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Adverse drug reactions of acyclovir – cases reports and literature review

Działania niepożądane acyklowiru – opisy przypadków i przegląd piśmiennictwa

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Abstract

Background. Acyclovir is an antiviral drug that is primarily used for the treatment of HSV (herpes simplex virus) infection but it has also an effect on varicella zoster and herpes zoster infections. This antiviral agent is available in numerous forms such as tablet, suspension, intravenous injection, ointment, cream, gel and skin stick. However, the use of acyclovir may contribute to the occurrence of many adverse effects, e.g. malaise, headache, nausea, vomiting, diarrhoea and renal damage. ***Material and methods.*** We present two case report of female patients aged 23 and 43, both taking acyclovir 5 days in a dose of 200 mg 5 times a day every 4 hours for HSV infection. Both of them developed adverse reactions lasting until the last (5th) day of the therapy- 23-year-old woman had headache and dizziness, while 43-year-old patient had persistent nausea and diarrhea. ***Results.*** The symptoms subsided after cessation of acyclovir treatment in both patients. ***Conclusion.*** Described cases confirm the risk of adverse reactions to acyclovir treatment. *(Farm Współ 2020; 13: 213-217)*

Keywords: acyclovir, herpes simplex virus, infection HSV

Streszczenie

Wstęp. Acyklowir jest lekiem przeciwwirusowym stosowanym głównie w leczeniu zakażenia HSV (wirusem opryszczki pospolitej), ale wykazuje również działanie na zakażenia wirusem ospy wietrznej i półpaśca. Omawiany środek przeciwwirusowy dostępny jest w wielu postaciach, takich jak tabletki, zawiesina, iniekcje dożylne, maści, żel i sztyft na skórę. Stosowanie acyklowiru może jednak przyczynić się do wystąpienia wielu działań niepożądanych, m.in. złego samopoczucia, bólów głowy, nudności, wymiotów, biegunki i uszkodzenia nerek. ***Materiał i metody.*** Przedstawiamy dwa opisy przypadków pacjentek w wieku 23 i 43 lat, obie odbyły terapię acyklowirem przez 5 dni w dawce 200 mg 5 razy dziennie co 4 godziny w celu leczenia infekcji wirusem HSV. U obu pacjentek wystąpiły działania niepożądane utrzymujące się do ostatniego (5) dnia terapii – 23-letnia kobieta odczuwała ból i zawroty głowy, natomiast 43-letnia pacjentka miała utrzymujące się nudności i biegunkę. **Wyniki**. U obu pacjentek objawy ustąpiły po zaprzestaniu leczenia acyklowirem. **Wnioski**. Opisane przypadki potwierdzają ryzyko wystąpienia działań niepożądanych w przypadku leczenia acyklowirem. *(Farm Współ 2020; 13: 213-217)*

Słowa kluczowe: acyklowir, herpes simplex virus, infekcja HSV

Introduction

Acyclovir, discovered in the 1970s, is a viral DNA polymerase inhibitor and most frequently prescribed antiviral agent [1]. It is an effective agent against Herpes simplex virus – HSV I and HSV II. Other viral infections that can benefit from acyclovir include varicella zoster (ten-fold less effectiveness), Epstein-Barr and cytomegalovirus (even smaller effectiveness due to lack of unique thymidine kinase and poor inhibition of viral DNA polymerase) [2]. It is approved by FDA to treat infections caused by the herpes simplex virus (HSV) – genital herpes and HSV encephalitis but despite the long term use of this agent to treat HSV encephalitis, there has not been a systematic review regarding the efficacy of this disease/treatment combination. Systematic reviews to address its safety and efficacy are

currently ongoing, with the primary outcome being mortality rate. A secondary outcome measure is the quality of life [1]. Regarding the off-label indications, acyclovir is applied for the treatment of herpes zoster (shingles), varicella-zoster (chickenpox) and muco-cutaneous HSV. The most common indications for the use of this drug are infections of the skin and mucous membranes (Herpes simplex type I and II) with recurrences in patients with immune deficiencies, Varicella zoster virus infections in patients with immune deficiencies, Herpetic meningitis in patients older than 6 months of age, and treatment of the initial phase of severe Herpes genitalis infection [3]. Acyclovir administered orally was also found effective in the treatment of HSV keratitis in pediatric patients. This drug is also helpful in HIV patients to treat eczema herpeticum, a rare condition but rapidly progressive if untreated. Acyclovir has been proven beneficial in treating diseases secondary to varicella-zoster (VZV) infection such as myelopathy and brachial plexus neuritis. The drug also turned out to be effective in the treatment of acute cerebellitis, a well-recognized complication of VZV infection in children, elderly or immunocompromised (rare in adults) and a rare motor complication such as herpes zoster abdominal paresis. In some cases, a prophylactic use of acyclovir should be considered, e.g. for herpes simplex virus and varicella-zoster reactivation in recipients of hematopoietic stem cell transplantation, in HSV-1 and HSV-2-seropositive organ recipients but also in juvenile-onset recurrent respiratory papillomatosis [4].

The recent issue of the pandemic of coronavirus causing severe respiratory failure has forced scientists around the world to search for a cure. The virus named 2019-nCoV is categorized as a beta genus coronavirus, similarly to the case of severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). Antiviral drugs that are possibly valid for 2019-nCoV are remdesivir, lopinavir/ritonavir, lopinavir/ritonavir combined with interferon-β, convalescent plasma, and monoclonal antibodies, but reliable information regarding the efficacy and safety of these drugs for 2019-nCoV pneumonia patients are still lacking and require further clinical trials. Antiviral drugs such as neuraminidase inhibitors (oseltamivir, paramivir, zanamivir), ganciclovir, acyclovir and ribavirin, which are frequently applied in clinical practice, are not efficient and not recommended for 2019-nCoV [5].

Case report

1st case: a 23-year-old female patient (no history of chronic diseases), taking supplements: Vit D 3 at a dose of 2000 U per day and biotin at a dose of 5 mg per day. She had been using an OTC acyclovir preparation for 5 days (200 mg 5 times a day every 4 hours, with a night break) for HSV infection without consulting the physician. After the first day of taking the drug, the patient experienced complaints such as headache and dizziness lasting until the last day (5th day) of the therapy. The patient treated her headache unsuccessfully with paracetamol in a dose of 2 g per day. The symptoms subsided after cessation of acyclovir treatment.

2nd case: a 43-year-old female patient (taking indapamide 1.5 mg per day and perindopril 5 mg per day for arterial hypertension and supplementing magnesium and vitamin D in a dose of 2000 U per day) treated HSV infection with acyclovir without consulting a doctor. She had been taking acyclovir for 5 days in a dose of 200 mg 5 times a day every 4 hours, with a night break. After the first day of taking the drug, the patient developed nausea and diarrhea lasting until the last day (5th day) of the therapy. She was given probiotic therapy for diarrhea. The symptoms resolved after discontinuation of acyclovir.

Acyclovir (9-[2-hydroxymethyl]guanine) is a synthetic purine nucleoside analog, demonstrating in vitro and in vivo inhibitory activity against HSV-1, HSV-2 and VZV. It is a precursor drug, that needs to be phosphorylated by viral kinase to acyclovir triphosphate. Acyclovir is converted by virally-encoded thymidine kinase to acycloguanosine monophosphate (acyclo-GMP) followed by phosphorylation by the cellular kinase into an active triphosphate form; acycloguanosine triphosphate (acyclo-GTP). The acyclo-GTP prevents viral DNA synthesis by inhibiting the viral DNA polymerase on the basis of competition with deoxyguanosine triphosphate (dGTP) as a substrate for this viral enzyme. Incorporation of acyclovir triphosphate into DNA results in the termination of the growing DNA chain as acycloguanosine triphosphate lacks the 3′-hydroxyl group required for the elongation (without 3′-hydroxyl group further nucleotides cannot be added to the strand). Acycloguanosine triphosphate which resembles the nucleotides has a much higher affinity for viral DNA polymerase than for dGTP, yielding a high therapeutic ratio with low toxicity of acyclovir in non-infected host cells. Eventually, the replication rate is slowed down, and moreover, there is more time for the immune response to intervene (Figure 1) [6-7].

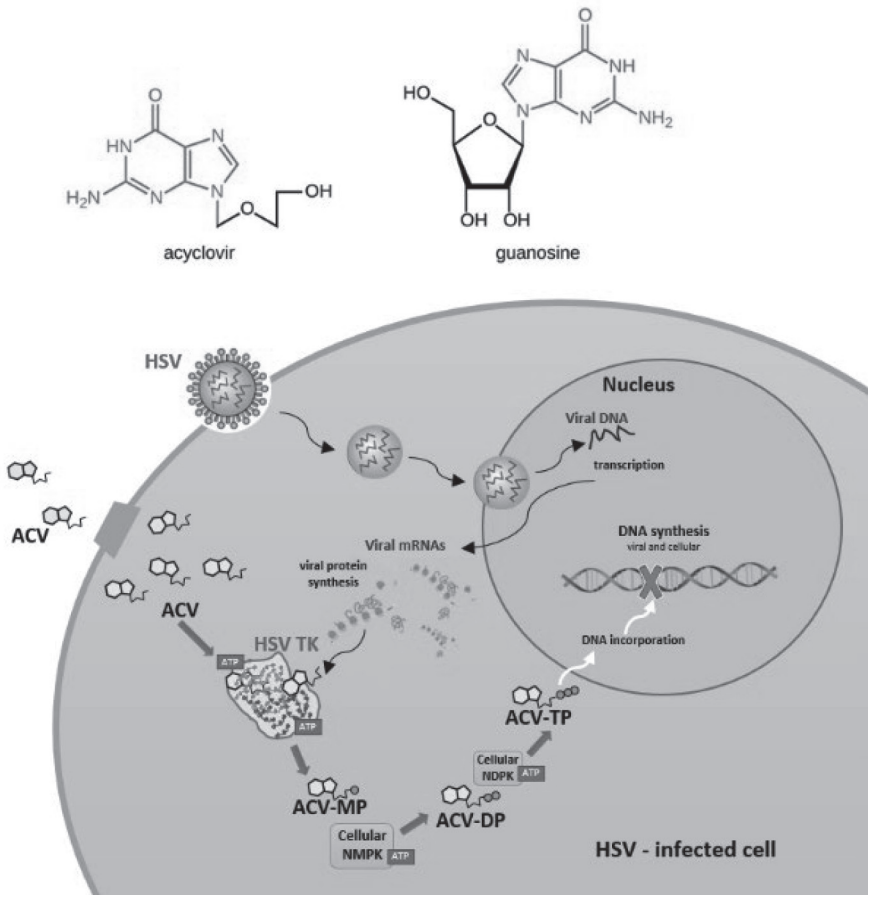

Figure 1. Schematic mechanism of action of acyclovir in inhibiting viral DNA synthesis on an example of HSV. ACVMP – Acyclovir, ACV-MP – Acyclovir monophosphate, ACV-DP – Acyclovir diphosphate, ACV-TP – Acyclovir triphosphate, HSV – Herpes simplex virus, HSV-TK – Herpes simplex virus thymidine kinase, NMPK- Nucleoside monophosphate kinase, NDPK- Nucleoside diphosphate kinase

Rycina 1. Schemat mechanizmu działania acykolowiru w hamowaniu syntezy wirusowego DNA na przykładzie HSV. ACV – Acyklowir, ACV-MP – Monofosforan acyklowiru, ACV-DP – Difosforan acyklowiru, ACV-TP – Trifosforan acyklowiru, HSV – Herpes simplex virus, HSV-TK- Kinaza tymidynowa HSV, NMPK – Kinaza monofosforanu nukleozydu, NDPK- Kinaza difosforanu nukleozydu

Discussion

Acyclovir, effective against diseases such as mucocutaneous herpes simplex infection, genital HSV, chickenpox and shingles (VZV), is available in numerous forms such as ointments, tablets, suspensions, and intravenous injection. Topical ointments or transdermal creams with acyclovir are recommended to treat skin lesion, cold sores, and blisters due to HSV infection, as applied directly at the site of infection, they improve the healing time of wounds and form a protective layer to prevent further virus entry and spread from a particular infection site. Unfortunately, acyclovir topical creams are slowly absorbed due to difficulties in penetrating the epidermal layer of the skin, frequent applications are required to attain its therapeutic effect and the efficacy of these ointments is only moderate, depending on the severity of the infection. In case of oral administration (the most preferred route), to attain desired concentration in plasma, and thus, significant pharmacological effect, acyclovir may be taken with or regardless of food intake 2 to 5 times a day for 5 to 10 days (typically a 200 mg tablet, taken 5 times a day for 10 days) as well as

up to 12 months. In case of serious infections which are disseminated, visceral, or affecting CNS (such as HSV encephalitis) and require high doses of the drug (100 mg/kg), acyclovir can be administered intravenously via injection (infusion over 1 hour in a diluted D5W solution or 0.9% NaCl to a final concentration of less than or equal to 7 mg/mL to prevent renal damage) [4], [7].

Acyclovir is an antiviral agent, most commonly used in the treatment and prophylaxis of Herpes virus infections (as well as Varicella zoster and Herpes zoster infections) which inhibits the viral DNA expression, and thus, accelerates the healing of lesions. It is very effective and well-tolerated by patients. Less than 1% of the population shows resistance to acyclovir (might be higher, up to 10%, in immunocompromised or immunosuppressed patients) [8]. Acyclovir is a substance characterized by rather inadequate bioavailability as it is poorly soluble in water and is rapidly cleared from the organism (the half-life of the drug is about three hours). This situation forces the use of higher oral doses of the drug, to obtain its higher serum concentration (200 mg tablet, five times daily for ten consecutive days or even higher doses of 400 mg), resulting in satisfactory therapeutic effects, however, the treatment with acyclovir in higher doses may contribute to the occurrence of adverse reactions. The common adverse effects of acyclovir administered orally are malaise, headache, nausea, vomiting and diarrhoea, some of which were reported in two women in presented case reports. Concerning the issue of acyclovir injections, patients may suffer from nausea, vomiting, transaminitis, and rash. Moreover, inflammation and phlebitis at the site of infection can also appear. Rotating the sites of injections and decreasing concentration to less than 10 mg/mL can help prevent inflammation at the injection site. Acyclovir given in high doses via bolus IV injection, may cause the deposition of acyclovir crystals in the kidney, resulting in intratubular renal damage and even acute kidney injury (it develops within 24–48 hours of acyclovir administration and is characterized by a decrease in renal function, indicated by a rapid rise in the serum creatinine). For this reason, it is necessary to modify the dose in patients with renal insufficiency, depending on the creatinine clearance. Increased risk of acute kidney injury may be associated with the concomitant use of acyclovir and some NSAIDs such as loxoprofen, diclofenac, etodolac, ketorolac, piroxicam or lornoxicam [9]. Particular caution should be taken in case of patients who are dehydrated, treated with high doses of acyclovir, with a history of renal disease or receiving concomitant nephrotoxic drugs-such patients should be carefully monitored throughout the treatment [4], [7]. There was also a case of a 54 year-old woman complaining of weakness and lower extremities paresis, nausea and vomiting after receiving oral acyclovir with a serum creatinine level of 2.1 mg/dL, serum potassium 2.1 mmol/L. Her kindey biopsy result confirmed the diagnosis of acute tubular necrosis and acute tubulointerstitial nephritis. The patient was advised to quit the acyclovir and to start oral and intravenous potassium supplement, which led to the improvement of symptoms [10]. A single-centre retrospective cohort study performed to identify the incidence, and risk factors for acute kidney injury in adults treated with parenteral acyclovir proved that overall incidence of this disease was 13% and it occurred more frequently in patients with pre-existing chronic kidney disease, diabetes, and in patients treated with higher daily doses of acyclovir [11]. Another case of a 69-year-old woman who had acyclovir-induced acute renal injury causing her creatinine level to rise up to 7.4 mg/dL, was characterized by symptoms such as mental status changes, word-finding difficulties and visual hallucinations [12]. Renal disease is a significant risk factor for acyclovir-induced neurotoxicity characterized by altered mentation and myoclonic movements. Neurological sequelae associated with acyclovir-induced neurotoxicity often resembles viral infections of the CNS. A 57-year-old male patient with end-stage renal disease, presenting vesicular herpetic lesions and associated symptoms of worsening burning pain on his anterior and posterior chest wall was diagnosed with dermatologic herpes zoster and at the same day he was discharged with a 10-day course of fulldose oral acyclovir (800 mg 5 times daily). Four days later he complaied of multiple episodes of diarrhea as well as swelling, fullness, pain, and redness in his right thigh. Clinical improvements in neurologic symptoms were observed after discontinuation of the drug and hemodialysis [13]. It has been shown, that IV injection of acyclovir may induce hypokalemia- intravenous acyclovir was administered to 423 patients and almost half of them (46%) developed hypokalemia. The rate of moderate to severe hypokalemia was more than threefold greater among patients treated with acyclovir than in the non-exposed group of 29,634 patients, 21% of whose acquired hypokalemia [14]. Patients treated with acyclovir may also experience many other symptoms such as dizziness, fatigue, abdominal pain,

confusion, agitation, alopecia, anaphylaxis, anemia, angioedema, anorexia, ataxia, coma, disseminated intravascular coagulation (DIC) and moreover decreased hemoglobin levels and the absolute neutrophil count in pediatric patients [4]. A rare clinical case of acyclovir-induced immune thrombocytopenia was reported in a 72-year-old female treated with acyclovir for typical herpes zoster. There was also four other cases of immune thrombocytopenia induced by acyclovir. It is an unusual adverse effect, with good prognosis [15]. There are no specific contraindications to acyclovir apart from hypersensitivity. Caution should be paid in case of pregnancy (acyclovir has been shown to cross the placenta), patients with renal impairments, immunocompromised patients, ones with potential risk of thrombotic thrombocytopenic purpura (TTP), and hemolytic uremic syndrome (HUS) [4].

Conclusion

Acyclovir is a widely prescribed, generally well-tolerated drug for the infections caused by human herpesvirus. However, the therapy with acyclovir, regardless of the method of administration, may cause various adverse reactions, from headache to serious renal damage. Although acyclovir is an over-the-counter drug, popular for HSV infections and ailments such as cold sores, it is worth consulting the general practitioner before the home treatment with this drug, especially in the current situation of the 2019-nCoV pandemic, when people seek for solutions that can prevent them from becoming infected.

Conflict of interest
None

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