

Review Article

Contact dermatitis from topical antiviral drugs

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The literature has been reviewed for contact dermatitis from topical antiviral drugs. 15 agents have been identified including acyclovir, imiquimod, podophyllin, podofilox, cidofovir, penciclovir, vidarabine, idoxuridine, trifluridine, tromantadine, lamivudine, interferon intralesional injections and ophthalmic solution, fomivirsen and foscarnet intravitreal injections and ganciclovir intraocular implants. Patch testing has been documented in certain individuals and cross-sensitization has been observed to contribute significantly to some allergic reactions.

Key words: antiviral drugs; contact dermatitis; patch test; adverse cutaneous reactions; cross-sensitivity; medicaments. © Munksgaard, 2001.

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Adverse cutaneous reactions following topical or injectable administration of antiviral drugs are an uncommonly observed entity. For the most part, skin eruptions are mild and transitory; however, systemic manifestations of varying intensity can occur and may sometimes be serious in nature. Even more rarely observed is the associated contact dermatitis following occupational or therapeutic exposure. Information concerning this aspect of antiviral therapy is sparse and scattered throughout the medical literature. A review of the available data identifies 15 agents including acyclovir, imiquimod, podophyllin, podofilox, cidofovir, penciclovir, vidarabine, idoxuridine, trifluridine, tromantadine, lamivudine, interferon intralesional injections and ophthalmic solution, fomivirsen and foscarnet intravitreal injections and ganciclovir intraocular implants.

Epidemiological studies have indicated seroprevalence rates to herpes virus vary from 1% in college freshmen in Columbia, South Carolina, to 9% in women attending a student health center at the University of Washington, to 22% of women attending family planning clinics in Pennsylvania, to 46% of women attending a sexually transmitted disease clinic in Seattle, Washington (1). Human papillomavirus types 6, 11, 16, 18, 31, 33, 35, 39, 45, 51 and 52 have been found in the cervical epi-

thelium of 50% of sexually active women (2). Types 6 and 11 account for 80% of genital condylomas; whereas, types 16 and 18 account for 80% of cervical cancers in the USA and UK. Thus, considering the number of individuals who receive antiviral chemotherapy, substantial potential exists for adverse cutaneous and contact related reactions to occur.

Documented Cases

Acyclovir

Phlebitis and erythema occurred in 16% of individuals receiving acyclovir intravenously (3). Severe local inflammation leading to necrosis of the skin has occurred from extravasation of intravenously administered acyclovir and has been considered a toxic reaction (4). However, a recent observation was suggestive of an immunologically based mechanism, as evidenced by histological examination indicative of a leukocytoclastic vasculitis (5). Approximately 1% of these individuals have manifested encephalopathic changes including lethargy, obtundation, tremors, confusion, hallucinations, seizures and coma. Rashes have rarely been reported and hematuria and nausea in clinical trials were not significantly different from that of placebo recipients.

Documented contact dermatitis from acyclovir was rare, with only 10 studies reported (6–15). Positive patch tests were confirmed to 5% aqueous acyclovir in 2 studies (6, 7) in which the patients developed vesicular eczematous eruptions after treating herpes simplex. Sensitivity to acyclovir 1%–5% in petrolatum was observed in other studies following treatment for recurrent herpes simplex (8, 9). Bourezane et al. (10) along with others (11–14) demonstrated negative patch testing to acyclovir 5% in petrolatum and suggested that most of the sensitivity to acyclovir cream was due to the vehicle components, including sodium lauryl sulfate and propylene glycol. However, with the low bioavailability of acyclovir dispersed in petrolatum compared to dissolved in propylene glycol one has to be skeptical of the conclusions of these studies that the skin reactions were being attributed only to the vehicle components. Corazza et al. (13) noted a concomitant sensitization to hydroxypropyl cellulose from a transdermal patch and the similar chemical structure of propylene glycol in the antiviral cream. Rodriguez-Serna et al. (15) recorded the first case of photoallergic contact dermatitis from acyclovir cream after treatment for recurrent labial herpes simplex. Punctate keratopathy was observed in 2 of 58 patients receiving 3% ophthalmic ointment for treatment of herpetic keratitis and confirmed by patch tests (16). In all of the above cases, tissue eruptions and pruritus resolved with discontinuation of the offending agents and/or topical application of corticosteroids.

As an interesting footnote, Porter et al. (17) published a case of an individual who presented with an indurated penile nodule following self-injection of acyclovir tablets dissolved in hydrogen peroxide into a genital herpetic lesion. A foreign body reaction was observed upon histological evaluation of the intralesional injection site and patch testing was not performed in this case.

Imiquimod

Numerous clinical trials have demonstrated 5% topical imiquimod to be an effective and safe treatment for anogenital warts caused by human papillomavirus. (18–20). Local skin reactions such as erythema, erosion, excoriation, flaking and edema occurred in up to 1.2% of patients with 3× per week application. Severe systemic reactions from topical application to anogenital warts included headache, influenza-like syndrome and myalgia. The most clinically serious adverse event recorded following multiple oral dosings of >200 mg was hypotension, which resolved with intravenous and oral fluid administration. Patients treated with this

chemical had a reaction rate of 50% versus 11% for those receiving the vehicle cream (18). Interestingly, females responded much better by 72% versus 33% for males and this was thought to be due to the differences in keratinization of the wart tissue (18).

Podophyllin and podofilox

Numerous studies have been published concerning the use of these 2 agents for treatment of anogenital warts (19, 21–23). Podophyllin is a plant compound that causes tissue necrosis by arresting cells in mitosis and is usually applied at concentrations of 10%–25% in tincture of benzoin. It is not a standardized compound and its efficacy may vary significantly from different batches. Other than intense local inflammatory dermatitis, rare systemic reactions include paresthesia, polyneuritis, paralytic ileus, leukopenia, thrombocytopenia and death (21). Podofilox, also known as podophyllo-toxin, is the biologically active lignin of podophyllin resin and is available in a 0.5% solution for self administration. Local cutaneous reactions following podophyllin application include pain, erythema, pruritus and edema. Rare severe systemic reactions include bone marrow suppression (24).

Podofilox, as opposed to podophyllin, can be self administered by the patient and studies indicated it was more effective, with faster resolution of the warts, over podophyllin (23). Rates of local side-effects 1 week after treatment were 57% inflammation, 48% burning, 47% pain, 44% pruritus and 39% erosion, which were mostly mild to moderate in intensity and diminished over time (22). Headaches were the most commonly reported systemic adverse event in 7% of clinical trials. Information in the literature was not available concerning patch testing and neither of these agents was used in pregnant patients.

Interferons

Interferons are naturally occurring substances used therapeutically for their properties of inducing an antiviral state in cells, thus inhibiting cellular proliferation and immunomodulation. The agents can be delivered by various routes including parenteral, topical and intralesional. Alpha-interferon has been used for intralesional treatment of condylomata acuminata and flu-like symptoms were a common effect (25). Localized reactions occurred at the site of injection in <5% of participants including injection site inflammation, pain and pruritus. Allergic contact dermatitis was observed from the application of beta-interferon eye drops including intense facial edema, erythema

and vesicular formation (26). Patch testing revealed positive reactions to the combined ingredients in the eye drops of beta-interferon but not to the excipients when patch tested separately.

Cidofovir, penciclovir and vidarabine

Cidofovir has been available for intravenous infusion and topical gel treatment of recurrent genital herpes and acyclovir-unresponsive mucocutaneous herpes simplex virus infection in patients with acquired immunodeficiency syndrome (27–29). Intravenous infusion in 89 humans resulted in adverse reactions of 53% nephrotoxicity, 20% neutropenia, 5.6% ocular hypotony and 2% Fanconi's syndrome (30). Lalezari et al. (27) noted 25% application site reactions (i.e., lesional burning, pain or pruritus) which occurred with 0.3%–1.0% cidofovir gel versus 20% for placebo-treated patients for acyclovir unresponsive mucocutaneous herpes simplex virus. 69 patients with recurrent genital herpes were treated with increasing strengths of 1%–5% cidofovir gel and application site reactions occurred in up to 22% of patients (28). Application site reactions consisted of pain, pruritus, skin changes (i.e., discoloration and hypertrophy) and ulceration and were dose dependent; only 1 patient treated with placebo experienced an adverse cutaneous reaction.

Penciclovir is made in a 1% gel and used for treatment of herpes viruses (31, 32) and was released for use in the United States in 1997. The most frequently reported adverse event was headache, which occurred in 5.3% of penciclovir patients versus 5.8% of placebo-treated patients. Spruance et al. (32) studied 1573 patients and found application site events (i.e., site irritation, hypesthesia and paresthesia) were related to the study medication in 0.5% for the penciclovir group and 1.1% for the placebo group.

Vidarabine 3% ophthalmic ointment has been used for topical treatment of epithelial keratitis caused by herpes simplex virus (33–35). Noted side-effects following ocular use included lacrimation, conjunctival infection, burning, irritation, superficial punctate keratitis, pain, photophobia, punctal occlusion and sensitivity in 10%–15% of patients. Patch testing was not performed for any of the above listed drugs.

Idoxuridine, trifluridine and tromantadine

Idoxuridine has been demonstrated to be too toxic for parenteral use and is now only applied topically (16, 36–41). Less toxic and more effective agents have been developed for treatment of this condition and idoxuridine was probably the most

well-known cause of chronic follicular conjunctivitis among the antiviral agents (36, 39). Contact dermatitis with patch testing has been documented in at least 7 studies (16, 38, 40–44). Less than 20 cases have confirmed patch test positive to this drug; whereas the others appeared to be due to the delivery vehicle components including propylene glycol and dimethylsulfoxide (41). Interestingly, Amon et al. (38) observed a pattern of cross-reactivity of this agent with other brominated and chlorinated, but not fluorinated, pyrimidine analogues.

Trifluridine 1% ophthalmic solution has proven more effective and less toxic than idoxuridine (36) and equally effective as cidofovir (20) in the treatment of ocular herpetic infections. The most noted reaction to this compound was contact dermatitis-conjunctivitis (36). Rarely have studies reported an allergic contact dermatitis from this agent in eye-drops (45, 46). Patch testing was confirmed to this chemical, and not the solution components, in the study by Millan-Parrilla & De La Cuadra (46).

Contact dermatitis from tromantadine, a derivative of amantadine, has also occurred in the treatment of recurrent herpes simplex (47–50). At least 100 cases of allergic contact dermatitis have been reported in the literature and patch testing has been used to identify this chemical. Fanta and Mischer (47) found that 8.3% of 240 patients affected with the herpes simplex virus treated with topical agents developed an allergic contact dermatitis. Of these, it was noted that 12 individuals or 5% had positive patch tests to this compound. Cross-sensitivity has been noted between tromantadine and amantadine using patch tests by Santucci et al. (48).

Miscellaneous drugs including lamivudine, fomivirsen, foscarnet and ganciclovir intraocular implants

Contact dermatitis has been reported only 1× from lamivudine in a case report of an individual handling the drug (51). After holding the agent for 30 min a pruritic eruption developed over the next 3 days and extended from the palm to the forearm. The reaction was confirmed by patch testing.

Fomivirsen has been administered by intravitreal injection for treatment of cytomegalovirus retinitis (52, 53). Mild intraocular inflammation occurred in 15% of cases, which were treated with topical corticosteroids, and rare serious events were marked by retinal toxicity.

Foscarnet has been used for intravitreal injections for cytomegalovirus infections and intraocular inflammation was the most commonly noted cutaneous reaction (54). Javalay et al. (55) studied topical 1% foscarnet cream for the treatment of

mucocutaneous herpes simplex virus infections unresponsive to acyclovir in 20 patients with acquired immunodeficiency syndrome. The most commonly associated adverse events were fever, headaches, new herpetic simplex lesions and skin ulcerations, while site application reactions (i.e., burning and irritation) occurred in only 2 individuals.

An interesting application of ganciclovir has been as intraocular implants for treatment of cytomegalovirus infections (54, 56–59). The implants allowed slow release of the agent over an extended period of 6–8 months, with decreased toxicity versus that of intravenous administration, and absence of the need for repeat intravitreal injections. Focal granulomatous inflammation was noted at the suture site (57) and surgical placement of the intraocular implants rarely resulted in vitreous hemorrhage, retinal detachment and endophthalmitis (58, 59).

Hyposensitization

A review of the literature has produced little information on the hyposensitization of these topical agents in humans. In consideration of the number of compounds available, the various routes of administration and combinations of chemotherapy, hyposensitization, specifically for any 1 topical compound, would seem to be of little clinical value.

Conclusions

The literature has been reviewed for contact dermatitis from 15 antiviral drugs. Most cutaneous reactions were mild and transitory; however, in rare cases some were extremely severe. Patch testing has revealed only rare instances of reactivity to the medications and skin reactions have also been attributable to the delivery vehicle components. However, it must be pointed out that there were probably more observed contact dermatitis reactions than have been published. Also, in many of the case reports incriminating vehicle components, the studies were not fully evaluated in detail to determine the allergenic potential of the active principles, such as changes in solution concentrations, changes in vehicles, ROATs and PUTs. A limited number of studies have indicated cross-sensitivity to idoxuridine and tromantadine when individuals were exposed to structurally related compounds. Thus, in consideration of the number of people who may receive these medications throughout the world, substantial potential exists for contact dermatitis to occur.

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