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EJHP Science • Volume 15 • 2009 • Issue 4 • P. 83-85
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www.ejhp.eu

Topical cidofovir for the treatment of resistant viral infections: a case report

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Abstract

Background: Numerous case reports and published studies have described the successful use of topical cidofovir to treat resistant and severe forms of viral infection.
Objective: To report a case of resistant human papilloma virus (HPV) infection treated with topical cidofovir.
Method: A 25-year-old woman presented with injury in the pubic region caused by HPV. Because of her resistance to conventional therapies she was treated with 1% topical cidofovir.
Results: All the lesions disappeared completely. The only adverse effect observed was irritation in the treated zone.
Conclusion: Topical cidofovir can be effective in resistant cutaneous viral infections.

Keywords

Anogenital warts, cidofovir, condylomata acuminate, human papilloma virus (HPV)

Introduction

Anogenital warts (condylomata acuminata) are caused by human papilloma virus (HPV) infection. HPV lesions can occur anywhere on the cutaneous surface, but are observed mainly on the extremities, genitalia and oral mucosa. HPV infections are most common in patients who are immunocompromised. These patients have more problems with extensive, recurrent and resistant infections compared with the general population.

HPV encompasses a family of highly infectious and, primarily, sexually transmitted double-stranded DNA viruses. Most infections are transient and they clear within two years. Persistent infections in the setting of other clinical risk factors (such as infection with the human immunodeficiency virus (HIV)) are associated with the development of squamous cell carcinoma. There are over 70 distinct HPV subtypes. Low-risk subtypes, such as HPV 6 and 11, are most frequently associated with benign condylomas and low-grade intraepithelial neoplasia.

Symptoms associated with condylomata acuminata vary depending upon the number of lesions and their location. Patients with a small number of warts are often asymptomatic although other patients can have pruritus, bleeding, burning, tenderness, vaginal discharge and/or pain. The diagnosis of condylomata can usually be made by visual inspection of the affected area. The lesions, which are skin-coloured or pink, range from smooth, flattened papules to a verrucous, papilliform appearance. A biopsy can be considered in the following circumstances: when the diagnosis is uncertain; in those who do not respond to therapy; in immunocompromised patients; in those with large lesions; or in the presence of atypical features.

Conventional therapies for HPV are classified as:

- Chemotherapeutic agents: podophyllotoxin, retinoic acid, trichloroacetic acid
- Cytodestructive methods: liquid nitrogen, electrocautery, carbon dioxide laser photocoagulation
- Immunostimulants: interferon alpha, imiquimod

However, all therapies for genital warts are somewhat unsatisfactory because of recurrence rates of 30% to 70%.

Cidofovir is a broad-spectrum antiviral agent, commercially available as an IV injection and approved for treatment

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Received: 19 December 2008; Revised manuscript received: 16 June 2009; Accepted: 16 June 2009

of cytomegalovirus retinitis in HIV patients. Several case reports and published studies, such as those by McElhiney [1] and others mentioned in the discussion section of this paper, describe successful use of topical cidofovir to treat resistant and severe forms of viral infections such as molluscum contagiosum, condylomata acuminata, genital warts and gingival infection with HPV, with minimal adverse events.

Case Report

A 25-year-old HIV-negative woman presented with papillomas in the pubic region; these were diagnosed as condylomata acuminata. After several cycles of treatment with imiquimod and podophyllotoxin, the lesions were refractory or reappeared and extended to the genital zone. The exudate from the papillomas was positive for papilloma virus type 6.

The patient was resistant to conventional treatments. In addition, because of the number and growth of the lesions, the medical team took the decision to avoid other more aggressive therapies such as surgical resection. Instead, she was prescribed a less aggressive treatment: 1% cidofovir cream once daily for five consecutive days for two weeks.

Preparation of topical cidofovir

Topical cidofovir cream or gel is compounded from the commercial parenteral cidofovir (Vistide) solution and a cream or aqueous gel base. Because of the drug's mutagenic properties, those involved in formulating this preparation should take cytotoxic or antineoplastic precautions. The National Institutes of Health recommends that cidofovir be prepared in a Class II laminar airflow biological safety cabinet or barrier isolator. Staff should wear chemotherapy gloves and closed-front surgical gowns with knitted cuffs during preparation of the compound. If the compounder is accidentally exposed to cidofovir, the exposed area should be washed and flushed with copious amounts of water. All materials in contact with cidofovir should be disposed of in a waterproof, puncture-proof container and incinerated. Because the amount of cream or gel compounded is usually less than 40 g, the syringe method of preparation is ideal (see Panel I).

There are several different cidofovir formulations and two are shown in Table 1; 1% cidofovir cream was used in the case study. Although no stability studies on cidofovir cream or gel have been published, it is reasonable to assign an expiry date of 30 days after preparation to allow for a full month of therapy.

Panel 1: Syringe method of preparation of topical cidofovir [1]
1. Weigh the vehicle base.
2. Place the vehicle base in a disposable 60-mL syringe.
3. Place the syringe in a barrier isolator.
4. Use a chemo-protective device to withdraw the desired amount of cidofovir into another disposable 60-mL syringe.
5. Detach the chemo-protective device from the syringe containing the cidofovir.
6. Attach a luer-lock-to-luer-lock connector to the syringe.
7. Connect the syringe containing the cream or gel base to the connector.
8. Inject the contents of the syringes back and forth between the two syringes until the cream or gel is thoroughly mixed with the cidofovir solution and the mixture is smooth and consistent in texture.
9. Detach the connector.
10. Empty the syringes.
11. Transfer the mixture to a clean ointment jar or ointment tube.
12. Cap, seal and label the jar or tube.

Results

All the lesions completely disappeared. The only adverse effect observed was irritation in the treated zone which resolved spontaneously. No recurrence was observed over an average follow-up period of 15 months.

Discussion

Numerous case reports and published studies describe successful use of topical cidofovir to treat resistant and severe forms of viral infection. Some of these are outlined below.

Snoeck et al. first reported the effective use of topical cidofovir for relapsing anogenital condylomas in three AIDS patients [2].

In another study, patients with genital condylomata acuminata treated with topical cidofovir experienced

Table 1: Formulations for topical cidofovir cream or gel [1]

	Cidofovir gel (1%)	Cidofovir cream (1%)
Cidofovir injection 75 mg/mL	5 mL	5 mL
Propylene glycol–based jelly	32.5 mL	
Eucerin cream		32.5 g

a complete response rate of 47% compared with 0% for patients on placebo in a double-blind trial with 30 HIV-negative individuals. Combined complete and partial response was 84% and 18% for the cidofovir and placebo groups, respectively. Adverse events most frequently reported were pain, pruritus and rash at the application site [3].

Calista et al. described the effectiveness of topical cidofovir for severe cutaneous HPV and molluscum contagiosum infections in HIV patients in a pilot study [4].

Matteelli et al. conducted a randomised, placebo-controlled, single-blinded study to determine the tolerability and efficacy of topical 1% cidofovir cream for the treatment of external anogenital warts in HIV-infected patients. More than a 50% reduction of the total wart area was achieved in 58% of the cidofovir group compared with 0% of the placebo group [5].

In a study published by Hengge et al., condylomata acuminata recalcitrant to laser treatment, podophyllin, and imiquimod resolved with topical 1.5% cidofovir [6]. A case report published by Shürmann et al. described resolution of a penile condylomata acuminata with topical cidofovir [7].

Tobin et al. described a case of a 9-year-old girl with a verruca that had proven refractory to conventional treatments; when 1% cidofovir ointment was applied topically the verruca was completely eradicated and no adverse effects or local irritation were observed [8].

A case report published by De Socio et al. described a 42-year-old man with AIDS and Hodgkin's lymphoma who had severe and recalcitrant cutaneous warts. The warts resolved following treatment with local 1% cidofovir [9].

In addition to this evidence, Field et al. presented a series of seven children treated with topical 1% cidofovir ointment for severe recalcitrant viral warts, which were limiting their quality of life. All the children had failed to respond to at least two other forms of therapy and the warts had persisted for a mean of two years. In this study, four of the seven children with recalcitrant viral warts achieved long-lasting clearance in response to topical 1% cidofovir [10].

Conclusion

Topical cidofovir has demonstrated its efficacy in resistant cutaneous viral infections in several studies, as shown above.

However, compounded cidofovir creams or gels are prohibitively expensive and should be reserved for cases in which all other conventional treatments have failed. Until a commercial product is developed, marketed and affordably priced to allow it to be routinely prescribed for these infections, the compounding pharmacist can provide this treatment option to treat infection, prevent severe disfigurement, improve self-esteem and social interaction, and, ultimately, enhance the quality of life for the patients.

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