A Study of Adverse Drug Reactions to Antihypertensive Drugs Perceived by Patients in a Rural Hospital

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Accepted 26 November 2004
Revised 9 June 2004
Received 17 July 2003

The detection of adverse drug reactions has become increasingly important. This study aimed to determine adverse drug reactions of currently-used antihypertensive drugs in a rural hospital, and to assess the effect of pharmacist's intervention on the process of antihypertensive therapy management. Patients were identified to have adverse reactions by interview, using laboratory investigation data and in consultation with physicians and other health care professionals. Patients randomized to pharmacist's intervention received counselling during course of study. Of the 138 patients enrolled, 42% were women, and the average age was approximately 51 y. The study identified adverse drug reactions in 56.5% of the patients. Significant changes in patient satisfaction were observed as result of counselling ($P < 0.001$).

An adverse drug reaction (ADR) may be defined as any response to a drug which is noxious, unintended and which occurs at doses normally used for prophylaxis, diagnosis or therapy[1]. Every drug, no matter how trivial its therapeutic actions, has risks. The problem of adverse drug reactions as significant cause of a morbidity and mortality has been demonstrated by a number of studies during last decades. Every year millions of patients in developed nations are hospitalized and die from complications relating to adverse reactions from drugs. In 1994, Lazarou *et al.*[2] estimated that adverse drug reactions were the fourth to sixth largest cause of death in the USA. Drug-related complication ultimately leads to increased cost of health care. In addition less serious ADRs, such as those not requiring admission to hospital, are under reported[3]. The ADR monitoring, reporting and prevention programmes to minimize drug related morbidity and mortality are well established in many developed nations. Many drugs have been withdrawn from the market in the recent years as a result of spontaneous reporting. Spontaneous reporting has proven to be an effective way to generate an early signal that a drug may be causing an adverse event[4].

Various adverse drug reactions are routinely observed in patients with antihypertensive therapy[5]. The ADRs of antihypertensive therapy for a number of drugs was previously reported[6-10]. In India, the patient demographics and prescribing pattern are quiet different compared to the advanced countries. The reporting of ADR is not mandatory in India and hence a majority of ADRs remain unreported. These observations prompted us to initiate a programme on monitoring of ADRs by pharmacists, in association with other health care professionals, in a rural hospital. The main objectives of the study were to evaluate ADRs of currently used antihypertensive drugs to the local population, to provide counselling to hypertensive patients and to analyze perceptions of the patients towards an intervention.

The study was conducted in the department of medicine, Rajah Muthiah Medical College (RMMC) Hospital, Annnamalai University, Chidambaram, Tamilnadu. It is located 244 km south of Chennai and is a 1200 bed tertiary teaching hospital. Ambulatory patients who had minimum 3 visits to the hospital and patients hospitalized up to 4 w for treatment during July 2002 to December 2002 were selected for study. Ambulatory patients were included in the study, since many hypertensive patients prefer not to be hospitalized in this area. Patients were approached for participation in this study only if they were hypertensives or hypertensives with diabetes. Patients receiving single drug antihypertensive drug therapy were selected for this study. Patients were

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excluded if they were below 25 y of age or pregnant or refused to provide verbal informed consent or non-compliant. Patients below 25 y were not selected with a presumption that hypertension and ADRs are less likely to occur among people below 25 y of age. The study didn't try to evaluate the possibility of ADRs to be a result of other medications that the patient is on.

Patients were identified to have ADRs[4] by a combination of a structured interview, patient's medical history or laboratory investigation data (these values were documented using an in-house format made by the hospital) and finally by discussion with concerned physicians and other health professionals (Table 1). The pharmacists identified the ADRs in consultation with the physicians (one of the authors is a physician in the medicine department). The laboratory investigation data collected was categorized as follows; serum K+, serum cholesterol, blood sugar, ECG, urine analysis, and chest X-ray. Verbal informed consent was obtained from all participants.

Patients were randomized to receive either counselling in connection with antihypertensive therapy or usual treatment. Randomization was carried out separately in each category of patients (ambulatory or hospitalized) by the authors using sealed opaque envelopes. Random assignment was done stratified for gender (male or female). The intervention counseling consisted of identification of ADRS, ver-

TABLE 1: ADVERSE REACTIONS OBSERVED

ADRs†	Patients affected* within treatment group				
	ß-B n=31	Ca^{2+} n=46	A-II n=8	Diuretics n=23	ACE Inhibitors n=30
Angio Oedema	-	-	01 (12.5)	-	06 (20.0)
Ankle Oedema	-	13 (28.2)	-	-	-
Bronchospasm	04 (12.9)	-	-	-	-
Constipation	12 (38.7)	-	-	-	-
Dizziness	-	18 (39.1)	04 (50.0)	-	08(26.6)
Dry cough	-	-	-	-	13(43.3)
Fatigue	-	18 (39.1)	-	-	-
Flushing	-	04 (08.7)	-	-	05(16.0)
Dyspepsia	-	14 (30.4)	-	-	-
Headache	-	16 (34.8)	-	-	12(40.0)
Hyperuricemia	-	-	-	02 (08.7)	-
Hypokalemia	-	-	-	04 (17.4)	-
Insomnia	16 (51.6)	-	-	-	-
Muscle cramp	-	-	-	13 (56.5)	-
Nausea/vomiting	-	-	-	16 (69.5)	12(40.0)
Palpitation	-	09 (19.5)	-	-	-
Tachycardia	-	-	03 (37.5)	-	-
Vivid dreams	19 (61.3)	-	-	-	-

*All data are given as numbers (percentages). † Not mutually exclusive. ß-B denotes Beta blockers, Ca^{2+} is Calcium channel blockers and A-II is Angiotensin II receptor blockers.

TABLE 2: PATIENT DEMOGRAPHICS*

Variable	n=138
Gender	
Male	80 (58.0)
Female	58 (42.0)
Category	
Ambulatory	55 (39.8)
Hospitalized	83 (60.2)
Age	
25 to 34	09 (06.5)
35 to 44	26 (18.9)
45 to 54	32 (23.2)
55 to 64	34 (24.6)
65 to 74	37 (26.8)
Average (±SD)	51 (10.4)
Personal habits	
Alcoholic	18 (13.0)
Smokers	24 (17.4)
Alcoholics and smokers	15 (10.9)
Non alcoholics and non smokers	81 (58.7)
Disease states	
Hypertension	57 (41.3)
Hypertension with IHD	28 (20.3)
Hypertension with diabetes	30 (21.7)
Hypertension with diabetes and IHD	23 (16.7)
Treatment received	
Beta-blockers	31 (22.5)
Calcium channel blockers	46 (33.3)
A-II Antagonist	08 (05.7)
ACE Inhibitors	30 (21.7)
Diuretics	23 (16.7)

*All data are given as numbers (percentages) unless otherwise indicated.

bal education and general advice on their complaints, and close follow-up. Patients assigned to usual treatment subjected to same identification of ADRs only. The intervention group received counseling at first and second visits. Counseling was performed to ensure and reinforce adherence to medications, to make further suggestion to the patient and to educate on antihypertensive therapy. Patients randomized to usual treatment group received minimal counselling. A patient's perception of their well being and distress during antihypertensive therapy was assessed on a 5 point scale, by measuring anxious versus relaxed and illness versus healthy, ranging from greatly anxious/ill (beginning of scale), anxious/ill (point 2 in scale), neutral (midpoint), relaxed/healthy (point 4 in scale) to highly relaxed/healthy (end of scale). Seventy one patients were randomized to intervention group and 67 to usual treatment group. The differences in satisfaction in patients between intervention and usual treatment groups were compared using independent samples student's't' test. A threshold of statistical significance of $P< 0.001$ was used.

A total of 138 patients were enrolled in the main study between July 1, 2002 and December 31, 2002. The patient demographics have been summarized in Table 2. The average age was about 51 y, with 42% of patients being women. Majority of them were hospitalized (60.2%). Over 40% of patients had a history of hypertension; 20.3% had hypertension with ischemic heart disease; 21.7% had hypertension with diabetes and 16.7% had hypertension with both diabetes and ischemic heart disease. When prescribing pattern was analyzed, it was observed that 22.5% patients received beta blockers, 33.3% calcium channel blockers, 5.7% angiotensin type II blockers, 217% ACE inhibitors and 16.7% diuretics.

During the period studied, beta blockers (mainly atenolol) were prescribed for hypertensive patients with ischemic heart disease. The most common ADRs identified (Table1) were constipation (38.7%), insomnia (51.6%) and vivid dreams (61.3%). The ADRs of calcium channel blockers observed were dizziness (39.1%), fatigue (39.1%), dyspepsia (30.4%) and headache (34.8%). Some patients had 2 or more ADRs, the details of which have been presented in Table 3. The ADRs such as fatigue and headache only seemed to make the patients anxious, depressed and disturbed. Of all ADRs of angiotensin type II blockers, 50% patients experienced dizziness and another 37.5% tachycardia. ADRs like hyperuricemia, hypokalemia and muscle cramp have been attributed to the use of diuretics. ACE inhibitors (captopril and lisinopril) were prescribed to patients

TABLE 3: NUMBERS AND INCIDENCE OF ADVERSE DRUG REACTIONS

Treatment Group	Patients affected with			Total No. of patients*
	1 ADR	2 ADRs	More than 2 ADRs	
Beta Blockers	2	4	12	18 (58.0)
Calcium channel blockers	4	5	17	26 (56.5)
Angiotensin II receptor blockers	2	3	-	05 (62.5)
Diuretics	2	3	09	14 (60.9)
ACE inhibitors	1	3	11	15 (50.0)

*Data are given as numbers (percentages)

with diabetes and hypertension. The Main ADRs of ACE inhibitors were found to be dry cough (43.3%). Other ADRs observed included headache (40%) and vomiting (40%). During the study period no reactions other than those listed in Table 1 have been observed.

Table 4 shows changes in patient satisfaction (antihypertensive therapy) with patient counselling by pharmacists. There were statistically significant changes in satisfaction with counselling as a result of the intervention. Comparing the satisfaction scale scores, it seemed that respondents were more satisfied with mental score status (mean scale score, 3.23 out of 5) than with physical health status (mean scale score, 2.83).

This pilot study suffers from a few limitations. The number of patients included in the study was small and was conducted only for a short period of time. An attempt was not made in this study to compare with control group. The study didn't use any ADR causality assessment scale. It is also possible that the information provided by respondents was inaccurate (considering their status of poor literacy and ignorance). Although many respondents may have been familiar with their illnesses and mental conditions, the idea of response to their perception of degree of illness/ health was new to almost all respondents. The study found that a wide selection of all the recently developed drugs have been routinely employed for treatment of hypertension. The findings of this study demonstrated that currently used antihypertensive drugs show various ADRs in the study patient population of this rural hospital. These observed ADRs coupled with a lack of general advice and education on antihypertensive therapy appeared to be a strong factor of patient dissatisfaction. Interventions by a pharmacist improved the responsiveness to antihypertensive drug therapy in patients.

In conclusion, this six months ADR study programme was successfully completed in collaboration with patients and physicians, by attempting to document the ADRs, for the first time in this hospital and the intervention by a pharmacist contributed towards positive outcome of therapy.

ACKNOWLEDGEMENTS

We are grateful to the referee of this manuscript for the valuable comments that helped in modifying this manuscript. The authors are thankful to the Department of Medicine, RMMC Hospital, Annamalai University for providing all possible assistance to carry out this work

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TABLE 4: CHANGES IN PATIENT SATISFACTION WITH COUNSELLING*

Variable	Usual treatment group (n=67)	Intervention Group (n=71)	P value
Mental Status	2.32 (0.74)	3.23 (0.94)	<0.001
Physical health status	2.03 (0.85)	2.83 (0.83)	<0.001

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Synthesis and Antimicrobial Activities of Some 5-(4'-Pyridyl)-4-Substituted Benzylideneamino-3-Mercapto(4H)-1,2,4-Triazoles

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Accepted 11 December 2004
Revised 16 June 2004
Received 3 March 2004

Certain 5-(4'-pyridyl)-4-substituted benzylideneamino-3-mercapto(4H)-1,2,4-triazoles having different substitutions on the aromatic ring possessing azomethine linkage were synthesized and evaluated for their antimicrobial activities. The compounds with a 4-dimethylamino, 3,4-dimethoxy, 2-nitro and 4-chloro group on the aromatic ring showed good antimicrobial activity.

Triazoles[1-5] have been reported to exhibit significant antibacterial and antifungal activities. Itraconazole is a well established triazole antifungal agent. Antimicrobial activity of 1,2,4-Triazoles having mercapto[6,7] or mercapto acetic acid[8] at different position have been reported. Compounds with azomethine linkage[9] were also shown to possess good antimicrobial activity. In view of these observations it was thought of interest to synthesize some new 5-(4'-pyridyl)-4-substituted benzylideneamino-3-mercapto(4H)-1,2,4-triazoles having an azomethine linkage. Isonicotinic acid hydrazide which is also a well established antitubercular drug has been incorporated with a view to enhance the activity of triazole derivatives (scheme 1).

All melting points were determined in open glass capillaries and are uncorrected. The purity of the compounds were ascertained by TLC on silica gel-G plates using the solvent systems; benzene:acetone (8:2), toluene:ethylacetate:formic acid (5:4:1) and iodine vapour as detecting agent. IR spectra were taken using the KBr disc technique on a Jasco FTIR 410 Spectrophotometer. ^{1}H NMR spectra were recorded on a Brucker DRX-300 NMR Spectrometer in $CDCl_3$ and DMSO-d_6 with TMS as internal standard. The mass spectra were recorded on a Jeol SX 102 (FAB) mass spectrometer. All the chemicals used were of LR and AR grade and was procured from S. D. Fine Chem. Ltd., New Delhi, E. Merck, Delhi and Central Drug House Pvt. Ltd., Delhi. Potassium isonicotinoyl dithiocarbazinate (1) was prepared using a method that has been reported in the literature[10].

For the synthesis of 5-(4'-pyridyl)-4-amino-3-mercapto(4H)-1,2,4-triazole (2), potassium dithiocarbazinate (0.02 mol) was dissolved in water (5 ml). To this solution, 99% hydrazine hydrate (0.04 mol) was added. The reaction mixture was refluxed on a water bath until the evolution of H_2S gas ceased. It was then diluted with water (20 ml) and carefully acidified with glacial acetic acid. The colourless solid thus separated was filtered, washed with water, dried

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