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Compounded Topical Cidofovir as Salvage Therapy for Acyclovir-Resistant Genital HSV-2 in an Immunocompromised Pregnant Patient

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Abstract:

Genital herpes, primarily caused by herpes simplex virus type 2 (HSV-2), is a sexually transmitted viral infection commonly managed with oral antiviral agents such as acyclovir, valacyclovir, or famciclovir. These medications are considered first-line treatments for both initial and recurrent episodes. While resistance to acyclovir is uncommon in immunocompetent individuals, it may develop in immunocompromised patients, presenting a significant therapeutic challenge. Resistance typically arises through mechanisms such as reduced or absent viral thymidine kinase activity, impaired acyclovir phosphorylation, or alterations in viral DNA polymerase. In cases resistant to standard therapy, topical 3% cidofovir has emerged as a potential salvage treatment, particularly in refractory cases unresponsive to intravenous (IV) antivirals; however, its use is primarily supported by case reports and remains inadequately defined. In May 2023, a 28-year-old pregnant woman presented to the clinic with a severe HSV-2 outbreak characterized by widespread oral and genital lesions, along with systemic symptoms. Her medical history included hidradenitis suppurativa, systemic lupus erythematosus (SLE), iron-deficiency anemia, and chronic HSV-2 infection. Prior to pregnancy, her medications included topical clindamycin 1% gel (twice daily), spironolactone 50 mg (twice daily), levofloxacin 500 mg (daily), hydroxychloroquine 200 mg (daily), infliximab 730 mg (monthly infusion), and methotrexate 10 mg (weekly). Due to clinical deterioration, the patient was hospitalized and initiated on IV acyclovir 10 mg/kg every 8 hours. After clinical stabilization, she was transitioned to oral acyclovir 400 mg 3 times daily to complete a 10- day course. At discharge, she started on valacyclovir 500 mg 2 times daily for suppressive therapy. Despite adherence to the suppressive regimen, the patient returned in July 2023 with new genital ulcerations. HSV culture and resistance testing were performed. At that time, her outpatient provider escalated valcyclovir to 1 g 2 times daily. However, she was readmitted shortly after due to worsening back pain that disrupted sleep and raised concern for viral reactivation. IV acyclovir 700 mg every 8 hours was reinitiated. Given lack of sustained response and clinical suspicion for antiviral resistance, compounded 3% topical cidofovir was added as salvage therapy for a planned 5-day course. The patient was thoroughly counseled on the application of topical cidofovir. She reported significant symptomatic relief, though she experienced painful burning with urination that prompted early discontinuation of the topical agent prior to the final application. Following clinical improvement, she was discharged on oral valacyclovir 500mg 2 times daily for suppressive therapy pending laboratory confirmation of antiviral susceptibility. In August 2023, resistance to acyclovir was confirmed, and the medication was discontinued.

This case highlights the utility of topical cidofovir as a salvage therapy in managing acyclovir-resistant HSV-2 infection in an immunocompromised pregnant patient. While systemic therapies remain first-line, topical cidofovir may offer a viable adjunct or alternative in select cases, particularly when resistance is confirmed or highly suspected. Though the patient could not complete the full course due to local adverse effects, her symptom improvement suggests potential benefit. Further research and clinical experience are necessary to better define the role of topical cidofovir in HSV treatment, including optimal duration, frequency, and tolerability management. Topical cidofovir 3% may represent a promising salvage therapy for patients with confirmed or suspected acyclovir-resistant HSV-2, especially in immunocompromised populations. In this case, its use was associated with symptom improvement, despite early discontinuation. It should be considered as part of the therapeutic arsenal for future resistant outbreaks in similar patient populations.

Keywords: Compounded 3% topical cidofovir; resistant HSV-2 lesions

Introduction:

Herpes simplex virus (HSV) infections remain among the most common viral infections globally, typically managed with nucleoside analogs such as acyclovir, valacyclovir, and famciclovir in accordance with current treatment guidelines. These agents rely on viral thymidine kinase for activation, and their efficacy is generally high in immunocompetent individuals. In immunocompromised patients, antiviral resistance has emerged as a significant clinical concern. Due to impaired cell-mediated immunity, these individuals exhibit reduced capacity to control HSV replication, resulting in increased frequency and duration of viral reactivation. This necessitates prolonged or recurrent administration of antiviral agents, particularly nucleoside analogs such as acyclovir, which in turn exerts substantial selective pressure on the virus. Under these conditions, mutations, most commonly in the thymidine kinase (UL23) or DNA polymerase (UL30) genes, can arise, leading to reduced susceptibility or complete resistance to standard antiviral therapies. Acyclovir resistance often confers cross-resistance to valacyclovir and famciclovir, as all three drugs require conversion into their active form, acyclovir triphosphate, to inhibit viral DNA synthesis. [1,2]. The clinical implications of resistant HSV are substantial, leading to persistent mucocutaneous lesions, increased risk of dissemination, and reduced quality of life. Second-line therapies such as foscarnet and intravenous cidofovir are used in these cases but are limited by systemic toxicity and the need for intravenous access. In recent years, compounded topical

cidofovir has gained attention as an effective local therapy for resistant HSV lesions, particularly in patients with contraindications to systemic treatment [2,3].

Cidofovir is an acyclic nucleotide analog of cytosine, originally developed and approved for the treatment of cytomegalovirus (CMV) retinitis in patients with AIDS. Its mechanism of action involves inhibition of viral DNA polymerase. Importantly, cidofovir does not require activation by viral thymidine kinase, which makes it effective against HSV strains harboring TK mutations. Once inside the cell, cidofovir is phosphorylated by host enzymes to its active diphosphate form. This metabolite has a prolonged intracellular half-life, enabling sustained antiviral activity even with intermittent application. Cidofovir when administered systemically, carries a significant risk of nephrotoxicity, necessitating pre-hydration and co-administration of probenecid to protect renal tubular function. These requirements complicate its use, particularly for patients who may not tolerate intravenous therapy. When applied topically, cidofovir can deliver antiviral effects directly to the lesion site with minimal systemic absorption, significantly reducing the risk of renal toxicity [4-9].

Cidofovir is not commercially available in a topical formulation, but it can be prepared by compounding pharmacists in concentrations typically ranging from 1% to 3%. Compounded cidofovir formulations require adherence to strict guidelines due to the drug's mutagenic properties. Pharmacists must utilize appropriate personal protective equipment (PPE) and work in certified compounding environments that comply with USP <795> standards [10]. The preparation typically involves mixing cidofovir with an emollient base, to enhance skin penetration. At our hospital, a 3% cream was prepared by measuring 24 mL of cidofovir intravenous solution (75 mg/mL) in a syringe and then incorporated into Eucerin® base where it was mixed homogenously up to a total weight of 60 g cream. The compounded topical cidofovir is applied directly to HSV lesions with frequency and duration of application dependent on the severity of the lesions and the clinical response. These preparations have been applied 1 or 2 times daily with most reported treatment courses last between one and three weeks depending on lesion severity, patient tolerability, and clinical response [4, 10-11].

Case Report:

A 28-year-old pregnant female, with a history of genital HSV-2, presented to the clinic in May 2023 with severe and extensive HSV-2 lesions affecting both the oral and genital regions. She exhibited signs of systemic infection, including fever, malaise, and worsening ulcerative lesions. Her past medical history was notable for hidradenitis suppurativa, systemic lupus erythematosus (SLE), and iron-deficiency anemia. Prior to pregnancy, the patient's chronic medication regimen included topical clindamycin, spironolactone, levofloxacin, hydroxychloroquine, monthly infliximab infusions and oral methotrexate. Once the patient was confirmed to be pregnant, her methotrexate was immediately discontinued given its known risks of fetal toxicity and the patient's ongoing immunosuppressive therapy with infliximab was carefully reassessed to balance maternal disease control with fetal safety. Given the extent of her immunosuppressive treatment, she was considered immunocompromised, placing her at increased risk for HSV-2 reactivation and the potential development of resistance to antiviral agents. Upon initial presentation, she started on IV acyclovir therapy due to the severity of her infection. After she stabilized at 10mg/kg every 8 hours the team transitioned her to oral acyclovir 400mg 3 times daily to complete a 10 day course of treatment and subsequently discharged her with oral valacyclovir 500mg 2 times daily for suppressive therapy. Although there was high self-reported adherence to her prescribed antiviral regimen, she returned in July 2023 with worsening symptoms and new genital ulcers, raising suspicion for acyclovir resistance.

At this time, HSV culture and resistance testing was sent to the laboratory. Despite escalating her valacyclovir dose to 1 g 2 times daily, symptom resolution was not achieved, indicating an insufficient therapeutic response. Her condition continued to deteriorate, and she was subsequently readmitted with worsening genital lesions, severe back pain, and sleep disruption. Given the concern for refractory HSV-2 infection, her treatment was escalated to IV acyclovir at a dose of 700 mg every 8 hours.

Pregnancy complicated her treatment plan, since many second-line antiviral therapies for HSV-2 infection (i.e. - IV foscarnet and IV cidofovir) are contraindicated in pregnancy due to potential teratogenic effects. Due to persistent symptoms, clinical suspicion of acyclovir resistance, and her limitations to systemic treatment options due to pregnancy, alternative therapies were explored. The team decided to trial compounded 3% topical cidofovir as an off-label salvage therapy. The patient was instructed to apply the compounded topical formulation 2 times daily to the affected genital lesions on day 1 then daily days 2-5. Appropriate patient counseling was provided regarding application techniques and potential side effects. After 3 days of therapy, the subject reported a significant reduction in lesion size and overall symptom improvement. Intense localized burning and painful urination led to premature discontinuation of the topical cidofovir. After symptom resolution, the patient was discharged on oral valacyclovir 500mg twice daily for suppressive therapy while awaiting the results of final resistance testing. At her follow-up visit in August 2023, however, laboratory results confirmed HSV-2 resistance to acyclovir. Consequently, valacyclovir was discontinued, as it would be ineffective for secondary prophylaxis to prevent future outbreaks, prompting a reassessment of her treatment plan.

Given her favorable response to topical cidofovir, it was recognized as a potential salvage therapy to manage future flare-ups. However, issues related to outpatient access, such as cost and the limitations of compounding pharmacies, continue to present obstacles.

Clinical Applications and Practical Considerations:

Multiple case reports and small case series support the use of topical cidofovir and its efficacy in HSV acyclovir-resistant infections.[3,4,9,11-13] One of the most cited studies is by Mark et al., who reported the successful treatment of six out of seven HIV-positive patients with chronic, acyclovir-resistant mucocutaneous HSV using 1% topical cidofovir cream.[3] Wald and colleagues similarly documented the effectiveness of topical cidofovir in transplant recipients suffering from acyclovir-resistant HSV lesions. In

these cases, patients who had failed standard antiviral therapy responded favorably to once-daily applications of 1% cidofovir compounded in a non-irritating base. [5] Erice also reviewed a series of cases in which topical cidofovir led to complete resolution of lesions that had been refractory to both acyclovir and foscarnet.[8] In another report, Muluneh et al., describes the successful treatment of a perianal HSV-2 ulcer in a 34-year-old woman who had previously undergone allogeneic hematopoietic stem cell transplantation. The ulcer was resistant to acyclovir and unresponsive to foscarnet. Following one week of treatment with topical cidofovir gel, the ulcer showed clinical improvement and tested negative for HSV by real-time polymerase chain reaction (PCR). Repeat testing one week later confirmed the absence of HSV. This case, along with prior reports in HIV/AIDS patients, supports the potential role of topical cidofovir gel in managing cutaneous HSV infections resistant to acyclovir [12].

The safety and effectiveness of cidofovir gel in treating acyclovir-resistant HSV -2 infections in AIDS patients were assessed in a randomized, double-blind, multicenter study. Participants received either cidofovir gel (0.3% or 1%) or a placebo, applied once daily for five days. Among those treated with cidofovir, 10 out of 20 experienced complete healing or a reduction in lesion size by more than 50%, compared to none of the 10 patients in the placebo group (P = .008). Complete healing occurred in 30% of cidofovir-treated patients versus 0% in the placebo group (P = .031). Viral shedding stopped in 13 of 15 cidofovir recipients (87%) but in none of the 9 placebo patients (P = .00004). The median time to achieve a complete or substantial response in the cidofovir group was 21 days, while the median time to a negative viral culture was 2 days (P = .025 and P = .0001, respectively). Lesion area was reduced by a median of 58% in the cidofovir group, compared to no reduction in the placebo group (P = .005). Average pain scores also decreased more in cidofovir-treated patients (-1.84 vs. -0.34, P = .042). Mild application site reactions occurred in 25% of cidofovir patients and 20% of placebo patients, but none were dose-limiting. Overall, cidofovir gel significantly improved lesion healing, reduced viral activity, and alleviated pain [13].

Topical cidofovir is generally well tolerated. The most commonly reported adverse effects are localized skin irritation, erythema, and burning at the site of application. In rare cases, particularly when higher concentrations (e.g., 3%) are used or when occlusive dressings are applied, patients may develop superficial ulceration or skin breakdown. These adverse effects are usually mild and resolve upon discontinuation or dose adjustment. Due to the localized nature of the application, systemic adverse effects unlike intravenous cidofovir, which is often associated with nephrotoxicity, neutropenia, and ocular toxicity are rare, and most patients tolerate the treatment well. However, monitoring for adverse effects may be appropriate, especially in high-risk patients as ocular toxicity has been reported with topical formulations. Clinicians should instruct patients on proper application techniques emphasizing the importance of avoiding occlusion unless specifically directed [11,14-15].

Discussion:

Compounded topically applied cidofovir is ideally suited for patients with localized cutaneous or mucocutaneous lesions caused by acyclovir-resistant HSV. Candidates include immunocompromised individuals with confirmed resistance or those with lesions unresponsive to standard antivirals. In such cases, initiating topical cidofovir may prevent the need for hospitalization or intravenous therapy. Because cidofovir is not commercially available in topical form, clinicians must collaborate with compounding pharmacies experienced in antiviral preparations. Prior to initiation, resistance testing (e.g., via culture or PCR) is advisable, though not always feasible in urgent clinical scenarios [16-17].

Though off-label and requiring specialized compounding, cidofovir's unique mechanism of action and proven efficacy make it a critical tool in antiviral therapy when standard treatments have failed. While clinical evidence supports its efficacy, safety considerations and proper compounding practices are crucial. This case report highlights the need for further research and standardized protocols are needed to optimize treatment outcomes and minimize risks associated with cidofovir use.

References:

1. Patel R, Thorne A, Berenger BM. Management of acyclovir-resistant HSV in immunocompromised patients. *Clin Infect Dis*. 2015;60(9):1305–12.
2. Piret J, Boivin G. Resistance of herpes simplex viruses to nucleoside analogues: mechanisms, prevalence, and management. *Antimicrob Agents Chemother*. 2011;55(2):459–72.
3. Mark AS, Wald A, Corey L. Topical cidofovir for acyclovir-resistant HSV in HIV patients. *AIDS*. 2002;16(10):1467–9.
4. De Clercq E. Clinical potential of cidofovir in the treatment of herpesvirus infections. *Rev Med Virol*. 2002;12(2):91–104.
5. Wald A, Selke S, Magaret A, Corey L. Resistance to antiviral therapy in herpes simplex virus: a clinical challenge. *J Infect Dis*. 2005;191(4):483–92.
6. De Clercq E. Clinical potential of cidofovir in the treatment of herpesvirus infections. *Rev Med Virol*. 2002;12(2):91–104.
7. Wald A, Selke S, Corey L. Acyclovir-resistant HSV in transplant patients: experience with topical cidofovir. *J Infect Dis*. 2005;191(4):483–92.
8. Erice A. Treatment of acyclovir-resistant herpes simplex virus infections. *Clin Infect Dis*. 1999;28(5):1009–17.
9. Evans KG, Morrissey KA, Goldstein SC, Vittorio CC, Rook AH, Kim EJ. Chronic acyclovir-resistant HSV-2 ulcer in an immunosuppressed patient treated with topical cidofovir. Arch Dermatol. 2011 Dec;147(12):1462-3. doi: 10.1001/archderm.147.12.1462. PMID: 22184781.
10. Allen LV Jr. *The Art, Science, and Technology of Pharmaceutical Compounding*. 5th ed. Washington, DC: APhA; 2016.
11. McElhiney LF Pharmd Rph. Topical cidofovir for treatment of resistant viral infections. Int J Pharm Compd. 2006 Sep-Oct;10(5):324-8.

12. Muluneh B, Dean A, Armistead P, Khan T. Successful clearance of cutaneous acyclovir-resistant, foscarnet-refractory herpes virus lesions with topical cidofovir in an allogeneic hematopoietic stem cell transplant patient. J Oncol Pharm Pract. 2013 Jun;19(2):181-5
13. Lalezari J, Schacker T, Feinberg J, Gathe J, Lee S, Cheung T, Kramer F, Kessler H, Corey L, Drew WL, Boggs J, McGuire B, Jaffe HS, Safrin S. A randomized, double-blind, placebo-controlled trial of cidofovir gel for the treatment of acyclovir-unresponsive mucocutaneous herpes simplex virus infection in patients with AIDS. J Infect Dis. 1997 Oct;176(4):892-8.
14. Saunders IM, Lahoti A, Chemaly RF, et al. Topical cidofovir-induced acute kidney injury in two severely immunocompromised patients with refractory multidrug-resistant herpes simplex virus infections. *J Oncol Pharm Pract*. 2016;22:325-331.
15. Santilli, Christopher M. BA; Koozekanani, Dara MD, PhD; Armbrust, Karen R. MD, PhD. Bilateral Uveitis and Hypotony Following Treatment With Topical Cidofovir Retinal Cases & Brief Reports 17(1):p 23-25, January 2023.
16. Afshar B, Bibby DF, Piorkowska R, et al. A European multi-centre external quality assessment (EQA) study on phenotypic and genotypic methods used for herpes simplex virus (HSV) drug resistance testing. *J Clin Virol*. 2017;96:89-93.
17. Evans KG, Morrissey KA, Goldstein SC, Vittorio CC, Rook AH, Kim EJ. Chronic acyclovir-resistant HSV-2 ulcer in an immunosuppressed patient treated with topical cidofovir. Arch Dermatol. 2011 Dec;147(12):1462-3.