Adverse drug reactions result in a substantial number of hospital admissions and inpatient events. Diagnosis usually is made with clinical judgment and circumstantiality without diagnostic testing. Furthermore, even in situations where diagnostic testing is performed, no safe gold standard tests exist. Oral rechallenge is currently the gold standard but carries the risk of recrudescence of severe allergic symptoms. Other tests include skin prick tests, the lymphocyte transformation test, immunohistochemistry, and patch testing. This article provides a review of patch testing in cases of adverse drug reactions and presents new data on this topic.

Adverse drug reactions account for 3% to 6% of hospital admissions in the United States and occur in 10% to 15% of hospitalized patients. The most common culprits are antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs). In most cases, diagnoses are made clinically without diagnostic testing. To identify drug allergies associated with diagnostic testing, one center selected patients with suspected cutaneous drug reactions (2006-2010) for further evaluation. Of 612 patients who were evaluated, 141 had a high suspicion of drug allergy and were included in the analysis. The excluded patients had pseudoallergic reactions, reactive exanthemas due to infection, histopathologic exclusion of drug allergy, angioedema, or other dermatological conditions such as contact dermatitis and eczema. Of the included patients, 107 were diagnosed with drug reactions, while the remainder had non-drug-related exanthemas or unknown etiology after testing. Identified culprit drugs were predominantly antibiotics (39.8%) and NSAIDs (21.2%); contrast media, anticoagulants, anticonvulsants, antimalarials, antifungals, glucocorticoids, antihypertensives, and proton pump inhibitors also were implicated. They were identified with skin prick, intradermal, and patch tests (62.6%); lymphocyte transformation test (17.7%); oral rechallenge (5.6%); or without skin testing (6.5%). One quarter of patients with a high suspicion for drug allergy did not have a confirmed drug eruption in this study. Another study found that 10% to 20% of patients with reported penicillin allergy had confirmation via skin prick testing. These findings suggest that confirmation of suspected drug allergy may require more than one diagnostic test.

Tests for Adverse Drug Reactions

The following tests have been shown to aid in the identification of cutaneous drug eruptions: (1) patch tests; (2) intradermal tests; (3) drug provocation tests; and (4) lymphocyte transformation tests. Intradermal or skin prick tests are most useful in urticarial eruptions but can be considered in nonurticarial eruptions with delayed inspection of test sites up to 1 week after testing. Drug provocation
tests are considered the gold standard but involve patient risk. Lymphocyte transformation tests use the principle that T lymphocytes proliferate in the presence of drugs to which the patient is sensitized. Patch tests will be discussed in greater detail below. Immunohistochemistry can determine immunologic mechanisms of eruptions but cannot identify causative agents.\(^{16,17,22}\)

A retrospective study of patients referred for evaluation of adverse drug reactions between 1996 and 2006 found the collective negative predictive value (NPV)—the percentage of truly negative skin tests based on provocation or substitution testing—of cutaneous drug tests including patch, prick, and intradermal tests to be 89.6% (95% confidence interval, 85.9%-93.3%).\(^{23}\) The NPVs of each test were not reported. Patients with negative cutaneous tests had subsequent oral rechallenge or substitution testing with medication from the same drug class.\(^{23}\) Another study\(^{16}\) found the NPV of patch testing to be at least 79% after review of data from other studies using patch and provocation testing.\(^{16,24}\) These studies suggest that cutaneous testing can be useful, albeit imperfect, in the evaluation and diagnosis of drug allergy.

**Review of the Patch Test**

Patch tests can be helpful in diagnosis of delayed hypersensitivities.\(^{18}\) Patch testing is most commonly and effectively used to diagnose allergic contact dermatitis, but its utility in other applications, such as diagnosis of cutaneous drug eruptions, has not been extensively studied.

The development of patch tests to diagnose systemic drug allergies is inhibited by the uncertainty of percutaneous drug penetration, a dearth of studies to determine the best test concentrations of active drug in the patch test, and the potential for nonimmunologic contact urticaria upon skin exposure. Furthermore, cutaneous metabolism of many antigens is well documented, but correlation to systemic metabolism often is unknown, which can confound patch test results and lead to false-negative results when the skin’s metabolic capacity does not match the body’s capacity to generate antigens capable of eliciting immunogenic responses.\(^{21}\) Additionally, the method used to suspend and disperse drugs in patch test vehicles is unfamiliar to most pharmacists, and standardized concentrations and vehicles are available only for some medications.\(^{25}\) Studies sufficient to obtain US Food and Drug Administration approval of patch tests for systemic drug eruptions would be costly and therefore prohibitive to investigators. The majority of the literature consists of case reports and data extrapolated from reviews.

Patch test results of many drugs have been reported in the literature, with the highest frequencies of positive results associated with anticonvulsants,\(^{26}\) antibiotics, corticosteroids, calcium channel blockers, and benzodiazepines.\(^{21}\)

Patch test placement affects the diagnostic value of the test. Placing patch tests on previously involved sites of fixed drug eruptions improves yield over placement on uninvolved skin.\(^{27}\) Placing patch tests on previously involved sites of other drug eruptions such as toxic epidermal necrolysis also may aid in diagnosis, though the literature is sparse.\(^{25,26,28}\)

**Patch Testing in Drug Eruptions**

Morbilliform eruptions account for 48% to 91% of patients with adverse drug reactions.\(^{4,6}\) Other drug eruptions include urticarial eruptions, acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, toxic epidermal necrolysis, Stevens-Johnson syndrome, lichenoid drug eruption, symmetric drug-related intertriginous and flexural exanthema (SDRIFE), erythema multiforme (EM), and systemic contact dermatitis. The Table summarizes reports of positive patch tests with various medications for these drug eruptions.

In general, antimicrobials and NSAIDs were the most implicated drugs with positive patch test results in AGEP, DRESS syndrome, EM, fixed drug eruptions, and morbilliform eruptions. In AGEP, positive results also were reported for other drugs, including terbinafine and morphine.\(^{29-38}\) In fixed drug eruptions, patch testing on involved skin showed positive results to NSAIDs, analgesics, platelet inhibitors, and antimicrobials.\(^{27,52-55}\) Patch testing in DRESS syndrome has shown many positive reactions to antiepileptics and antipsychotics.\(^{39-43}\)

One study used patch tests in SDRIFE, reporting positive results with antimicrobials, antineoplastics, decongestants, and glucocorticoids.\(^{61}\) Nonsteroidal anti-inflammatory drugs, antimicrobials, calcium channel blockers, and histamine antagonists were implicated in EM.\(^{47-51}\) Positive patch tests were seen in morbilliform eruptions with selective serotonin reuptake inhibitors, antiepileptics/benzodiazepines, NSAIDs, and antimicrobials.\(^{28,57-60}\) In toxic epidermal necrolysis, diagnosis with patch testing was made using patches placed on previously involved skin with sulfamethoxazole.\(^{62}\)

**Systemic Contact Dermatitis**

Drugs historically recognized as causing allergic contact dermatitis (eg, topical gentamycin) can cause systemic contact dermatitis, which can be patch tested. In these situations, systemic contact dermatitis may
### Positive Patch Test Results for Adverse Drug Reactions

<table>
<thead>
<tr>
<th>Class of Drug(s)</th>
<th>Patch-Tested Medication(s)</th>
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</thead>
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<td>Antimicrobial</td>
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<tr>
<td>Antiepileptics/benzodiazepines</td>
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<td><strong>SDRIFE</strong></td>
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<tr>
<td>Antimicrobials/antifungals</td>
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Abbreviations: AGEP, acute generalized exanthematous pustulosis; NSAID, nonsteroidal anti-inflammatory drug; DRESS, drug reaction with eosinophilia and systemic symptoms; SSRI, selective serotonin reuptake inhibitor; SDRIFE, symmetric drug-related intertriginous and flexural exanthema; TEN, toxic epidermal necrolysis.
be due to either the active drug or excipients in the medication formulation. Excipients are inactive ingredients in medications that provide a suitable consistency, appearance, or form. Often overlooked as culprits of drug hypersensitivity because they are theoretically inert, excipients are increasingly implicated in drug allergy. Swerlick and Campbell described 11 cases in which chronic unexplained pruritus responded to medication changes to avoid coloring agents. The most common culprits were FD&C Blue No. 1 and FD&C Blue No. 2. Patch testing for allergies to dyes can be clinically useful, though a lack of commercially available patch tests makes diagnosis difficult.

Other excipients can cause cutaneous reactions. Propylene glycol, commonly implicated in allergic contact dermatitis, can also cause cutaneous eruptions upon systemic exposure. Corticosteroid-induced systemic contact dermatitis has been reported, though it is less prevalent than allergic contact dermatitis. These reactions usually are due to nonmethylated and nonhalogenated corticosteroids including budesonide, cortisone, hydrocortisone, prednisolone, and methylprednisolone.

Patch testing in these situations is complicated by the possibility of false-negative results due to the anti-inflammatory effects of the corticosteroids. Therefore, patch testing should be performed using standardized and not treatment concentrations.

In our clinic, we have anecdotally observed several patients with chronic dermatitis and suspected NSAID allergies have positive patch test results with propylene glycol and not the suspected drug. Excipients encountered in multiple drugs and foods are more likely to present as chronic dermatitis, while active drug ingredients started in hospital settings more often present as acute dermatitis.

**Our Experience**

We have patch tested a handful of patients with suspected drug eruptions (University Hospitals Cleveland Medical Center institutional review board #07-12-27). Medications, excipients, and their concentrations (in % weight per weight) and vehicles that were tested include ibuprofen (10% petrolatum), aspirin (10% petrolatum), hydrochlorothiazide (10% petrolatum), captopril (5% petrolatum), and propylene glycol (30% water or 5% petrolatum). Patch tests were read at 48 and 72 hours and scored according to the International Contact Dermatitis Research Group patch test scoring guidelines. Two patients tested for ibuprofen reacted positively only to propylene glycol; the 3 other patients did not react to aspirin, hydrochlorothiazide, and captopril. Overall, we observed no positive patch tests to medications and 2 positive tests to propylene glycol in 5 patients tested (unpublished data).

**Areas of Uncertainty**

Although tests for immediate-type hypersensitivity reactions to drugs exist as skin prick tests, diagnostic testing for the majority of drug reactions does not exist. Drug allergy diagnosis is made with history and temporality, potentially resulting in unnecessary avoidance of helpful medications. Ideal patch test concentrations and vehicles as well as the sensitivity and specificity of these tests are unknown.

**Guidelines From Professional Societies**

Drug allergy testing guidelines are available from the British Society for Allergy and Clinical Immunology and American Academy of Allergy, Asthma and Immunology. The guidelines recommend diagnosis by history and temporality, and it is stated that patch testing is potentially useful in maculopapular rashes, AGEP, fixed drug eruptions, and DRESS syndrome.

**Conclusion**

Case reports in the literature suggest the utility of patch testing in some drug allergies. We suggest testing excipients such as propylene glycol and benzoic acid to rule out systemic contact dermatitis when patch testing with active drugs to confirm cause of suspected adverse cutaneous reactions to medications.

**REFERENCES**


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