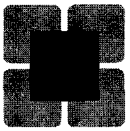

Fixed drug eruptions and oral rechallenge

ADVERSE REACTIONS to drugs remain a problem in medicine, despite our increased understanding of drug hypersensitivity and the trend toward production of hypoallergenic drugs. It is important to detect the causative drug because the eruption may become more severe with every exposure.

Drug-induced hypersensitivity reactions most commonly affect the skin, and have several different presentations.[1] Since even the same agent may cause different types of eruptions, it is impossible to detect the causative agent from the appearance of the eruption. A detailed history of drug use is important but, in many cases, insufficient to make the diagnosis. Oral drug provocation is a practical way to identify the agent responsible for a fixed drug eruption.

An extensive number of agents can cause fixed drug eruptions. The agents implicated most commonly vary among different countries, probably because of different usage patterns.[2–5] Furthermore, several case reports document fixed drug eruption caused by agents that are infrequently used.[6]

■ *See Nedorost and associates (pp 33–34).*

Nedorost and associates report the first case of fixed drug eruption to pamabrom (2-amino-2-methyl-1-propanol-8-bromo-theophyllinate). The causative agent, an ingredient of a compound drug, was confirmed by oral rechallenge. Theophylline and its derivatives are widely used, but their implication in skin reactions is rare. One case of fixed drug eruption caused by 8-chlorotheophyllin has been reported.[7] In the case reported by Nedorost, pamabrom was used periodically for menstrual pain; unusual mucosal symptoms reappeared that resembled those of herpes simplex. Similar cases of fixed drug eruptions with mucosal involvement causing diagnostic difficulties have been reported.[8,9]

VALUE OF ORAL PROVOCATION

Up-to-date records

It is often difficult to select the agent for a rechallenge test. Many patients take multiple medications and have no history of previous drug reactions. Lists based on critical studies of the agents that most frequently cause drug eruption are of great help.[6] Since usage of drugs varies from time to time, it is important to keep these lists up to date by adding any new, critically studied substance known to have caused an eruption. In this respect, Nedorost's report of the case of fixed drug eruption to pamabrom documented by rechallenge is valuable, and the agent should be added to the lists of agents that have caused fixed drug eruptions.

Reliable results

Oral drug provocation is widely used for detecting the causative agent in drug eruptions, especially in Finland[8] and Asia,[3–5] but is used infrequently in the United States. Yet, it is the most reliable test and, when performed rationally, serious rechallenge reactions can be avoided.

The aim of a drug challenge test is to elicit the reappearance of an eruption in mild form after the original eruption has disappeared, preferably after 1 to 2 months. The test is carried out in controlled circumstances, preferably in the hospital, both to ensure safety and to enable recording of flare-up of the eruption, fever, and other clinical symptoms.

Topical provocation of fixed drug eruption has been studied[10] as an alternative to oral rechallenge. The suspected drug, diluted in a vehicle, was applied as an open test on both normal skin and on previous lesion sites. Local provocation was obtained in most cases. It occurred only at sites of previous eruptions but never on clinically normal skin.[10]

Despite the importance of detecting the causative agent in drug eruptions, especially fixed drug eruptions,

some authorities recommend avoiding oral rechallenge, at least routinely, preferring to avert any possible risk associated with oral rechallenge.[6] Others suggest that patch testing the eruption site prior to systemic challenge is worthwhile because it may confirm the causative agent in some cases; thus, no oral challenge would be needed.[11]

ORAL RECHALLENGE METHODS

The type of reaction should be considered when evaluating the need for a drug challenge test. Challenge testing is inadvisable if the original reaction was anaphylaxis, severe urticaria, severe angioedema, toxic epidermal necrolysis (Lyell's syndrome), maximal variant of erythema multiforme (Stevens-Johnson syndrome), or a systemic lupus erythematosus-like reaction.

The test dose of drug to be used in a challenge test must be individualized. Drug-induced hypersensitivity reactions are dose-dependent and the dose that provokes a reaction in a sensitized person varies. There are no standard test doses for each drug that would definitely give a positive result.

Important considerations when choosing a test dose include the severity of the original reaction, the nature of the suspected drug, and the interval between the original eruption and the challenge test. As a rule, if the primary reaction was intense and the drug is known to provoke strong reactions, the initial test dose should be small and great care should be taken when increasing the dose. One-tenth of a standard single dose or even less may cause reappearance of the reaction.[12] One-fourth to one-half of a single dose is the most common dosage used in rechallenge testing. A test dose equal to or larger than the single standard dose is seldom needed.

The challenge test result is considered positive if eruption, fever, or both appear. A negative result may indicate that the agent used was not the causative drug, or that the test dose was too small.

CONCLUSION

No laboratory or topical skin test can dependably elucidate the responsible agent in drug eruptions. An oral drug challenge, performed rationally, can detect the causative agent, and is reliable and safe.

KIRSTI KAUPPINEN, MD
Department of Dermatology
Helsinki University Central Hospital
Snellmaninkatu 14
SF-00170 Helsinki
Finland

REFERENCES

1. Alanko K, Stubb S, Kauppinen K. Cutaneous drug reactions: clinical types and causative agents. Acta Derm Venereol (Stockh) 1989; **69**:223–226.
2. Kauppinen K, Stubb S. Fixed eruptions: causative drugs and challenge tests. Br J Dermatol 1985; **112**:575–578.
3. Shukla SR. Drugs causing fixed drug eruptions. Dermatologica 1981; **163**:160–163.
4. Chan HL. Fixed drug eruptions. A study of 20 occurrences in Singapore. Int J Dermatol 1984; **23**:607–609.
5. Kanwar AJ, Bharija SC, Singh M, Belhaj MS. Ninety-eight fixed drug eruptions with provocation tests. Dermatologica 1988; **177**:274–279.
6. Bruisma W. A guide to drug eruptions. The European file of side effects in dermatology, 3rd ed. The Netherlands: Oosthuizen; 1990.
7. Stritzler C, Kopf AW. Fixed drug eruptions caused by 8-chlorotheophyllin in Dramamine with clinical and histologic studies. J Invest Dermatol 1960; **34**:319–330.
8. Loveman AB, Simon FA. Fixed eruption and stomatitis due to sulfanilamide. Arch Derm Syph 1939; **48**:1034.
9. Kuokkanen K. Erythema fixum of the genitals and the mucous membranes. Int J Dermatol 1974; **13(1)**:4–8.
10. Alanko K, Stubb S, Reitamo S. Topical provocation of fixed drug eruption. Br J Dermatol 1987; **116**:561–567.
11. Habbema L, Bruynzeel DP. Fixed eruption due to naproxen. Dermatologica 1987; **174**:184–185.
12. Kauppinen K, Alanko K. Oral provocation: uses. Seminars in Dermatology 1989; **8(13)**:187–191.