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General review

Effectiveness of antiviral treatment on acute phase of herpes zoster and development of post herpetic neuralgia: Review of international publications

Efficacité des traitements antiviraux sur la douleur de la phase éruptive du zona et sur la survenue de douleurs post-zostériennes chez des sujets immunocompétents: revue de publications internationales

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Abstract

Herpes zoster is due to the reactivation of the virus causing varicella, called varicella-zoster virus. It affects peripheral nerves and causes painful skin and nerve lesions. This pain may last for months, or years after the initial lesions have resolved: post-herpetic neuralgia is the most frequent complication. Antiviral drugs, acting directly on the infectious agent are prescribed to reduce or block viral replication, relieve pain, and shorten symptom duration, especially for people of 50 years of age or more. However, there is currently no systematic collection of data concerning the effectiveness of antiviral drugs administered outside of clinical trials. This review evaluates the effectiveness of antiviral drugs on: (a) the intensity of pain and progression of the rash during the acute phase of herpes zoster, and (b) the frequency, intensity, and duration of post-herpetic neuralgia. During the acute phase, antiviral drugs (acyclovir, valacyclovir and famcyclovir) significantly reduce the intensity of acute pain, accelerate the healing of the vesicular rash, and reduce the duration of viral excretion. According to some authors, these drugs taken at an early stage of the disease would help to prevent the development of post herpetic neuralgia. But for others, there is no convincing evidence that antiviral drugs reduce the risk of painful complications.

Keywords: Herpes zoster; Antiviral drugs; Acute herpes zoster pain; Post herpetic neuralgia

Résumé

Le zona est dû à la réactivation du virus qui cause la varicelle, appelé virus de la varicelle et du zona. Il affecte les nerfs périphériques et provoque des lésions nerveuses et cutanées douloureuses. Ces douleurs peuvent persister pendant des mois ou même des années après la guérison de l'éruption : il s'agit alors de douleurs post-zostériennes, qui dominent les complications. En bloquant la réplication du virus de la varicelle et du zona, le traitement antiviral, notamment prescrit chez les personnes âgées de 50 ans ou plus, permet de diminuer la douleur et la durée des symptômes. En dehors du cadre des essais cliniques, il n'existe cependant aucun dispositif de recueil systématique des données sur l'efficacité des traitements antiviraux administrés. Cette revue évalue le niveau d'efficacité de ces antiviraux, d'une part, sur l'intensité des douleurs et l'évolution de l'éruption à la phase aiguë du zona, et d'autre part, sur la fréquence, l'intensité et la durée des douleurs post-zostériennes. Lors de la phase aiguë du zona, les médicaments antiviraux (acyclovir, valacyclovir et famcyclovir) réduisent nettement l'intensité de la douleur aiguë, accélèrent la guérison de l'éruption vésiculaire et écourtent la période d'excrétion virale. S'ils sont pris à un stade suffisamment précoce de la maladie, ils contribueraient, selon certains auteurs, à prévenir le développement des douleurs post-zostériennes, mais pour d'autres, aucun élément ne prouve de façon convaincante que les antiviraux réduisent le risque de complications douloureuses.

Mots clés : Zona ; Antiviraux ; Douleur aiguë du zona ; Douleurs post-zostériennes

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1. Objectives

This literature review was made to assess the level of effectiveness of antiviral drugs on the intensity of pain and on the evolution of the rash in the acute phase of herpes zoster on one hand, and on the other hand, the frequency, the intensity, and the duration of post herpetic neuralgia (PHN), persisting beyond the cure of herpes zoster cutaneous lesions.

2. Patients and methods

A request was made in the *National Library of Medicine* Medline database and in all Cochrane Library reviews to search for articles published (in English or in French) between January 2002 and December 2009. The keywords used were "herpes zoster" or "post herpetic neuralgia" and "treatment" or "therapy". This review was made with meta-analyses, randomized controlled trials (RCT), of reviews made on international publications, or of recommendations for the practice, prevention, and management of herpes zoster issued by experts under the aegis of the *Advisory Committee on Immunization Practice*, of the French Ministry, or published by the International Herpes Management Forum (IHMF) or by European Scientific Societies.

3. Results

3.1. Introduction

Herpes zoster is due to a neurological and dermatological infection caused by the reactivation of the varicella and herpes zoster virus (VZV), latent after the varicella episode in the sensitive spinal and cranial ganglia. Once reactivated, the virus moves along sensitive fibers up to the skin area they innervate. Herpes zoster presents as a rash with flabby vesicles, with unilateral topography, and usually concerns one to three dermatomes. The reactivation of VZV usually occurs only once in a lifetime, and most often in elderly patients or in case of immunodepression due to various diseases such as HIV infection or cancer, or in the course of treatments modifying immunity (corticosteroids, immunosuppressive drugs). Pain associated with herpes zoster is permanent in the acute phase. After the healing phase of vesicles, some patients still feel pain that can persist several months, or even several years. This post herpetic neuralgia (PHN), even if not life threatening, is associated to an important loss of autonomy and poorer quality of life; it can also induce a significant cost for the patient and healthcare providers [1].

The treatment of acute herpes zoster, the prevention of PHN in immunocompetent patients presenting with acute herpes zoster, and the management of PHN patients remains a complex clinical issue for which there are still numerous questions and ongoing research [2].

3.2. Effectiveness of antiviral drug treatment on acute herpes zoster

Table 1 is a list of available drugs to treat acute herpes zoster in adult immunocompetent patients.

Table 1
Oral antiviral therapy of acute herpes zoster in patients 50 years of age or older. *Traitement du zona en phase aiguë chez les patients de plus de 50 ans.*

In immunocompetent patients	
Drug	Dose
Acyclovir	5 × 800 mg/day p.o. – 7 days
Valacyclovir	3 × 1 g/day p.o. – 7 days
Famcyclovir	3 × 500 mg/day p.o. – 7 days

Adapted from Kempf et al. [54].

3.2.1. Acyclovir

Acyclovir was the first antiviral treatment studied for patients presenting with acute herpes zoster, no other antiviral treatment has ever been analyzed so thoroughly [3]. Acyclovir was used as the reference treatment to assess valacyclovir and famcyclovir effectiveness [4].

Compared to a placebo, acyclovir significantly decreases the delay of onset of new lesions (1.7 days vs. 2.2 with the placebo, $P = 0.005$), the delay before resolution of vesicles (6.4 days vs. 8.2 with the placebo, $P < 0.001$) and the delay before formation of scabs (7.8 days vs. 10.0 with the placebo, $P = 0.02$) in patients treated within 48 hours, following the onset of the rash [5]. But, acyclovir was not more effective than the placebo if it was prescribed 4 or 5 days after the onset of the rash. Its drawback is a weak bioavailability after oral administration, and thus the need to administer the drug in five daily intakes [6]. The reported adverse effects are usually limited, headaches and nausea, and their incidence was similar in the treated group and control group [3]. Acyclovir is cheaper than famcyclovir and valacyclovir, since it is available as a generic drug [2,7].

3.2.2. Famcyclovir

Famcyclovir is the oral prodrug of pencyclovir and was approved by the Food and Drug Administration (FDA) in June 1994 for the treatment of acute herpes zoster [8]. The effectiveness of oral famcyclovir for the treatment of herpes zoster was analyzed in several multicentric randomized double-blind clinical trials on large cohorts, comparing this agent to a placebo [8–10], to acyclovir [11,12] and to valacyclovir [13] in immunocompetent patients. The effectiveness on healing of lesions compared to a placebo was demonstrated: it was similar to that of acyclovir [11,12] and valacyclovir [13], to prevent new lesions and for the delay before resolution of scabs. The decrease of acute pain intensity in the eruptive phase obtained with famcyclovir was also comparable to that of acyclovir [7,10–12].

The analysis of the safety profile from 13 clinical trials demonstrated that famcyclovir was well tolerated [10,14]. Famcyclovir can be administered at a lower dose and with less frequent intakes than acyclovir, and is an effective treatment for patients presenting with uncomplicated herpes zoster [6,10–12,14,15]. Its main alternative is valacyclovir, the oral prodrug of acyclovir [16].

3.2.3. Valacyclovir

Valacyclovir, the oral prodrug of acyclovir [6], was approved by FDA in 1995 for the treatment of herpes zoster [17].