# Clinical and Laboratory Assays in the Diagnosis of Cutaneous Adverse Drug Reactions

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An adverse cutaneous reaction caused by a drug is any undesirable change in the structure or function of the skin, its appendages, or mucous membranes as a result of a drug given in any way (systemic or topical). Many mechanisms, allergic and non-allergic, may be involved in the pathogenesis of skin reactions to drugs. The non-allergic mechanisms (without immunologic background) include: overdose, pharmacologic or idiosyncratic side effects, reciprocal drug interactions, Jarisch-Herxheimer reaction, etc. Allergic rash is an expression of hypersensitivity that is created by one of four known allergic mechanisms (types I-IV hypersensitivity reactions) [1].

The data on the prevalence of skin reactions to drugs are gathered from hospital projects, epidemiologic surveys, and case reports. The true prevalence of this phenomenon is much greater than that reported, even without taking into consideration diagnoses where the connection to undesirable drug reaction was not determined.

The clinical diagnosis of skin reactions to drugs is not an easy one. Not only are there many types of skin reactions to drugs, but many of them mimic skin diseases, such as bullous diseases, psoriasis, etc. [2,3]. These reactions are now called "the great imitator." Another difficulty in diagnosis is when the patient is taking more than one drug at the same time. A further obstacle is the existence of a latent period that can last a few days to over a year between taking the drug and the appearance of the skin reaction.

According to the literature, there are several clinical and laboratory methods that can be used to discover the different mechanisms of drug rash and that prove the connection between a suspected drug and the reaction [4–12]. *In vivo* tests, like the challenge test, are potentially hazardous and are usually not recommended in most clinical situations. Skin tests such as prick tests, patch tests and delayed (tuberculin-type) tests have only limited value in the diagnosis of cutaneous drug reactions.

These limitations prompted the development of *in vitro* tests. However, one of the problems with these tests is that the immunologic reaction sometimes occurs due to a metabolite of a drug and not to the drug itself. Furthermore, the antigenic determinant may include a binding protein in addition to the drug having a false negative result in an *in vitro* test.

Examples of *in vitro* tests include:

- **RAST (radioallergosorbent test)**

This test is used to measure specific immunoglobulin E antibodies in serum. Allergen extract is coupled to a solid matrix. This immunosorbent is reacted with serum and washed and then reacted with radiolabeled anti-human IgE antibody and washed. Uptake of the labeled antibody is proportional to the level of specific serum IgE antibodies to the allergen. This test is limited to reactions that are mediated by IgE antibody and to drugs in which the epitope has been defined [4].

- **Mast cell degranulation test**

This is an assay that tests the amount of histamine release from mast cells after incubation with the suspected drug. This test is related to type I hypersensitivity reaction. The specificity and sensitivity of the test have not been defined [5].

- **Lymphocyte transformation test**

In this test lymphocytes are incubated with and without the suspected drug for several days. Later, $^{3}$H-thymidine is added for a few hours. Lymphocyte proliferation is expressed as the ratio between thymidine uptake with the drug and uptake without the drug. Usually, only minor proliferation occurs and it is difficult to distinguish between false positive or negative results [6,7].

- **Diagnosis of reactions that involve immune complexes**

Immune complexes cause elevated levels of lysosomal enzymes such as β-glucuronidase. In the test leukocytes are incubated with the drug and β-glucuronidase levels are measured in the supernatant [8].

- **Lymphocyte toxicity assay**

This assay attempts to identify defects in the detoxification of toxic metabolites in drugs. The drug is incubated with lymphocytes of the patient in the presence of human-like microsome, which includes cytochrome p450. This test is useful in hypersensitivity syndrome.

Ig = immunoglobulin

- **Macrophage migratory inhibition factor test**

MIF is a lymphokine released from sensitized T lymphocytes by an appropriate antigen. The expression of MIF activity correlates with delayed hypersensitivity and cellular immunity. Macrophage migration is compared in the presence and absence of the drug, and the ratio is expressed as a migration index. A migration index of 0.80 or less with the drug is considered a positive MIF test. The sensitivity of this test is estimated to be 57% with specificity of 96% [9–11].

- **Interferon-gamma release test**

Th1 lymphocytes are activated in delayed-type hypersensitivity reactions and produce interleukin-2 and IFNγ. Th2 lymphocytes are activated in immediate-type hypersensitivity and produce IL-4, IL-5 and IL-10. Recent studies demonstrated the diagnostic potential of a test based on release of IFNγ from lymphocytes after exposure to a suspected drug.

Lymphocytes of patients are incubated with and without the drug. IFNγ is collected from the supernatant and its level is measured by enzyme-linked immunosorbent assay. The increase in IFNγ release is calculated. The test has a sensitivity of 54% and specificity of 92% [12].

In the present issue of *IMAJ*, Halevy et al. [13] evaluated the IFNγ release test in diagnosing a case of erythema nodosum. Erythema nodosum is a septal panniculitis. It is a reactive hypersensitivity reaction that may be induced by a variety of systemic diseases, infections, malignancies, as well as drugs. The latter include sulfonamides, bromides, iodides, oral contraceptives, gold, penicillin, minocycline, salicylates and other analgetics. In the presented case the suspected drugs were estradiol, progesterone and paracetamol. The IFNγ test was positive only for estradiol. The authors suggest, therefore, that this test may serve as a diagnostic test in drug-induced erythema nodosum. Their results emphasized the role of Th1 lymphocytes in the pathogenesis of erythema nodosum.

The IFNγ release assay is currently the preferred test and the one most widely used. The aim of future investigations in the field of drug allergies is to find assays with greater sensitivity and specificity for assessing the different mechanisms of adverse reactions to drugs.

MIF = macrophage migratory inhibition factor test
IFN = interferon-gamma
IL = interleukin

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