

MONITORING THE ADVERSE PROFILE OF ATENOLOL - A COLIABORATIVE STUDY

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Abstract : Atenolol, a cardio selective β -adrenergic blocker, frequently prescribed in various cardiac ailments, has not been thoroughly investigated for its adverse reaction profile in Indian patient. The present ADR monitoring study which was open, prospective and collaborative was therefore planned. A total of 440 patients with various heart disease were enrolled after a strict inclusion and exclusion criteria from Maulana Azad Medical College, New Delhi and J.N. Medical College, Aligarh. fifteen patients dropped out leaving 435 for final analysis. Cold extremities occurred in 1.18% headache and dizziness in 1.41% breathlessness in 0.94% oedema in 0.70% and bradycardia in 0.47%. Adverse drug reaction in our study were less than those reported from Western countries. Better patient selection, optimal dose could have reduced the frequency of ADR in the present study. Racial factor and season might be operating to bring down ADR to atenolol in Indian patients.

Key words : atenolol adverse drug reaction β -adrenergic blockers

INTRODUCTION

Atenolol a cardoselective β -adrenergic antagonist without any partial agonist activity (1) is extensively used in hypertension (2-6), ischemic heart disease (7-11), and cardiac arrhythmias (12-13). Although, the incidence of adverse drug reaction (ADR) with its use is low, but these do occur and occasionally are of serious nature (11, 14-22). The overall incidence of ADR's are variable and these depend on the method of recording, study duration, disease state and season. ADR's may also have some racial predisposition.

A number of ADR related studies have been reported in Western literature but the data on Indian patients is very meagre. Only a few case reports are available. The present prospective adverse drug reaction monitoring study was therefore planned to monitor ADR to atenolol in patients with cardiovascular ailments in hospital set up.

METHODS

A total of 440 patients attending Hypertensive Clinic and Medical Units of Maulana Azad Medical College, New Delhi and Medical Unit of J.N. Medical College, A.M.U., Aligarh were included in this open, prospective, I.C.M.R. sponsored collaborative study. Patients selected for ADR monitoring were subjected to physical examination, routine hematology, blood chemistry (blood sugar, blood urea, serum creatinine, serum electrolyte, serum uric acid, serum cholesterol and serum triglycerides) urine examination, electrocardiogram and X-ray chest. The record was maintained on a uniform ADR monitoring proforma. Exclusion criteria were airway obstruction, peripheral circulatory insufficiency, intermittent claudication, heart block, heart failure, pheochromocytoma and diabetes mellitus, patients with hepersensitivity to β -blockers, evidence of hepatic or renal damage. Patients were advised atenolol in a a dose range of 50-100 mg/day and were

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asked to report every 2 weeks. On each visit, the resting pulse rate, blood pressure, ECG were recorded. Lung bases, ankles, jugular venous pressure were examined for evidence suggesting of early decompensation. Any other relevant complaint was noted and investigations were done whenever necessary.

To ascertain the cause affect relationship of drug, dechallenge was attempted. Rechallenge was done in only selected few cases where the drug was not likely to produce any harm to the patients.

RESULTS

Fifteen patients out of 440 failed to report for follow up. These were excluded from the trial leaving only 425 patients for the final analysis. The mean age of the patients was 55 years and weight 60 kg. The ADR occurred in 20 patients manifesting as bradycardia (0.47%), oedema (0.70%), cold extremities (1.18%), headache and dizziness (1.41%) and breathlessness (0.94%) (Table I). The ADR's observed were only the extension of pharmacological actions (Type A) and in

none of the patients Type B reactions were observed.

DISCUSSION

Atenolol, in therapeutic doses, due to its β -adrenoceptor blocking action can be predicted to reduce rate and force of contraction of heart, lower blood pressure and some reduction in cardiac output. Thus bradycardia observed in 0.47% patients can directly be correlated to its effect in β -adrenoceptors. The two patients who developed severe bradycardia merits mention. Both were male doctors aged 40 and 42 years respectively with moderate hypertension. First developed severe bradycardia (pulse rate 42/mt) with fall in blood pressure from 154/100 to 90/72 within 30 mts of ingestion of 50 mg atenolol tablet. The other developed only bradycardia (pulse rate 58/mt) after 3 days of atenolol administration (50 mg/day). Both of them recovered following withdrawal of drug and rest and were put on alternative antihypertensive therapy which was tolerated well.

Though atenolol is a cardio selective β -adrenoceptor blocker but its selectivity is relative

TABLE I: Percent incidence of ADR's in the present study compared with similar studies by other workers.

| | <i>Present study (%)</i> | <i>Study I (%) Herman et al 1983 (4)</i> | <i>Study II (%) Zacharias et al 1977 (29)</i> | <i>Study III (%) Steiner et al 1980 (30)</i> |
|--------------------------------|--------------------------|--|---|--|
| n | 425 | 39,000 | 390 | 91 |
| <i>C.V.S.</i> | | | | |
| Bradycardia | 0.47 | -0.90 | 0.18 | 10.00 |
| Oedema | 0.70 | 0.60 | 0.37 | — |
| Cold extremities | 1.18 | — | 4.05 | — |
| <i>C.N.S.</i> | | | | |
| Headache or dizziness | 1.41 | 2.50 | 0.92 | 10.00 |
| Fatigue and weakness | — | 2.80 | 3.87 | 9.00 |
| Depression and nervousness | — | 0.5 | 0.74 | 0.40 |
| Sleep disturbance | — | — | 0.92 | 7.00 |
| Paresthesia and Ataxia | — | — | 0.55 | — |
| <i>Respiratory system</i> | | | | |
| Breathlessness | 0.94 | — | 3.31 | — |
| <i>Gastrointestinal system</i> | | | | |
| G.I.T. Symptom | — | 1.80 | 1.80 | 13.00 |
| <i>Genital system</i> | | | | |
| Sexual disturbance | — | — | 0.18 | 1.20 |

n is number of patients in each study.

rather than absolute (23-28) and it is inversely related to the dose. Higher doses and even therapeutic doses in susceptible patient may show some B₂-adrenoceptor blocking action (23-26) manifesting as cold extremities, deterioration of airway function and oedema. Blockade of B₁-adrenoceptor may lead to reflex increase in α -adrenergic activity. This may contribute to the causation of cold extremities. In the present study cold extremities, without fatigue and weakness were observed in 1.18% of patients (Table I), commonly during winter months and when the dose of atenolol was 100 mg/day. Only in one patient, the symptoms warranted withdrawal of the drug. The lower incidence of cold extremities could be attributed to climatic difference as the other studies (29) taken into consideration for comparison were from Western countries where the climate is cold. Oedema was observed in 0.70% of the patients in the present study. Such effect has also been reported by other workers (4, 29). Oedema a cardinal manifestation of congestive heart failure was seen in patients. Although care was taken for observing exclusion criteria strictly, it is possible that some patient might have been in impending failure which was precipitated by atenolol by its cardiac depressant action. The lower incidence of breathlessness (0.94%) in the present study as compared to the reports from Western countries (29)

could be due to climatic and racial variations.

The CNS related ADR's were lower in incidence in the present study and were confined to headache and dizziness (1.41%). The higher incidence of such reaction has been reported by other workers (4, 29, 30) and the profile of CNS related ADR's included depression and nervousness, sleep disturbance, paresthesia and ataxia (Table I).

The frequency of ADR in comparative studies also depend on the method of recording, study duration and the age of the patient population. On compiling 6 ADR related comparative studies (30-35) of atenolol it was found that the ADR to atenolol ranged from 2 to 10% for bradycardia, 2 to 3.5% of cold extremities, 7 to 17% of headache, 2 to 51% of fatigue, 6 to 26% of sleep disturbance and 1 to 14% of sexual disturbances.

The incidence of ADR was lower in the present study as compared to reported by others (4, 29, 30). Reason may be put forward that it could be due to stringent criteria for inclusion and inclusion of patient, racial and climatic variation. Further, atenolol is B₁ blocker in smaller dose while it loses specificity with higher doses. This might have contributed to higher incidence of ADRs observed by other investigators.

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