PHARMACOEPIDEMIOLOGY AND DRUG SAFETY, VOL. 5: 325–332 (1996)

REVIEW

Safety of Acyclovir in General Practice: A Review of the Literature

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SUMMARY

Published data has been reviewed with the intent to determine the safety with which topical or oral acyclovir may be prescribed to immunocompetent patients outside specialist centres. The extent of the pre- and post-marketing development programme has made it possible to assess the main adverse effects associated with the drug, including the effects of high dosage, prolonged treatment and maternal exposure during the course of pregnancy. Possible risk factors are discussed and the overall reliability of the observations are considered. In conclusion it appears that with certain precautions there is little risk attached to the wider use of these formulations of acyclovir.

KEY WORDS — acyclovir; safety review; general practice

INTRODUCTION

The incidence of herpes infections is rising in the developed countries and up to 90% of those affected will suffer recurring outbreaks.[1–6] Acyclovir, an analogue of the nucleoside, 2′-deoxyguanoside, selectively inhibits replication of DNA viruses[7] and has provided an effective and generally well-tolerated treatment for most herpes infections since its introduction into clinical practice in the early 1980s.[8–12] In addition to offering a life-saving intervention for patients with herpes encephalitis, for instance, it is capable of providing symptomatic relief to patients suffering the physical and psychological pain of genital or oral herpes eruptions. The latter outnumber those with life-threatening illnesses by orders of magnitude, but the question of drug safety becomes paramount when considering the treatment of 'trivial' disease.

The purpose of this paper is to review the published information relevant to the safety of acyclovir when used in topical or oral formulations for the more minor manifestations of herpetic illness, in the belief that sufferers should not be deprived of valuable symptomatic relief solely because of fears of the sort of adverse experience that has been noted in more seriously ill patients treated in specialist centres.

METHODS

By searching a variety of bibliographic databanks (including Medline, Excerpta Medica and the database maintained by the manufacturer) an attempt has been made to retrieve all publications in the English or French languages that might contain information concerning the safety of acyclovir. While not exhaustive, it is believed that this search has revealed the great majority of relevant texts.

Subsequent analysis of the information has relied on a qualitative assessment of all the data, by contrast with the more formal statistical procedure of meta-analysis which inevitably requires careful selection of data and the consequent risk of selection bias.

Unpublished data in the form of spontaneous reports to government agencies or the manufacturer were not considered. It is the author's opinion that any event suggested in such reports that is not also revealed in the published literature is likely to be exceedingly uncommon.

CCC 1053–8569/96/050325–08

Received 8 March 1995
Accepted 14 May 1996

RESULTS

Clinical safety

Gastrointestinal tract and 'general' symptoms. Relatively trivial symptoms such as nausea, tiredness, headache and so forth are amongst the most frequent adverse events reported in any clinical trial, often described as 'adverse non-drug reactions'.[13] In trials of acyclovir generally, gastrointestinal symptoms, particularly nausea, were the most commonly reported, albeit at a low rate.

The relationship to drug use of common, subjective complaints such as these can only be assessed in controlled trials. There the incidence of nausea appeared to be below 5% at an acyclovir dose of 800 mg/day.[14–21] One large study involving 596 patients revealed a rate of 4.8% nausea in the active arm and 1.5% in the placebo arm, but other studies showed no difference in rates or even the reverse, with the placebo arm more severely affected. The situation was similar at higher doses up to 4000 mg/day.[17,22–26] Only occasionally was nausea sufficiently severe to be associated with vomiting and treatment was rarely discontinued because of it.

Other GI symptoms reported have included diarrhoea[27] and loose stools,[18] at similar rates in active and placebo arms. One patient developed chronic diarrhoea that was found to be due to intolerance of lactose excipient in the tablet formulation.[28]

Cutaneous effects. Minor skin conditions are very common and it is inevitable that they have been seen in association with acyclovir usage. As with nausea, however, controlled trials suggest the improbability of a causal relationship.[16,29] Two publications describe cases where cutaneous events were ascribed to the drug[30,31] but in only one of the three patients does the evidence seem compelling (positive rechallenge with no prior history of allergy).

Local reactions have been reported infrequently following use of topical acyclovir preparations. Drug sensitivity is difficult to distinguish from the effects of the underlying disease however, and skin irritation may be more severe when placebo is used.[32–34] In a trial involving four applications of dermal cream every day for 16 weeks, no cutaneous complication was observed in a group of 23 patients.[35] Seven other publications describe a total of nine patients who developed a local contact dermatitis at the site of application;[36–42] in two instances sensitivity testing revealed an allergy to the excipient propylene glycol but more often no individual component could be implicated.

Renal effects. High dose and pre-existent impairment of renal function appear to be risk factors for renal complications of acyclovir treatment.

Two publications describe the onset of acute renal insufficiency associated with coma and convulsion in two elderly patients, both of whom were receiving 4000 mg/day. One patient had a plasma acyclovir level three times higher than the upper therapeutic limit.[43,44] A third report describes a 52-year-old patient with chronic renal insufficiency whose plasma creatinine rose during treatment first with intravenous and then oral acyclovir.[45] All three patients recovered rapidly after drug withdrawal.

No renal complications have yet been reported in association with oral dosage of up to 1000 mg daily in patients with normal renal function. In such patients oral overdoses of up to 4500 mg/m^2 should have no renal consequence.[46] A published report of four patients who had developed creatininaemia after intravenous acyclovir at a dose of 1500 mg/m^2 noted that the renal dysfunction did not return during subsequent exposure to oral drug at doses up to 1600 mg/day for a month or more.[47]

There is no evidence in the literature to suggest that acyclovir has any chronic toxic effect on the kidney.

Neurological effects. A number of publications document the occurrence of neurological adverse events during treatment with intravenous acyclovir, usually at a high dose in renally compromised patients, often given with concomitant drugs of potential neurotoxicity.[48] Such complications are very much less commonly reported with oral medication. In addition to the two cases associated with renal impairment described above,[43,44] eight published case reports detail episodes of confusion in patients all of whom had pre-existent renal failure and received doses of at least 1000 mg/day.[49–52]

Neurological effects are no doubt associated with penetration of the blood–brain barrier; while this is essential to the efficacy of acyclovir in the treatment of herpes encephalitis,[53] neurological adverse effects of the drug may be difficult to distinguish from symptoms caused by the underlying disease.[27,48,54]

Laboratory tests

Placebo-controlled trials have shown no significant abnormality of laboratory test values due to the use of acyclovir dermal cream.[34,55] The same can be said for oral preparations when used in immunocompetent patients of any age for the treatment of *Herpes simplex*,[16,18,21,56–58] *H. varicella*[25–27,59] or *H. zoster*[17,22,23] in doses up to 4000 mg/day. Specifically, minor liver-related abnormalities seen in uncontrolled trials[60] were not found to be more frequently associated with acyclovir than placebo in controlled trials. Safety is maintained during long-term treatment.[61,62] Even high-dose intravenous therapy in patients after bone marrow transplantation appeared to be free of adverse haematological effects.[63]

Treatment compliance and quality of life

The low rate of premature withdrawal from treatment in long-term clinical trials of acyclovir was very striking. Kroon *et al.* found two (of 20) patients had to withdraw within a year for non-treatment related reasons;[61] Mindel *et al.*[60] found three (of 134) patients had withdrawn within a year, none for safety reasons. In the Acyclovir Study Group trial involving 575 patients receiving continuous treatment, 9% withdrew in the first year (one patient for safety reasons);[14] in the fourth and fifth years withdrawal rates were 10% and 9.7% respectively (0.8% and 0.5% for reasons of adverse experience).[62]

This unusually good compliance with long-term treatment by generally healthy young adults contrasts with that seen in antihypertensive therapy[64,65] and post-menopausal hormone replacement.[66,67] The psychological effects of recurrent herpes attacks can be very severe;[68–72] the continuing efficacy of acyclovir increases psychological well-being[73] and the resultant improvement in quality of life no doubt encourages long-term compliance with treatment.

Modulation of immune response

Treatment with acyclovir reduces the extent of the immune response to herpes virus.[74,75] Although this might be thought to make the patient more vulnerable than before to recurrent attacks after stopping treatment,[12,14] there is no obvious correlation between level of antibody and severity of disease.[74] Assessment of the risk is complicated by the unpredictable course of the disease and a tendency for attacks to become less frequent with time[3,5,76,77] but the experience gathered from long-term studies so far suggests that anxiety is unwarranted.[61,62,75,77,78]

Resistant strains of virus

There is natural concern over the possibility that resistant strains of herpes virus might emerge as a result of widespread or indiscriminate use of acyclovir. Although virus strains vary in sensitivity, no clear correlation has been seen between the level of *in vitro* resistance and the clinical efficacy of treatment in immunocompetent patients,[3,12,65,77,79,81,82] although the same is not true of patients with impaired immune systems.[78–80]

Drug interactions

There have been relatively few reports of possible interactions between acyclovir and other drugs, and virtually none relevant to the use of oral or topical formulations in general practice. A report of two patients with severe concomitant disease who developed marked dependent oedema associated with oral acyclovir treatment[83] suggests a possible interaction with diuretics (triamterene in one patient, frusemide in the other). There have been no confirmatory reports of such an effect, however, despite a no doubt large number of similar concomitant exposures in elderly patients treated for *H. zoster*.

Risk factors for toxicity

Neither dose level nor duration of dosage appear to be positively correlated with adverse experience in patients with normal renal function. The proportion of orally-administered acyclovir absorbed reduces with increasing dose and the *Physician Desk Reference* mentions overdoses of up to 20 g which were without significant harmful effect.

Acyclovir is mostly eliminated by glomerular filtration, with a half life of 3 h which will increase to about 20 h in patients with renal failure.[9,84] Although complications related to acyclovir accumulation are rare in the elderly and other patients with mild to moderate renal impairment, dosage should be reduced in cases of severe renal failure.

Fertility and second-generation effects

Despite natural concern over the possible harmful effects of treating sexually active young people with a purine base analogue, with all its potential for damaging DNA, there have been no reports of a deleterious effect on fertility. A 6-month study of 20 male subjects revealed no change in spermatozoal morphology or mortality, although acyclovir appeared to concentrate in spermatozoa.[1]

Acyclovir crosses the placental barrier[85-88] and the possibility of foetal developmental abnormality is of obvious importance. While standard animal studies of teratogenicity in mice, rats and rabbits have shown no effect, Stahlmann and colleagues reported foetal abnormalities in the offspring of rats treated with a single, very large subcutaneous dose of acyclovir;[89] the authors considered these findings to be of uncertain relevance to human medicine.[90]

The human experience of acyclovir use in pregnancy is unusually well documented. In a collaboration between the manufacturer and the US Centers for Disease Control and Prevention, an Acyclovir in Pregnancy Registry was established shortly after the drug was placed on the market, with the aim of collecting and evaluating information from as many exposed pregnancies as possible. Up to the end of 1993 a total of 651 pregnancies had been prospectively recorded (with first registration before the outcome of pregnancy was known) and a further 249 had been reported retrospectively. The frequency and type of birth defect notified to the Registry were compatible with those expected in the general population (Wellcome, personal communication).

Nursing mothers secrete acyclovir in breast milk[91,92] although the amount ingested by the infant is only about 1/1000 of the maternal dose. Deliberate treatment of infants with much higher doses appears to have been safe,[91,93] so inadvertent exposure to the drug in mother's milk gives no cause for anxiety.

DISCUSSION

As usual with an important and effective medicine, acyclovir has been used in a wide range of clinical conditions, including a variety of serious illnesses such as viral encephalitis and AIDS. As a result, there has been a good deal of associated adverse experience, much of which may be judged to be due to the underlying diseases. It is unfortunate that this experience also affects the general perception of the risks posed by the use of acyclovir in its main indication, the symptomatic and prophylactic treatment of recurrent *Herpes simplex* lesions in otherwise healthy, immunocompetent individuals.

To summarize the potentially serious reactions to acyclovir, it would seem that renal toxicity is rare and almost exclusively associated with intravenous treatment; the few cases associated with the oral drug have occurred in the context of pre-existing renal impairment. Reports of neuropsychiatric effects now number 35 cases, almost all following parenteral treatment. Finally, the risks presented by resistant strains of virus appear to affect only immunosuppressed patients.

By contrast, adverse events experienced by the generally healthy, immunocompetent patient with *Herpes simplex* eruptions have for the most part been reported to be trivial and, in controlled trials, to be equally associated with placebo treatment. The lack of any report of major toxicity is no guarantee that it does not exist, but there are a number of features of the clinical development of acyclovir that increase the level of confidence that can be placed in this negative observation. The size and diversity (age, indication, dose range, treatment duration) of the patient groups covered in published studies is unusually great; the methodology was rigorous as well as diverse,[11] with many placebo-controlled trials possible because of the lack of any other acceptable treatment for viral disease. Clinical trials have been supplemented by a very extensive programme of formal post-marketing surveillance studies, many conducted by independent experts of international repute[94,95] with a total of more than 70,000 patients observed in routine clinical practice (Wellcome, personal communication). Finally, there is a striking consistency in the reports from all sources, adding further weight to the message of relative safety.

No matter how large or well-conducted formal studies may be, they will have limitation of size or duration that make it impossible to deny that some risks may still exist. Events that are too rare or too long-delayed in onset to have been observed in the population studied may still exist for acyclovir as for any other drug. Thus, it always makes good clinical sense to avoid treating pregnant women unless the balance of benefit and risk clearly favours it (but there is no evidence to warrant termination if a pregnant woman is accidentally exposed to acyclovir). Wherever possible, children should be given topical treatment rather than oral

acyclovir, because of the lack of knowledge concerning very long-term outcomes. Any patient with impaired renal function should be considered with care: dosage may need adjustment and adequate hydration should be ensured.

The growing epidemic of genital herpes that gave rise to such concern in the 1970s is now perceived with less alarm. While this is in part due to the emergence of other more serious challenges to health, such as AIDS, distracting attention from less life-threatening conditions, it is certainly true that acyclovir has played a part in reducing the burden of morbidity and consequent social and psychological suffering. Nevertheless, the fear of severe adverse reactions associated with potent drugs inevitably, and properly, argues against their use in 'trivial' conditions. It is to be hoped that the lack of serious toxicity revealed by this search of the published literature will help to allay the anxieties of non-specialist physicians and thus allow them to prescribe acyclovir to all who could benefit thereby.

ACKNOWLEDGEMENTS

The author is indebted to Wellcome France for its financial support and to Drs F. Ponchie and A. Saint-Croix for their help in collecting the documentation. He thanks O. Blakoe and an anonymous reviewer for assistance in preparing the English manuscript.

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