REVIEW ARTICLES

ADVERSE DRUG REACTION: A COMMON DERMATOLOGICAL EMERGENCY

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Abstract

In the evaluation of patients with a history of adverse cutaneous drug reactions, it is important to obtain a detailed medication therapy including over-the-counter drugs, herbal and neuropathic remedies. There are a significant number of offending drugs causing adverse cutaneous drug reactions. If we can find out the clinical pattern of drug reaction along with their risk and aggravating factors, a good number of lives can be saved. If the offending drugs can be identified, proper preventive measures can be taken by individual or policy makers. Many of the cutaneous drug reactions can be prevented if diagnosed early.

Introduction

Adverse drug reactions are a common cause of dermatologic consultation. Simple exanthems (75%-95%) and urticaria (5%-6%) account for the vast majority of drug eruptions. Females are 1.3 to 1.5 times more likely to develop drug eruptions, except in children under the age of 3 where boys are more likely affected.[1] Complications of drug therapy are a major cause of patient morbidity and account for a significant number of patient deaths. Drug reactions may be solely limited to the skin or they may be part of a systemic reaction, such as drug hypersensitivity syndrome or toxic epidermal necrolysis.[2]

Cutaneous drug reactions have become very common in recent times. The incidence of cutaneous drug reactions is about 2.2% and is reported to be higher among inpatients and females. Fatal reactions to drugs occur even though benign reactions are more common. The incidence increases in proportion to the number of drugs prescribed. Cutaneous drug reactions are the most common adverse reactions attributed to drugs. Any skin disorder can be initated, induced or aggravated by drugs.[3]

Adverse drug reactions (ADRs) are unwanted or unintended effects of drugs, which occur during proper use of a drug. The safe use of medicines is an important issue for prescribers, pharmacists, nurses, regulatory authorities, the pharmaceutical industry, and the public. Healthcare professionals have a responsibility to their patients, who themselves are increasingly aware of the problems associated with drug therapy. It is essential that the practicing pharmacist should have a thorough knowledge about the various adverse effects of the drugs, including its predictability and reversibility, frequency and severity, predisposing factors and recognition, relationship to dosage, and duration of treatment and prevention. Adverse reactions are responsible for a significant number of hospital admissions, among these; cutaneous ADRs (2 to 3%) are one of the frequent reasons for patients to visit the physicians. Although majority of ADRs are minor reactions and are self limiting, sometimes severe and potentially life threatening situations like Stevens-Johnson Syndrome (SJS) and Toxic epidermal necrolysis (TEN) can occur, which constitute from 2.6 to 7% of all drug reactions. Drugs, no matter how safe and efficacious, are always coupled with unavoidable risk of adverse reactions. ADRs are a cause of significant morbidity and mortality in patients of all areas of healthcare today. It has been estimated, that from one third to as high as one half of ADRs, are believed to be preventable. The incidence and severity of ADRs can be influenced by patient-related factors like age, sex, concurrent diseases, genetic factors, and drug related factors like type of drug, route of administration, duration of therapy, and dosage. The other important risk factors associated with adverse drug reactions are gender, increased number of drug exposures, advanced age, length of hospital stay, and function of excreting organs. The incidence of cutaneous drug

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reactions varies from 15 to 30%. Studies on the epidemiology of common cutaneous ADRs have rarely been reported, since such studies can only be successfully conducted in clinics of internal medicine, who employ consultant dermatologists and where there is a comprehensive or intensive ADR monitoring system. Such evaluations of ADR in dermatology are yet to evolve in India.[4]

Cutaneous adverse drug reactions (ADR) can be caused by a wide variety of agents. They are responsible for approximately 3% of all disabling injuries during hospitalization and complications of drug therapy are the most common type of adverse event in hospitalized patients. Many of the commonly used drugs have reaction rates above one percent.[5]

A morbilliform rash is the most common reaction to phenytoin, occurring in as many as 5% of cases overall. However, a wide variety of cutaneous reactions can occur, including acneiform lesions, exfoliative dermatitis, erythema multiforme, SJS, vasculitis, gingival hyperplasia, heel pad thickening, and lupus-like reaction. In a hospital-based adverse drug reaction reporting program from an Indian tertiary care hospital, phenytoin was the individual drug most frequently reported as a cause of adverse drug reaction. As calculated by Naranjo's adverse drug reaction probability score, the causable relationship between phenytoin and TEN in our case is 'probable'. TEN can also occur as a complication of other drugs.

Toxic epidermal necrolysis (TEN) is the most serious of the cutaneous drug reactions. It is blistering disorder, with erosions of multiple mucous membranes and small skin blisters developing on dusky or purpuric macules. The onset is usually acute, as in our case and epidermal necrosis involves >30% of body surface area. It can be distinguished from Stevens-Johnson syndrome (SJS), where the total surface of body surface area detachment is <10%, by definition.[6]

Fixed drug eruptions characteristically recur in the same site or sites each time the drug is administered; with each exposure, however the number of involved site may increase. Usually just one drug is involved. Although, independent lesion from more than one drug have been described. Cross-sensitivity to related drug may occur such as between phenylbutazone and oxyphenbutazone and between tetracycline type drugs, and there are occasional reports of recurrences at the same site induced by drugs which appear to be clinically unrelated, e.g. oxyphenbutazone and tetracycline. Sometimes the inducing drugs can be re-administered without exacerbation, and there may be a refractory period after the occurance of a FDE. Acute lesions are sharply marginated round or oval plaques of erythema and oedema becoming dusky and violaceous or brown in colour, and sometimes surmounted by a large bulla. They usually develop within 30 minutes to 8 hours of drug administration. Lesions are sometimes solitary at first but with repeated attacks, new lesions usually appear and existing lesions may increase in size. Lesions are commoner in the limbs than the trunks; the hands and feet, genitalia (glans penis) and peri-anal areas are favourite sites. Peri-oral and peri-orbital lesions may occur. Genital and oral mucous membranes may be involved in association with skin lesions or alone. Pigmentation of the tongue may occur as a form of fixed drug eruption in heroin addicts. A curious linear fixed drug eruption to intramuscular cephazolin occurred. As healing occurs, crusting and scaling are followed by pigmentation, which may be very persistent and occasionally extensive, and all that is seen between attacks. Local or constitutional symptoms are mild or absent. Diffuse hypermelanosis of extensive areas of trunk, face or limbs is perhaps more common in Negroids. Non-pigmenting fixed reactions have been reported in association with pseudoephendrine, tetrahydrozoline or piroxicam.

The number of drugs capable of producing fixed eruptions is very large but most are due to tetracyclines, sulphonamides (including co-trimoxazole), barbiturates, oxyphenbutazone, metamizol, acetylsalicylic acid, hyoscine butylbromide, ibuprofen, chlordiazepoxide, dapsone, phenazone, phenolphthalein, quinine and derivatives, paracetamol, benzodiazepines. Earlier series incriminated analgesics, sulphonamides and tetracyclines. In a recent report from Finland, phenazones caused most eruptions, with barbiturates, sulphonamides, tetracyclines and carbamazepine causing fewer reactions. Patch testing in a previously involved site may yield a positive response in a high proportion of cases. The mechanism of the reaction is unknown; serum factors and localized skin factors have been postulated, while the results of skin autotransplantation have been equivocal. Lesional skin contains T cells with suppressor/cytotoxic phenotype. Keratinocytes express the intercellular adhesion molecule ICAM-1, which is involved in interaction between keratinocytes and lymphocytes in lesional but not in normal skin, which may be of relevance to the preferential site specificity of the condition.

Erythema multiforme is more commonly precipitated by various interactions, and therefore many instances may have been wrongly blamed on drugs. Clinically,

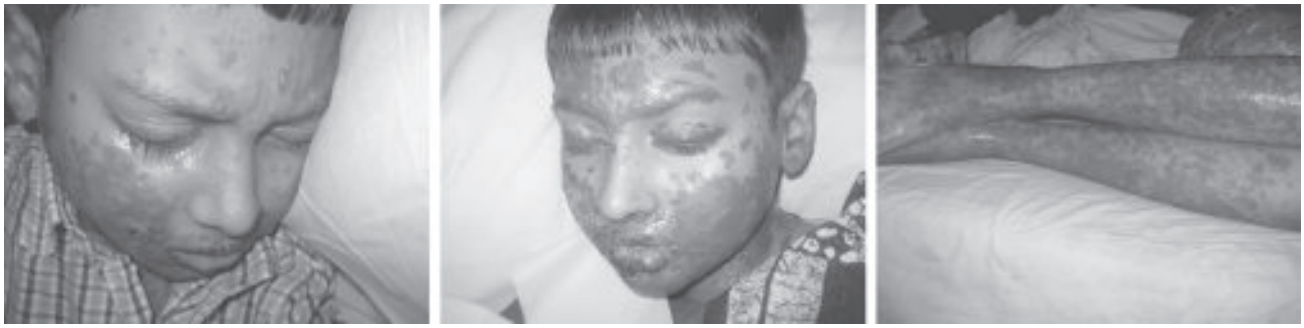

Figure: *Multiple bullous eruption with erythematous base involving skin and mucosa in a 9 years old patient of TEN.*

macular, papular, or urticarial lesions, as well as the classical iris or 'target lesions', sometimes with central vesicles, bullae or purpura, are distributed preferentially on the distal extremities, especially the dorsa of the hands and the extensor forearms. Lesions may involve the palms or trunk. In the Stevens-Johnson syndrome, there is in addition involvement of conjunctival, corneal, iris, buccal, labial and genital mucous membranes; occasionally mucous membrane involvement is all that is seen. Deposits of IgM and C3 may be found in the walls of superficial blood vessels, especially in lesions less than 24 hours old. Circulating immune complexes have been reported, suggesting that immune complex deposition may be important in the pathogenesis.[7]

Discussion

Cutaneous drug reactions are the most common adverse reactions attributed to drugs. Any skin disorder can be limitated, induced or aggravated by drugs. A study was carried out by Patel et al to determine the age, sex incidence and clinical pattern of drug eruptions, to recognize offending drugs (self medication or prescribed), to evaluate mortality and morbidity associated with drugs, to educate the patients, and to avoid self-administration of drugs and re-administration of the offending drugs. The diagnosis of cutaneous drug reactions is mainly based on detailed history and correlation between drug intake and the onset of rash. Two hundred patients (112 males and 88 females) presenting with cutaneous drug reactions were studied. Fixed drug eruption was seen in 61(30.5%) patients; others being urticaria and angioedema 39(18.5%), morbilliform rash in 37(18%), pruritus in 25(12.5%), Stevens-Johnson (SJS) syndrome in six, purpura in six, exfoliative dermatitis in five, photosensitivity in five, Toxic Epidermal Necrolysis in two, acneiform eruption in three, and erythema multiforme in two patients. The most frequently affected age group was 41-50 years, followed by the 21-30 and 31-40 years age groups. The youngest patient was one year old and the oldest was 80 years old. The period of development of lesions after the intake of drug(s) varies from 01-45 days. Cotrimoxazole was the offending drug in 26 cases, followed by Ibuprofen in 20 cases. Fixed drug eruption was the most common drug eruption seen. Cotrimoxazole was the most common cause of drug eruptions. The study finding of Patel et at-where majority of causative drugs in fixed drug reaction are co-trimoxazole 26(29.5%) and NSAIDs 20(22.8%) in number. NSAIDs were also the main offenders in causing urticaria, angioedema and morbilliform rash. Photosensitivity was seen mainly due to ciprofloxacin and sparfloxacin in four cases. Five cases of exfoliative dermatitis (2.5%) occurring due to carbamazepine (two), ibuprofen and NSAIDs and dapsone were seen. There were four cases of purpura-the offending drugs being aspirin, chloroquine, griseofulvin and an unknown drug. One case of angular cheilitis was due to isotretinoin.[3]

Ghosh et al did a study at Kasturba Hospital (KH), Manipal, a 1400 bedded tertiary care hospital. The study was focused on extending the ADR reporting and monitoring program to the dermatology department, with the objective to implement ADR reporting and monitoring system in the department of dermatology of Kasturba Hospital, Manipal; to categorize and analyze the reported cutaneous ADRs, which were reported during the study period; to evaluate the management and outcome of ADRs; and to assess the causality, severity and preventability of the reported cutaneous ADRs, using different scales. The study was a prospective one, conducted in the dermatology department of KH Manipal, for a period of six months, between November 2002 and April 2003. All the inpatients and the outpatients who visited the department during the study period, were monitored for ADRs. Patient case notes/files and suspected ADR notification forms were used as main sources of data collection. For the study purpose, the following documents were used. Suspected ADR notification form, ADR reporting and

documentation form, ADR alert card, Thank you card, Causality assessment scale (Naranjo's scale), Severity assessment and Preventability assessment scale (Hartwig *et al.* scale). The clinical pharmacist who was posted in the dermatology department, used to take part in the ward rounds along with other dermatologists, and actively monitor for any ADRs. To strengthen the awareness of the ADR reporting system posters were displayed, oral campaign, and formal speeches about the importance of reporting ADRs, were done. On intimation of suspected ADRs by the dermatologist, the notification form was filled up by the pharmacist, and the case was followed up for further details, and were documented in the ADR reporting and documentation forms. 'ADR alert card ' was given to the patients who exhibited hypersensitivity type of reaction, or near fatal reaction with any component of the drug. Thank you cards were issued to those dermatologists who reported ADR, so as to encourage further reporting. All the documented ADRs were analyzed for incidence, purpose of visit to the hospital, types of ADRs, drug classes, and individual drug causing cutaneous reaction, association of cutaneous reaction with drugs, predisposing factors, management and outcome of ADRs. ADRs were also assessed for causality using Naranjo's scale, severity and preventability, using Hartwig *et al.* scale. Severities of the reported ADRs were assessed at various levels, ranging between 1 and 7. Level 1 and 2 indicates mild, 3 and 4 as moderate and level 5 and above, as severe ADRs. The study of Ghosh et al was seen that majority of adverse reactions were Stevens-Johnson syndrome, erythema multiforme and urticaria among the 53 patients of adverse drug reactions. Ghosh et al was also seen that majority of adverse drug reactions were due to antibiotic 16(30%), anticonvulsants 13 (25%), anti-tubercular drugs 6(11%), antipyretics 5(9%) and ayurvedic 2(4%).[4]

A study was carried out by Sharma et al in the Department of Dermatology, Venereology and Leprology of Nehru Hospital attached to Postgraduate Institute of Medical Education and Research, Chandigarh, India. All patients suspected of having drug reactions seen in various outpatient departments and admitted in the wards during the period of six years were evaluated. In every case a detailed history was elicited and a thorough clinical examination was carried out as suggested by Sacerdots et al. to establish the etiologic agent for a particular type of reaction, attention was paid to the drug history, temporal correlation with the drug, duration of the rash, approximate incubation period, morphology of the eruption, associated mucosal or systemic involvement, improvement of lesions on withdrawal of drug and recurrence of lesion on rechallenge. If more than one drug was thought to be responsible, the most likely offending agent was noted and the impression was confirmed by subsidence of the rash on withdrawing the drug. The rashes were attributed to a drug following the guidelines of Boston collaborative drug reaction surveillance-programme. All the information was carefully recorded in a specially designed. A total of 500 patients with cutaneous ADR were enrolled during the study period. There were 298 (59.6%) males and 202 (40.4%) females, with an age range of 4 months to 76 years (mean 34.5 years). Maximum number of patients 252 (50.4%) were in the age group of 21-40 years, 126 (25.2%) below 20 years and 72 (14.4%) above 60 years. The incubation period for maculopapular rash and urticaria varied from 30 minutes to 3 weeks. Fixed drug eruption (FDE) had an incubation period ranging from two days to two months. The incubation period for serious drug reactions viz. Stevens-Johnson syndrome (SJS) and TEN varied from a few hours to one-week. Various clinical types of cutaneous ADR and the causative drugs are shown. Serious systemic complications were more frequently seen in cases of TEN. Septicaemia and/or renal failure or other organ dysfunction were seen in 14 patients with TEN and of these, 10 patients died. Other complications recorded were bronchopneumonia, altered liver and renal function tests. Two patients with SJS had major systemic complications (bronchopneumonia and septicaemia with hepatitis in one patient each). The complications observed in erythroderma were acute renal failure (1 patient) and impaired hepatic and renal function (1 patient). Fever was recorded in most of the patients with maculopapular rash, SJS, TEN and erythroderma. Pre-existing renal disease was seen in 2 patients and none of the patients had pre-existing liver disease. Only one patient was HIV positive. In 8 (1.6%) patients, more than one type of rash was observed. Anticonvulsants- phenytoin, carbamazepine & phenobarbitone were implicated in 41.6% of patients with maculopapular rashes. Sulfonamides accounted for 43.3% and NSAIDs for 30.7% of FDE; Urticaria was caused mainly by NSAIDs (24.3%) and penicillins (20%). Anticonvulsants were responsible for 43.8% of life-threatening reactions-TEN and SJS.

To study the changing clinical reaction patterns and the causative drugs over a period of 6 years, the results were tabulated year wise. The statistical analysis was done by using linear trend analysis. It shows –2.6 times decreasing incidence of sulfonamide induced reaction and +1.1 times increasing incidence of

reactions to fluoroquinolones. Among the anticonvulsants phenytoin shows +1.5 times increasing incidence and carbamazepine +3.7 times increasing incidence-of-reactions. Sharma et al was also observed that adverse drug reactions were due to antimicrobials 42.6%, anticonvulsants 22.2%, NSAIDs 18% among the 500 patients of adverse drug reactions. Among the 14% cases of urticaria, 24.3% were due to NSAIDs and 20% were due to penicillin.[5]

Ahmad et al done a study where, life-threatening cutaneous adverse drug reaction, TEN was developed by sparfloxacin. TEN is known to occur with the fluoroquinolones. However, the incidence of sparfloxacin induced TEN is very low, with only four cases having been reported to the WHO database. Ahmad et al reported one more case. A 17-year-old boy with a three-day history of cough and fever was treated with sparfloxacin 400 mg on day one and 200 mg on the following two days. On day three of treatment the patient was hospitalized at their centre for an extensive blistering rash and involvement of the eyes, oral and nasal mucosa. He had greater than 60% cutaneous detachment and was diagnosed as drug induced toxic epidermal necrolysis (TEN). Except for electrolyte imbalance, all the hematological tests and liver and renal functions were within normal limits. Sparfloxacin was stopped and the patient was treated with injections of pheniramine maleate and methyl prednisolone 1 g o.d. intravenously for 4 days. The oral mucosa was treated with metronidazole 1% gel and chlorhexidine mouth wash. Oral prednisolone 40 mg o.d. was begun on the fifth day of admission and was continued until day 19, with constant monitoring of the patient's condition in an intensive care area. Based on culture sensitivity reports, he was treated with various injectible antibiotics during his hospital stay. These included amoxicillin + sulbactam 1.5 g b.i.d., ceftriaxone 1 g b.i.d., cefoperazone 1 g b.i.d. and gentamicin 120 mg o.d. on different days. During this period he was gradually improving, but on the day 22 of hospitalization, he died of suspected pulmonary emboli. The causality assessment of the reaction was 'probable' by both the WHO probability scale and Naranjo's ADR probability scale. A 50-year-old man was admitted for treatment of a posterior fossa cyst with hydrocephalus. It was planned to do a ventriculoperitoneal (VP) shunt for rapid relief of pressure symptoms, followed by endoscopic decompression of the cyst through the fourth ventricle in the same admission, but different sitting. Phenytoin was started after VP shunt was done. However, two days later, the patient started developing an erythematous rash, beginning in the perioral and periorbital areas, which spread to involve the whole trunk and limbs centrifugally over the next one day. Over 50% of the total surface area was involved. Next day, wrinkling and sloughing of the skin began and sloughing could be provoked by gentle stroking of the skin (Nikolsky's sign), even in areas apparently uninvolved. Large flaccid bullae developed and exfoliation continued in large sheets over the front and back of trunk, leaving behind denuded areas of red, glistening, but non-purulent skin. Since he was being treated with multiple drugs, including netilmycin, chloramphenicol, phenytoin, and NSAIDs, drug eruption was considered a strong possibility and all medications were stopped. In consultation with dermatologists, he was managed with topical antibiotics for the skin, eyes, and oral cavity, along with systemic steroids. Prophylactic intravenous antibiotics (vancomycin, levofloxacin, and piperacillin-tazobactam) were added when the patient developed fever after one week of illness. High dose cyclophosphamide/cyclosporin/intravenous immunoglobulin were considered in treatment but were not used in view of their side effects and improvement in patient's condition with the ongoing treatment. Multiple cultures from blood and raw areas of skin were either sterile or grew multiple contaminants. Other drugs were slowly restarted but phenytoin was replaced with sodium valproate. Care was taken to maintain the fluid and electrolyte balance.

A morbilliform rash is the most common reaction to phenytoin, occurring in as many as 5% of cases overall. However, a wide variety of cutaneous reactions can occur, including acneiform lesions, exfoliative dermatitis, erythema multiforme, SJS, vasculitis, gingival hyperplasia, heel pad thickening, and lupus like reaction. In a hospital-based adverse drug reaction reporting program from an Indian tertiary care hospital, phenytoin was the individual drug most frequently reported as a cause of adverse drug reaction. As calculated by Naranjo's adverse drug reaction probability score, the causable relationship between phenytoin and TEN in our case is 'probable'. TEN can also occur as a complication of other drugs. Steroids are the treatment of choice in severe cases, to limit the inflammatory process, along with prophylactic systemic and topical antibiotics. If severe drug reactions such as TEN occur, the suspected drugs, including antiepileptic drugs (AED), should be stopped immediately. A new AED can be started, if necessary, before the resolution of the rash without increasing the risk of further reactions. [6]

Conclusion and recommendations

Although some cutaneous drug reactions may not cause any significant harm to an individual and may cure spontaneously or require very minimum treatments but some are dangerous enough to cause serious harmful effects on the body even may lead to death if not diagnosed early and not promptly and efficiently treated. Hence, each of these cutaneous reactions are to be considered with great importance as it may cause deleterious effect on the working capability. To reduce the cutaneous drug reactions the following are the recommendations:

- The person must be meticulous about taking the drugs.
- Injudicious use of the drugs should be avoided.
- Drug having adverse effects should be carefully considered before prescribing to any diseased and co-morbid person.
- Careful history should be taken about any drug allergy on a particular drug on any previous occasions.
- Individual should stop the drug immediately and report to the doctor as early as possible when he develops any cutaneous lesions.
- Disposal and instruction given by dermatologist regarding individual's cutaneous reactions should be followed by individual and authority should supervise it.

References

1. James WD, Berger TG and Elston D. Andrew's Disease of the skin-Clinical Dermatology. 10th edition. U.S.A: Saunders Elsevier; 2006:115
2. Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA and Katz SI. Fitzpatrick's Dermatology in General Medicine. 7th edition. New York :The McGraw- Hill Companies; 2003:355.
3. Patel RM, Marfatia YS. Clinical study of cutaneous drug reaction in 200 patients. Indian J Dermatol Venereol Leprol 2008; 74: 430.
4. Ghosh S, Acharya LD, Rao PGM.Study and evaluation of the various cutaneous adverse drug reactions in Kasturba hospital, Manipal. Indian J Pharm Sci 2006; 68(2): 212-215
5. Sharma VK, Sethuraman G, Kumar B. Cutaneous adverse drug reactions: Clinical pattern and causative agents- a 6 year series from Chandigarh, India. J Postgrad Med 2001; 47(2): page 95-99.
6. Ahmad FU, Mahapatra AK. Phenytoin-induced toxic epidermal necrolysis in a neurosurgical patient. Neurol India 2007;55:181-2.
7. Champion RH, Burton JL, Ebling FJG, Rook/ Wilkinson/Ebling. Textbook of Dermatology. 5th Edition, 1992;4(5): 2973
8. Jhaj R, Uppal R, Malhotra S, Bhargava VK. Cutaneous adverse reactions in in-patients in a tertiary care hospital. Indian J Dermatol Venereol Leprol 1999; 65:14-7
9. Shrivastava D, Kumar A, Singh SK. Adverse drug reaction monitoring in patients attending skin O.P.D at a teaching hospital. Indian J Pharmacol 2004;36:S42.
10. Devi K, George Sandhya, Criton S, Suja V. Carbamazepine- The commonest cause of toxic epidermal necrolysis and Steven Johnson syndrome: A study of 7 years. Indian J Dermatol Venereol Leprol 2005;71:325-8.
11. Dreskin SC, Andrews KY. The thyroid and urticaria. Curr Opin Allergy Clin Immunol. 2005;5:408-12.
12. Verneuil L, Leconte C, Ballet JJ, Coffi n C, Laroche D, Izard JP,Reznik Y, Leroy D. Association between chronic urticaria and thyroid autoimmunity: a prospective study involving 99 patients.Dermatology. 2004;208:98-103.
13. Ryhal B, DeMera RS, Shoenfeld Y, Peter JB, Gershwin ME. Are autoantibodies present in patients with subacute and chronic urticaria? J Investig Allergol Clin Immunol. 2001;11:16-20.
14. Sehgal S, Balachandran C, Shenoi SD. Clinical study of cutaneous drug reaction in 80 patients. Indian J Dermatol Venereol Leprol 2003;69:6-7.
15. Roujeau JC, Kelly J, Naldi L, Berthold R, Stern R, Anderson T, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med*. 1995;333:1600–1607
16. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N Engl J Med*. 1994;331:1272–1285
17. Garcia-Doval I, LeCleach L, Bocquet H, Otero XL, Rojeau JC. Toxic epidermal necrolysis and Stevens-Johnson syndrome. Does early withdrawal of causative drugs decrease the risk of death?. *Arch Dermatol*. 2000;136:326–327
18. Mockenhaupt M, Schöpf E. Cutaneous drug reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis). *Curr Opin Dermatol*. 1997;4:269–275
19. Moshfeghi M, Mandler HD. Ciprofloxacin-induced toxic epidermal necrolysis. *Ann Pharmacother*. 1993;27:1467–1469.
20. Livasy CA, Kaplan AM. Ciprofloxacin-induced toxic epidermal necrolysis (a case report). *Dermatology*. 1997;195:173–175
21. Tham TCK, Allen G, Hayes D, McGrady B, Riddell JG. Possible association between toxic epidermal necrolysis and ciprofloxacin. *Lancet*. 1991;338:522.