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Resolution of Hand, Foot, and Mouth Disease With Valacyclovir

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ABSTRACT

Hand, foot, and mouth disease (HFMD) is a common viral illness that predominantly affects young children, with approximately 95% of cases occurring in individuals under the age of 5. While typically self-limiting, a subset of cases may present with more severe cardiopulmonary and neurological sequelae, such as myocarditis, pneumonia, meningitis, and encephalitis. Management is primarily supportive, as no standard antiviral therapy currently exists. However, previous case reports have suggested that acyclovir may offer therapeutic benefits. We present a case of a healthy 39-year-old female who experienced dramatic symptomatic improvement within 10 hours and complete resolution within 48 hours following off-label valacyclovir use. This case raises the possibility of valacyclovir use in adults with HFMD and highlights the need for further research to validate its role.

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INTRODUCTION

Hand, foot, and mouth disease (HFMD) is a contagious viral infection most commonly caused by Coxsackievirus A16 (CVA16) and Enterovirus A71 (EVA71), members of the *Enterovirus* genus within the *Picornaviridae* family. Symptoms typically include fever, malaise, pharyngitis, and a papulovesicular rash, characteristically appearing on the hands, feet, groin/buttock, and mouth, which resolves in 7 to 10 days without intervention. Most cases are mild (86.2%) or asymptomatic (12.7%).[1] A small percentage of cases develop neurological complications (eg, aseptic meningitis, encephalitis) and cardiopulmonary failure, with EVA71 and CVA6 more likely to cause severe disease in 1.1% and death in 0.03% of cases.[1]

Infection occurs primarily through fecal-oral transmission and direct contact with lesions. On average, symptoms begin 3 to 6 days post-exposure, and supportive care remains the standard of treatment. No antiviral therapy is standard. However, multiple case reports have indicated that early oral acyclovir can accelerate symptom resolution, particularly in prolonged or severe cases.[2-6]

We present the first published case of HFMD successfully treated with valacyclovir, a prodrug of acyclovir. Valacyclovir and acyclovir are antiviral drugs used to treat herpesvirus infections and are not recommended for HFMD due to the lack of viral thymidine kinase within the Enterovirus genus. Nonetheless, symptom overlap with herpesvirus infections has led to the empirical use of antivirals with unexpected clinical benefits.

CASE PRESENTATION

A 39-year-old healthy female developed tender vesicles and papules on her palms and soles. These symptoms began 7 days after her school-aged child developed similar symptoms, which were diagnosed as HFMD. On day 2, she developed herpangina and an increased number of acral blisters. The patient alternated over-the-counter oral acetaminophen and naproxen for analgesia. Symptoms progressed on day 4, with the emergence of a low-grade fever of 100.4°F, malaise, and worsening of oral and palmoplantar lesions. At 21:00 on day 4, she self-administered 2 g of valacyclovir. She awoke the next morning (day 5) with a significant reduction in pain and inflammation, then took 2 g of valacyclovir in the morning and 1 g at bedtime. Analgesia was no longer needed and was discontinued. There were no new lesions on day 6, and the patient was symptom-free. On day 7, she remained lesion-free, suggesting resolution ahead of the expected 7 to 10-day course.

FIGURE 1. Erythematous vesicles and erosions involving the mucosal surface of the lower lip. Before (top) and 10 hours after (bottom) the first treatment with valacyclovir 2g on day 5 after symptom onset.

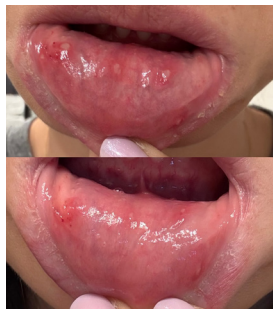
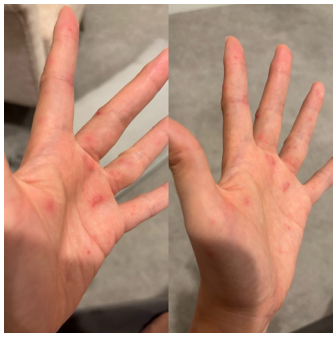


FIGURE 2. Multiple papulovesicular eruptions on an erythematous base were observed on the palmar surfaces. Before (left) and 10 hours after (right) treatment with valacyclovir on day 5 after symptom onset.



DISCUSSION

The case presented here demonstrates significant symptom reduction of HFMD within 10 hours of valacyclovir treatment and complete resolution within 48 hours. In addition to clinical improvement, the period of infectivity may also have been reduced as well, as it is most prominent during the first week of illness and in the presence of skin lesions.

The current standard of care is supportive, including hydration, oral analgesics/antipyretics, and topical anesthetics. IV fluids can be administered when extensive oral involvement, accompanied by odynophagia, limits oral intake.

Antiviral therapy with acyclovir has been explored to hasten symptom resolution.[2-6] A 1996 trial of 12 children and one adult reported symptomatic abatement within 24 hours and disease clearance by day 5 of oral acyclovir, initiated within 1 to 2 days of rash onset and dosed at 200 mg to 300 mg 5 times per day.[2] A 2019 series of 3 intra-familial cases (2 children and 1 immunocompetent adult) revealed symptomatic resolution of pruritus and fever, with lesion involution and halted spread within 1 day of acyclovir initiation.[3] The children received 200 mg 4 times daily and had fully resolved in 3 days, while their mother received 800 mg 4 times daily, with her single lesion resolving after 1 day. A 2020 case also supports early acyclovir initiation leading to defervescence and complete lesion resolution within 48 hours in a 37-year-old female treated with acyclovir 800 mg 3 times daily who presented with a 2-day history of fever, pharyngitis, and the characteristic papulovesicular rash.[4] Benefits of acyclovir have been reported in cases of severe HFMD, as seen in a 2018 case series of 3 children with rapidly progressive, widespread HFMD who were treated with early administration of oral acyclovir at a dose of 10 mg/kg 4 times a day for 7 days. All 3 patients had accelerated clinical recovery with constitutional symptoms improvement and lesion involution noted within 48 hours of treatment.[5] Furthermore, a case of a 27-year-old immunosuppressed male from recent chemotherapy and a prolonged 3.5-week history of HFMD experienced complete symptom resolution within 5 days of treatment with acyclovir 200 mg × 5 daily.[6]

Acyclovir is a nucleoside analog that inhibits viral DNA polymerase to halt DNA synthesis. Acyclovir becomes pharmacologically active through phosphorylation, first by viral thymidine kinase – found in herpesviruses – and then by host cellular enzymes, producing acyclovir triphosphate. This active metabolite competes with deoxyguanosine triphosphate (dGTP) for binding to viral DNA polymerase. Once incorporated into the viral DNA, its lack of a 3'-hydroxyl group prevents the addition of further nucleotides, inhibiting viral proliferation.

Valacyclovir is the valine ester prodrug of acyclovir that undergoes rapid hepatic conversion to acyclovir after oral administration. In our case, the 10-hour symptomatic improvement and 1 to 2-day shorter disease course mirror patterns seen with acyclovir. Moreover, the greater bioavailability of valacyclovir yields higher, more consistent serum levels, which allow for less frequent dosing.

However, enteroviruses are RNA viruses that lack thymidine kinase, and therefore, acyclovir should theoretically be ineffective in treating HFMD. The observed clinical benefit may be achieved through indirect mechanisms, possibly by potentiation of host interferon (IFN) pathways, which can enhance innate immune system antiviral activity. IFNs are proinflammatory cytokines frequently activated by viral infections, which induce the activation of IFN-stimulated genes and result in the inhibition of enterovirus replication.[7-9]

While a placebo effect or unaltered course of the disease are possible in this case, the magnitude and speed of improvement coinciding with treatment support the efficacy of valacyclovir. Clinical improvement may have been due to the treatment of a confounding herpetic coinfection. This is unlikely in our case, considering the epidemiological context and enteroviral dominance in lesion patterns.

CONCLUSION

While supportive care remains the standard treatment for HFMD, especially in mild cases, this case adds to a growing body of evidence suggesting a role for nucleoside analogs like acyclovir and valacyclovir. These diverse cases, spanning pediatric to adult and immunosuppressed individuals, consistently show accelerated recovery post-acyclovir – despite a lack of direct antiviral activity. Our case demonstrates that valacyclovir may alter the disease course of HFMD in adults, particularly when administered early, underscoring the need for controlled studies to evaluate the efficacy, safety, and mechanism of action in HFMD. Further research could help define its role in managing more severe or prolonged cases and contribute to the broader development of targeted antiviral therapies for HFMD.

DISCLOSURES

The authors have no conflicts to declare.

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