of omeprazole on day-8 after 8th dose of Trade-B between the same time intervals

**Table-III**

*The AUC of individual subject after 1st dose of omeperazole on day-1 of Trade–A and Trade–B in different time intervals.*

| Subjects | Time (hours) | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0.0 – 0.5 | 0.5 – 1.0 | 1.0 -1.5 | 1.5 – 2.0 | 2.0 – 2.5 | 2.5 – 3.0 | 3.0 -6.0 |
| | Trade –A | | | | | | |
| 1 | 60.35 | 301.30 | 624.25 | 815.80 | 1073.35 | 1327.38 | 8973.60 |
| 2 | 59.58 | 301.33 | 616.82 | 815.00 | 1080.83 | 1320.25 | 8874.40 |
| 3 | 60.38 | 294.05 | 613.58 | 812.28 | 1069.73 | 1325.68 | 8846.70 |
| 4 | 59.50 | 298.55 | 626.93 | 820.03 | 1068.43 | 1313.73 | 8855.40 |
| 5 | 61.35 | 303.85 | 638.28 | 835.83 | 1075.83 | 1320.88 | 8842.50 |
| 6 | 62.13 | 309.48 | 676.63 | 893.20 | 1117.80 | 1353.65 | 8995.50 |
| | Trade-B | | | | | | |
| 1 | 61.63 | 320.18 | 679.55 | 878.70 | 1100.53 | 1353.88 | 9072.60 |
| 2 | 60.55 | 307.75 | 662.25 | 877.48 | 1115.43 | 1369.15 | 9044.70 |
| 3 | 62.02 | 310.28 | 672.45 | 897.98 | 1134.55 | 1382.90 | 9100.20 |
| 4 | 62.95 | 320.58 | 664.48 | 871.20 | 1149.00 | 1448.73 | 9379.80 |
| 5 | 61.15 | 327.38 | 681.40 | 887.08 | 1164.48 | 1472.33 | 9484.80 |
| 6 | 62.23 | 572.73 | 936.55 | 899.35 | 1181.85 | 1498.65 | 9547.05 |

**Table-IV**

*The AUC of individual subject after 8th dose of omeperazole on day-8 of Trade–A and Trade-B in different time intervals.*

| Subjects | Time (hours) | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0.0 – 0.5 | 0.5 – 1.0 | 1.0 -1.5 | 1.5 – 2.0 | 2.0 – 2.5 | 2.5 – 3.0 | 3.0 -6.0 |
| | Trade –A | | | | | | |
| 1 | 740.05 | 797.85 | 845.13 | 909.05 | 986.65 | 1051.93 | 7078.80 |
| 2 | 732.18 | 793.10 | 836.78 | 904.98 | 981.38 | 1047.28 | 7083.00 |
| 3 | 741.58 | 794.03 | 833.88 | 902.55 | 997.23 | 1071.83 | 7143.00 |
| 4 | 765.53 | 801.25 | 841.80 | 916.43 | 1018.63 | 1092.25 | 7168.65 |
| 5 | 744.80 | 797.68 | 875.08 | 964.43 | 1045.25 | 1108.70 | 7267.65 |
| 6 | 781.83 | 812.70 | 891.58 | 979.58 | 1060.78 | 1131.88 | 7404.90 |
| | Trade-B | | | | | | |
| 1 | 791.4 | 814.08 | 899.63 | 987.23 | 1066.25 | 1143.25 | 7491.15 |
| 2 | 775.65 | 812.8 | 915.78 | 1005.23 | 1084.35 | 1156.6 | 7560.6 |
| 3 | 789.5 | 826.65 | 932.13 | 1018.93 | 1082.58 | 1156.48 | 7648.5 |
| 4 | 789.38 | 845.63 | 956.38 | 1046.25 | 1127.08 | 1227.55 | 8033.7 |
| 5 | 793.63 | 859.98 | 971.7 | 1069.25 | 1156.48 | 1248.88 | 8059.65 |
| 6 | 809.3 | 912.9 | 1014.2 | 1103.53 | 1176.45 | 1263.48 | 8093.1 |

were 791.47 ± 9.84, 845.34 ± 34.55, 948.30 ± 37.95, 1038.40 ±39.48, 1115.53 ± 40.84, 1199.37 ± 48.60, and 7814.45 ± 252.43 ng-hr/rnl respectively.

From the plasma concentration data of Trade-A, the mean AUCs of day-1 in respective time intervals were compared with the mean AUCs of day-8 statistically using paired t-test, where the comparison was only within the same group of samples in respect of timing after dose. Here the result showed a significant difference between the AUC values on day-1 and day-8 at $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.0014$, $p<0.001$ and $p<0.001$ level.

Similarly, from the plasma concentration data of Trade-B, the mean AUCs of Day-1 in respective time intervals were compared with the mean AUCs of Day-8 statistically using paired t-test. Here the result also exhibited a significant difference between the AUC values on day-1 and day-8 at $p<0.001$, $p<0.001$, $p<0.009$, $p<0.002$, $p<0.0162$, $p<0.001$ and $p<0.001$ level.

**Discussion**

The plasma concentration data of omeperazole of Trade-A and Trade-B on day-1 and day-8 in different time intervals were used to determine the area under the plasma omeperazole concentration (AUC). In this study the AUC-time curve was used to determine the availability of the drug. As the degree of suppression of gastric acid secretion is correlated with the area under the plasma omeperazole concentration (AUC)-time curve, but is not related directly to the time course of plasma drug concentration[23].

The mean AUCs of Trade-A and Trade-B were increased with time intervals on day-1 and day-8 in both study groups. This increased AUC may be due to decreased first-pass elimination during repeated treatment and/or by a reduced degradation of omeperazole in the stomach secondary to the profound decrease in intragastric acidity caused by the drug.[24].

The increased AUC of omeperazole on day-8 in both the study group may be due to steady state concentration after repeated once daily dosing. This observation is correlated with the findings of Howden *et al* [17, 19, 22] with increased absorption of omeperazole after repeated once daily administration to reach a plateau by the 5th day. This steady state level may be explained by the progressive increased absorption of omeperazole from its standard capsule formulation over the first few days of dosing, because of a progessive inhibition of intragastric acidity and a consequent increase in the amount of omeperazole that is not denatured by acid and so is available for absorption [16]. The clinical relevance of this increase in AUC with repeated dosing of the drug may contribute to the increase in the pharmacodynamic effect on day-8 of administration [19].

From the result it was observed that the plasma concentration of omeperazole was increased up to 6 hours in both Trade-A and Trade-B in day-1 and day-8 . Thus the AUC (ng.hr/ml) of omeperazole was also increased. But most of the studies in western population showed that the maximum plasma concentration was within 0.5 to 2.0 hours[17, 19, 22]. So the increasing pattern of plasma concentration and AUC of omeperazole in our study showed a difference from that of western studies. The observation may be correlated with the report on pharmacokinetic studies of single 20mg omeperazole administration with increase in AUC of approximately four-fold higher in Asian subjects compared to Caucasians [24]

In this study all the subjects exhibited increased plasma concentration and AUC which may be due to the genetic variation of omeperazole metabolism as an Asian which may be due to slow or "poor metabolizers" (PMs), of the study population, who are deficient in CYP2C19.

It is revealed that the plasma concentration and AUCs of both the products after single and repeated doses of omeperazole capsule were higher in comparison to other studies in western population. So, the systemic availability of omeperazole in Bangladeshi healthy population is good and the quality of the products, used in the study, manufactured by Bangladeshi pharmaceuticals is also good.

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# COMPARISON OF THE EFFICACY OF OMEPRAZOLE FOR THE TREATMENT OF EROSIVE AND NON-EROSIVE GASTROESOPHAGEAL REFLUX DISEASE

M M R BHUIYAM, BISWAJIT DATTA, A S M A RAIHAN, P K ROY, M HASAN, H MASUD

**Summary**

*Eighty patients with symptomatic gastroesophageal reflux disease (GERD) were enrolled from outpatient clinic of BSMMU. Presence of heartburn for more than 3 months and also presence of heartburn at least 3 days in the last 7days were the inclusion criteria. Pregnant women, lactating mothers, known cases of peptic ulcer, GIT bleeding, Zollinger Ellison syndrome, cardiac, liver and renal diseases were excluded from the study. Patient taking any anti-ulcer drug was advised to stop the drug at least 15 days as washout period. Endoscopy was done in all cases to level erosive and non-erosive group and to exclude other disease. Patients were randomly allocated to receive 20 mg of omeprazole or placebo twice daily for 28 days and maintained their daily diary. Among 80 patients, 40 were in omeprazole group and 40 in placebo group. Total number of drop out patients was 9. Out of the remaining 71 patients, 37 in omeprazole group and 34 in placebo group completed the follow up. Among 37 patients with omeprazole, 26 were endoscopy negative and in 34 patients with placebo therapy, 29 were endoscopy negative GERD.*

*A daily diary of improvement of heartburn, acid regurgitation, epigastric pain, nausea and dysphagia for 28 days was maintained. At end of 4 week, it was observed that in endoscopy negative group, improvement in patients taking omeprazole was 77% for heartburn, 90% for acid regurgitation, 80% for epigastric pain, 75% for dysphagia in comparison to 10% for heartburn, 19% for acid regurgitation, 26% for epigastic pain, 0% for dysphagia in the placebo group which indicated a statistically significant difference in symptom improvement with omeprazole than placebo therapy. In endoscopy positive cases, improvements of symptoms with omeprazole were 63% for heartburn, 80% for regurgitation, and 89% for epigastic pain. Whereas 40% for heartburn, 40% for acid regurgitation, 100% for epigastic pain in the placebo group. In erosive variety, on any given day of 28 day, the odds of having no heartburn were 0 to 4 times for patients with omeprazole group compared with placebo group that is symptomatic improvement is less with omeprazole and not significantly higher than placebo. In conclusion, PPI is significantly effective in relieving symptoms of non- erosive variety of GERD.*

**Introduction:**

GERD can be defined as any symptomatic condition or anatomical alteration caused by the reflux of noxious material from the stomach into the oesophagus[1].. Findings of reflux esophagitis on endoscopic examination confirm the diagnosis of GERD but a normal esophagoscopy does not rule out GERD as a cause of symptoms [1].The classical symptom of GERD is heartburn and others are acid regurgitation, dysphagia and epigastric pain. GERD is as a spectrum of disease where patient may have non-erosive GERD, erosive GERD and Barrett's oesophagus[2, 3,4].

There is geographical variation in the prevalence of GERD. It is common in the western population[5] and was thought to be uncommon in Asians[6] but the prevalence of GERD is rising in the western and in some Asian countries [7,8,9.] In population-based studies in western countries, approximately 40% of the adult experience heartburn, and 10% to 20% have heartburn at least once a week and 4 to 10% have daily heartburn episodes[10-13] .The prevalence among Indians is 7.5% and in Malays is 3 %[9] .The prevalence of GERD at least once a week is 3.5% in Korea[14].

GERD is diagnosed on the basis of symptoms as there is no single diagnosed test and symptoms are assessed by structured interview or questionnaire[15.]

GERD has considerable morbidity and complications without treatment [5, 11]. There is a strong association between GERD symptoms and oesophageal acid exposure [16] and gastric acid suppression improves symptoms of GERD[17, 18.] Acid suppression with Histamine-2 receptor antagonists (H2RA) and proton pump inhibitor has become the main stay of treatment of GERD and omeprazole 20mg twice daily is more effective for relief of symptoms of symptoms [19,20].

Department of Gastroenterology, Chittagong Medical College, Department of Gastroenterology BSMMU

**Bangladesh J Medicine 2009; 20: 7-12**

In Bangladesh there are few studies on management of GERD and there is no study on efficacy of proton pump inhibitor for the treatment of symptomatic erosive and non-erosive variety of reflux disease. The aim of the double blind placebo controlled study was to assess the efficacy of omeprazole for the treatment of symptomatic endoscopy positive and endoscopy negative acid reflux disease.

**Materials and methods:**

This prospective double blind placebo controlled trial included patients of 18 to 60 years ages of both sexes. Study period was from November 2004 to June 2005.Patients were recruited from the outpatient of gastroenterology department of BSMMU. Diagnosis was made on the basis of presence of heartburn. Patient having heartburn for more than three months and also its presence for at least 3 days in the last 7 days were included. Exclusion criteria were, patients below 18 and above 60 years of age, presence of peptic ulcer, GIT bleeding, Zollinger Elison syndrome, pregnancy, lactating mother, co-morbid cardiac, renal and liver disease. If any patient was taking anti ulcer drugs, was advised to stop the drug for at least 15 days as a wash out period. Included patients under went upper GIT endoscopy to level erosive and non-erosive GERD and to exclude other pathology. A daily diary was developed to record daily presence of heartburn (none, mild, moderate, severe), acid regurgitation, dysphagia, epigastic pain and nausea during treatment along with any antacid consumption. The daily dairy was converted into Bengali by forward and backward translation.

Patients were randomly allocated to receive 20mg of omeprazole or placebo twice daily for 28 days and maintain their daily dairy.

Assessment of efficacy of treatment:

A complete clinical examination was done at baseline and at the end of the study. All patients were assessed on 2nd and 4th week by analyzing daily dairy maintained by the patients. Following parameters were analyzed to determine the efficacy:

1.Daily occurrence of heartburn i.e. proportion of patients with heartburn on each day of the study period.

2.Complete resolution of heartburn i.e. no heartburn of any sort in the last 7 days prior to evaluation at week 2nd and 4th.

3.Improvement of other symptoms like regurgitation, dysphagia, epigastic pain and nausea at baseline and at the end of 4th week of the follow up.

4.Development of any side effects or complication during the period of study.

**Statistical analysis**

The chi-square test was used to evaluate the difference between groups and values of $p<0.05$ was considered significant in case of symptoms analysis. All analysis was done with the help of statistical package for social science (SPSS).

**Results:**

A total of 80 patients were enrolled in the study. Endoscopy was performed in all cases. Following randomization 40 (male 33, female 07) patients received omeprazole and 40 patients (male31, female 09) received placebo.

Baseline characteristics are shown in table-I, Total nine patients were dropped from the study of which 3 were from omeprazole group and 6 from placebo group. Among the remaining 71 patients, 55 patients had endoscopy negative (nonerosive) and 16 had endoscopy positive (erosive) GERD. Among 37 patients of omeprazole group, 26 patients were found to be non-erosive, and 11 patients erosive GERD. Among 34 patients of placebo group, 29 patients were non-erosive and 5 were erosive for GERD.

Compliance with treatment was monitored by completion of daily dairy and pill counting at 14th and 28th day and this was found to be satisfactory.

**Table-I**

*Base line characteristics of the two groups*

| Parameter | Omeprazole group (N= 37) n(%) | Placebo group (N= 34) n(%) |
|---|---|---|
| Age | 29.9±7.39 | 29.9±7.9 |
| Sex | | |
| Male | 32(87%) | 27(79%) |
| Female | 05(13%) | 07(21%) |
| Weight(kg) | 68.34 | 67.90 |
| Height | 164 | 165 |
| Smoker | 1(2.7%) | 8 (23.5%) |
| Alcohol user | 0 | 0 |
| Average income per month(taka) | 3419 | 3819 |
| Endoscopic changes of reflux oesophagitis | | |
| Endo. | (+) 26 | 29 |
| Endo. (-) | 11 | 05 |

Number of patients with symptoms at entry and at the end of 2nd and 4th week is shown in table II.

**Table-II**

*Number of patients with symptoms at entry and at the end of the 2nd, 4th week: In endoscopic negative and positive patients:*

| | Endoscopic negative patients | | | | | | Endoscopic positive patients | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Drug group (N=26) | | | Placebo group (N=29) | | | Drug group (N=11) | | | Placebo group (N=05) | | |
| Symptom | 1st Day | 28th Day | P value | Day | 28th day | n value | 1st day | 28th, day | P value | 1st day | 28th day | P value |
| Heartburn | 26 | 06 | <.001 | 29 | 26 | >.05 | 11 | 03 | <05 | 05 | 02 | >.05 |
| Acid regurgitation | 20 | 02 | <.001 | 27 | 22 | >.05 | 08 | 01 | <.05 | 05 | 03 | >.05 |
| Dysphagia | 08 | 02 | >.05 | it | 11 | >.05 | 03 | 02 | >.05 | 03 | 02 | >.05 |
| Epigastricpain | 19 | 04 | <.001 | 15 | 11 | >.05 | 09 | Of | <.05 | 03 | 00 | >.05 |
| Nausea | 09 | 04 | >.05 | 02 | 01 | >.05 | 03 | 0 1 | >.05 | 00 | 00 | |

**Resolution of heartburn**

Success of treatment was recorded by the percentage of patients with no heartburn at each day. Complete resolution of heartburn on 7th, 14th, 21st and 28th day are shown in table- table III**.**

**In endoscopy negative group (drug-26, placebo-29**)- all patients initially had heartburn. Following treatment the daily proportion of patients with no heartburn in drug group were 8(31%) on day 7, 7(27%) on day 14, 19(73%) on day 21 and 20(77%) on day 28 and in placebo group were 1(3%) on day 7, 2(7%) on day 14, 6(20%) on day 21and 3(10%) on day 28.The difference in improvement of heartburn between omeprazole and placebo group in endoscopy negative group at the end of 1st, 3rd and 4th week was significant p<0.01, p<0.001, p<0.001) but not significant (p>0.05) at the end of 2nd week Table- III.. Thus it is noted that in endoscopy negative group, complete resolution **of** heartburn at 7th, 21stand 28th day was relatively higher in the omeprazole group in comparison to the placebo group.

**In endoscopy positive group (drug-11, placebo-5)-** all patients initially had heartburn following treatment, the daily proportion of patients with no heartburn in the drug group were 3(27%) on day 7, 3(27%) on day 14, 6(54%) on day 21 and 8(73%) on day 28 and in control group, it was 0 on day 7, 2(40%) on day 14, 2(40%) on day 21 and 3(60%) on day 28. The difference in improvement of heartburn between omeprazole and placebo group in endoscopy positive group were not significant at the end of 1st, 2nd, 3rd and 4th week (Table-III).

Comparison of daily odds between omeprazole (nonerosive and erosive) and placebo (nonerosive and erosive) group-

**In endoscopy negative group**- on any given day in 1st week, the odds of having no heartburn were approximately 6(95%C.I.=0.724-0.619) to 17(95% C.I. = 2.084-149) times for patients in the omeprazole group compared with these in the placebo group; in 2nd and 3rd week, it is 2(95%C.I.=0.724-10.65) to 10(95% C.I. =1.172-0.9078) and in the 4th week, it is 16(95% C.I. 4.243-60.31) to 36(95% C.I.= 7.784-170.2).

**In group-endoscopy positive**- on any given day in 1st, 2nd, 3rd week, the odds of having no heartburn were 0(95% C.I. =0) to 2 (95%C.I. =. 185-28.186) times for patients in the omeprazole group compared with that in the placebo group and patients in 4th week, it was 1(95%C.I. = .135 to 22) to 4(95%C.I. 0.431 –37.108).

**Table-III**

*Complete resolution of Heartburn on 7th, 14th, 21st and 28th day: In endoscopic negative and positive patients:*

| | Endoscopic negative(N=55) | | | Endoscopic positive(N=16) | | |
|---|---|---|---|---|---|---|
| | Druggroup (n=26) | PlaceboGroup (n=29) | P value | DrugGroup (n=11) | PlaceboGroup (n=05) | P value |
| T" day | 8(31%) | 1(3%) | >0.05 | 3(27%) | 0(0%) | >0.05 |
| 14[0]'day | 7(27%) | 2(7%) | <0.05 | 3(27%) | 2(40%) | >0.05 |
| 21thday | 19(73%) | 6(6%) | >0.001 | 6(55%) | 2(40%) | >0.05 |
| '2e'day | 20(77%) | 3(3%) | >0.001 | 8(77%) | 3(60%) | >0.05 |

Complete resolution of heartburn for the whole week in 2nd and 4th week between omeprazole group (nonerosive and erosive) and placebo group (nonerosive and erosive): **(**Table IV**).**

**In endoscopy negative group**- complete resolution of heartburn every day during a full week of treatment in 2nd and 4th week were 5 (19.2%) and 19(73%) in omeprazole group and 1(3.4%) and 3(10%) in placebo group. That means a higher proportion of patients in the omeprazole group experienced complete resolution of heartburn in comparison to the placebo group during 4th week [19(73%) versus 3(3.4%), p< 0.001] but not significantly greater in 2nd week [5(19%) versus 1(3.4%), p>0.05] Table-IV.

**In endoscopy positive group**- the proportion of complete resolution of heartburn every day during a full week of treatment in the 2nd and 4th week were 2(18%) and7 (63%) in omeprazole group and 1(20%) and 2(40%) in placebo group. So complete resolution of heartburn was not significantly higher in omeprazole group compared with the placebo group during 2nd an 4th week [2(18%) versus 1 (20%), p> .05] [7(63%) versus 2(40%), p>.05] (Table- IV).

**Resolution of other symptoms (**Table V**)**

**In endoscopy negative patients**- at baseline, symptom free patients in drug group were: acid regurgitation 23(76%), dysphagia 18(69%), epigastic pain 7(26%), nausea 17 (65%). In placebo group, the following proportion of patients reported to be symptom free; acid regurgitation 2(7%), dyashagia 18(62%), epigastric pain 14(48%) and nausea 27(93%). At 28th day, the proportion of patients who had symptoms on first day, reported to be symptom free in omeprazole group; acid regurgitation 18(90%), dysphagia 6(75%), epigastric pain 15(79%), nausea 5(56%). In placebo group, acid regurgitation5 (18%), dysphagia 0(%), epigastic pain 4(22%), nausea 1(5%). In endoscopy negative patients, at the end of 4th week, the proportion of patients experiencing no acid regurgitation, dysphagia, and epigastric pain were significantly (p<0.001, p<0.05, p<0.05) higher in omeprazole group then in placebo group but for nausea, the improvement was not significantly (p>0.05) higher in omeprazole group (Table- v).

**In endoscopy positive patients**- at baseline, the following proportion of patients reported to be symptom free in drug group: acid regurgitation 3(28%), dysphagia 8(73%), epigastic pain 2(18%), nausea 08 (73%). In placebo group, the following proportion of patients reported to be symptom free: acid regurgitation 0(0%), dyashagia 02(40%), epigastric pain 02(48%) and nausea 05(100%). At 28th day, the proportion of patients who had symptoms on first day, reported to be symptom free in omeprazole group; acid regurgitation 8(80%), dysphagia 1(33%), epigastric pain 8(89%), nausea 2(66%). In placebo group, acid regurgitation 2(40%), dysphagia 1(33%), epigastic pain 5(100%), nausea 0(0%). So, in endoscopy positive patients, at the end of 4th week, the proportion of patients experiencing no dysphagia, epigastric pain and nauses were not significantly (p>0.05, p>0.05, p>0.05) higher in omeprazole group then in placebo group but for acid regurgitation it was significantly (p<0.05) higher (Table- v).

**Table-IV**

*Complete resolution of heartburn for the whole week in 2ndd and 4th week:*

| | Endoscopic negative (N=55) | | | Endoscopic positive (N=16) | | |
|---|---|---|---|---|---|---|
| | Drug group (n=26) | Placebo group (n=29) | P value | Drug group (n=11) | Placebo Group n=05) | P value |
| 2ndweek | 05(19.2%) | 01(3.4%) | 0.05 | 02(18%) | 01(20%) | 0.05 |
| 4t'week | 19(73%) | 03(10%) | >0.001 | 07(63%) | 02(40%) | <0.05 |

**Table-V**

*Complete resolution of other symptoms at the end of 4th week:*
*In endoscopic negative and positive patients:*

| | Endoscopic negativepatients | | | Endoscopic positivepatients | | |
|---|---|---|---|---|---|---|
| SymptomI | Drug group | Placebo Group | value | Drug Group | Placebo Group | value |
| Acidregurgitation | 18(90%) | 5(18%) | <.001 ! | 8(80%) | 2(40%) | .05 |
| Dysphagia | 6(75%) | 0(0%) | <.001 | 1(33%) | 2(40%) | .05 |
| ; EpigastriciPain | 15(79%) | 4(22%) | <.OS | 8(89%) | 3(100%) | *.05* |
| Nausia | 5(56%) | 1(50%) | >.OS | 2(66%) | 0(0%) | .OS |

**Discussion:**

The term gastroesophageal reflux disease describes any symptomatic condition or histopathologic alteration resulting from episodes of gastroesophageal reflux[21]. Genval workshop defined Gastroesophageal reflux disease as being present in all individuals who are exposed to the risk of physical complications of gastroesophageal reflux or who experience clinically significant impairment of health related well being due to reflux related symptoms[22]. Heartburn is a classical symptom of GERD but other symptoms like acid regurgitation, epigastic pain, dysphagia, and nausea are also common[23, 24]. In a population-based study in western country, approximately 20% to 40% have heartburn at least once a week and 4% to 10% have daily heartburn episodes[10, 11,12].

GERD is a chronic medical disorder and affects quality of life[22]. There may be waxing and waning of symptoms with no permanent cure with the conventional presently available treatment[22]. It is expensive both for the individual and the society in terms of drug, surgery and absence from work[19]. The risks of complications of GERD are erosions, strictures, Barrett's oesophagus and malignancy[11].

A strong association between GERD symptoms and esophageal acid suppression has been demonstrated in many studies [16]. Trials have shown that suppression of gastric acid secretion is associated with improvement of symptoms of GERD[17, 18]. H2RA and PPI are the main stay in the treatment of GERD.

Although omeprazole is widely used for the treatment of GERD, there is no comparative study on efficacy of proton pump inhibitor for the treatment of erosive and no erosive variety of GERD in Bangladesh. This is the first prospective double blind placebo controlled study on the efficacy of omeprazole 20mg twice daily in erosive and non-erosive variety of GERD patients.

In our endoscopy negative nonerosive GERD patients, complete resolution of heartburn at the end of 28$^{th}$ day was 77% in omeprazole getting patients and 10% in placebo group and the effect of the drug in relieving symptoms was statistically significantly. In endoscopy positive group, complete resolution of heartburn at the end of 28$^{th}$ day was 73% and 60 % in drug and placebo groups respectively and the difference was not statistically significant. From this trial it is found that omeprazole is more effective in relieving heartburn in non-erosive group of patients. Armstrong et al, a in randomized control comparison study found that PPI like pantoprazole results complete heartburn relief in GERD higher than that of placebo therapy but the incidence of complete heartburn relief did not significantly differ between the erosive and nonerosive GERD patients[25]. Richter et al in their study showed that lansoprazole is more effective than ranitidine and placebo in relieving heartburn with non-erosive GERD[26].

Carlson et al. used 10mg and 20 mg of omeprazole to treat both erosive and non-erosive patients with GERD symptoms. After 4 week of treatment, resolution of heartburn was approximately the same in both groups [27] .In comparison; our trial showed that endoscopy negative patients responds more than endoscopy positive group to omeprazole. Less response in erosive group cannot be explained but it might be due to small sample size.

In endoscopy negative group, on any given day of 28days, the odds of having no heartburn were approximately 6(95%C.I.= .724- 619) to 36(95% C.I. = 7.7 170) times for patients in the omeprazole group compared to that in the placebo group.

In endoscopy positive group, on any given day of 28days, the odds of having no heartburn were approximately 0(95%C.I.= 0) to 4(95% C.I. = .431-37.10) times for patients in the omeprazole group compared to that in the placebo group. Richter at al. in a similar study showed on any given day, the odds of having no heartburn were significantly higher in omeprazole group than that of the placebo group[28]

In endoscopy negative group, complete resolution of heartburn every day during a full week of treatment was experienced by a significantly greater proportion of patients in the omeprazole group compared to the placebo group during 4 week (73% versus3.4%).

In endoscopy positive group, complete resolution of heartburn every day during a full week of treatment was not experienced by a significantly greater proportion of patients in the omeprazole group compared to the placebo group. Lack of response might be explained by small sample size in this group.

**Resolution of the other symptoms of GERD:**

In endoscopy negative group: Acid regurgitation (90% versus 19%), epigastric pain (80% versus 26%), nausea (58% versus 00%), dysphagia(75% versus0%) were significantly higher in the omeprazole group than in the placebo group but for nausea, it was not higher.

In endoscopy positive group: only acid regurgitation (90% versus 40%) and epigastric pain (89% versus 0%) were significantly higher in the omeprazole group than in the placebo group but for nausea, it was not higher. Carlsson et al. in his study showed, after 4 weeks of treatment by omeprazole, symptoms of acid regurgitation, epigastric pain, nausea, dysphagia were

resolved more often in endoscopy positive patients than in endoscopy group [27]. This dissimilar finding in our study might be due to small sample size in endoscopy positive patients.

In conclusion, from this study omeprazole was found to be more effective than placebo in relieving symptoms of gastroesophageal disease. This effect was significantly more in non-erosive group. In erosive group the difference did not reached the level of significance.

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# LIPID ABNORMALITIES IN HYPOTHYROID PATIENTS

M FARIDUDDIN[1], MI MAJUMDER[2], MA JALIL CHOWDHURY[3], SA HAQ[3], NA CHOWDHURY[4], A R HOWLADAR[5],F H MOLLAH[5]

**Abstract**

*Dyslipidaemia frequently found in hypothyroid patient. Early diagnosis & management is very important for better out come. This study was carried out in the THYROID CLINIC,Bangabandhu Sheikh Mujib Medical University (BSMMU) to find out the lipid abnormalities in hypothyroid patients. After thorough examination, and relevant investigations, 80 (eighty) hypothyroid patients (male-9 & female-46) and 30 (thirty) healthy euthyroid controls (male-15 & female-15) were taken in this study. Mean (M±SD) of total cholesterol (TC), LDL cholesterol (LDL-C) and triglyceride (TG) of patient group were 231.6±62.9mg/dl, 152.4±59.4mg/dl and 186.9±95.3mg/dl respectively. On the other hand mean (M±SD) of TC, LDL-C and TG of control group were 146.9±23.6mg/dl, 70.6±25.6mg/dl and 100.5±39.2mg/dl respectively. Mean (M±SD) of HDL-C of the patient group and control group was 41.4±3.8mg/dl and 56.3±11.5mg/dl respectively. TC (P=0.000), LDL-C (p=0.000), TG (P=0.000) were significantly higher but HLD-C (P=0.000) was significantly lower in the patients group compared to control group. This study reveals that atherogenic lipids are present in hypothyroid patient*

## Introduction

Hypothyroid is a common endocrine disorder. The prevalence rate of hypothyroidism depends upon population studied. The study was done in Colorado where prevalence was about 9.5[1,2]. According to study of thyroid clinic, IPGMR, and INM, 10.12% patients were presented with hypothyroidism[3]. At the 20 years follow up of the Whickman cohort provided incidence data and allowed the determination of risk factors for hypothyroidism in this period[4,5]. The mean incidence of spontaneous hypothyroidism in the surviving women over the 20 years follow up was 3.5 per 1000 per year, rising to 4.1 per 1000 per year and in men was 0.6 per 1000 per year[5]. Hypothyroidism is associated with many biochemical abnormalities including lipids. Serum TSH levels were related to the levels of LDL-C and HDL-C[6,7]. In study from the Mayo Clinic, the lipid profiles of 268 consecutive patients with overt hypothyroidism were reviewed and it was found that 91.4% of these patients had abnormal lipid values[8]. Staub et al.[9] and Althus et al.[10] showed higher LDL-C levels in patients with slightly elevated TSH as compared with euthyroid controls. So hypothyroidism is a major cause of secondary dyslipidemia[1,6,8], the cause of which resides in a decrease of cholesterol excretion and in a marked increase in apoB-lipoproteins because of decrease catabolism and turnover by reduced number of LDL-receptors on the liver cell surface. LDL-C and LDL-C are also increased due to decrease activity of LDL receptors resulting in decreased receptor mediated catabolism of LDL-C and IDL-C in hypothyroid patients. In hypothyroid patients, a reduced removal rate of TG from plasma and accumulation of VLDL and IDL have been reproted[2]. This decreased clearance of TG is due to decreased activity of lipoprotein lipase[2]. Dyslipidemias are a well known risk factor for cardiovascular diseases. Early diagnosis and proper management can significantly reduce the mortality and morbidity of dyslipidemic cardiovascular diseases. Our aim of this study was to find out the lipid abnormalities in our hypothyroid patients.

## Subjects and Methods

The study was carried out in the Thyroid Clinic, Bangabandhu Sheikh Mujib Medical University, Dhaka during the period of July 2003 to June 2005. The patients were selected from the Endocrine Out Patient Department of BSMMU. Investigations were done in the Biochemistry Department, BSMMU. The clinical course of the disease was explained with each patient in details and they were enrolled after obtaining informed written consent. Permission of the study and ethical clearance was taken from the concerned department prior to the study.

1. Department of Medicine (Endocrine Wing), BSMMU, Dhaka
2. Department of Medicine, BSMMU),Dhaka
3. Department of Medicine, BSMMU, Dhaka
4. Department of Medicine (Endocrine Wing), BSMMU, Dhaka
5. Department of Medicine (Endocrine Wing), BSMMU, Dhaka
6. Department of Bio chemistry, BSMMU, Dhaka

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**Subjects**

The patients who presented with signs and symptoms of hypothyroidism were initially considered for inclusion in the study. After thorough examination and relevant investigations, the patient who fulfilled the inclusion criteria were initially selected for the study. The diagnosis of hypothyroidism was based on clinical findings and low serum FT4 and high serum TSH concentration. Diagnosis of hypothyroidism was confirmed by the author. The subjects who seemed to be healthy were taken as control subjects. None of control subjects was diabetic and had clinical or biochemical evidence of thyroid, liver and renal disease.

**Inclusion Criteria:**

i. Age e" 20 d" 60 years, male-female both
ii. Recent clinically detected and biochemically confirmed hypothyroidism.
iii. No dietary restrictions during study period

Exclusion Criteria:

Associated other diseases or conditions known to alter TSH secretion and/or interfere with lipoprotein metabolism.

Such as-

Chronic renal failure ,liver disease ,diabetes mellitus ,neoplastic, pregnancy ,less than 20 or more than 60 years age, coronary artery diseases, metabolic syndrome ,history of intake of L-thyroxine within past six weeks, history of intake of lipid lowering drugs, oral contraceptive pill, estrogen, steroid and B-blockers during treatment period.

The conditions listed in the exclusion criteria were diagnosed by liver function tests, renal function tests, fasting blood sugar, ECG and imaging. The particulars of each patients, detailed history and physical examination were noted in the data collection sheet.

**Data Analysis**

All data were analyzed with the help of SPSS software programme (version -10.0) and expressed as mean±SD. Person correlation co-efficient test was done to see the correlation of lipid profile with the severity of hypothyroidism. 'p' values < 0.05 were considered significant.

**Results and Observations**

During the period from July 2003 to June 2005, 80 (eighty) hypothyroid patients and 30 (thirty) healthy controls included in the study.

Age of patients ranged from 20-60 years. Peak age of the subjects at presentation was observed at 3rd and 4th decade. In the patient group the mean age (M±SD) was 34.4±11.2 years and in the control group was 37.7±5.7 years respectively. Female to male ratio was about 5:1 in patient group and 1:1 in control group (Table-I).

**Table-I**

*Study Subjects by Age & Sex*

| Parameters | | Study Subjects | |
|---|---|---|---|
| | | Patient group (N=55) | Control group (N=30) |
| Age in years (Mean±SD) | | 34.4±11.2 | 37.75.7 |
| Sex | Male | 9 | 15 |
| | Female | 46 | 15 |
| Total | | 55 | 30 |

Mean TSH (M±SD) of patient group at presentation was 60.0±31.7 miu/L and control group was 1.6±1.4miu/L. Mean TSH (M±SD) of the patient group was much higher than control group. Mean $FT_4$ (M±SD) of patient group was 5.4±2.9poml/L (Table-II).

**Table-II**

*TSH and $FT_4$ levels in the patient and control group*

| Parameters | Patient group (n=55) | Control group | Reference Values |
|---|---|---|---|
| TSH (mIU/L) | 60.0 ± 31.7 | 1.6±1.4 | 0.4 – 5.0 |
| $FT_4$ (pmol/L) | 5.4 2.9 | | 9.1 – 23.8 |

Mean (M±SD) of total cholesterol (TC), LDL cholesterol (LDL-C) & triglyceride (TG) of patient group were 231.6 ± 62.9 mg/dl, 152.4 ± 59.4mg/dl & 186.9 ± 95.3mg/dl respectively. On the other hand mean (M±SD) of TC, LDL-C & TG of control group were 146.9 ± 23.6 mg/dl, 70.6 ± 25.6 mg/dl & 100.5±39.2mg/dl respectively. Mean (M±SD) of HDL-C of the patient group and control group was 41.4±3.8mg/dl & 56.3±11.5mg/dl respectively. TC (p=0.000), LDL-C (p=0.000), TG (p=0.000) were significantly higher but HDL-C (p=0.000) was significantly lower in the patient group compared to control group (Table-III)

TSH always showed positive correlation with total cholesterol (r=0.276, p=0.041) & LDL- Cholesterol (r=0.306, p=0.022) and no correlation with triglyceride (r=0.002, p=0.986) & HDL- cholesterol (r=-0.070, p= 0.610) (Table-IV).

$FT_4$ showed no correlation with total cholesterol (r= -0.229, p=0.126), LDL- cholesterol (r= -0.212, p=0.158), triglyceride (r= -0.146, p=0.334) & HDL- cholesterol (r=0.280, p=0.060) (Table-V).

**Table-III**

*Lipid profile in the patient group & Control group*

| Parameters | Patient group (Before treatment) (Mean±SD)(n=55) | Control group (Mean±SD)(n=30) | P-Values |
|---|---|---|---|
| Total Cholesterol120-200mg/dl | 231.6±62.9 | 146.9±23.6 | 0.000 |
| HDL CholesterolM=>40mg/dlF=>50mg/dl | 41.4±3.8 | 56.3±11.5 | 0.000 |
| LDL Cholesterol<130mg/dl | 152.4±59.4 | 70.6±25.6 | 0.000 |
| Triglyceride<150mg/dl | 186.9±95.3 | 100.5±39.2 | 0.000 |

**Table-IV**

*Correlation between TSH levels & lipid profile of the patient group*

| Parameters | Lipid Profile(Mean±SD) (mg/dl) | r-value | P-Value | |
|---|---|---|---|---|
| TSH (Mean±SD) 60.04±31.79(miu/L) | Total Cholesterol | 231.6±62.9 | 0.276 | 0.041 |
| | HDL Cholesterol | 41.4±3.8 | -0.070 | 0.610 |
| | LDL Cholesterol | 152.4±59.4 | 0.306 | 0.022 |
| | Triglyceride | 186.9±95.3 | 0.002 | 0.986 |

**Table-V**

*Correlation between $FT_4$ levels and lipid profile of the patient group*

| Parameters | Lipid Profile(Mean±SD) (mg/dl) | r-value | P-value | |
|---|---|---|---|---|
| $FT_4$ (Mean±SD) 5.47±2.94(pmol/L) | Total Cholesterol | 231.6±62.9 | -0.229 | 0.126 |
| | HDL Cholesterol | 41.4±3.8 | 0.280 | 0.060 |
| | LDL Cholesterol | 152.4±59.4 | -0.212 | 0.158 |
| | Triglyceride | 186.9±95.3 | -0.146 | 0.334 |

## Discussion

Hypothyroidism is a common metabolic disorder in the general population. Levels of TC and LDL-C tend to increase as the thyroid function declines. Therefore, hypothyroidism constitutes a significant cause of secondary dyslipidemia[1,2].

Tosimihodimos et al.[1] studied for 2 years in their lipid clinic and they admitted 248 patients for the diagnosis and management of dyslipidemia. They found seven female asymptomatic patients (2.8%) had frank biochemical hypothyroidism,&11(4.4%) had subclinical hypothyroidism. In general, overt and subclinical hypothyroidism is associated with hypercholesterolemia mainly due to elevation of LDL-C levels, HDL-C concentration is usually normal or even elevated[2,8]. Staub et al.[9] also concluded that the magnitude of changes in lipoprotein fractions in hypothyroid patients correlate with severity of thyroid hormone deficiency.

In the present study it was observed that mean of TC, LDL-C and TG of patient group was significantly higher than control group which is similar with the findings of earlier studies. On the otherhand mean of HDL-C was significantly lower in the patient group compared to control group, which is consistent with previous findings. In our study HDL-C levels of patient group is significantly lower compared to control which is inconsistent with studies was done by Dullaart et al. So our study regarding HDL-C is consistent with some studies and inconsistent with the others. Hypothyroidism is associated with atherogenic dyslipidaemia .So in a dyslipidaeic patient hypothyroidism should be excluded.

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# ENDOSCOPIC FINDINGS IN A DISTRICT PRIVATE HOSPITAL OF BANGLADESH

ABM SAFIULLAH, MMR BHUYIAN, H MASUD[2,] PK ROY

**Summary:**
*Upper GI endoscopy is the most accurate and cost effective diagnostic tool to physicians when confronted with patients with digestive complaints. Objectives of this study are to demonstrate indications r and the findings of endoscopy in a district private hospital of Bangladesh. We retrospectively reviewed the medical records for endoscopy indications and results of adult who referred for endoscopy in a private hospital of Noakhali during the period from July 2007 to October 2008. We analyzed 512 adults who had upper GI endoscopy. The age range was 12 to 82 years. Male & female ratio was 1.2:1.The most common indications were upper abdominal pain, heartburn, dyspepsia. Overall yield was 17.19%. Normal upper GI endocopy was 82.81%and common diagnosis was duodenal ulcer disease. Duodenal ulcer disease, Gastric ulcer, Carcinoma stomach, Gastric outlet obstruction, Esophageal varices, Oesophagititis and Ascariasis were found in 10.35%, 3.32%, 1.56%, 0.58%, 0.58%, 0.58%, 0.39% patients respectively. In conclusion, the most common presenting complaint was upper abdominal pain and common endoscopic finding was duodenal ulcer disease.*

**Introduction:**

The upper gastrointestinal flexible fiber optic endoscope was first used in 1968 and proved to be a major break through in the diagnosis of oesophago-gastro-duodenal lesions[1]. This procedure is used in diagnosis of GI disease, obtain tissue to confirm a diagnosis and to deliver specific therapy. Estimates of number of procedures performed in the United States[2] and United Kingdoms [3] are 1.2 examination per 1000 age 65 years age and older and 650 to 1000 procedures per 100000 respectively.

Peptic ulcer disease is common in Bangladesh [4, 5] and point prevalence was 15% in eighties[6]. There is strong association between H. Pyloric infection and peptic ulcer disease. One of the studies on H.pylori infection and peptic ulcer disease in Bangladesh where there is a high prevalence of peptic ulcer disease. A study conducted in four villages five miles away from Dhaka city has shown the point prevalence of duodenal ulcer (DU) to be 11.98% and that of gastric ulcer to be 3.5%[7]. The prevalence of H. pylori infection is also very high. Studies conducted in Bangladesh children by scientists of the International Center of Diarrhoeal Disease Research, Bangladesh (ICDDRB) has shown that 60% of the children are infected by the age of three months and 80% are infected by the age of three years[8]. A seroprevalence study of 268 apparently healthy subjects between the age of 15 and 40 years showed 91% to be positive for H. pylori antibody[9].

Aim of this paper is to report on the endoscopic indication and yield of endoscopy at peripheral district hospital of Bangladesh.

**Material and Method**

This is a retrospective study in which we reviewed the endoscopy records of 512 patients that underwent upper gastrointestinal endoscopy at Rabeya Private hospital, Noakhali from July 2007 to October 2008. The patient's biodata, indications and findings during endoscopic examinations as well as any adverse outcomes were documented.

All patients above the age of 12 irrespective of sex were included. All patients were given pharyngeal anesthesia by 10% Xylocaine spray. Endoscopic diagnosis was based on the macroscopic appearance using standard criteria. Endoscopy was considered negative when no abnormality was seen. The common endoscopic findings were duodenal ulcer disease and gastric erosions.Lesions in esophagus, stomach and duodenum were recorded. The procedures were well tolerated by the most of the subjects. None had any complications due to procedure.

**Results:**

A total of 512 upper GI endoscopies were performed during period of the study.Age range was 18 to 82 years. Male & female ratio was 1.2:1 (Table I). Majority of the patients were under age of 40 (table II). The most common indications were upper abdominal pain, heartburn, dyspepsia.

Department of Gastroenterology Bangabandu Sheikh Mojib Medical University, Dhaka,Bangladesh

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**Table-I**
*Sex distribution*

| Sex | Frequency | Percentage |
|---|---|---|
| Male | 285 | 55.66 |
| Female | 227 | 44.33 |

**Table-II**
*Distribution of patients by age*

| Age in years | Frequency | Percentage |
|---|---|---|
| 18-29 | 180 | 35.15 |
| 30-39 | 132 | 25.78 |
| 40-49 | 76 | 14.84 |
| 50-59 | 56 | 10.93 |
| 60-69 | 34 | 6.64 |
| 70 >= | 34 | 6.64 |

Overall yield was 17.19%. Normal upper GI endocopy was 82.81%. Finally common diagnosis was duodenal ulcer disease. Duodenal ulcer disease, Gastric ulcer, Carcinoma stomach, Gastric outlet obstruction, Esophageal varices, Oesophagititis and Ascariasis was 10.35%, 3.32%, 1.56%, 0.58%, 0.58%, 0.58%, 0.39% patients respectively (Table III).

**Table-III**
*Endoscopic findings*

| Findings | Frequency | Percentage |
|---|---|---|
| Duodenal ulcer disease | 53 | 10.35 |
| Gastric erosions | 17 | 3.32 |
| Ca-stomach | 8 | 1.56 |
| Gastric outlet obstruction | 3 | 0.58 |
| Oesophageal varices | 3 | 0.58 |
| Oesophagititis | 3 | 0.58 |
| Ascariasis | 2 | 0.39 |

**Discussion:**

Gastrointestinal diseases affect people worldwide. Endoscopy is the gold standard tool to reach a diagnosis[10].

The age range of the patients was 12 to 82 years. There are 285 males (55.66%) and 227 (44.33%0 females in the study. The most common indications for endoscopy in this study were upper abdominal pain, heart burn, and dyspepsia. There are several studies about endoscopic findings of upper GIT. A retrospective study by Onyewere CA[11] in which they reviewed the upper GI endoscopy records of 170 patients in the Lagos State University, Nigeria. This study showed that the indications for upper GI endoscopy were; Dyspepsia, Upper abdominal pain, upper GI haemorrage and 10.39% patients had duodenal ulcer disease, 3.37% Gastric ulcer, 1.55% Ca-stomach, 0.58% Gastric outlet obstruction at endoscopy. Oesophageal varices were found 0.58%, GERD-0.26% and Ascariasis 0.39% of the patients. Another study by Arfen Ahmed[12] in a review of 500 endoscopies report at Sheikh Zayed Medical College, Pakistan showed that 57% patients were referred due to upper GI bleeding, 9%due to dysphagia, 8% due to persisting vomiting and 7% due to dyspeptic symptoms. Common endoscopic diagnoses were oesophageal varices, reflux oesophagitis, gastritis and gastric ulcer.

Raihan et al[13]reported in a study conducted in Bangabandu Sheikh Mojib Medical University, Bangladesh that total number of endoscopies performed in the period from 1985 to 1989 was 7177, from 1990 to 1994 was 4658, from 1995 to 1999 was 3143 and from 2000 to 2004 was 4347.Gastric erosion was found in 10.16%, 5.98%, 7.9% and 10.5%, Duodenal erosions were found in 2.2%, 3.6%, 3% and 3.9%in the four groups respectively. Esophageal ulcer was found in 6.54, 3.20, 7.31 and 19.09 persons per thousand endoscopies respectively. Esophageal varices were found 1.8%, 3.6%, 2.8% 11.07%and 12.5% persons endoscopies respectively. Carcinoma of the stomach was found in 2.7, 3, 4.1 and 60.6 persons per hundred endoscopies respectively. Carcinoma of the esophagus was found in 1.1, 1.15, 1.9 and 2 persons per hundred endoscopies respectively.

Study done by P.K.Roy[14] et al showed that prevalence of peptic ulcer disease in Bangladeshi general population is 14.45% with duodenal ulcer 10%, Gastric ulcer4%, Gastric outlet obstruction 0.45%, Gastric erosion 3.16% and Carcinoma stomach 2.29%. Study reported that esophagal abnormalities such as Ca-oesophagus 0.86%, oesophageal varices 1.43%. All these data are almost similar to the previous studies in home and abroad.

**Conclusion:**

In our experience upper GI endoscopy is very much sensitive procedure to dectect any suspected lesion in the esophagus, stomach and duodenum. A large proportion of patients 17.19% with gastrointestinal complaints have positive upper GI endoscopy. The most common indications for upper GI endoscopy in adults are epigastric pain, dyspepsia. Gastritis and duodenal ulcer diseases are common disease in adult.

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# COMPARATIVE BIOAVAILABILITY OF TWO ORAL FORMULATIONS OF KETOROLAC TROMETHAMINE

SHEIK SAYEED HASAN[1], CHANCHAL KUMAR GHOSH[3] , M AFTAB UDDIN[2], AHAMED HASAN-AL BAIZYD[1], NIGAR SULTANA TITHI[1], SITESH CHANDRA BACHAR[1]

**Abstract**

*The bioavailability study of ketorolac after oral administration of two formulations containing 10 mg of ketorolac tromethamine tablet namely Toradol® as reference product and Torax® as test product was compared by using serum data. The open label, randomized two way crossover study was conducted on 12 healthy Bangladeshi volunteers. Each subject received both formulations under fasting condition according to a randomized crossover design. Following oral administration, blood samples were drawn at selected times during 12hours. Ketorolac plasma concentrations were determined by using a validated HPLC assay method with UV detection and individual plasma concentration against time curves were constructed. The pharmacokinetic parameters were determined by the non-compartmental method. From serum data, the obtained values for test and reference products were 0.0183±0.0028 and 0.0203±0.0011µg/ml for $C_{max}$; 0.0427±0.0094 and 0.0557±0.0157 µg-hr/ml for $AUC_{0-12}$ and 0.0455±0.0097 and 0.0622±0.0165 µg-hr/ml for $AUC_{0-\infty}$; 0.2651±0.0464 and 0.2179±0.0872 for $K_{el}$; 2.69±0.457 hr and 3.582±1.212 hr for $t_{1/2}$ respectively. From the study, it is concluded that the two oral formulations are bioequivalent and the test product (Torax®) may be the true substitution for the reference product (Toradol®).*

## Introduction

Ketorolac is a potent analgesic agent currently used in the treatment of moderate to severe pain.[1] Clinical studies have shown that the potency and efficacy of ketorolac are similar to those of morphine,[2-4] but that it does not exhibit the untoward effects related to opioid drugs.[1] It is quite evident that the analgesic activity of ketorolac could be due to prostaglandin synthesis inhibition.[1,5] It has also been suggested that endogenous opioid release could also be involved.[6] Animal studies have shown that ketorolac is about 100 times more potent than aspirin as an analgesic agent, although its anti- inflammatory activity is limited.[5] Comparative clinical studies have confirmed that ketorolac is remarkably more potent in pain relief than currently used non-steroidal anti-inflammatory drugs.[7] One major advantage of ketorolac over other non-steroidal anti-inflammatory drugs is that the salt ketorolac tromethamine can be administered either intravenously, intramuscularly, or orally.[8,9] Therefore, it can be used in a wide variety of clinical situations. Forbes et al. reported that ketorolac is completely and rapidly absorbed after oral administration of ketorolac tromethamine,[8] resulting in fast pain relief.[7] However, the complete and better absorption with prompt pharmacological effect is related to the bioavailability of the drug. But this bioavailability and the related pharmacokinetic is to determine in different demographic population. This present study compared the bioavailability of two ketorolac tromethamine after oral administration for the first time among the Bangladeshi volunteers.

## Materials and Methods

### Drugs and reagents

Commercially available Torax® tablets were manufactured by Square Pharmaceutical Ltd. Dhaka, Bangladesh. Toradol® tablets were made available from a reliable source manufactured by Roche Ireland Ltd.( Ireland.). The internal standard naproxen was a gift of Incepta Pharmaceutical Ltd. Dhaka, Bangladesh. Deionized water was prepared using Milli-Q system (Continental Water Systems, El Paso, TX, U.S.A.). HPLC grade methanol was obtained from Merck (Darmstadt, Federal Republic of Germany). All other reagents were of analytical grade

### Subjects

Twelve young healthy male Bangladeshi volunteers participated in the study. No abnormalities were detected in routine clinical and laboratory (biochemical and haematological) tests. Demographic data are given in Table 1. None of the subjects was an alcohol or drug abuser nor taking any concomitant medication

1. Department of Pharmaceutical Technology, University of Dhaka;
2. Department of Biochemistry & Molecular biology, University of Dhaka;
3. Department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University, Dhaka.

at the time of the study. All subjects read the protocol approved by the Clinical Review Committee of Faculty of Pharmacy at University of Dhaka and gave written consent for participation before entering the study.

**Study plan**

The study was carried out according to the recommendations of the Declaration of Helsinki. All subjects received two oral pharmaceutical formulations containing 10 mg of ketorolac tromethamine in two separate trial sessions according to a randomized crossover design. A one-week washout period was allowed between the sessions. At each session, all volunteers had abstained from alcohol and caffeine-containing beverages for 24 hrs. After an overnight fast (10 h), they received a tablet of 10 mg ketorolac tromethamine with 200 ml water. The formulations were marked Toradol® as (A) and Torax® as (B); the treatment sequence for each subject is indicated in Table-1. The study was started at 7:00 a.m. Before medication, an indwelling catheter with a heparin lock was placed in a suitable forearm vein and blood samples were drawn at 0, 10, 20, 40 min and at 1, 1.5, 2, 4, 6, 8, 12 h after drug administration. Plasma was obtained by centrifugation, immediately frozen in liquid nitrogen and stored at - 40 $^0$C until analysed. Subjects remained fasting for 4 h after medication. Standard lunch was given to the volunteers.

**Determination of ketorolac in plasma**

Ketorolac plasma concentrations were determined by a high-performance liquid chromatographic (HPLC) method. To prepare 200µL of serum samples, 200µL of methanol solution were added. The mixture was vortexed for 15 sec and then centrifuged at 10,000 rpm for 5 minutes. The supernatant was transferred to disposable eppendrof and kept at -40$^0$C until analysis. Twenty microliters (20µL) of the sample was injected into the column after filtering through 0.2µ syringe filter and analyzed by HPLC with UV detection. A series of control serum samples were prepared by drug free serum with required amount of ketorolac and naproxen (I.S.) and also prepared the final serum samples of 0.12, 0.09, 0.06, 0.03 µg/mL of ketorolac. A typical chromatogram obtained with the retention time of naproxen and ketorolac was shown in Figure-1.

The chromatographic system consisted of a Shimadzu (Columbia, MD, USA) HPLC system was used in quantification of keorolac in tablets, which consisting of a SCL-20Avp system controller, two LC-8A pumps. The drug analysis data were acquired and processed using LC solution (Version 1.03 SP3, Shimadzu Corporation USA) software running under windows XP on a Pentium PC, Ultraviolet detection was achieved with a SPD-20Avp UV-VIS detector (Shimadzu Corporation, MD, USA) , a 250×4.6 mm Lichrosorb RP-18 column (particle size 5µm), and a 460 multiwavelength detector. The column was eluted with a mixture of Methanol, water and acetic acid and the mixture ratio is 55:44:1 at a constant flow rate of 1 ml/min. The effluent from the column was detected at 322 nm. Analyses were performed at room temperature. Since ketorolac tromethamine dissociates into the anion form of ketorolac at physiological pH after absorption, the measured concentrations are referred to ketorolac.

**Pharmacokinetic and statistical analysis**

The pharmacokinetics of ketorolac in serum was analyzed by non-compartmental method and program kinetica (version 4.4.1, Thermo Electron Corporation, UK) maximal plasma concentration ($C_{max}$) and time to reach the maximal concentration ($t_{max}$), half-life ($t_{1/2}$), area under the curves ($AUC_{0-12,}$ $AUC_{0-\infty}$) were directly determined from the Trykinetica software. The elimination rate constant ($k_{el}$) was determined from the half-life.

From ANOVA, it was found that the $p>0.05$ for all the parameters from the different source of variations likes formulation, period and sequence except subjects. But this variation is usual due to wide inter-individual differences. So from ANOVA it can be claimed that the difference between these two formulations (reference and test) was not significant and may produce the similar therapeutic efficacy. According to the FDA, at 90% confidence interval, the acceptable range is 80% to 125% for two drug products to be bioequivalent. From the table-2 we found that all the values are within the acceptable range. From these we can conclude that these two products are bioequivalent in respect of rate and extent of drug absorption and this can be evaluated by using both serum data.

**Results**

The bioavailability of ketorolac tablet first time in Bangladeshi healthy populations with two preparations manufactured by two different Bangladeshi pharmaceuticals was studied. The retention times of ketorolac and Naproxen were 10.49 and 16.77 minutes respectively; no interfering peaks occurred at these times (Fig-1). Calibration curves were constructed over a range of 00-0.12µg/mL. A linear relationship (r =0.9967) was obtained when the ratio of the peak areas of ketorolac and naproxen was plotted against ketorolac concentration. The coefficient of variation was always lower than 8%.

The method had a precision of 98.99±4.89% and its detection limit was 0.005µg/mL. The HPLC method thus proved to be suitable for pharmacokinetic studies.

The mean plasma concentrations of ketorolac observed in the 12 healthy volunteers studied with two oral pharmaceutical formulations: Toradol® and Torax® (Fig.-2). Ketorolac kinetics exhibited a similar pattern after administration of either formulation. Inter-individual variability in ketorolac plasma concentrations was small. For all subjects, there was a very fast absorption, a peak concentration of about 0.018µg/ml and 0.020µg/ml being attained in about 30 min and about 26 min for test and reference formulation respectively. The half-lives of the test and reference products were determined 2.69 hours and 3.58 hours. Pharmacokinetic parameters calculated from mean plasma level time curves were shown in Table-2. No statistically significant difference was observed in pharmacokinetic parameters when both formulations were compared by analysis of variance (ANOVA). Moreover, paired t-test was also done for all the parameters at 5% level of significance. All the P-values from paired t-test were greater than 0.05 which indicate that there was no significance difference except $AUC_{0-12}$ among these two formulations by using Minitab software.

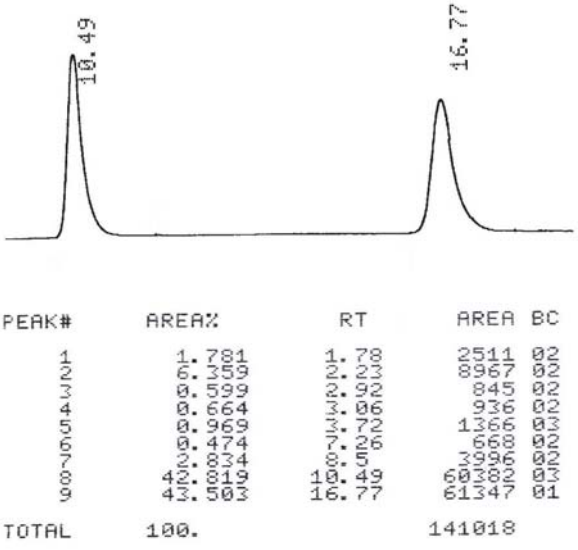


**Fig.-1:** *Chromatogram of calibrator serum sample spiked with 0.012µg/ml ketorolac and internal standard (Naproxen, 0.12µg/ml)*

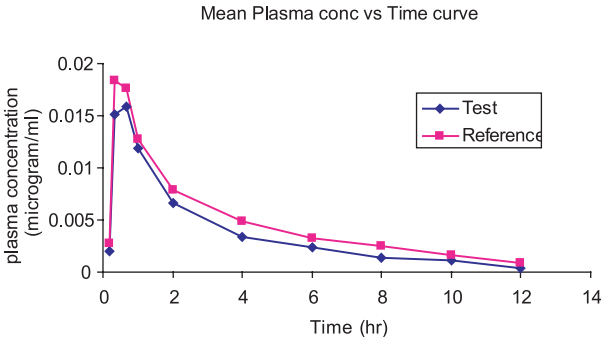


**Fig.-2**: *Mean plasma-concentration-against-time curves of ketorolac after administration of two oral formulations-Reference (Toradol®) and Test (Torax® ) products to 12 healthy volunteers.*

**Table-I**

*Demographic data and sequence of administration of ketorolac subjects who volunteered for participation in the comparison of two oral formulations of ketorolac tromethamine.*

| SL No. | Volunteer code | Age (Yrs) | Weight (Kg) | Height (m) | Sequence of administration | |
|---|---|---|---|---|---|---|
| | | | | | First session | Second session |
| 1 | Subject-UGA | 25 | 68 | 1.678 | A | B |
| 2 | Subject-JCC | 27 | 55 | 1.7 | B | A |
| 3 | Subject-ATF | 25 | 63 | 1.627 | A | B |
| 4 | Subject-RMN | 27 | 64 | 1.751 | B | A |
| 5 | Subject-EGM | 24 | 65 | 1.59 | A | B |
| 6 | Subject-MTF | 23 | 62 | 1.706 | B | A |
| 7 | Subject-NBB | 26 | 62 | 1.622 | A | B |
| 8 | Subject-MGM | 27 | 61 | 1.582 | B | A |
| 9 | Subject-JRG | 26 | 62 | 1.636 | A | B |
| 10 | Subject-NCM | 24 | 65 | 1.713 | B | A |
| 11 | Subject-JAM | 26 | 64 | 1.623 | A | B |
| 12 | Subject-MCH | 25 | 61 | 1.72 | B | A |

**Table-II**

*Pharmacokinetic parameters of ketorolac after administration of 10 mg ketorolac tromethamine in two different oral formulatiom to 12 healthy volunteers*

| Pharmacokinetic parameters | Test Formulation | Reference Formulation |
|---|---|---|
| | Mean±SD (n=12) | Mean±SD (n=12) |
| $C_{max}$ (mg/mL) | 0.018±0.0028 | 0.020±0.0011 |
| $t_{max}$ (hr) | 0.527±0.2254 | 0.443±0.2191 |
| $AUC_{o-12}$ (hr ug/mL) | 0.043±0.0094 | 0.055±0.0157 |
| $AUC_{o-\infty}$ (hr ug/mL) | 0.045±0.0096 | 0.062±0.0165 |
| MRT | 3.81±0.6385 | 4.897±1.209 |
| $AUMC_{o-12}$ ($hr^2$ ug/mL) | 0.163±0.0533 | 0.274±0.1017 |
| $AUMC_{o-\infty}$ ($hr^2$ ug/mL) | 0.175±0.0562 | 0.311±0.1295 |
| $K_{el}$ | 0.265±0.0464 | 0.218±0.0872 |
| $t_{1/2}$ (hr) | 2.69±0.4569 | 3.582±1.211 |
| $C_{max}$ / $AUC_{o-\infty}$ | 0.410±0.0717 | 0.352±0.1064 |

**Table-III**

*P-values for different pharmacokinetic parameters of two formulations calculated by paired t-test (n=12)*

| **Parameters** | $C_{max}$ | $t_{max}$ | $AUC_{o-12}$ | $AUC_{o-\infty}$ | MRT | $AUMC_{o-12}$ | $AUMC_{o-\infty}$ | $K_{el}$ | $t_{1/2}$ | $C_{max}$ / $AUC_{o-\infty}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| p-values | 0.06 | 0.78 | 0.043 | 0.057 | 0.063 | 0.045 | 0.059 | 0.061 | 0.061 | 0.062 |

## Discussion

The plasma level versus time curves of two pharmaceutical formulations of ketorolac tromethamine was compared for equivalency. It has been reported that ketorolac bioavailability after oral administration of ketorolac tromethamine is 100%, as absorption from the gastrointestinal tract is complete and there is practically no first-pass effect.[8] Since inter-individual variability in bioavailability was small, few subjects were required to detect significant differences.[14] The sample size was calculated according to the equation proposed by Stolley and Strom,[15] considering the variability reported by Jung and coworkers.[8] It appeared that from paired t-test, no significant difference were found between these two formulations as all the p-values for different pharmacokinetic parameters were greater than 0.05, except $AUC_{0-12.}$ The experimental design allowed the conclusion that the two oral formulations containing 10 mg of ketorolac tromethamine, Toradol® and Torax® were bioequivalent in both rate and extent of absorption. So, Torax® 10 mg tablet may be the good substitution of Toradol® 10 mg tablet.

## Acknowledgements

The authors are very much grateful to the Incepta Pharmaceuticals for providing internal standard Naproxen for fruitful completion of this research.

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# THE EVALUATION OF THE SOCIO-DEMOGRAPHIC AND CLINICAL FEATURES OF PSORIASIS PATIENTS: STUDY IN A TERTIARY HOSPITAL IN BANGLADESH

MT ISLAM[1], HK PAUL[2], ASM ZAKARIA[3], MJ ISLAM[4], AM CHOUDHURY[5], AZMM ISLAM[5]

**Summary**

*This cross-sectional study was conducted on 102 cases having clinical manifestation of psoriasis attending the Department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from January 2005 to June 2005 with a view to evaluate Socio-demographic and Clinical Features of Psoriasis. Seventy patients (68.6%) were males and 32 (31.4%) were females with a male to female ratio of 2.18:1. The mean age of onset was 29.56 ± 13.79 years with 30.76 ± 13.17 years in male and 26.94 ± 14.94 years in female. The mean age of onset was higher in males than in females. Sixteen (15.7%) patients had one or more family member having psoriasis with male and female in equal frequency. Plaque type of psoriasis (87.3%) was most frequent clinical presentation followed by erythrodermic pattern (5.9%). Nail changes were found in 61.8% and arthritis was found in 9.8% of psoriatics. Pruritus was experienced in 81.4% and Köbner's phenomenon was observed in 37.3% of cases. Initial site of involvement was leg (42.2%) followed by scalp (38.2%). It was concluded that males were predominant sufferer of psoriasis; the mean age of onset was lower in women. Plaque type psoriasis was the most common presentation.*

## Introduction

Psoriasis is a chronic, relapsing, inflammatory dermatosis and is characterized by well-demarcated, pruritic, salmon-pink plaques with thick, silvery-white scales. Lesions are usually symmetrically on extensor surfaces of the knees and elbows, the scalp and intertriginous areas.[1] Psoriasis occurs worldwide.[2] The prevalence is between 0.6 and 4.8% in worldwide population,[3-6] and varies according to race, ethnicity and geographic location.[6,11] Psoriasis can begin at any age, most frequently beginning in the young adult with male and female affected almost equally.[7-12] Although the cause is not completely understood,[13.14] psoriasis is a multifactorial and polygenetically inherited disease.[15,16]

Plaque psoriasis, the most common clinical presentation characterized by symmetrically distributed and well demarcated, erythematous plaques topped by white-silvery scales.[17,18] Nail involvement occurs in 10 to 50%,[10,20] and psoriatic arthritis develops in 5 to 42% of psoriatics.[21,22]

Psoriasis is an incurable and chronic disease, persisting through out life,[5,10] and profoundly impacts physical, psychological and social health and 5 to 30% of patients contemplate suicide. The negative effects of psoriasis on the quality of life can be even greater than that caused by life threatening illness.[17,18,23] The physical and psychosocial impact of the disease has stimulated a growing international interest and concern about psoriasis.[24]

**T**here have been no formal studies in our country to evaluate the Socio-demographic and Clinical Features of Psoriasis. So, this study was designed to evaluate Socio-demographic and Clinical Features of Psoriasis in a tertiary hospital in Bangladesh.

## Materials and Methods

One hundred and two patients with psoriasis were evaluated in this cross-sectional study in the Department Dermatology and Venereology, BSMMU, a tertiary hospital in Dhaka, Bangladesh during the study period from January 2005 to June 2005. Each and every patient was examined; the diagnosis was made from the morphology of the lesions and was confirmed by histopathology when in doubt.

The information included the age of onset, sex, occupation, marital status, family history of psoriasis, socioeconomic status.

1. Department of Dermatology and Venereology, Sylhet MAG Osmani Medical College Hospital, Sylhet, Bangladesh.
2. Department of Dermatology and Venereology, BSMMU, Dhaka, Bangladesh.
3. Department of Dermatology and Venereology, BSMMU, Dhaka, Bangladesh.
4. Community Medicine, Sylhet MAG Osmani Medical College Hospital, Sylhet, Bangladesh.
5. Department of Dermatology and Venereology, BSMMU, Dhaka, Bangladesh.

**Bangladesh J Medicine 2009; 20: 25-29**

Patients were classified according to the clinical pattern of the disease, body surface involvement presence, or absence of nail involvement and psoriatic arthropathy at the time of initial examination.

All the data were checked and edited after collection. Then the data were entered into computer and analyzed with the help of SPSS (Statistical package for social sciences) win version 12.0. An analysis plan was developed keeping in view with the objectives of the study.

**Results**

The data obtained from 102 psoriatic patients was as follows:

Seventy patients (68.6%) were male and 32 (31.4%) were female that indicated male preponderance. The male/female ratio was 2.19:1. The onset of disease showed a wide range of ages from 9 months to 65 years with the mean age of onset was 29.56 ± 13.79 years. The mean age of onset for male was 30.76 ± 13.17 years and female was 26.94 ± 14.94 years. The mean age at onset of psoriasis was higher in males than in females. Distribution of psoriatic patients by age of onset was shown in figure –1.

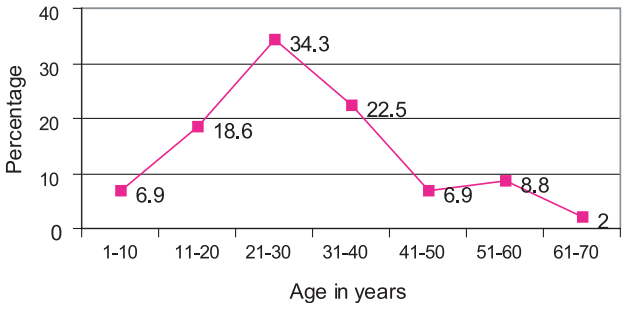


**Fig.-1:** *Distribution of psoriatics according to age of onset groups*

Of the 102 cases, 16 (15.7%) patients had one or more family member having psoriasis with equal frequency in male and female. The study also revealed that among the psoriatics with positive family history, 87.5% had the first-degree and 12.5% had the second-degree relatives with psoriasis. Our patients' marital statuses were as follows: 20 (19.6%) single, 76 (74.5%) married, 6 (5.9%) divorced or widowed. The surveyed occupations included 22 (21.6%) housewives, 14 (13.7%) business, 13 (12.7%) non-government service, 5 (4.9%) government service, 11 (10.8%) students, 10 (9.8%) day labourer, 10 (9.8%) farmer and 17 (16.7%) others.

Regarding socio-economic status, 55 (53.9%) were in lower middle class followed by 22 (21.65) poor, 21 (20.6%) upper middle class and 4 (3.9%) rich.

Plaque type of psoriasis was the most clinical types of psoriatic lesions 89 (87.2%), followed by erythrodermic pattern 6 (5.9%), guttate 4 (3.9%), nail alone 2 (2%) and generalized pustular psoriasis 1 (1%). Pruritus was experienced by 83 (81.4%) psoriatics and Köbner's phenomenon was observed in 38 (37.3%) psoriatcs.

Percentage of body surface involvement was shown in figure-2.

The initial site of involvement at the time of presentation was shown in figure-3.

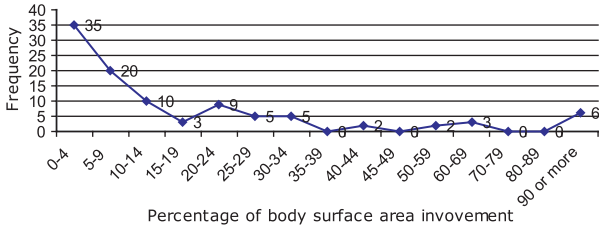


**Fig.-2:** *Distribution of psoriatics according to body surface*

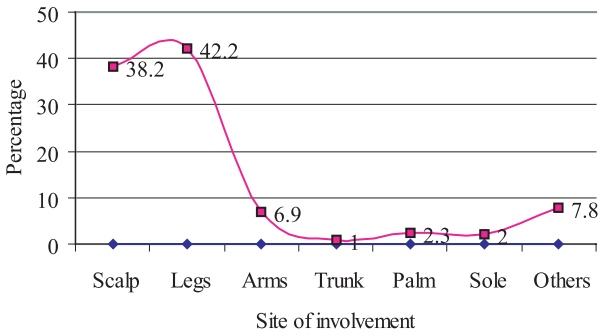


**Fig.-3:** *Site of involvement at the onset of psoriasis*

Nail changes were found in 63 (61.8%) cases. Different types of nail changes are shown in table-1.

**Table-I**

*Types of nail changes in psoriatics at the time of presentation.*

| Type of nail changes | Number of patients | Percentage |
|---|---|---|
| Nail pitting | 43 | 42.2 |
| Subungual hyperkeratosis | 23 | 22.5 |
| Nail discolouration | 18 | 17.6 |
| Longitudinal ridges | 14 | 13.7 |
| Onycholysis | 9 | 8.8 |
| Nail thickening | 9 | 8.8 |
| Opaque nail | 6 | 5.9 |
| Beaus' line | 6 | 5.9 |
| Oil spot | 2 | 2 |

Arthritis was found in 10 (9.8%) psoriatcs, the most frequent type of joint involvement was asymmetric oligoarthritis in 6 (60%) followed by arthritis in distal interphalangeal joints in 2 (20%), symmetric polyarthritis in 1 (10%) and arthritis mutilans in 1 (10%) cases among the patients with arthritis.

Arthritis was the most frequent co-morbidity (9.8%), followed by diabetes mellitus (5.9%), hypertension (4.9%) and psychosis (1.0%).

**Discussion**

This cross-sectional study was conducted among 102 patients with psoriasis attending the Department of Dermatology and Venereology, BSMMU, Dhaka, Bangladesh from January 2005 to June 2005 with a view to evaluate the socio-demographic and clinical features of psoriasis patients.

A lot of studies revealed that psoriasis in men and women was equal,[8,11,12,24,25] but male preponderance was reported in some.[33-35,37,39-43] whereas females in others.[4,9,26-30] In the current study 68.6% were males and 31.4% were females. This result was supported by Kaur et al, [31] and Kawada et al.[32] The male preponderance was supprted by others.[31-39]

Psoriasis can be present at any age and has been reported at birth and older people of advanced age of 108.[2,8,9] By this study it was also revealed that the disease had started at a wide range of ages from 9 months to 65 years.

In this study, the mean age of onset was 29.56 ± 13.79 years. Which was near similar to Ferrándiz et al, [35] and Farber et al.[26]

This study also revealed that the mean age of onset for male was 30.76 ± 13.18 years and for female was 26.94 14.94 years. Ferrándiz et al, [35] nearly supported this result. Females tend to develop psoriasis earlier than males was also supported by some other studies.[19,11,31,33,40]

Present study revealed that 34.3% had the age of onset between 21 to 30 years and no late onset peak (figure-1). Naysmith and Rees,[12] partially supported this where they had reported the first peak at late adolescent or early adult life; and no late onset peak had supported by Farber et al, [26] and Kaur et al.[31] But It was differed from others where bimodal distribution of age of onset had reported.[2,11,12,41-43]

We found a positive family history of psoriasis in 15.7% of cases. This was supported by Ferrándiz et al,[24] Kaur et al,[31] and Gunawardena et al,[33] but was differed from Ferrándiz et al,[35] Farber et al,[26] Ingram,[28] Malbris et al,[29] and three different studies conducted by Naldi et al.[30,36,37] The study also revealed that among the psoriatics with positive family history, 87.5% had the first-degree and 12.5% had the second-degree relatives with psoriasis, similar results were reported by Kaur et al,[31] (80% and 18.2% respectively).

Current study showed that vast majority of cases (87.2%) were of plaque type psoriasis followed by erythrodermic pattern in 5.9%, guttate in 3.9% and generalized pustular psoriasis in 1% and nail alone in 2% of cases. This result was nearly supported by some other findings.[31,32,35] Kaur et al,[31] had found plaque type in 90.5%, guttate in 7.41%, erythrodermic in 1.15% and nail alone in 0.51%; Kawada et al,[32] had observed plaque psoriasis in 86%, guttate in 2.8%, erythrodermic in 0.8% and generalized pustulosis in 0.9%; and Ferrándiz et al,[35] had observed plaque psoriasis in 78.8%, guttate in 14.8%, erythrodermic in 4.4% and generalized pustular in 1.5% of their psoriasis patients.

In this study pruritus was experienced by 81.4% of psoriatics, which was concordance with Szepietowski et al, [44] (80%) and nearly correlated with Krueger et al,[23] (79.7%).

It was found from this study that 37.3% psoriatics had Köbner's phenomenon. It was supported by Naldi et al, [3] (33%), and was nearly supported by Kaur et al,[31] (29.1%), and Kumar et al,[34] (27.9%), but was differed from Mallbris et al,[29] (5%), and Gunawardena et al,[33] (1.7%).

Kaur et al, [31] found the site of first involvement was scalp (32.99%), legs (24.3%) followed by other regions. Kawada et al, [32] found that onset psoriasis was mostly seen in the scalp (33.7%), followed by lower extremities (26.9%) and by other sites. But current study showed that 42.2% had their site of first involvement in legs followed by scalp (38.2%). This result was differed from the above-mentioned two studies,[31,32] but the pattern of involvement was accorded with Kumar et al,[34] who observed the site of first involvement was extensors of the legs (25%), followed by the scalp (20.7%).

From the current study it was found that 61.8% psoriatics had shown some degree of nail changes. It was supported by Kaur et al,[31] (62.2%), but was differed from Kundakci et al,[9] (16%), Kumar et al,[34] (31%) and Ferrándiz et al.[35] (39.8%).

The nail changes were recorded as pitting (42.2%), subungual hyperkeratosis (22.5%), discoloration (17.6%), longitudinal ridges (13.7%), onycholysis (8.8%) nail thickening (8.8%), opaque nail (5.9%), Beau's line (5.9%), and oil spot (2%) which were nearly

supported other studies,[31,34] Kaur et al,[31] had found pitting (56.3%), thickening (5.7%), discoloration (31.8%), subungual hyperkeratosis (10.1%), onycholysis (7%), yellow brown discoloration of nail plate (22%), nail only (0.51%) of cases; and Kumar et al,[34] had found pitting (28.8, ridging (13.3%), discolouration (11.2%), subungual hyperkeratosis (6.6%), onycholysis (6.6%), Beau's line (4.2%) among patients with nail involvement. But it was varied from Kundakci et al,[9] who observed pitting (12.8%), oily spot (0.9%), 7% subungual hyperkeratosis (7%), onycholysis (2.1%), discoloration (1.5%), splinter hemorrhages (0.3%).

From the present study it was revealed that joints were involved in 9.8% of psoriatics. Kaur et al,[31] supported this (10.24%), and nearly correlated with Ingram,[28] (7.0%) but was differed from Kundakci et al,[9] (1.5%), Kawada et al,[32] (1%), and Kumar et al,[34] (1.1%).

James et al,[45] reported asymmetric oligoarthritis (70%) was the most common type of joint involvement followed by arthritis in distal interphalangeal joints (16%), symmetric polyarthritis (15%) spondylitis (5%) and arthritis mutilans (5%). In this regard we also found, asymmetric oligoarthritis (60%), arthritis in distal interphalangeal joints (20%), symmetric polyarthritis (10%) and arthritis mutilans (10%) in the present study.

A number of diseases are associated with psoriasis, including arthritis, Crohn's disease, cardiovascular disease, hypertension, and diabetes.[8,32] Our study revealed arthritis (9.8%) as the most frequent co-morbidity, followed by diabetes mellitus (5.9%), hypertension (4.9%) and psychosis (1.0%).

## Conclusion

Males are predominant (68.8%) sufferer of psoriasis, and the mean age of onset is lower in female (26.94 ± 14.94 years vs 30.76 ± 13.17 years). Positive family history is observed in 15.7% with male and female in equal frequency. Plaque type psoriasis is the most common presentation (87.3%). Psoriatic arthritis is observed in 9.8% of psoriatics. Nails are involved in 61.8% with pitting is the most common abnormality of the nails (42.2%). Initial involvement is in legs (42.2%) followed by scalp (38.2%). Based on these result and subsequent discussion with other literature it is clear that the findings of the present study may be a useful basis for future research and planning for the control of psoriasis and its complications and also to reduce morbidity from the disease.

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# EPIDEMIOLOGIC PROFILE OF ALOPECIA AREATA - STUDY IN A TERTIARY HOSPITAL IN BANGLADESH

ASM ZAKARIA[1], HK PAUL[1], MT ISLAM[1], AZMM ISLAM[2]

**Summary**

*This cross-sectional study was conducted on 90 cases having alopecia areata (AA) with a view to evaluate the epidemiological profile of the disease. The prevalence of alopecia areata among the dermatological patients was 0.41%. 55.55% of patients were male and 44.44% were female with a male to female ratio of 1.25:1. Peak age of onset for either sex was 21-30 years constituting 46 (51.1%) of the total patients. In 31% of patients alopecia started before 20 years of age. Patchy hair loss was the commonest clinical presentation (97.77%). Diffuse hair loss was seen only in 2.22% of patients. Nail involvement was seen in 27.7% of patients and pitting was found to be the commonest change (13.3%). Personal history of atopy was present in 20% cases. Family history of atopy and alopecia areata was present in 30% and 10% of patients respectively.*

*Precipitating factors were associated with alopecia areata in 13.3% of patients. Emotional stress was the most common precipitating factor (6.6%). Associated cutaneous and systemic diseases were found in 14.4% and 10% of patients respectively.*

## Introduction

Alopecia areata is an unpredictable usually patchy, non-scarring hair loss condition affecting any of the hair bearing surfaces of the body, hypothesized to be an organ specific auto-immune disease mediated by T-lymphocytes directed to hair follicles.[1]

Alopecia areata (AA) especially when severe, often profoundly affects the lives of those afflicted. The severe hair loss produces not only cosmetic concern, but also evokes feelings of vulnerability, loss of self-esteem, alterations in self-image and perhaps even of self-identity.[2]

The epidemiology of a disease is a powerful tool that can help in the understanding of the disease. There are several epidemiologic studies, mostly from USA, United Kingdom, European countries and Japan.[2] A few reports from India are also there. There is a scarcity of published data about alopecia areata from Bangladesh. The purpose of our study is to review the epidemiology of alopecia areata in a tertiary hospital in Bangladesh. This study will certainly enrich our epidemiological records.

## Materials and methods

The study was carried out in the department of Dermatology & Venereology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. Twenty one thousand eight hundred and forty three individuals were attended in the Department of Dermatology and Venereology, BSMMU, a tertiary hospital in Dhaka, Bangladesh during the study period from April 2004 to December 2005 among them 90 patients were diagnosed as alopecia areata and were enrolled in the study. The diagnosis was made on clinical ground. Each patient was enrolled only once in the study.

A detailed history regarding age, sex, occupation, socioeconomic status, age of onset, site and pattern of alopecia, extent of hair loss, presence or absence of exclamation point hair, duration of disease, family history of alopecia, personal and family history of atopy, precipitating factors, any associated cutaneous or systemic disease was noted. Nail changes were also recorded. We adopted the alopecia areata investigational assessment guidelines collated by Olsen E et al. [44/3] The extent of hair loss was classified as S: scalp hair loss; S0= no hair loss, S1= d”25% hair loss, S2= 26-50% hair loss, S3=51-75% hair loss, S4=76-99% hair loss, S5=100% hair loss. B: body hair loss; B0= no body hair loss, B1= some body hair loss, B2= 100% body (excluding scalp) hair loss.[3] All the data were checked and edited after

1. Dept. of Dermatology & Venereology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.
2. Medical Officer, Dept. of Dermatology & Venereology, Sylhet MAG Osmani Medical College, Sylhet, Bangladesh.

**Bangladesh J Medicine 2009; 20: 30-34**

collection. Then the data were entered into computer and analyzed with the help of SPSS (Statistical package for social sciences) win version 12.0. An analysis plan was developed keeping in view with the objectives of the study.

Results

Ninety patients with alopecia areata were studied. Age range varies from1year to 40 years with mean age 22.80±9.328 years. Alopecia areata was accounted for 0.41% of the new out-patient attendance in the study period. The findings of the study were presented hereunder.

**Table-I**

*Socio-demographic variables.*

| Variables | Number(Percentage) |
|---|---|
| Age (years) | |
| 10-Jan | 10 (11.11%) |
| 20-Nov | 18 (20.00%) |
| 21-30 | 45 (50.00%) |
| 31-40 | 17 (18.88%) |
| Sex | |
| Male | 50 (55.55%) |
| Female | 40 (44.44%) |
| Occupation | |
| Student | 40 (44.44%) |
| Service holder | 28 (31.11%) |
| House wife | 18 (20%) |
| Others | 4 (4.44%) |
| Socioeconomic status | |
| Poor | 18 (20%) |
| Middle class | 63 (70%) |
| Upper class | 9 (10%) |

Table-1: Shows out of 90 patients 50 (55.55%) are male and 40 (44.44%) patients are female with a male female ratio of 1.25:1. Majority of the patients, 45(50.00%) are in the age range of 21-30 years followed by 18(20.00%) in 11-20 years age group. 44.44% patients are student followed by service holder 31.11%. 20% of the patient is house wife.70% of the patients are of middle class, 20% poor and only 10% come of the upper class.

**Table II**

*Clinical aspects of alopecia areata*

| Variables | Number (Percentage) |
|---|---|
| Age of onset | |
| (mean21.95±9.322 years) | |
| ≤1-10 | 12 (13.33%) |
| 20-Nov | 16(17.77%) |
| 21-30 | 46 (51.11%) |
| 31-40 | 16 (17.77%) |
| Site of alopecia | |
| Scalp | 80 (88.88%) |
| Bearded area | 7 (7.77%) |
| Extremity | 2 (2.22%) |
| Eye brow | 1 (1.11%) |
| Pattern of alopecia | |
| Patchy | 88 (97.77%) |
| Diffuse | 2 (2.22%) |
| Extent of hair loss | |
| d”25% scalp hair loss | 88 (97.77%) |
| AT (100% scalp hair loss) | 1 (1.11%) |
| AU (100% scalp & body hair loss) | 1 (1.11%) |
| Family history of alopecia | |
| Present | 9 (10%) |
| Absent | 81 (90%) |
| History of atopy | |
| Personal | |
| Present | 18 (20%) |
| Absent | 72 (80%) |
| Family | |
| Present | 27 (30%) |
| Absent | 63 (70%) |
| Exclamation point hair | |
| Present | 70 (77.77%) |
| Absent | 20 (22.22%) |
| Duration of alopecia | |
| d” 2 years | 81 (90%) |
| >2 years | 9 (10%) |

Table-II shows age of onset of alopecia areata in 51.11% patients are 21-30 years followed by

17.77 % each in both 11-20 years and 31-40 years age group. In 13.33% onset occurs in d” 1-10 years age group. Scalp is the involved site in 88.88% cases, bearded area in 7.77%, 2.22% in extremity and 1.11% in eye brow. Patchy hair loss seen in 97.77% cases and diffuse hair loss is only in 2.22% cases. d”25% of the scalp area is involved in 97.77% cases, 100% scalp hair loss (Alopecia totalis, AT) in 1.11% and 100% scalp and body hair loss (Alopecia universalis, AU) in 1.11% cases. Family history of alopecia areata was present in 9(10%) of patients. Exclamation mark hairs are present in 77.77% patients on the edges of fresh

or extending lesions. Personal history of atopy including rhinitis, bronchial asthma and atopic dermatitis is present in 20% of patients. Evidence of atopy in family members is present in 30% of patients. Duration of alopecia is d"2years in 81(90%) of patients and more than 2 years in 9(10%) of patients.

**Table-III**

*Nail changes in alopecia areata.*

| Nail changes | Nubmer of patients (percentage) |
|---|---|
| Nail changes | |
| Present | 25 (27.77%) |
| Absent | 65 (72.22%) |
| Types of nail changes | |
| Nail pitting | 12(13.3%) |
| Longitudinal ridges | 7 (7.7%) |
| Shiny nails | 3 (3.3%) |
| Lustreless nails | 2 (2.2%) |
| Terminal 'V' nick | 1 (1.1%) |

Table-III shows nail involvement in 27.7% patients. Pitting is the commonest change in 13.3% cases, followed by longitudinal ridging 7.7%, shinny nails 3.3%, lusterless nail 2.2%, terminal 'V' nick in 1.1% of cases.

**Table-IV**

*Precipitating factors and associated diseases in alopecia areata*

| Variables | Number (Percentage) |
|---|---|
| Precipitating factors | |
| Present | 13.30% |
| Absent | 86.66% |
| Emotional state | 6 (6.6%) |
| Febrile illness | 4 (4.4%) |
| Death of a close relative | 1 (1.1%) |
| Malabsorption | 1 (1.1%) |
| | |
| Associated skin diseases | 13 (14.4%) |
| Superficial fungal infection | 4 (4.4%) |
| Acne vulgaris | 8(8.8%) |
| Vitiligo | 1 (1.1%) |
| | |
| Associated systemic diseases | 9 (10%) |
| Hypertensoin | 1 (1.1%) |
| Diabetes mellitus | 1 (1.1%) |
| Malabsorption | 1 (1.1%) |
| Anaemia | 6 (6.7%) |

Table-IV shows precipitating factors associated with alopecia areata in 12(13.3%) of patients. Emotional stress is the most common precipitating factor in 6.6%, followed by febrile episode in 4.4%, death of close relative in 1.1%, and malabsorption in 1.1% cases.

Associated skin diseases are present in 14.4% patients, included mostly superficial fungal infections and acne vulgaris. Vitiligo is present in 2.2% patients.

Associated systemic diseases are seen in 10% of patients including hypertension, diabetes mellitus, malabsorption in1.1%, cases each and anaemia in 6.7% cases.

## Discussion

This cross sectional study was conducted with a view to review the epidemiologic profile of alopecia areata. As there is no recorded study in this field, it happens to be first of its kind in Bangladesh.

AA and its variants were found worldwide. Its prevalence across the globe varies from 0.05% to 0.1%.[5] In the present study alopecia areata was accounted for 0.41% of the new out-patient attendance in the study period.

In the present study a male-to-female ratio was 1.25:1,that is males were slightly predominant than females consistent with another study from India.[6] This could be due to the fact that men were subject to more stress, being the main earning members of the family.

Although no age group is spared, the majority of patients with AA have been found in the age group of 21-30 years. Among the patients 46.66% were within this age group (Table-I). This finding was supported by Sharma VK et al. They found 40% patients were in 20-29 years age group.[18/2]

The occupational profile varied widely among the patients. Students comprised the majority of patients (44.44%) with AA, followed by service holders (31.11%). 20% of the patients were house wife.

Dutta Banik RL. had reported similar findings.[7] He had reported that 53.3% patients were student. Probably it is due to awareness to seek medical care and also due to the fact that they are usually in the age group 20-29 years.

Seventy percent of the patients were of middle class, 20% poor and only 10% come of the upper class. This result was quite different from the study done by Sehgal V N et al. They had reported 58.5% patients belonged to the higher income group, 23.1% in the middle income and 18.5% in the low income groups.[8]

Age of onset of alopecia areata in 51.11% patients was 21-30 years followed by17.77 % each in both 11-

20 years and 31-40 years age group. In 13.33% onset occurs in d" 1-10 years age group (Table-II). This is supported by Sharma VK et al.[2] Sharma VK et al. had found the peak age of onset for either sex was 20-29 years.

Scalp was the involved site in 88.88% cases, bearded area in 7.77%, 2.22% in extremity and 1.11% in eye brow (Table-II). This finding is more or less similar to that of Sharma VK et al. Sharma VK et al. had reported scalp involvement in 77.6% of cases./[9]

We found patchy hair loss in 97.77% cases and diffuse hair loss in 2.22% of cases. This is a bit different from that of Sharma V K et al. Sharma V K et al had reported patchy alopecia over the scalp in 74.4% of cases.[2]

Pender AJ and Madani S et al had reported alopecia totalis and alopecia universalis variants in 30% to 50% of patients, [1,10] This is quiet different from that of our study. We found each of alopecia totalis and alopecia universalis in 1.11% of cases (Table-II).

The family occurrence varies from 10% to 20% in most studies,[11] but our study had only an 10% family occurrence rate.

Personal history of atopy including rhinitis, bronchial asthma, atopic dermatitis was present in 20% and evidence of atopy in family members were present in 30% of patients in our cases. These results were similar to that of Sharma et al. Sharma et al. has reported the evidence of atopy in patients and/or family members in 18% [9] Atopy has been associated with an earlier age of onset, longer duration of disease, and more severe AA compared with nonatopics,[10,12,13]as was observed in our study.

Alopecia areata generally presents as an anagen effluvium with an inflammatory insult to the hair matrix resulting in tapering of hair shaft and resulting in fracture of anagen hairs. As the hair miniaturizes or converts from anagen to telogen, the remaining lower portion of the hair rises above the level of the scalp, producing the exclamation point hair.[14]A common finding of a patchy alopecia areata is 'exclamation point' hair present at the margin.[7]We also found exclamation mark hairs in 77.77% of patients on the edges of fresh or extending lesions.

Alopecia areata produces nails changes. The reported incidence of nail changes in alopecia areata ranges from 10 to 66% depending on how diligently it is looked for. Changes can be seen in one nail, several nails or all of the nails.[1]The present study showed nail involvement in 27.7% patients. Pitting was the commonest change in 13.3% cases, followed by longitudinal ridging 7.7%, shinny nails 3.3%, lusterless nail 2.2%, terminal 'V' nick in 1.1% of cases (Table-III).

Sharma V K et al had reported that pitting was the commonest change (50.6%), followed by longitudinal ridging (27.1%), trachyonychia (rough nail)(14.8%), stippled leukonychia (13.6%), yellow brown discolouration (10.5%), pigmented bands (5.5%), shiny nails (4.3%), lusterless nail (3.7%), distal fraying (3.1%), terminal 'v' nicks (1.9%), onycholysis (1.2%). Platynychia, racket-shaped nail, congenital deformity, splinter hemorrhage, Beau's line, fissured eponychium, paronychia and suffused nails were seen in one patient each.[2]

Stress is suggested an environmental trigger in people predisposed to alopecia areata development rather than the primary basis for alopecia areata.[15]Attempts at objective evaluation using standard psychiatric procedures such as the Rorschach test showed over 90% of patients with alopecia areata to be psychologically abnormal and up to 29% to have psychological factors and family situations that may have affected the onset or course of disease.[16] We also found emotional stress as the precipitating factor in 6.6% of the patients (Table-IV).

Alopecia areata usually occurs without associated diseases. However, there is a higher incidence than usual in patients with atopic dermatitis, downs syndrome, lichen planus and such autoimmune diseases as systemic lupus erythematosus, thyroiditis, myasthenia gravis, and vitiligo.[17] We found associated other skin diseases in 14.4% of patients, included mostly superficial fungal infections and acne vulgaris. Vitiligo was present in 2.2% patients. Associated systemic diseases were seen in 10% of patients including hypertension, diabetes mellitus, malabsorption in1.1%, cases each and anaemia in 6.7% cases (Table-IV).

**Conclusions:**

Alopecia areata in Bangladesh showed a preponderance in men (M:F =1.25:1) and the majority of patients with disease (51.1%) were below 30 years of age. Patchy hair loss was the commonest clinical presentation (97.77%). The incidence of severe alopecia was seen only in 2.22% of patients. Atopy was found to be associated in 20% of patients and 10% of the family members. Precipitating factors were associated with alopecia areata in 13.3% of patients. Emotional stress was the most common precipitating factor (6.6%). Associated cutaneous and systemic diseases were found in 14.4% and 10% of patients

respectively. In 97.77% of cases d"25% scalp area is involved where the out-come is favourable.

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## CASE REPORTS

# WILSON'S DISEASE IN A YOUNG MAN PRESENTING WITH RECURRENT DARK URINE: A CASE REPORT

N C NATH[A], B JAHAN[B], MMR KHAN[C], S A ZAMAN[D], AHM FIROZ[E]

**Summary :**
*A 25 year young man presented with persistant jaundice, severe anaemia and recurrent dark urine for the last 7 years along with Hepatosplenomegaly. Evidence of haemolysis and persistantly elevated SGPT raised the suspicion of CLD with haemolytic anaemia. Decreased serum ceruloplasmin level, increased 24 hrs urinary copper excretion & provocation test after giving penicillamine therapy confirmed the diagnosis of Wilson's Disease.*

**Introduction :**

Wilson's Disease is a disorder of abnormal copper metabolism in which copper accumulates in tissues that manifests as neurological or psychiatric symptoms & liver disease rarely with feature of Haemolysis.[1] The fulminant presentation of Wilson's Disease is more common in female than in male (4:1): Symptoms usually arises between the ages of 5 to 45 years. It occurs in about 1 in 40,000.[2] It is named after Dr. Samuel Alexander Kinnier Wilson, the British neurologist who first described the condition in 1912. In 1953, Bearn discovered an autosomal recessive mode of inheritance of this disease.

There are only few reported cases of Wilson's Disease with feature of haemolysis.[3] In this situation, a 25 years young man presented with persistant jaundice, severe anaemia and dark urine with no feature of neurological, psychaiatric or eye involvement.

**Case history :**

A 25 year old man, was a garment worker, smoker, non alcoholic, normotensive presented with 7 years history of generalized weakness, persistent jaundice and recurrent dark urine. His sufferings started from 2001 when he was only 18. He stated that yellow coloration of his eyes never disappeared but fluctuant in nature. Patient noticed passage of recurrent dark urine which was intermittent, interval varies from 2 weeks to 3 months occurs averagely 3 times a year. Patient consulted with many physicians in last 7 years and took 2 bags blood transfusion. Patient states that both dark urine & jaundice increases after transfusion. There is no consanguinal marital history between his parents and no history of such illness in his brothers & sister but clumsiness of movement is described in one of his maternal aunt. He has travelling history to Chittagong hill tracks.

On general exanimation, he was depressive, ill looking, afebrile, severely anaemic, deeply icteric, vital signs are normal and there is no other finding of CLD. On systemic examination, liver is enlarged, lower border is 10 cm away from the costal margin in the mid clavicular line, surface is smooth, non tender, firm in consistency, and upper border of liver dullness in the 5$^{th}$ intercostal space. Spleen is just palpable. Examinations of other systems were unrevealing. Fundoscopy revealed no abnormality.

Before proceeding to investigation we extensively studied the previous records. The patient was found althrough anaemic with features of haemolysis with raised reticulocyte count, Serum bilirubin and SGPT persistantly high, all viral markers were negative. In USG of Hepatobiliary System,we found multiple echogenic structures in gall bladder which reveals multiple stones. Hb electrophoresis was normal, G6PD level is normal, HAM's test is negative, osmotic fragility decreased, Coomb's test is negative, serum vit-B12 level is normal, tests for IMN, VDRL, TPHA & HIV were negative. U/R/E & Renal function test reveal normal. After meticulous history taking, clinical examination and studying the previous investigation reports our impression was haemolytic anaemia with persistantly raised SGPT. Investigations done in this time CBC with PBF – Hb-35% & feature of haemolysis with increased reticulocyte count (7.50%), LFT reveals - Serum bilirubin 18.2 mg/dl, all viral markers were negative, Blood for MP negative, normal Upper GIT at

1. 200 Bedded Hospital Narayangonj.
2. 200 Bedded Hospital Narayangonj.
3. Dept. of Gastroenterology, BSMMU.
4. 200 Bedded Hospital Narayangonj.
5. Begum Khaleda Zia Medical College.

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endoscopy. After that we did following investigations Serum ceruloplasmin (205 U/L) (Normal value 280U-570 U/L),[4] 24 hours urinary copper excretion rate-7.62 micromole/day) ( Normal value <0.6 micromole/day), provocation test – 27.5 micromole/day(Normal value < 25 micromole/day),Kayser-Fleischer ring was absent.[5] So, with these clinical & libratory scenario, this patient was diagnosed as a case of Wilson's Disease and was initially treated with repeated blood transfusion under steroid covering for correction of anaemia and Tab. D-penicillamine (250 mg) 2 tab BD at least 30 min before or 2 hr after meal,Tab.Pyridoxine (25mg once daily).There was marked improvement of general well being, anaemia and jaundice and dark urine completely subsided, liver is decreased in size and spleen is impalpable & 24 hours urinary copper excretion rate decreased. We have discharged the patient with the advice of monthly follow up with physical examination and CBC, LFT, RFT & 24 hr urinary copper excretion rate to monitor effectiveness of therapy & late drug toxicity. When 24 hours urinary copper excretion rate will come to within normal limit we may expect to switch over to tab.Zinc (50 mg) 1 tab tds (150 mg daily doses) as maintenance therapy for life long.

**Discussion :**

Wilson's Disease (Hepatolenticular Degeneration) is an autosomal recessive genetic disorder which occurs due to mutations in the ATP7B gene on chromosome 13 which encodes for a copper transporting protein (ATPase) that exports copper out of the cells such transports it into the bile and incorporates it into ceruloplasmin.[6] Defects in this gene causes copper accumulation in the brain (pre dominantly in the basal ganglia), liver, kidney, cornea and many other organs.

In people with Wilson's Disease copper begins accumulating in the liver immediately after birth but signs and symptoms rarely occurs before the age of 5 or 6. The disease almost always becomes apparent before the age 30 but Wilson's Disease symptoms sometimes appear much later in life. New cases have been reported in people aged between 2 to 72 years. The increased frequency in certain country is due to high rate of consanguinal marriage. The heterogygotes carrier rate is 1 case per 100 person.

Any unexplained chronic liver disease specially in individuals younger than 40 years Wilson's Disease should be considered.[7] The condition may also manifest as acute hepatitis. Hepatic dysfunction is the presenting feature in more than half of the patients. The 3 major patterns of hepatic involvement are as follows (1) chronic active hepatitis (2) cirrhosis 3) fulminant hepatic failure. The most common presentation is cirrhosis.[8]

Most patients who present with neuropsychiatric manifestation have cirrhosis.The most common presenting neurological feature is asymmetric tremor occuring in half of individuals with Wilson's Disease. Frequently early symptorns include difficulty in speech, excessive salivation, ataxia, clumsiness with the hands and personality changes.[9] Late manifestations (now rare because of earlier diagnosis and treatment ) include dystonia, spasticity, grandmal seizure, rigidity and flexor cortracture: Psychiatric features include emotional lability, impulsiveness, disinhibition and self injuries behaviour. The reported percentage of patient with psychiatric symptoms as the presenting clinical feature is 10-20%. The range of psychiatric abnormality associated with Wilson's Disease has been divided into basic four categories as follows- Behavioral, affective disorder, schizophrenia and cognitive disorder.

In Wilson's Disease KF rings are formed by the deposition of copper in the Descemate's membrane of cornea always found bilaterally, first appeared at the superior pale of the cornea, then the inferior pole and ultimately circumferentially. The color ranges from greenish gold to brown. When well developed, ring may be readily visible to the naked eye or with an ophthalmoscope set at +40. When not visible to the unaided eye, the rings may be identified by using silt lamp examination or gonioscopy. KF ring observed in upto 90% of individuals with symptomatic Wilson's Disease and are almost invariably present in those with neurological manifestations. It is no longer considered pathognomonic unless accompanied by neurologic manifestations. This may be observed in patient with chronic chalestatic disorders such as partial biliary atresia, primary biliary cirrhosis, primary sclerosing cholangitis & cryptogenic cirrhosis.Sunflower cataract has been reported occasionally due to deposition of copper in lens.[10]

Musculoskeletal problem is common feature of Wilson's Disease. It is a degenerative process that resembles premature osteoarthritis.[11] Symptomatic joint Disease which occurs in 20-50% of patients frequently occurs after the age of 20 yrs. The arthropathy generally involves the spine and large appendicular joints such as knees, wrists & hips.

In 10-15% cases Coomb's negative acute intravascular haemolysis occurs as a complication of Wilson's Disease. [12] It is not clear why Wilson's Disease causes haemolysis but various lines of evidence suggest that high levels of free (non ceruloplasmin bound) copper have a direct effect on either oxidation

of haemoglobin, inhibition of energy supplying enzymes in the red blood cells or direct oxidative damage to the red cell membrane by the higher copper concentration. [13]

The Wilson's Disease gene is expressed in kidney tissue, therefore any renal manifestation may be primary or secondary to release of copper from the liver. Clinically, patient may resemble those with Fanconi's syndrome, defective renal acidification and excess renal losses of amino acid, glucose, fructose, galactose, pentose, uric acid, phosphate and calcium. Urolithiasis found in upto 16% of Wilson's Disease may be result of hypercalciuria or poor acidification. Haematuria and nepbrocalcinosis are reported and proteinuria and peptiduria can occur both before & after treatment of penicillamine.[14]

Wilson's Disease is diagnosed through the physical examination and laboratory testing. During the physical examination , a doctor will look for visible sign of Wilson's Disease. On slit lamp microscopy, kayser- Fleischer ring in the eyes are present in almost all people and Wilson's Disease who show signs of neurological damage. A low serum ceruloplasmin is the best single labratory clue to the diagnosis.Other features of disorderd copper metabolism should be sought;such as high free serum copper concentration ,high urine copper excretion of greater than 0.6 micromole/24 hrs and a very high hepatic copper content (on liver biopsy 250 microgram/gram dry liver weight).Measuring 24 hours urinary copper excretion whilst giving D- penicillamine (500 mg BD in 24 hours ) is a useful confirmatory test. More than 25 micromole/24 hrs is considered diagnostic of Wilson's Disease.[15] Genetic testing is termed by the existence of multiple genetic defects, but may be useful in screening families once the abnormality has been identified in an affected individual.

The Goal of Wilson's Disease treatment is two fold- To remove excess copper & to prevent copper from building up again. On treatment starting, the disease stops progressing and many sign & symptoms improve. But, liver scarring and certain neurological or psychological symptoms may not be completely reversible. Untreated Wilson's Disease is always fatal. Doctors usually prescribe one of the following medications to treat Wilson's disease. Penicillamine was the first copper chelating drug approved for use in Wilson's Disease.[16] It works by binding to copper and creating a water soluble complex that is excreted in urine. Although it is an effective treatment, penicillamine can cause serious side effects including Nephrotic syndrome, Goodpasture's syndrome,SLE, myasthenia, bonemarrow suppression,severe arthralgia.[17] As it has an antipyridoxine effect 25 mg/ day of pyridoxine should also be given. Trientine: Another chellating agent. As it is less toxic than penicillamine many doctors consider it as a first line therapy, specially in people with liver or neurological symptoms.[18] Zinc acetate or gluconate. It prevents absorption of copper from stomach and small intestine. It is effective as maintenance therapy at doses of 150 mg/day of elemental zinc; [19] For patients who are asymptomatic or have improved maximally on penicillamine or trientine. Tetrathiomolybdate : This copper binders agent is being studied in clinical trials.[20] Besides these drugs, copper containing diet-tapwater containing more than 100 microgram of copper per litre,copper containing vitamins & minerals supplements and foods such as liver,shell fish, mushroom, nuts, chocolate,dried fruits should be avoided. For people with severe cirrhosis,fulminant hepatitis or other severe liver disorders, a liver transplant may be the only option.[21]

**Conclusion:**

Anyone with unexplained liver disease or neurological symptoms with evidence of liver disease should be screened for Wilson's Disease. It requires life long treatment to reduce and control the amount of copper into the body. If the disorder is detected early & treated effectively people with Wilson's disease can enjoy good health.

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# GASTRIC LYMPHOMA PRESENTING AS REFRACTORY ASCITES – A CASE REPORT

M A RAHIM MIAH, QUAMRUL HASAN, BINOY PAUL, MASHIUR RAHMAN, ASMA RAIHAN, PK Roy, H Masud

**Introduction:**

Primary Gastrointestinal Lymphoma accounts for one fourth of malignant lymphomas; the stomach and the small bowel are the most frequently involved sites.[1] Stomach is involved in >50% of all metastatic lymphomas. Primary Gastric Lymphoma (PGL) comprised up to 5% of all the stomach tumors.[2] Multiple intra-abdominal organ infiltration or disseminated peritoneal lymphoma called 'Peritoneal Lymphomatosis' receives much less attention than peritoneal carcinomatosis in clinical practice possibly due to its relatively infrequent occurrence.[3]

**Case note:**

A 35 years old male cultivator who is non-diabetic, normotensive, non-asthmatic, non-alcoholic, was admitted into the Gastroenterology unit of the BSMMU hospital on 31st December, 2008 with the complaints of

1. mild vague upper abdominal pain for 18 months
2. Anorexia with significant weight loss, progressively increasing swelling of abdomen and legs and occasional vomiting for two months.

No history of fever, jaundice, haematemesis/melena, any heart disease, renal disease, tuberculosis or exposure to any patient with active tuberculosis. Physical examination revealed presence of mild anaemia, bipedal pitting oedema with huge ascites and an irregular, firm to hard, non-tender intra abdominal lump in the epigastrium which moves with respiration and is separated from the liver. No lymphadenopathy or hepatosplenomegaly. Heart and lungs are found to be normal. Investigation data showed that his haemoglobin level is – 12 gm/dl, ESR – 45 mm in 1st hour, Total count of WBC - $5\times10^9$/L, polymorphs-76%, platelet count - $300\times10^9$/L, RBG – 4.5 mmol/L, serum ALT – 57 u/L, serum albumin – 16 gm/L, Prothrombin time – 12.4(c-12) sec, serum amylase – 46 u/L, Blood electrolytes - $Na^+$ - 141 mmol/L, $k^+$ -4.4 mmol/L, $Cl^-$-99 mmol/L, $Tco_2$ – 22 mmol/L, CEA level – 20.3 ng/ml; HBsAg – negative, Anti-HCV – negative; X-Ray chest PA view – NAD. USG of abdomen revealed ascites with bilateral basal pleural effusion. At endoscopy – stomach showed mucosal irregularities, nodularity with surface ulceration and contact bleeding involving the distal body, antrum and pre-pyloric area, highly suggestive of Ca-stomach or gastric lymphoma (Fig.-1). Histopathology of gastric tissue showed gastric mucosa with granulation tissue and fibrino-purulent exudates; Lamina propria packed with atypical lymphocytes compatible with diffuse non- Hodgekin's lymphoma of intermediate grade.Ascitic fluid study showed protein content – 10 gm/L, albumin – 7 gm/l, amylase – 20 u/L, ADA (Adenosine Deaminase) – 26.5 u/L; cytology revealed TC – 2400 cells/ul, polymorphs – 45%, lymphocytes – 55%, no malignant cell seen. The patient was on symptomatic treatment with all possible supportive measures including transfusion of 6 units of fresh frozen plasma but there was no significant clinical improvement rather his condition was deteriorating with development of refractory ascites.

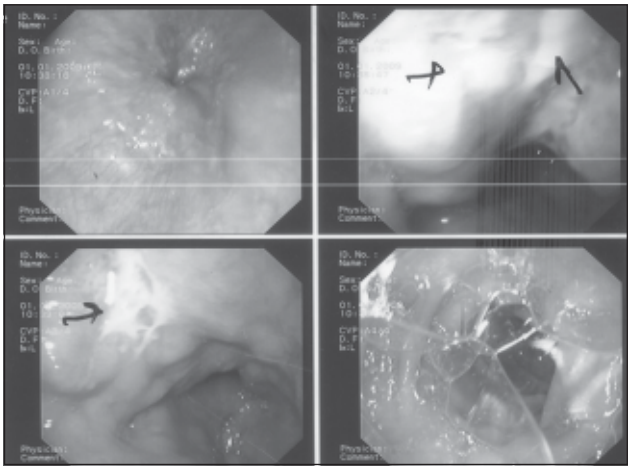

**Fig.-1:** *Findings showing mucosal irregularities & nodularity*

**Discussion:**

Primary Gastrointestinal Lymphoma is the most common extra-nodal site of involvement of all lymphomas.[4] The most common sites being the stomach, small intestine, ileo-caecum and colon in a descending order of frequency.[1, 5] Primary gastric lymphoma accounts for 5% of stomach tumors;[2] the

Depertment of Gastroenterology, Bangabandhu Sheikh Mujib Medical University (BSMMU)

most common location being the distal two third of the stomach along the posterior wall and lesser curvature. About 25% of all cases may have multiple cancer foci. Gastric outlet obstruction is rare.[6] Our patient also had endoscopic evidences of involvement of the distal body, antrum and pre-pyloric area, without any gastric outlet obstruction. Although lymphoma can involve any site of the body, diffuse and extensive involvement of the peritoneal cavity is rare[7], so lymphoma presenting as peritoneal lymphomatosis is also rare. Because of considerable overlapping of clinical features, it is very difficult to differentiate peritoneal lymphomatosis from tuberculus peritonitis, peritoneal carcinomatosis, peritoneal mesothelioma and infiltrating fibromatosis.[3]

Most common symptoms are the epigastric pain that lasted for an average of 30 months before the definitive diagnosis is made. Many patient may present with anorexia and weight loss but cachexia is less common.[8] Gastric outlet obstruction with vomiting is uncommon.[8] On physical examination an abdominal mass may be present in as many as one third of the patients.[8] This patient also presented with history of abdominal pain for 18 months, anorexia with weight loss, epigastric lump and ascites for two months, which are consistent with the clinical features of gastric lymphoma mentioned above. Sterile ascitic fluid with elevated level of protein and LDH, low glucose concentration, high ADA content are the diagnostic features of peritoneal lymphomatosis. This reporting case had ascites with low protein (10 gm/L), normal ADA level (26.5 u/L), absence of any malignant cells which are against the diagnosis of peritoneal carcinomatosis [9].In our case the transudative ascitis with bilateral basal pleural effusion might be due to associated hypoalbuminemia (serum albumin -16 gm/L).However, ascites refractory to diuretic therapy plus transfusion of several units of fresh frozen plasma and supplementary albumin infusion is unlikely in case of hypoalbuminemia. On the other hand, ascitic fluid negative for malignant cells with normal ADA level do not exclude the diagnosis of peritoneal lymohomatosis. Microscopic findings of gastric lymphoma reveal a diffuse histocytic non-Hodgekin's lymphoma in > 50% cases with well-differentiated lymphocytic and mixed cell lymphocytic pattern in about 33% of cases. [10, 11] Microscopy of the endoscopic gastric biopsy of our patient also revealed diffuse non-Hodgekin's lymphoma of intermediate grade.

Considering all the clinical and investigation data, the case is diagnosed as gastric lymphoma presenting with refractory ascitis.An oncologist was consulted and CHOP therapy started on the 8th January 2009 as per advice with reporting of marked clinical improvement after 2 cycles of therapy. In conclusion, disseminated peritoneal involvement of extra-nodal and gastrointestinal lymphoma is very unusual and needs further attention.

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# GASTROINTESTINAL STROMAL TUMOR (GIST) PRESENTING AS ABDOMINAL TUMOR - A CASE REPORT

M A RAHIM MIAH, QUAMRUL HASAN, BINOY PAUL, MASHIUR RAHMAN, HASAN MASUD
PK ROY, ASMA RAIHAN

**Introduction:**

Gastrointestinal Stromal Tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. Stromal tumors represent less than 1% of all the gastrointestinal tract tumors.[1, 2]. It has been assumed that GIST arise from the myenteric ganglion cells-so called interstitial cells of Cajal or its precursors.[3,4] Approximately 60% of the GISTs occur in the stomach, 25% in the small intestine, and 10% in the colon and rectum. The remainder arise from other sites in the GI tract or rare other locations such as the gall bladder, appendix, omentum or mesentery. GISTs account for approximately 2% of all the stomach tumors, 14% of small intestine tumors, and 0.1% of colon tumors.[5,6] The prevalence of stromal tumors amounts to 20-40 per million inhabitants per year.[7] In the United States, the incidence is approximately 5000 new cases annually.[8] The median age at diagnosis is approximately 58 years.[1] As early as the 1940s , the GISTs were often diagnosed smooth muscle tumors of the GI tract ( GI leiomyosarcoma, leiomyoblastoma and leiomyoma), but advances in histopathology later provided evidence that the GISTs are distinct from the smooth muscle tumors. GISTs may be submucosal, mural or subserosal. In the majority of cases (54%), metastasis are found in the liver, in 22% they are isolated lesions, and in 32% coexist with intra-peritoneal dissemination.[9]

**Case Note:**

A 55 year old male, who is non-diabetic, non-asthmatic, non-alcoholic, normotensive, got admitted in the Gastroenterology unit of BSMMU hospital, on the 20th November, 2008 with the complaints of

1. Anorexia with significant weight loss ( 6 kg ) for 4 months and
2. altered bowel habit for 1 month

He had no complain of fever, pain abdomen, vomiting, respiratory or urinary symptoms or any sort of GI bleeding. No history of pulmonary TB or exposure to any patient with tuberculosis. On examination he was severely anemic but non-icteric and had no edema or palpable lymph nodes. There was an intra-abdominal firm to hard irregular lump measuring 8 × 10 cm in size in the epigastrium which moves with respiration. No hepatosplenomegaly, no ascites. Examination of other system revealed no abnormality. Investigation data showed that his hemoglobin level is 6.25 gm/dl, ESR-70 mm in 1st hour. Total count of WBC-$12.3\times10^9$/L with Polymorphs -60% and Lymphocytes-30%; Platelet count-$300\times10^9$/l, PBF-combined deficiency anemia ,FBG-6 mmol/l, ALT-59 u/l,AST-70u/l,ALP-235u/l, S. bilirubin-12µmol/l,Serum creatinine-1.3mg/dl, CEA-2.4 ng/ml, M.T-02 mm (negative). Endoscopy of upper GI tract revealed no abnormality. USG of whole abdomen showed a hypoechoic irregular mass measuring 9.3×9.0 cm in size in the left upper abdomen which is separated from the liver, spleen and left kidney suggestive of bowel mass/lymphoma. CT scan of upper abdomen revealed a fairly large irregular soft tissue mass in the left upper quadrant of the abdomen in between stomach and spleen suggesting a possibility of colonic mass lesion. Colonoscopy revealed no abnormality. CT guided FNAC from the mass revealed evidences of malignant tumor cells with glandular differentiation suggestive of gastrointestinal stromal tumor. For confirmation CD 117 immunohistochemical analysis of the sample was done and found to be CD 117 positive.

**Discussion:**

Gastrointestinal stromal tumors are the most common mesenchymal tumor of the GI tract.[1] Gastrointestinal stromal tumors have been diagnosed during the recent several years. The prevalence of stromal tumors accounts to 20-40 per million people per year.[7] EORTC study showed that the incidence rate is approximately 4-5 cases per million per year.[9] The prevalence of clinically significant GIST that is inoperable, metastatic and high risk GISTs amounts to 20-30%, equivalent to approximately 3-4 cases per million.[9, 10] The prevalence of GISTs is similar in men and women. GISTs usually appear in patients above the age of 50 years with the highest incidence in the 5th and 6th decade of life. The mean age at the diagnosis is 55-63 years.[8] The majority of GIST (40-70%) are found in the stomach, usually in the fundus and accounts 1-3% of stomach neoplasms. About 20-50% of GISTs are localized in the small intestine usually in the jejunum, very rarely found in the large intestine and rectum (5%), less than 5% in the oesophagus.[5,6] In about 6% cases due to the

Depertment of Gastroenterology, Bangabandhu Sheikh Mujib Medical University (BSMMU) Hospital.

progression of the disease and multi-focal intra-peritoneal dissemination it is impossible to determine the primary site of the tumor. Metastasis are usually limited to the abdominal cavity and liver is the most common site of secondaries, rarely metastasized to lungs.[11] Usually no metastasis is found in the regional lymphnodes.[9]

The clinical presentation of GISTs depends on site and size of the tumor. About 10-30% of the GISTs are completely asymptomatic and discovered incidentally during the endoscopic, radiologic investigation including ultrasonography, CT scan, endosonography as well as during surgical interventions performed in order to diagnose various non-specific symptoms. When present, the symptoms are non-specific and include: abdominal pain (20-30%), early satiety, flatulence, subileus or ileus (10-30%), prolonged gastrointestinal bleeding (about 50%), unexplained anemia, weight loss, vomiting and acute abdomen.[12-14] Gastrointestinal stromal tumors may present as an abdominal tumor on physical examination.[15,16] Stomach tumors may cause epigastric pain , anorexia, nausea, vomiting and weight loss .[7,9,16,17] Small intestine GISTs usually present with abdominal pain, sometimes mimicking biliary colic, duodenal tumors may cause jaundice. Colonic lesions may be manifested with abdominal pain or altered bowel habits. Independently of localization of GIST may cause ileus, perforation, acute abdomen as well as GI bleeding. Majority i.e. about 95% of the GISTs are CD-117 antigen positive whereas 60-70% express antigen CD 34.[7,9,16,17]

This patient presented with 4 months history of anorexia, weight loss, altered bowel habit with an intra-abdominal mass. His oesophagogastro-duodenoscopy and colonoscopy revealed no abnormal finding. USG of abdomen revealed a hyopoechoic irregular mass in left upper quadrant of the abdomen. CT guided FNAC from the mass revealed features highly suggestive of GIST with positivity for CD-117 on immunohistochemical staining.

Considering all the clinical features, investigation data including CD-117 positivity the reporting case is diagnosed as GIST presenting as abdominal tumor, although the primary site could not be identified. A surgeon was consulted and the case was transferred to surgery unit for surgical intervention.

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# IDIOPATHIC DILATED CARDIOMYOPATHY IN PREGNANCY: CASE REPORT WITH BRIEF REVIEW

S A BEGUM[1], M FARIDUDDIN[2], A K M AKHTARUZZAMAN[3], R K KAZAL[1]

**Abstract**

*Peripartum cardiomyopathy (PPCM) is a dilated cardiomyopathy with impaired systolic function that occurs usually between the last month of pregnancy and the five months following delivery. Peripartum cardiomyopathy is a rare disease of unclear etiology with a frequent poor outcome, despite optimal medical therapy. It is associated with high mortality rate (60%). Echocardiography confirms the diagnosis by showing a left ventricular dilatation and a decreased ejection fraction. Up to date, the treatment remains symptomatic. In case of peripartum cardiomyopathy; first clinical manifestation is respiratory distress and exhaustion. Pregnancy with respiratory distress must be evaluated meticulously. We present two patients with peripartum cardiomyopathy requiring Cesarean section (CS) who was managed with spinal (SE) anesthesia and combined spinal-epidural anesthesia (CSE).*

## Introduction

Peripartum cardiomyopathy (PPCM) is a rare and life-threatening disease of unknown aetiology[1].Unlike other parts of the world in which cardiomyopathy are rare, dilated cardiomyopathy is a major cause of heart failure throughout Africa[2]. Its aetiopathogenesis is still poorly understood, but recent evidence supports inflammation, viral infection and autoimmunity as the leading causative hypotheses[3]. This diagnosis should be limited to previously healthy women who present with congestive heart failure (CHF) and decreased left ventricular systolic function in the last month of pregnancy or within 5 months after delivery. Recently, introduction of echocardiography has made diagnosis of PPCM easier and more accurate. Conventional treatment consists of diuretics, vasodilators, and sometimes digoxin and anticoagulants, usually in combination[4]. Patients who fail to recover may require inotropic therapy. In resistant cases, newer therapeutic modalities such as immunomodulation, immunoglobulin and immunosuppressant may be considered. Prognosis is highly related to reversal of ventricular dysfunction. Compared to historically higher mortality rates, recent reports describe better outcome, probably because of advances in medical care. Based on current information, future pregnancy is usually not recommended in patients who fail to recover normal heart function. Peripartum cardiomyopathy occurs in approximately 1/10,000 deliveries[1] and can result in severe ventricular dysfunction during late pregnancy or early puerperium.[2]

## Case Reports

Case – 1: 26 year old 2nd gravid lady had been suffering from 34weaks twin pregnancy with severe respiratory distress was admitted at the city clinic. Her first baby was delivered by caesarean section due to pregnancy induced hypertension at her 37weeks pregnancy. She was on regular antenatal check up but not to a fixed obstetrician. From the beginning of her pregnancy she feels fatigability weakness. At her 16 weeks of pregnancy she was diagnosed as twin pregnancy by ultrasound. She was underwent all routine investigation those were within normal limit. But one thing was that she never underwent any investigation like ECG, Echocardiogram and thyroid profile. There were no clinical findings regarding her heart and lungs in her prescription. In each visit when she complaints of respiratory distress, she was counseled it was due to her twin pregnancy. After delivery she will be OK. After admission she was under observation.2nd day of her admission she had underwent caesarean section under coverage of spinal anesthesia. During operative procedure she developed intractable hypotension and cardiac arrest during spinal anesthesia for elective caesarean section. Cardiopulmonary resuscitation was not successful for mother and baby made a good recovery. Postoperative investigation revealed a dilated cardiomyopathy related to pregnancy. .After diagnosis in spite of vigorous treatment poor lady expired keeping her two female babies in this world.

CASE – 2: In another case in which 32 years old parturient with the diagnosis of peripartum

1. Department of Gynae & Obstetrics, BSMMU, Dhaka
2. Department of Endocrine Medicine, BSMMU, Dhaka
3. Department of Anaesthesia, BSMMU, Dhaka

**Bangladesh J Medicine 2009; 20: 43-45**

cardiomyopathy presented in congestive heart failure for emergent Cesarean section. Continuous spinal anesthesia and combined spinal-epidural anesthesia were successfully employed as the anesthetic techniques for the procedures. Patient remained hemodynamically stable during surgery and was discharged home on postoperative day 8. During the period she was under the combined treatment of Obstetrician and Cardiologist.

**Discussion**

Although the etiology of peripartum cardiomyopathy is uncertain, viral, autoimmune and idiopathic causes have been considered.[3] Cardiomyopathy is usually a diagnosis of exclusion. Common misdiagnoses include other types of cardiomyopathy, valvulopathies, accelerated hypertension, diastolic ventricular dysfunction, systemic infection, pulmonary embolism, etc.[4] There is an increased incidence with multiple gestation, preeclampsia, obesity, advanced maternal age,[1] African descent and prolonged tocolysis.[4] Treatment includes digitalis, diuretics, vasodilators, and anticoagulants[4]. If supportive treatment fails, cardiac transplantation may be indicated[5].

The prognosis is related to the recovery of ventricular function.[4] The mortality rate of peripartum cardiomyopathy is 30–60% and may be caused by severe pulmonary congestion, and/or thrombo-embolic events.[2,6] Survivors have a 50–80% risk of developing cardiac failure during future pregnancies, with an associated mortality rate of 60%[7]. Cardiovascular status may benefit from prompt vaginal delivery or CS.[1]

There is scant information in the literature regarding the anesthetic management of peripartum cardiomyopathy, although several anesthetic options for CS have been reported. Malinow presented two patients undergoing CS under spinal anesthesia and general anesthesia (GA) respectively.[8] Both had full cardiac recovery within seven to eight days. Epidural lidocaine, titrated in small aliquots together with fentanyl, has been successfully employed in a patient with pulmonary hypertension and cardiomyopathy.[9]

GA may be necessary for urgent CS.[6] However, performing a rapid sequence induction on a patient with compromised cardiac function can be very challenging. When time permits, a carefully administered regional anesthetic would seem to be advantageous. In addition to avoiding the stress of GA, the vasodilatation produced by regional anesthesia is beneficial with isolated left ventricular dysfunction.[10]

If time permits, hemodynamics should be optimized by careful fluid replacement under the control of invasive monitoring prior to surgery. We chose to monitor CVP rather than pulmonary capillary wedge pressure for assessing the cardiac filling pressures primarily because the patient was asymptomatic and hemodynamically stable despite the low EF. Successful outcome using only non-invasive monitoring has been reported[11]. Intraoperative monitoring with trans-esophageal echocardiography has been reported in obstetric patients with hypertrophic cardiomyopathy[12].

We preferred CSE to epidural anesthesia (EA) for several reasons. First, CSE has a lower failure rate than EA[13]. Secondly, intra-operative patient satisfaction, anxiolysis, and post-operative pain scores have been superior with CSE[14]. Furthermore, some authors report a lower incidence of hypotensive episodes with CSE compared to EA[13]. Another advantage of CSE includes a lower maternal and umbilical cord blood concentration of local anesthetics[13].

There are also disadvantages associated with using CSE. Local anesthetics should be injected into the epidural space in small increments to avoid severe hypotension[15] in case the catheter has accidentally migrated into the subarachnoid space. The epidural injection of opiates with the CSE technique may be dangerous because of the potential for accidental catheter migration and injection of a large dose of opioid into the subarachnoid space with the ensuing risk of respiratory arrest[16]. The incidence of meningitis after CSE may be higher than after spinal or EA.[17] In our case, careful fluid administration under the guidance of invasive monitoring and a well-tailored regional anesthetic satisfied the anesthetic goals emphasized above[9].

To our knowledge this is the first report of the use of CSE anesthesia in a patient with peripartum dilated cardiomyopathy. Although a single case has no role in predicting anesthetic outcome, we believe this case demonstrates that CSE anesthesia is an acceptable option for patients with peripartum dilated cardiomyopathy undergoing CS. In general, treatment consists of the use of ACE inhibitors in asymptomatic or symptomatic patients, the use of diuretics in volume-overloaded subjects, and the use of digoxin in subjects who remain symptomatic on the former medications.

An emerging treatment strategy is the use of beta-adrenergic blocking agents in mild to moderately symptomatic subjects. Whereas in both ischemic and

nonischemic dilated cardiomyopathies, second- and third-generation compounds improve LV function, reduces hospitalizations, and lower mortality. Additionally, adjunctive therapy includes anticoagulation in subjects with lower LV ejection fractions to prevent thromboembolic complications. Amiodarone is used to treat symptomatic arrhythmias. It is mandatory to maintain potassium levels in the high normal (4.3-5.0 meq/L) range to prevent sudden death. Frequent clinic visits need be ensured to adjust medications. Aggressive approach should be taken to treat ischemia & revascularization must be maintained.

**Conclusions**

Subjects who have developed peripartum cardiomyopathy should never become pregnant again, even if myocardial function has recovered fully. In management of dilated cardiomyopathy full cooperation of Cardiologist, Obstetrician & Anesthetist are mandatory for better outcome.

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# PSEUDOHYPOPARATHYROIDISM: A RARE CAUSE OF RESISTANT TETANY

M FARIDUDDIN [1], P SENGUPTA [2], H BANU [2], M A HASANAT[1], A R HOWLADAR [3], N A CHOWDHURY [4]

**Abstract**

*Tetany is not an uncommon condition. Hypocalcaemia results in increased neuromuscular irritability and tetany. Here we are reporting a case of resistant tetany. Mrs. Tamanna, a 24-year-old female patient, mother of two children has been suffering from recurrent attacks of carpopedal spasm since she was 9 years old. She was diagnosed as a case of pseudohypoparathyroidism in 2005 and has been on tab. calcium 2gm/day and cap. Dicaltrol 0.25 microgram/day. Despite these drugs she experienced repeated attacks of tetany and her symptoms deteriorated after she became pregnant 9 months back. She got admitted in BSMMU on 6/4/2008 with similar complaints. Her serum calcium was 7.3 mg/dl*

*(corrected calcium 8.8 mg/dl) ,serum phosphate 4.4 mg/dl , serum alkaline phosphatase 900 u/L , serum PTH 91.8 pg/ml, serum albumin 27g/l. Her calcium level did not come to normal level despite she was being treated with injectable calcium and high doses of oral calcium 3 g/day, dicaltrol 2 mg/day. But after correcting hypomagnesaemia with intravenous magnesium sulfate her serum calcium and magnesium level became normal and she clinically became symptom free. She was finally discharged with oral magnesium supplement (syp magnesium hydroxide 1 tsf b.d) and tab calcium carbonate 1.5 g/day and tab dicaltrol 1 mg/day and was advised for follow up. In her follow up visit after one month she was symptom free, her serum calcium level was 9 mg/dl, serum magnesium 1.5 mg/dl. Hypomagnesaemia may present with the same constellation of symptoms and signs of hypocalcaemia. Sustained correction of hypocalcaemia cannot be achieved by administration of calcium alone in patients of hypomagnesaemia. Correction of hypomagnesaemia can correct hypocalcaemia and reverse symptoms of hypocalcaemia such as tetany. So in any resistant case of tetany hypomagnesaemia should be excluded.*

## Introduction

Tetany occurs in all syndromes in which ionized calcium concentrations are low. In the absence of alkalosis, tetany usually occurs in adults only if total serum calcium is <2.0 mmol/l (8 mg/dl).[1]

A decrease in the concentration of free calcium ions in plasma results in increased neuromuscular irritability and tetany. This syndrome is characterized by peripheral and perioral paresthesia, carpopedal spasm, anxiety, seizures, bronchospasm, laryngospasm, Chvostek's sign, Trousseau's sign, and Erb's sign, and lengthening of the QT interval of the electrocardiogram. The level of calcium ions that determines which features of tetany will be manifested varies among individuals. Tetany is also influenced by conditions like hypomagnesaemia and alkalosis. Acidosis raises the threshold for tetany. [2]

Chronic hypocalcaemia is less common than hypercalcaemia; causes of hypocalcaemia include chronic renal failure, hereditary and acquired hypoparathyroidism, vitamin D deficiency, pseudohypoparathyroidism, and hypomagnesaemia. [2]

Pseudohypoparathyroidism (PHP) is a heterogeneous group of disorders characterized by hypocalcaemia, hyperphosphataemia, increased serum concentration of parathyroid hormone (PTH), and insensitivity to the biological activity of PTH .[4]

PTH is responsible for minute-to-minute regulation of plasma calcium concentration. Therefore, the occurrence of hypocalcaemia must mean a failure of the homeostatic action of PTH. Failure of the PTH response can occur due to hereditary or acquired parathyroid gland failure, if PTH is ineffective in target organs, or if the action of the hormone is overwhelmed by the loss of calcium from the ECF at a rate faster than it can be replaced. [2]

Hypomagnesaemia may present with the same constellation of symptoms and signs; hence, ideally, serum magnesium levels should also be measured in each patient having these symptoms. Sustained

Department of Medicine (Endocrine), BSMMU

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correction of hypocalcaemia cannot be achieved by administration of calcium alone in patients of hypomagnesaemia; instead, administration of magnesium corrects the hypocalcaemia in such patients.[3]

**Case report**

Mrs. Tamanna, 24 year old female patient, mother of two children has been suffering from recurrent attacks of carpopedal spasm since she was 9 years old. She had no history of thyroid surgery, or neck surgery, external neck irradiation, no family history of similar illness. She comes of a middle class family with normal dietary history. She got admitted in Dhaka Medical College Hospital in 2005 with carpopedal spasm, vomiting and fever. Her serum calcium was 0.5 mol/l, PTH 208 pg/ml, serum magnesium and phosphate was normal. CT scan of brain revealed bilateral calcification of basal ganglia. She was diagnosed as a case of psedohypoparathyroidism and was referred to endocrinology unit of BSMMU. She has been on tab. calcium 2gm/day and cap. Dicaltrol 0.25 microgram/day. Despite these drugs she experienced repeated attacks of tetany and her symptoms deteriorated after she became pregnant 9 months back. She got admitted in BSMMU on 6/4/2008 with similar complaints .This time her serum calcium was 7.3 mg/dl (corrected calcium 8.8 mg/dl), serum phosphate 4.4 mg/dl, serum alkaline phosphatase 900 u/L, serum PTH 91.8 pg/ml, serum magnesium was 1.4 mg/dl. Serum albumin 27g/l. Her calcium level did not come to normal level despite she was being treated with injectable calcium and high doses of oral calcium 3 g/day, dicaltrol 2 mg/day. But after correcting hypomagnesaemia with intravenous magnesium sulfate her serum calcium and magnesium level became normal and she clinically became symptom free. She was finally discharged with oral magnesium supplement (syp magnesium hydroxide 1 tsf b.d) and tab calcium carbonate 1.5 g/day and tab dicaltrol 1 mg/day and was advised for follow up.

In her follow up visit after one month she was symptom free, her serum calcium level was 9 mg/dl, serum magnesium 2 mg/dl.

**Discussion**

Hypocalcaemia is frequently encountered in patients who are hospitalized. Presentations vary widely, from asymptomatic to life-threatening situations. [5]In order of frequency, hypocalcaemia occurs in patients with chronic and acute renal failure; vitamin D deficiency; magnesium (Mg) deficiency; acute pancreatitis; hypoparathyroidism and pseudohypoparathyroidism; and infusion of phosphate, citrate, or calcium-free albumin [5]

Ionized calcium is the necessary plasma fraction for normal physiologic processes. In the neuromuscular system, ionized calcium levels facilitate nerve conduction, muscle contraction, and muscle relaxation. Calcium is necessary for bone mineralization and is an important cofactor for hormonal secretion in endocrine organs. At the cellular level, calcium is an important regulator of ion transport and membrane integrity. The calcium turnover is estimated at 10-20 mEq/d. Approximately 500 mg of calcium are removed from the bones daily and replaced by an equal amount. Normally, the amount of calcium absorbed by the intestines is matched by urinary calcium excretion. Despite these enormous fluxes of calcium, the levels of ionized calcium remain stable because of the rigid control of parathyroid hormone (PTH) and vitamin D levels. Normocalcemia requires PTH and normal target-organ response to PTH. The parathyroid gland has a remarkable sensitivity to ionized serum calcium changes.[3]

In 1942, Fuller Albright first introduced the term pseudohypoparathyroidism to describe patients who presented with PTH-resistant hypocalcaemia and hyperphosphatemia along with an unusual constellation of developmental and skeletal defects, collectively termed Albright hereditary osteodystrophy (AHO). These features include short stature, rounded face, shortened fourth metacarpals and other bones of the hand and feet, obesity, dental hypoplasia, and soft tissue calcifications/ossifications. In addition, administration of PTH failed to produce the expected phosphaturia or to stimulate renal production of cyclic adenosine monophosphate (cAMP). [4]

There are various types of pseudohypoparathyroidism:

* Type 1a pseudohypoparathyroidism has a characteristic phenotypic appearance (Albright's hereditary osteodystrophy), including short fourth and fifth metacarpals and a rounded facies. It is most likely an autosomal dominant disorder.

*Type 1b pseudohypoparathyroidism lacks the physical appearance of type 1a, but is biochemically similar.

* Type 2 pseudohypoparathyroidism also lacks the physical appearance of type 1a. While biochemically similar.Type 1 and 2 disease may be distinguished by the differing urinary excretion of cyclic AMP in response to exogenous PTH. Type 2 show normal urinary cyclic AMP excretion.[6]

The reported case is considered as type 1b pseudohypoparathyroidism as she lacks the physical appearance although urinary excretion of cyclic AMP in response to exogenous PTH could not be demonstrated because of lack of availability.

The pathophysiology of intracerebral calcification in hypoparathyroidism, which appears paradoxical, is unknown. It is usually asymptomatic. When neurological effects occur, they are thought to be caused by microvascular degeneration from massive perivascular calcium deposition in high-metabolic areas.[7] Basal ganglia calcification and extrapyramidal syndromes are more common and earlier in onset in hereditary hypoparathyroidism [2]. The CT scan of brain of our reported case revealed bilateral calcification of basal ganglia which indicate the presence of chronic hypocalcaemia.

Hypocalcaemia associated with hypomagnesaemia is usually associated with both deficient PTH release and impaired responsiveness to the hormone. Patients with hypocalcaemia secondary to hypomagnesaemia have absent or low levels of circulating PTH, indicative of diminished hormone release despite maximum physiologic stimulus by hypocalcaemia. Plasma PTH levels return to normal with correction of the hypomagnesaemia. Thus hypoparathyroidism with low levels of PTH in blood can be due to hereditary gland failure, acquired gland failure, or acute but reversible gland dysfunction (hypomagnesaemia).[2]

In our case it was very difficult to control s. calcium level despite the use of very high dose of oral calcium (3 gm/day) and dicaltrol (2 mg/ day). But after correcting hypomagnesaemia with intravenous magnesium sulfate her serum calcium and magnesium level became normal and she clinically became symptom free with normalization of serum calcium.

Magnesium is a cofactor in more than 300 enzyme regulated reactions. Most importantly forming and using ATP, i.e. kinase. There is a direct effect of magnesium on sodium- (Na), potassium- (K) and calcium (Ca)channels. It has several effects:Potassium channels are inhibited by magnesium. Hypomagnesaemia results in increased efflux of intracellular Mg. The cell loses potassium which then is excreted by the kidneys, resulting in hypokalaemia.

Release of calcium from the sarcoplasmic reticulum is inhibited by magnesium. Low levels of magnesium stimulate the release of calcium and thereby an intracellular level of calcium. This effect similar to calcium inhibitors makes it “nature’s calcium inhibitor.” Lack of magnesium inhibits the release of parathyroid hormone, which can result in hypoparathyroidism and hypocalcemia. Furthermore, it makes skeletal and muscle receptors less sensitive to parathyroid hormone. [2]

The effects of magnesium on PTH secretion are similar to those of calcium; hypomagnesaemia suppresses and hypomagnesaemia stimulates PTH secretion. The effects of magnesium on PTH secretion are normally of little significance, however, because the calcium effects dominate. Greater change in magnesium than in calcium is needed to influence hormone secretion. Nonetheless, hypomagnesaemia might be expected to increase hormone secretion. It is therefore surprising to find that severe hypomagnesaemia is associated with blunted secretion of PTH. The explanation for the paradox is that severe, chronic hypomagnesaemia leads to intracellular magnesium deficiency, which interferes with secretion and peripheral responses to PTH. The mechanism of the cellular abnormalities caused by hypomagnesaemia is unknown, although effects on adenylate cyclase (for which magnesium is a cofactor) have been proposed.[2]

Hypocalcaemia and tetany improved in our case after correcting hypomagnesaemia reflecting the importance of correcting hypomagnesaemia in resistant cases of tetany. She was put on oral magnesium supplement and discharged with advice for follow up.

In conclusion, we can say, in any resistant case of tetany hypomagnesaemia should be excluded.

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