Cutaneous drug reactions to antihypertensive agents: a report from a single center in Pakistan

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Background: This study was conducted because up to now, the investigations performed on cutaneous manifestations of antihypertensive agents' reactions, especially in Pakistan, are negligible even though these drugs are taken by a large number of people. The aim of this study was to determine the cutaneous manifestations of different antihypertensive agents in terms of dosage and duration.

Method: The study was carried out at the Departments of Dermatology and Cardiology, Civil Hospital, Karachi. The study was carried out from June 2007 to December 2007. The inclusion criteria included all patients taking a single antihypertensive agent with cutaneous manifestations. Patients taking antihypertensive drugs but suffering from some other dermatological diseases and those taking more than one drug were excluded. After informed consent, history, specifically regarding the type of drug dosage and duration of drug intake was taken. Specific investigations such as biopsy were done if indicated.

Result: Out of 100 patients, 37 were male and 63 were female. Most of the patients were in the age group 46–60 years. The majority (97%) of patients experienced the onset of lesions between 4–8 weeks of therapy and only 2% had lesions within 4 weeks. Moderate lesions were markedly more common and were found in 65% followed by mild lesions in 26%, severe in 6%, and lethal in 3% of the patients. The most common lesions were pruritis and eczema, followed by flushing, lichenoid eruptions, oral ulcers, purpuras, psoriasis, exanthematous reactions, urticaria, gingival hyperplasia, lichen planus, morbilliform rashes, oral lichen planus and butterfly rash.

Conclusion: No relation was noted between a drug dose and the severity of skin lesions. Most patients started having skin lesions 4 to 8 weeks after therapy.

Keywords: antihypertensive agents, cutaneous drug reactions, side effect

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INTRODUCTION

Hypertension is the most common ailment the modern society is facing [1]. Antihypertensive agents are among the most widely prescribed medications as raised blood pressure is becoming a common problem of our society and hypertensive patients are taking these drugs for longer periods. These drugs have many side effects including electrolyte imbalance, cough, renal dysfunction, dysguesia (an unpleasant metallic taste), flushing, palpitations, fluid retention, constipation, first dose hypotension,

tachycardia as well as cutaneous side effects.

The incidence of cutaneous manifestations is approximately 2% to 3% of all drug reactions and approximately 1 in 1000 hospitalized patients have severe cutaneous reactions [2]. Cutaneous drug reactions are also a challenging diagnostic problem since they can mimic a large variety of skin diseases, including viral exanthema, collagen vascular disease, neoplasia, bacterial infection, psoriasis, and autoimmune blistering disease. Therefore, clinical approach to the diagnosis and management of adverse cutaneous drug reactions is very important and a careful physical and dermatological examination is essential [3].

This study was conducted because up to now, the investigations performed on cutaneous manifestations of antihypertensive agents' reactions, especially in Pakistan, are negligible even though these drugs are taken by a large number of people. The information obtained by different studies shows that 10-60% of adverse drug reactions (ADR) [4] from diuretics, beta blockers and other antihypertensives agents are dermatological in origin. However, determining that a particular medication has caused an eruption is often difficult when the patient is taking multiple drugs [5].

The rationale of the study was that the collected data for cutaneous side effects of antihypertensive agents is minimal, keeping in view the extensive use of these drugs. I tried my best to collect maximum literature review and to compile all the collected cases in a simple way.

Following are the groups of antihypertensive agents which are more commonly involved in adverse skin reactions.

Beta-blockers are widely used antihypertensive agents. They frequently cause skin reactions which include lichenoid, exanthematous, eczematous, psoriasiform rashes, exfoliative dermatitis, oculo-mucocutaneous reactions, fibrosing polyserositis and drug induced systemic lupus erythematosus (SLE) [6].

Calcium channel blockers are also a commonly used group of antihypertensive drugs and cause frequent skin reactions. The frequency of these reactions may be as high as 48% [6] including flushing, facial or truncal telangiectasia, photosensitivity reactions, new onset psoriasis, purpuric exanthemas, pemphigoid, subcutaneous lupus erythematosus (SCLE), steven-johnson syndrome, toxic epidermal necrolysis and oral ulcers and exanthematous pustulosis [7].

Vasodilators cause various cutaneous side effects such as lupus like syndrome, orogenital ulceration, leg ulceration, cutaneous vasculitis, fixed drug eruption, hypertrichosis, bullous eruptions and erythema multiforme [8].

Side effects of diuretics are rare especially with frusemide. Reported side effects are erythema multiforme, bullous pemphigoid, generalized exfoliative dermatitis, necrotizing vasculitis and porphyria like bullous eruptions. Different studies on angiotensin converting enzyme (ACE)-inhibitors have reported that most frequent side effects are taste disturbance, dizziness and dry cough. The cutaneous manifestations include oral ulcers, pruritus, lichenoid eruptions, drug induced angioedema, generalized pustular eruptions, drug induced linear IgA, mycosis fungoides and psoriasis [9-14].

To the best of our knowledge, there is no such study on the subject available in literature from Pakistan. We undertook this study to determine the scope and magnitude of the problem in the local population.

PATIENTS AND METHODS

This study was conducted in Civil Hospital Karachi, a tertiary care centre in which there are 1700 beds. This referral centre serves the largest population of the metropolitan city Karachi. It also serves the population living in the rural areas of Sindh and Baluchistan. Patients were collected from both the dermatology ward and outpatient department (OPD) as well as the cardiology ward and outpatient department. All the patients who came to OPD and ward were registered.

The sampling technique was non-probability, consecutive and convenient. The duration of the study was 6 months from June 2007 to December 2007. Detailed physical examination from head to toe, both by naked eye and with magnifying glass was done. In all, 100 patients who were on antihypertensive therapy were selected from OPD and wards of both dermatology and cardiology departments. The personal and clinical information of the patients were recorded on the proforma. Detailed history was taken regarding the specific drug used, its dosage, duration of taking the drug,

onset of eruptions, and site of lesions. Patients on antihypertensive drugs suffering from some other dermatological diseases and those taking more than one antihypertensive drug were excluded. Patients on other drugs, e.g. drugs relevant to other cardiac diseases, were also excluded. On examination, special attention was paid to rule out other dermatoses. Systemic examination was done to rule out systemic diseases.

Statistical analysis was carried out using SPSS version 10 (SPSS, Chicago, IL, USA). Simple descriptive statistics such as mean ± SD were used for continuous variables such as age and dose of hypertensive agents. Numbers (percentages) were used for categorical data.

RESULTS

Out of 100 patients, 37 were male and 63 female with a male to female ratio of 1: 1.7. The mean age of the patients was 57.96 ± 9.96 (range: 35-77) years. Two age groups, 46-50 years and 56-60 years, were equally common age groups (44%).

Regarding the type of antihypertensive drugs, ACE inhibitors and calcium channel blockers were equally common groups of drugs (26% each), followed by beta blockers (21%), diuretics (18%), methyldopa (5%) and vasodilators (4%).

The majority of the patients (82%) reported the duration of treatment up to 4 weeks followed by 17% up to 8 weeks; one patient just started the treatment 2 hours before. Onset of lesions was up to 8 weeks after initiating treatment in 97% followed by 4 weeks in 2% and up to 2 hours in only one patient.

Captopril was the commonest hypertensive agent used, reported by 21 patients followed by nifidipine by 16, frusemide by 14, propanolol by 12, amlodipine by 10, atenolol by 7, Methyldopa in 5, enalapril by 4, prazosin by 4, spironolactone by 4, metoprolol by 2 and lisinopril by one patient. Moderate lesions were markedly more common, found in 65% followed by mild lesions in 26%, severe in 6% and lethal in 3% of the patients.

Pruritus and eczema were equally common lesions each seen in 16% followed by flushing in 10%, lichenoid eruption in 9%, oral ulcer in 9%, purpura in 7%, psoriasis in 5%, exanthematous lesions in 4%, urticaria in 4%, gingival hyperplasia in 3%, lichen planus in 2%, morbilliform rashes in 2%, oral lichen planus in 2%, and butterfly rash in 2% of the patients. Each of the following lesions, angioedema, aphthous ulcers, bullous formation, fixed drug eruption, petechial eruption, photosensivity rash, Raynaud's phenomenon, toxic epidermal necrolysis (TEN) and vasculitis were observed in one patient. Some common examples of skin manifestations are shown in figures 1 to 4.

Out of 26 patients who had a positive history of ACE inhibitor use, 8 (30.8%) patients were diagnosed with mild, 14 (53.8%) with moderate, 2 (7.7%) with severe and 2 (7.7%) with lethal drug reactions. Out of 26 patients who were taking calcium channel blockers, 5 (19.2%) were diagnosed with mild, 20 (76.9%) with moderate and 1 (3.8%) with severe drug reactions. Out of 21 patients who were taking beta blockers, 6 (28.6%) were diagnosed with mild, 13 (61.9%) with moderate and 2 (9.5%) with

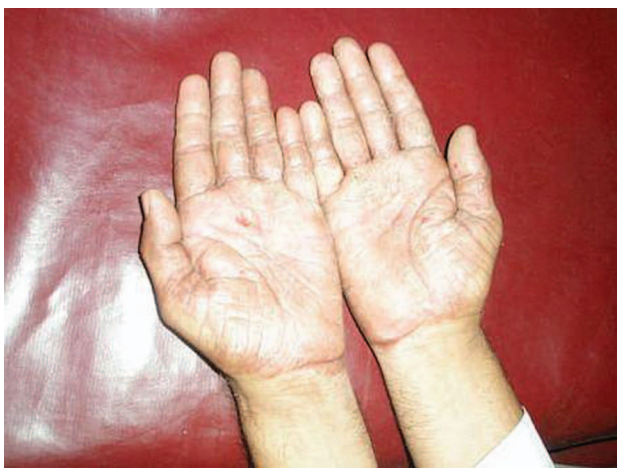

Figure 1. Palmar psoriasis started 6 weeks after taking beta blocker.

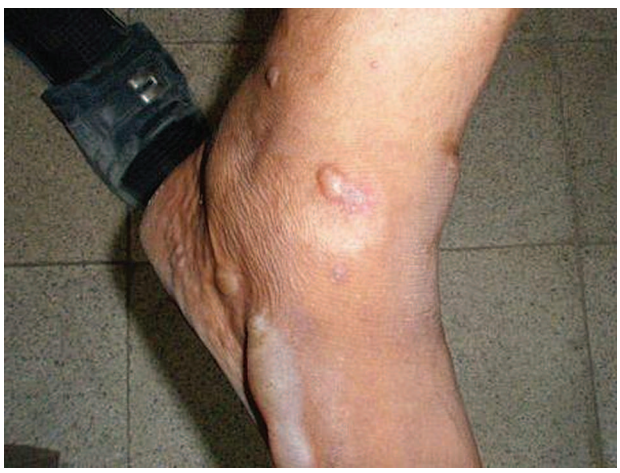

Figure 2. Bullous eruption in a patient on calcium channel blocker.

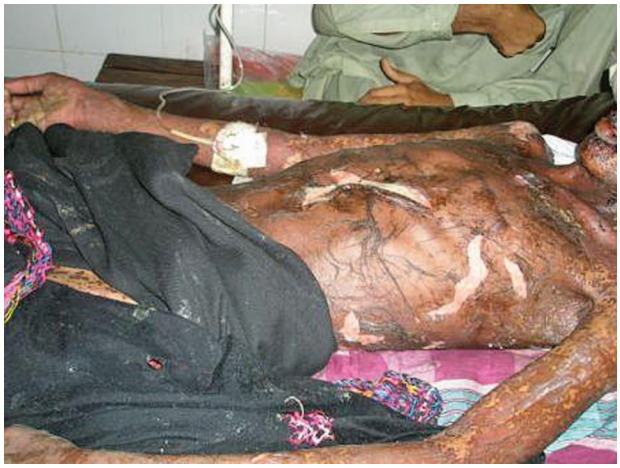

Figure 3. Toxic epidermal necrolysis in a patient on diuretic (frusemide).

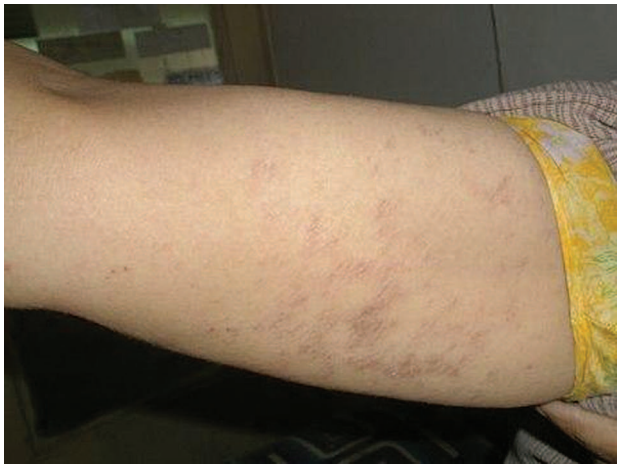

Figure 4. Lichenoid eruptions in a patient on methyldopa.

severe drug reactions. Out of 18 patients who were taking diuretic drugs, 5 (27.8%) were diagnosed with mild, 11 (61.1%) with moderate, 1 (5.6%) with severe and 1 (5.6%) with lethal drug reactions. Out of 5 patients who were taking methyldopa, 1 (20%) patient was with mild and 4 (80%) were diagnosed with moderate drug reactions. Out of 4 patients who were taking vasodilators, 1 (25%) was diagnosed with mild and 3 (75%) were diagnosed with moderate drug reactions.

DISCUSSION

Cutaneous reactions to antihypertensive agents are not infrequently seen, but are mostly neglected by clinicians or mistaken by some other dermatosis because presentations mimic other skin diseases. Therefore, a careful systemic and dermatological examination is essential and should always be included in the differential diagnosis of various dermatoses. Standard text books and literature review provide minimal information regarding this group of drugs. As antihypertensive agents are among the most commonly prescribed medications, one should be aware of skin manifestations of these drugs. This study was difficult because most patients were taking more than one anti-hypertensive drug for their blood pressure control; therefore, finding patients who took one agent and had skin manifestations was a difficult task [4-9].

In this study, 100 patients were included. All patients were on one antihypertensive agent for a minimum period of 2 days and maximum of 2 months and presented with skin manifestations. Regarding sex distribution, 37 were male and 63 were female with a male to female ratio of 1:1.7. It is evident that the cutaneous manifestations are more commonly seen in females as compared to males. This is explained by the fact that there are frequent periods in a female life like menarche, pregnancy, lactation and menopause, when there is alteration of pharmacokinetics of drugs. Also, women may seek medical advice more frequently than men. A study conducted in Pakistan showed that women had more drug adverse effects than men [15]. This is somewhat lower than what we noted in our study.

If we analyze the result of this study for age specific incidence, it becomes evident that two age groups, 46-50 years and 56-60 years, are commonly affected, implying that skin manifestations are commonly seen in adults and elderly population. A study done at the University of Manchester showed that the rates for adults and elderly patients were 6.3% and 10.7% [11]. In contrast, our results showed that cutaneous manifestations were equally seen in both groups .i.e. 44%, while it was 9% and 24% in younger and older age groups, respectively. ACE-inhibitors and calcium channel blockers were equally the most common group of drugs taken by these patients, followed by beta blockers, diuretics, methyldopa and vasodilators.

Cutaneous lesions can arise hours, days or even weeks after therapy is started and even after drug is withdrawn. In our study, we divided the duration of drug therapy into two groups; group 1 were those patients whose skin manifestations started within 2 days to 4 weeks and group 2 were the

patients whose lesions started between 4 weeks to 8 weeks after therapy. The majority of the patients (97%) fell in group 2, experiencing the onset of the lesions within 4-8 weeks, followed by 2% experiencing the onset of lesions within 4 weeks.

Regarding the clinical manifestations of lesions, pruritus and eczema were the commonest lesions. This is in contrast to a study which reported the most common cutaneous manifestations as exanthematic eruptions in 57%, urticaria in 7%, and vasculitis in 4% of the patients [13]. Rather similar results have been found in other studies, as well [16,17]. The variation in the distribution of cutaneous manifestations may be related to genetic or environmental factors.

In conclusion, our study showed that the cutaneous reactions were more common in females as compared to males. The incidence of these cutaneous manifestations in adults and elderly population was higher as compared to younger population. The majority of the patients developed lesions between 4 to 8 weeks of therapy. Among individual drugs, captopril was the commonest drug used. The lesions were not related to the prescribed dose of that particular drug and the severity of the lesions was not correlated with the increase in dosage. In this study, moderate lesions were markedly more common than mild or severe cases. However, further study with larger sample size could be more beneficial to elucidate the frequency and pattern of cutaneous reaction to antihypertensive agents.

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