

Current Dermatological Therapy

A series of articles on the current dermatological therapy will feature in the pages of the journal this year. This issue presents the sixth of the series. Articles are contributed by Dr. J. S. Pasricha, M.D., Ph.D., Department of Dermato-Venereology, All India Institute of Medical Sciences, New Delhi.

MANAGEMENT OF ALLERGIC CUTANEOUS REACTIONS TO DRUGS

In most references to adverse reactions to drugs, it is customary to use the phrase 'due to the addition of new drugs every now and then, the incidence of adverse drug reactions continues to rise'. In my opinion, however, there is no valid basis for making such a statement. Firstly, we have no system for monitoring adverse reactions to drugs and therefore do not know about the incidence of such reactions and secondly, a new drug does not necessarily mean more adverse reactions. Our only source of information about adverse drug reactions is, initially the studies undertaken by the pharmaceutical firm before the introduction of the drug and subsequently the reports which may appear in the literature after the drug has been in use. It is however important to bear in mind that majority of the adverse drug reactions are mild and may not be reported¹, while severe drug reactions sometimes remain undetected because of ignorance and non-availability of proper medical facilities. On the other hand, many patients attribute any symptom that may appear during the course of treatment, to the drug(s) being used at that time and most physicians as well as the patients are too scared to prove or disprove the association. Moreover, reports^{1,2} that are based on unconfirmed drug reactions are likely to be wrong

and misleading. Therefore, the first duty of all clinicians should be to sort out the truth from falsehood.

Out of all the various types of adverse reactions to drugs, allergic reactions are one of the most frequent and skin is the most commonly affected organ^{1,3}. The clinical manifestations include urticaria, angio-odema; exanthematous eruptions manifesting as macular, papular, papulo-vesicular, vesicular, purpuric or erythematous-squamous lesions, erythema multiforme, Stevens-Johnson syndrome, epidermal necrolysis, exfoliative dermatitis, SLE-like syndrome, lichenoid eruptions and fixed drug eruptions^{1,4,12}. It is often said that like syphilis (which is not so frequent now) drug eruptions can mimic most of the skin diseases including vesicular eruptions and many of these eruptions are severe enough to warrant emergency treatment.

The first thing that needs to be done in a case of drug eruption is to withdraw all the drugs including vitamins being taken by the patient¹³. The only exception to this rule is when the withdrawal of a particular drug is likely to be more serious than the drug reaction itself. It may however be noted that in many conditions, withdrawal of the drug for a few days does not necessarily lead to

serious complications. A correct decision at that stage is very important. In case the treatment of the original disease cannot be interrupted, it is safer to employ those drugs which the patient has not used earlier; but while making the choice, care should be taken to ensure that these drugs do not have any chemical resemblance to the previous drugs, otherwise cross-sensitive reactions may develop^{14,22}. It is also preferable to admit the patient particularly in severer drug reactions, so that the progress of the disease and that of the drug reaction can be watched almost continuously and readjustments in the treatment can be made as and when necessary.

In most cases, the drug reaction tends to subside spontaneously after the causative drug has been withdrawn¹¹ and in mild cases, no further treatment may be necessary. The process of spontaneous regression however is slow and in severer drug reactions, it is as a rule necessary to control it rapidly. Cases of urticaria and angio-odema may be controlled only with oral and/or parenteral antihistamines but in case the lesions tend to appear at important locations such as the larynx, it is important to use adrenaline immediately^{11,12}. A subcutaneous injection of 0.5 ml of 0.1% adrenaline is usually enough, but the dose can be repeated if there is no improvement in the condition within 5 minutes. Subsequently, treatment with an adequate dose of antihistamines has got to be continued till the effect of the drug wears off spontaneously. This may take between one and four weeks. Some physicians tend to use corticosteroids if the patient does not respond to the usual doses of antihistamines. Use of corticosteroids in urticaria is justifiable only if the reaction is based on type III immunologic reactions (serum sickness type)¹². In all other types of urticaria, an adequate dose of antihistamines as a rule, is sufficient.

Exanthematous eruptions manifesting as macular, papular, papulo-vesicular, vesicular, purpuric or scaly lesions and even erythema multiforme may be very mild and require only local applications of soothing lotions and the antipruritic effect of oral antihistamines, but severe exanthematous eruptions and all cases of Stevens-Johnson syndrome, epidermal necrolysis, exfoliative dermatitis and SLE-like syndrome as a rule require systemic corticosteroids. The dose of corticosteroids has to be determined arbitrarily, but it is preferable to err on the higher side of the dose to control the drug reaction as quickly as possible. In case new lesions do not stop appearing within 2 days, the dose must be increased proportionately. Some dermatologists hesitate to administer corticosteroids in patients who are having tuberculosis, diabetes or some other similar disease, but experience shows that a week or so of corticosteroid therapy even without specific therapy for the original disease is not really that dangerous. In fact at that stage, one has to select the lesser evil and in case the situation demands, corticosteroids should not be withheld. It may also be borne in mind that a half-hearted treatment with corticosteroids delays control of the drug reaction and is therefore more risky. In the case of fixed drug eruptions, 10-15 mg prednisolone a day is usually sufficient to control the reaction within 2-3 days.

Once the drug reaction has been controlled, it is important to withdraw corticosteroids as quickly as possible¹¹ and this can usually be accomplished within a week or two. The important question however, remains, how to find out the drug responsible for the drug reaction and how to treat the original disease. The simplest course is to avoid all the drugs being taken at the time of the reaction and to treat the patient with alternative drugs. This however may not be possible or economical in all the cases. Moreover, if a patient is advised to avoid a large

number of drugs, there are far greater chances that the patient will take some such drug or its analogue and develop another drug reaction. Worse still, even this time the patient may take more than one drug and once again the opportunity to find out the causative drug will be missed. Moreover, this second drug reaction may occur under such circumstances where adequate medical facilities for recognition and treatment of the drug reaction may not be available leading to serious consequences. It is also wrong to presume that the drug most commonly known to produce a drug reaction is the one responsible in every case. Sometimes at least, drugs not previously known to produce a drug reaction are found to be the causative drugs^{23, 24}. Thus it seems to be very important to find out the drug responsible for the reaction. For this, several *in vivo* and *in vitro* tests such as intradermal tests, basophil degranulation tests, histamine release tests, monkey ileum tests, radio-allergo-sorbent test, haemagglutination test, complement fixation test, lymphoblast transformation test, leucocyte migration inhibition test and several others have been recommended from time to time,^{1, 12, 25-28} but the general consensus is that none of these tests is fool-proof^{1, 3, 29}. Some of these tests such as the intradermal test give a high incidence of false positive or false negative results,^{7, 30} while others such as the radio-allergo-sorbent test are too complicated to be clinically practicable. It is therefore generally agreed that provocation test is the simplest and the most reliable method for finding out the causative drug^{1, 22, 31, 32}. Some dermatologists however, do not favour provocation tests for fear of fatal reactions^{6, 8, 12}. There is no doubt that the provocation test can be risky and should not be resorted to when the drug reaction was anaphylactic in nature^{12, 24}. But in cases manifesting as urticaria and when the drug is not to

be injected, the provocation test can be undertaken with due precautions. The patient should be kept available in the hospital and all resuscitative measures should be available if required. One capsule or tablet of the drug can be given and the patient kept under observation for the next 1 to 2 hours. In case there is no reaction, the next drug can be tested the next day.

Provocation test can also be undertaken in cases who developed exanthematous eruptions, erythema multiforme, Stevens-Johnson syndrome, epidermal necrolysis or exfoliative dermatitis^{1, 13} provided the patient can be available for observation. It is preferable to admit the patient though it is not absolutely necessary if the patient can report as soon as the reaction occurs. On the first day, the patient is given one half of a single therapeutic dose. In case there is no reaction during the next 24 hours, the patient should be given one full therapeutic dose of the same drug on the second day. If still there is no reaction, on the third day the patient should be given one day's full therapeutic dose. If there is no reaction with even this dose, the patient can be considered not allergic to this drug and one can proceed to test with the next drug. Using a small dose on the first day helps to minimise the reaction whenever it occurs, but since the reactions are dose dependent,^{12, 22, 33} it is necessary to use a day's full therapeutic dose before declaring the drug safe. In lichenoid eruptions or SLE-like syndrome, it is necessary to give a drug for a week or so before changing over to the next test drug because these eruptions are slow to develop. In the case of fixed drug eruptions, there is no need to hospitalise the patient. One drug (one tablet or a capsule) can be given per day to watch which of these reactivates the lesions²². Once some drug leads to recurrence of the symptoms, further testing should be suspended and the drug reaction should be

controlled as described previously. Generally, there is no need to resume provocation with other drugs, but occasionally, cases allergic to more than one drug have been recorded^{17, 34, 35} and therefore it may be preferable to complete the provocation test with the remaining drugs.

Contact dermatitis due to locally applied drugs is an altogether different problem in which there is hardly any risk of fatality, but the patient is very much inconvenienced for no fault of his. Quite often a patient who starts using a medicine for a minor injury or a skin lesion, finds that after a few days the lesion starts becoming worse with the appearance of new papular and papulo-vesicular lesions and extension into the adjoining areas³⁶. In such a case patch tests can be undertaken immediately in contravention of the general rule that patch tests should be avoided as long as contact dermatitis is active, because it is important to find out which drug(s) can be used to treat the patient. Although neomycin is known to be a very potent contact sensitizer all over the world,^{37, 39} in our experience^{36, 40} nitrofurazone tops the list. Even then a patient may be allergic to an altogether different agent. Moreover, our findings show that some patients are allergic to as many as six antibacterial agents⁴⁰. In case patch tests cannot be performed, gentian violet or brilliant green can be safely used as antibacterial agents.

References

1. Kauppinen K : Cutaneous reactions to drugs. *Acta Dermato-Venerol*, 52 : (Suppl 68), 1972.
2. Jesiotr M : Ethambutol in the treatment of 26 patients with chronic active pulmonary tuberculosis. *Tubercle*, 50 : 54, 1969.
3. Demis JD : Allergy and drug sensitivity of skin. *Ann Rev Pharmacol*, 9 : 457, 1969.
4. Ashby DW and Lazar T : Erythema multiforme exudativum major (Stevens-Johnson syndrome). *Lancet*, 1 : 1091, 1951.
5. Lyell A : Toxic epidermal necrolysis : An eruption resembling scalding of skin. *Brit J Derm*, 68 : 355, 1956.
6. Rostenberg A and Fagelson HJ : Life threatening drug eruptions. *J Amer Med Ass*, 194 : 660, 1965.
7. Halpern SR : Chronic hives in children. An analysis of 75 cases. *Ann Allergy*, 23 : 589, 1965.
8. Carroll OM, Bryan PA and Robinson RJ : Stevens-Johnson syndrome associated with long acting sulphonamides. *J Amer Med Ass*, 195 : 691, 1966.
9. Lyell A : A review of toxic epidermal necrolysis in Britain. *Brit J Derm*, 79 : 662, 1967.
10. Champion RH, Roberts SOB, Carpenter RG and Roger JH : Urticaria and angio-oedema. A review of 554 patients. *Brit J Derm*, 81 : 588, 1969.
11. Beerman H and Kirshbaum BA : Drug eruptions. In *Dermatology*. Editors, Moschella SL, Pillsbury DM and Hurley HJ Jr : WB Saunders Company, Philadelphia, 1975.
12. Baker H : Drug eruptions. In *Textbook of Dermatology*. Editors, Rook A, Wilkinson DS and Ebling FJG : Blackwell Scientific Publications. Oxford, 1975.
13. Pasricha JS : *Treatment of Skin Diseases*. Arnold Heinemann Publishers, New Delhi, 1976.
14. Welsh AL : Crossed fixed drug eruption from two antibiotics. *Arch Derm and Syph*, 65 : 232, 1952.
15. Dougherty JW : Fixed drug eruption due both to aureomycin and to terramycin. *Arch Derm and Syph*, 65 : 485, 1952.
16. Welsh AL : Crossed fixed drug eruption from three antibiotics. *Arch Derm and Syph*, 71 : 521, 1955.
17. Welsh AL : *The fixed eruption*. Charles C Thomas. Springfield, 1961.

18. Browne SG: Fixed eruption in deeply pigmented subjects: Clinical observations on 350 patients. *Brit Med J*, ii: 1041, 1964.
19. Fitzpatrick TB: Fixed drug eruption (Phenacetin). *Arch Derm*, 92: 484, 1965.
20. Nayyar KC and Pasricha JS: Fixed drug eruption to oxyphenbutazone and phenylbutazone. *Dermatologica*, 144: 214, 1972.
21. Pandhi RK and Bedi TR: Fixed skin eruption caused by oxyphenbutazone with cross sensitivity to phenylbutazone. *Arch Derm*, 111: 131, 1975.
22. Pasricha JS: Drugs causing fixed eruptions. *Brit J Derm*, (in press).
23. Pasricha JS and Nayyar KC: Skin rash as a side effect of l-tetramisole. *Toxicol Appl Pharmacol*, 20: 602, 1971.
24. Pasricha JS and Kanwar AJ: Skin eruption caused by ethambutol. *Arch Derm*, 113: 1122, 1977.
25. Shelley WB: New serological test for allergy in man. *Nature*, 195: 1181, 1962.
26. Shelley WB and Comaish JS: New test for penicillin allergy-Fluorometric assay of histamine release. *J Amer Med Ass*, 192: 36, 1965.
27. Virolainen M: Blast transformation in vivo and in vitro in carbamazepin hypersensitivity. *Clin Exp Immunol*, 9: 429, 1971.
28. Foucard T: Immunochemical and biological determination of reagins. A comparison between the radio-allergosorbent test (RAST) and the test for histamine release from passively sensitized chopped human lung. *Int Arch Allergy*, 42: 711, 1972.
29. Sherman WB: Drug allergy. *S Med J*, 64: 22, 1971.
30. Pedersen-Bjergaard J: The clinical diagnosis of penicillin allergy. *Acta Allergol*, 25: 89, 1970.
31. Casebolt JM: A safe approach to drug testing. Provocation titration. *Rev Allergy*, 24: 156, 1970.
32. Stubb S: Blood leucocytes, with special reference to basophils and eosinophils during provocation tests in fixed eruption and drug exanthema. *Acta Dermatovenereol*, 56: (Suppl 76), 1976.
33. Dostrovski A and Sagher F: Fixed erythema due to sulfanilamide with gradually lessening sensitivity. *Arch Derm and Syph* 49: 418, 1944.
34. Chargin L: Fixed eruption in a patient sensitive to arsphenamine and phenolphthalein in different areas. *Arch Derm and Syph*, 38: 474, 1938.
35. Pasricha JS and Shukla SR: Independent lesions of fixed eruption due to two unrelated drugs in the same patient. *Brit J Derm*, (in press).
36. Pasricha JS and Kanwar AJ: Substances causing contact dermatitis. *Ind J Derm Vener and Leprol*, 44: 264, 1978.
37. Reynolds H, Hildebrand JF, Livingood CS and Fosnaugh RP: Clinical features of contact dermatitis due to neomycin. *Arch Derm*, 80: 455, 1959.
38. Epstein E: Detection of neomycin sensitivity. *Arch Derm*, 91: 50, 1965.
39. Pirila V, Forstrom L and Rouhunkoskin S: Twelve years of sensitization to neomycin in Finland. *Acta Dermato-Venereol*, 47: 419, 1967.
40. Pasricha JS and Guru B: Contact hypersensitivity to local antibacterial agents (Unpublished).