Drugs 41 (1): 104-129, 1991
0012-6667/91/0001-0104/$13.00/0

DRE1 129

Foscarnet

A Review of its Antiviral Activity, Pharmacokinetic Properties and Therapeutic Use in Immunocompromised Patients with Cytomegalovirus Retinitis

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Contents

Summary

Synopsis

The pyrophosphate analogue, foscarnet, selectively inhibits the DNA polymerase of human herpes viruses, including cytomegalovirus, and the reverse transcriptase of HIV. Viral replication is therefore prevented, but resumes when the drug is cleared from infected cells. In vitro, *the combination of foscarnet and zidovudine (azidothymidine) has an additive effect against cytomegalovirus and acts synergistically against HIV.*

An improvement in cytomegalovirus retinitis is obtained in over 85% of affected AIDS patients during foscarnet induction therapy, but relapse usually occurs within a month of ceasing treatment. There is a similar duration of remission during maintenance therapy given for 5 days each week, but this can be extended 4- to 5-fold with daily administration of higher doses. In allograft recipients, progression of retinitis can be halted by foscarnet until immune function recovers and eradicates the virus. The incidence of acute renal failure, which is common during foscarnet therapy, may be reduced by dosage adjustment and adequate prehydration. Anaemia, phlebitis, nausea and vomiting, and disturbances in serum calcium and phosphate levels, perhaps resulting from uptake of foscarnet into bone or chelation with ionised calcium, have also been associated with administration of the drug.

Cytomegalovirus retinitis is difficult to treat, with few therapeutic options available. Although treatment with foscarnet produces some severe adverse effects, with care these can be minimised, and the drug produces clinical improvement in a large proportion of patients; this is a highly encouraging finding at this stage in its development. Preliminary comparative data indicate that foscarnet and ganciclovir are similarly effective, but foscarnet may have some theoretical advantages in AIDS patients since it can be used in combination with zidovudine without potentiating myelosuppression.

Antiviral Activity

Foscarnet is a pyrophosphate analogue which prevents replication of herpesviruses, including cytomegalovirus, by inhibiting viral DNA polymerases. 50% inhibition of cytomegalovirus DNA polymerase is achieved by foscarnet 0.3 μmol/L; other herpesvirus enzymes are similarly sensitive. Foscarnet also inhibits HIV reverse transcriptase, causing 50% reduction in activity at concentrations of 0.1 to 0.5 μmol/L. In contrast, inhibition of mammalian DNA polymerase by foscarnet is negligible, with 50% inhibition achieved at a concentration of 40 or 50 μmol/L. Exposure for at least 18 hours to foscarnet 1000 μmol/L was required to inhibit DNA synthesis and division of human cell lines by 50%.

Human cytomegalovirus plaque formation was inhibited by 50% by foscarnet concentrations between 25 and 34 μmol/L; clinical isolates were about 3 to 8 times less sensitive. Late antigen expression, a marker of cell death, was prevented by foscarnet 500 μmol/L only if human fibroblasts were exposed to the drug within 24 hours of cytomegalovirus infection. The virustatic activity of foscarnet is reversible, with antigens to cytomegalovirus expressed 3 to 9 days after foscarnet was removed from cell culture. *In vivo*, intraperitoneal administration of foscarnet reduced the mortality rate of cytomegalovirus-infected mice by 40%, but was ineffective in guinea-pigs. Foscarnet 10 to 25 μmol/L inhibited *in vitro* HIV replication by 50%, and 132 μmol/L caused 98% inhibition of the virus. Inhibition of cytomegalovirus replication in human cell lines is additive when foscarnet is combined with zidovudine and synergistic with trifluridine (trifluorothymidine). Synergistic inhibition of HIV replication occurred with the combination of foscarnet and zidovudine, particularly at higher ratios of foscarnet.

Although resistance of cytomegalovirus to foscarnet has not been reported either *in vitro* or clinically, resistant mutants of herpes simplex are readily produced. The lack of susceptibility to foscarnet is conferred by changes in the viral DNA polymerase; at least 3 different drug-resistant variants have been identified.

In summary, foscarnet reversibly inhibits cytomegalovirus and HIV replication by blocking DNA polymerase and reverse transcriptase, respectively, at concentrations relatively harmless to host cellular enzymes and division.

Pharmacokinetic Properties

Mean steady-state plasma concentrations of foscarnet, achieved after 6 to 21 days' continuous intravenous infusion of foscarnet 0.09 to 0.19 mg/kg/min, were between 228 and 261 μmol/L in AIDS patients, although there was substantial variation between individuals. With 2-hour infusions of foscarnet 60 mg/kg given every 8 hours, mean peak and trough plasma concentrations of 495 and 126 μmol/L were reached after 14 days. The mean apparent volume of distribution of foscarnet in 13 patients with HIV infection was 5.1 L/kg, indicating extensive distribution out of the plasma.

No metabolites of foscarnet have been detected. In HIV-infected patients, 83% of a cumulative intravenous dose of foscarnet was recovered unchanged in the urine during the first 36 hours of stopping the infusion, with 88% recovered within a week. The remainder was accounted for by deposition into bone, assuming that excretion of foscarnet is exclusively through the kidneys. Glomerular filtration and tubular secretion contribute almost equally to renal clearance which accounts for 82 to 86% of total plasma clearance of foscarnet. Uptake into bone matrix appears to be responsible for the balance.

Sequestration into bone may be responsible for the long terminal phase half-life of foscarnet which was up to a mean of 88 hours. Of more practical value in terms of a dosage schedule are the first and second phase elimination half-lives of foscarnet which were 0.5 to 1.4 hours and 3.3 to 6.8 hours, respectively.

Based on *in vitro* activity of foscarnet against cytomegalovirus, most investigators have aimed at keeping drug plasma concentrations between 333 and 500 μmol/L to ensure that virustatic levels are maintained.

Therapeutic Use

In common with other agents used in this condition, clinical experience with foscarnet in the management of patients with cytomegalovirus retinitis is largely limited to noncomparative studies involving AIDS patients, and to isolated case reports.

Both continuous and intermittent intravenous infusions have been investigated as induction therapy, with the latter approach now preferred because of apparently greater efficacy, convenience and reduced toxicity. Induction therapy commencing with an intravenous bolus injection of foscarnet 20 or 30 mg/kg followed by a continuous infusion of 230 mg/kg/day for 2 to 4 weeks elicits a complete response in 50 to 75% of patients, and a partial response in about 10 to 50%. The overall response rate is over 85%.

Continuous infusions have now largely been superseded by the alternative induction regimen of infusion of foscarnet 60 mg/kg every 8 hours or 100 mg/kg every 12 hours for 2 to 4 weeks, resulting in an overall response rate of over 88%, with partial responses predominating.

Because relapse occurs in approximately 66% of surviving patients within a month of stopping induction therapy, subsequent maintenance treatment is given. Over 60% of patients receiving maintenance schedules of 2-hour intravenous infusions of foscarnet 60 to 90 mg/kg/day for 5 days each week relapsed within 2 to 4 weeks. In contrast, administration of foscarnet 100 or 120 mg/kg each day delayed retinitis progression for 17 to 23 weeks on average, with no increase in toxicity.

The clinical response is clearly related to the virological outcome. Cytomegalovirus was eliminated from over 83% of buffy coat, blood and urine samples during induction treament, a rate which corresponded to clinical response.

In published case reports, maintenance foscarnet therapy was given at home to 2 AIDS patients, and coadministration of zidovudine, discontinued during previous ganciclovir therapy, was recommenced. Furthermore, foscarnet prevented retinitis progression until immunological status recovered sufficiently to eradicate the virus in a bone marrow transplant recipient.

Limited comparative data suggest that the efficacy of foscarnet is similar to that of ganciclovir in managing AIDS-related cytomegalovirus retinitis.

Adverse Effects

The most frequent dose-limiting adverse effect of foscarnet therapy is a 2- to 3-fold increase in serum creatinine in about 45% of patients. Loin pain has been reported and haemodialysis may be required in severe cases of renal impairment. The cause appears to be acute tubular necrosis, which tends to be reversible on foscarnet withdrawal, even in renal allograft recipients. The incidence and severity of renal dysfunction is reduced by adjusting the dosage of foscarnet depending on the serum creatinine level, using intermittent rather than continuous infusions, providing adequate prehydration and avoiding other potentially nephrotoxic drugs. Nausea and vomiting, which occurs in 20 to 30% of patients, could precipitate renal damage. Reversible hypercalcaemia and hyperphosphataemia occur in over 66% of foscarnet recipients, although symptomatic hypocalcaemia has also been observed. These disturbances are possibly due to foscarnet deposition in bone, chelation with ionised calcium, or to the drug inhibiting renal phosphate excretion.

Foscarnet causes anaemia in 20 to 50% of patients, but does not appear to be associated with neutropenia. Penile ulceration, resembling fixed drug eruption, associated with foscarnet use is increasingly being reported. It appears to be due to local irritation from unchanged drug in the urine, and therefore thorough personal hygiene is advised.

Thrombophlebitis of peripheral veins during continuous infusion, mild elevations in liver function, transient neurological disturbances, diarrhoea and headache have occasionally been reported.

Drug Interactions

The concomitant use of foscarnet and intravenous pentamidine appears to be contraindicated because of additive renal toxicity and severe hypocalcaemia.

Dosage and Administration

The recommended dosage of foscarnet in the management of patients with cytomegalovirus retinitis is a bolus infusion of 20 to 30 mg/kg over 30 minutes followed by infusion of 180 to 200 mg/kg/day, adjusted according to renal function. Intermittent 2-hour infusions of 60 mg/kg every 8 hours or 100 mg/kg every 12 hours are preferred over continuous infusion. Induction treatment can last for up to 4 weeks.

Maintenance therapy is usually necessary to prevent relapse. Daily 2-hour intravenous infusions of foscarnet 90 to 120 mg/kg are currently considered to be more effective in prolonging remission than 60 to 90 mg/kg/day administered for 5 days each week.

Serum creatinine and calcium levels should be closely monitored, and saline or dextrose hydration given before and during treatment to minimise the risk of acute renal damage. Foscarnet (24 mg/ml) stock solution can be diluted by 50% and administered centrally rather than peripherally to reduce the risk of thrombophlebitis.

1. Antiviral Activity

Foscarnet is the trisodium salt of phosphonoformic acid (fig. 1). Although first synthesised in 1924, it was 54 years later that the antiviral properties of foscarnet were discovered, when Helgstrand et al. reported in 1978 that concentrations of 20 and 3.5 μmol/L, respectively, inhibited influenza virus RNA polymerase and herpes simplex virus type 1 DNA polymerase by 50%. Foscarnet was subsequently found to inhibit the DNA polymerase activity of 5 of the 7 known types of herpesvirus which occur in humans, namely herpes simplex types 1 and 2, varicella zoster, Epstein-Barr virus and cytomegalovirus (see reviews by Eriksson & Öberg 1984, 1989; Wood & Geddes 1987).

The focus of this review is the virustatic activity of foscarnet against cytomegalovirus and, to a lesser extent, HIV, and its use in the management of cytomegalovirus retinitis in immunocompro-

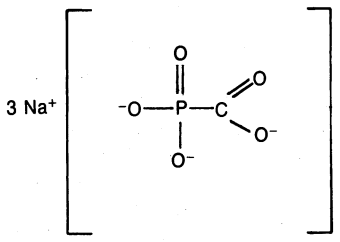

Fig. 1. Structural formula of foscarnet.

mised, mostly HIV-infected AIDS patients. The effects of foscarnet on other herpesviruses will therefore only be discussed to supplement or support its use in cytomegalovirus infection.

1.1 *In Vitro* Activity

1.1.1 Effects on Viral Enzymes

DNA Polymerase

DNA polymerases catalyse the linking by phosphodiester bonds of the 4 deoxynucleoside triphosphates (deoxyadenine, deoxythymine, deoxyguanine and deoxycytosine triphosphates) to elongate the DNA chain. The sequence in which the triphosphates add on to the polymer is governed by pairing with the complementary base on a preexisting DNA or RNA template (fig. 2). Pyrophosphate is produced in the polymerisation process. In infected cells, herpesviruses induce DNA polymerases which differ biochemically and kinetically from the DNA polymerases found in healthy cells, and are therefore potential targets for specific antiviral compounds (see section 2).

Foscarnet inhibits the DNA polymerase activity of human cytomegalovirus (Eriksson et al. 1982), herpes simplex virus types 1 and 2 (Eriksson & Öberg 1979; Helgstrand et al. 1978; Ostrander & Cheng 1980), varicella zoster virus (Öberg 1986) and Epstein-Barr virus (Datta & Hood 1981). Cytomegalovirus DNA polymerase was inhibited 50% by foscarnet 0.3 μmol/L, while slightly higher concentrations were required to inhibit other herpesvirus polymerases to the same extent (see reviews by Öberg 1986, 1989) [table I]. This activity is reflected in a 50% reduction in DNA synthesis in cytomegalovirus isolates exposed to a mean foscarnet concentration of 179 μmol/L (Gadler 1983).

Kinetic studies reveal that inhibition of herpesvirus DNA polymerases by foscarnet is noncompetitive with respect to deoxynucleoside triphosphates, uncompetitive with the activated DNA template primer, and competitive with pyrophosphate (Derse et al. 1982; Eriksson et al. 1980, 1982; Ostrander & Cheng 1980). These observations indicate that foscarnet blocks the pyrophosphate binding site of the viral DNA polymerase, thus preventing cleavage of pyrophosphate from the deoxynucleoside triphosphates. Further evidence for such a mechanism is provided by the findings that foscarnet-resistant herpes simplex DNA polymerases are also less sensitive to inhibition by pyrophosphate (Eriksson & Öberg 1979), and that the presence of pyrophosphate diminishes the inhibitory activity of foscarnet (Datta & Hood 1981). However, it appears that foscarnet and pyrophosphate are bound to distinct, although similar, sites on the enzyme, since the inhibition constants of the 2 compounds differ (Derse et al. 1982).

Reverse Transcriptase

The enzyme reverse transcriptase catalyses the process of reverse transcription, whereby viral RNA of a retrovirus, such as HIV, is converted into DNA which is then integrated into human DNA to direct further viral replication.

Foscarnet inhibited HIV reverse transcriptase by 50% at concentrations of 0.1 to 0.5 μmol/L (Sandström et al. 1985; Vrang & Öberg 1986; Vrang et al. 1988), and by 100% at 5 μmol/L (Sandström et al 1985). Inhibition of reverse transcriptase by foscarnet was noncompetitive with respect to deoxynucleoside triphosphates and uncompetitive towards the template primer (Vrang & Öberg 1986).

1.1.2 Effects on Viral Replication

Cytomegalovirus

While *in vitro* testing provides some indication of the sensitivity of cytomegalovirus to foscarnet, a number of factors including methodology, viral strain and multiplicity of infection introduce var-

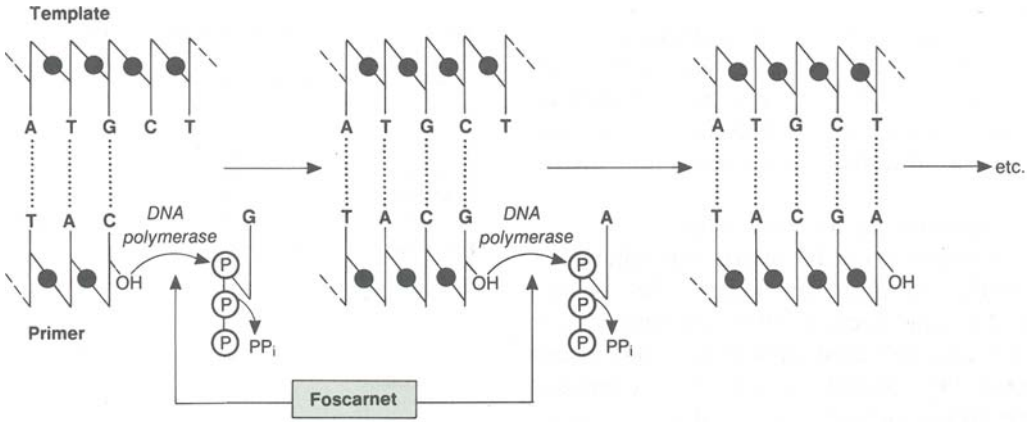

Fig. 2. Schematic representation of DNA chain elongation catalysed by DNA polymerase showing target site of foscarnet. *Abbreviations and symbols:* A = adenine; C = cytosine; G = guanine; T = thymine; ● = phosphodiester bond; P = phosphate; PP_i = pyrophosphate; •••• = base pairing.

iability to the results. Furthermore, *in vitro* susceptibility may not be predictive of the likely clinical response of a viral infection to a drug.

50% inhibition of plaque or focus formation was achieved with foscarnet 190 μmol/L against murine cytomegalovirus (Kern et al. 1978), and by 130 μmol/L with human cytomegalovirus strain Ad169 at a multiplicity of infection of 1 (Wahren & Öberg 1980). At the much lower multiplicity of infection value of 0.01, human cytomegalovirus Ad169 foci were 50% inhibited by foscarnet 25 μmol/L, and by over 90% with 100 μmol/L (Wahren & Öberg 1980). Four clinical isolates of cytomegalovirus were about 3 to 8 times less sensitive to foscarnet than the laboratory strain Ad169 (Wahren & Öberg 1980). A mean concentration of foscarnet 179 μmol/L was required for 50% inhibition of 6 other clinical isolates of human cytomegalovirus and strain Ad169 using DNA hybridisation to determine replication (Gadler 1983).

Table I. Activity of foscarnet against the herpesvirus DNA polymerases as estimated by the concentration required to inhibit purified DNA polymerase activity by 50% (IC_{50})

Virus	IC_{50} (μmol/L)	References
Cytomegalovirus	0.3	Eriksson et al. (1982)
Herpes simplex type 1	0.4-3.5	Eriksson & Öberg (1979), Helgstrand et al. (1978)
Herpes simplex type 2	0.6-22	Ostrander & Cheng (1980)
Varicella zoster	0.4	Öberg (1986)
Epstein-Barr	0.5-3	Datta & Hood (1981), Öberg (1986)

Exposing human embryonic fibroblast cultures infected with cytomegalovirus to inhibitory concentrations of foscarnet (300 to 500 μmol/L) failed to prevent the appearance of early antigens, but did inhibit late antigen and inclusion body development (Wahren & Öberg 1979, 1980). The appearance of late antigens occurs after viral DNA replication has commenced about 20 hours after infection, and is predictive of infected cell death. Foscarnet 500 μmol/L was only effective in preventing late antigen expression, focus formation and cytopathic effects if cells were exposed to the drug within 24 hours of being infected (Wahren & Öberg 1980).

Inhibition of cytomegalovirus replication in human embryonic lung fibroblasts by foscarnet was reversible. Cytopathic effects of the virus were restored within 6 or 10 days after 7 or 35 days' exposure to foscarnet 500 μmol/L (Wahren & Öberg 1980). Early antigen levels increased and late anti-

gens were detected within 3 to 9 days of infected cells no longer being exposed to virustatic concentrations of the drug (Wahren & Öberg 1980; Wahren et al. 1985). The viral genome thus persisted throughout the period of incubation and was reactivated once foscarnet was cleared from the cells.

Human Immunodeficiency Virus

HIV replication in H9 human cell cultures was completely prevented by foscarnet 680 μmol/L while 132 μmol/L caused 98% inhibition, and 10 to 25 μmol/L inhibited replication by 50% (Koshida et al. 1989; Sandström et al. 1985). Expression of the HIV-associated proteins p15 and p24 was also diminished by 2 to 6 days' exposure to foscarnet, particularly at concentrations of 150 μmol/L or more, indicating inhibition of viral multiplication in infected H9 cells (Sarin et al. 1985).

1.2 *In Vivo* Activity

Topical foscarnet has shown activity in animal models of cutaneous, genital and corneal herpes simplex infections (see reviews by Eriksson & Öberg 1984; Öberg 1983, 1989) which has been corroborated in clinical trials (Barton et al. 1986; Lawee et al. 1988; Lim et al. 1986; Safrin et al. 1990). Results obtained with foscarnet against cytomegalovirus *in vivo* may not be representative of efficacy in humans due to species specificity of the virus.

Intraperitoneal administration of foscarnet 250 mg/kg twice daily for 5 days reduced the mortality rate of mice with disseminated cytomegalovirus infection by about 40% (Kern et al. 1978). Foscarnet 20 or 200 mg/kg given intranasally for 9 days to mice with cytomegalovirus lung infections reduced pulmonary viral titres by 60 or 68% (Debs et al. 1986). However, in cytomegalovirus-infected guinea-pigs, considered to be a more appropriate model of human disease, foscarnet 100 mg/kg/day administered intraperitoneally for 5 days was ineffective (Lucia et al. 1984). Mortality, viraemia and virus distribution were similar in animals given foscarnet or placebo. Moreover, interstitial pneumonia was more prevalent and virulent in animals receiving foscarnet or aciclovir compared with placebo.

Table II. *In vitro* activity of foscarnet and zidovudine alone and in combination against human cytomegalovirus and HIV-1 replication

Drug	IC_{50} (μmol/L)[a]	
	cytomegalovirus	HIV-1
Foscarnet	34	22
Zidovudine	383	0.006
Foscarnet : zidovudine		
1 : 1	61	
2 : 1	41	
5 : 1	52	
10 : 1	33	
1000 : 1		3.5
4000 : 1		8.5

a IC_{50} = concentration which causes 50% inhibition of cytomegalovirus plaque formation in human embryonic lung fibroblasts or HIV-1 reverse transcriptase activity in human peripheral blood mononuclear cells.

1.3 Activity of Foscarnet Combined with Other Antiviral Drugs

To determine whether various antiviral drugs have additive or synergistic properties when used in combination, *in vitro* experiments have been performed with foscarnet and ganciclovir, zidovudine (azidothymidine), trifluridine (trifluorothymidine), interferon-α and aphidicolin.

Exposure of cytomegalovirus-infected human embryonic lung fibroblasts to foscarnet and zidovudine revealed that the additive activity was attributable to foscarnet, since zidovudine alone was relatively ineffective (table II) [Eriksson & Schinazi 1989]. Although zidovudine was about 30 times less active than foscarnet in inhibiting cytomegalovirus DNA polymerase, the 2 agents were mutually exclusive inhibitors of the enzyme, apparently possessing overlapping binding sites (Eriksson & Schinazi 1989). Inhibition of herpes simplex type 1 DNA polymerase by foscarnet, aphidicolin and the activated triphosphate forms of aciclovir and ganciclovir was also mutually exclusive, again implying receptor sites with common physical or kinetic characteristics (Frank & Cheng 1985). Combining foscarnet 30, 60 or 90 μmol/L with

ganciclovir 1, 2, 4 or 8 μmol/L produced a synergistic decrease in plaque formation by clinical isolates and strain Ad169 of cytomegalovirus (Manischewitz et al. 1990), as did foscarnet 25 μmol/L in combination with trifluridine 0.17 μmol/L (Spector et al. 1983).

Replication of HIV was inhibited synergistically by foscarnet combined with interferon-αA in human H9 cells (Hartshorn et al. 1986) and by foscarnet plus zidovudine in human peripheral blood mononuclear cells (Eriksson & Schinazi 1989; Koshida et al. 1989). The synergy was greatest with increased ratios of foscarnet to zidovudine, particularly at higher concentrations (table II). Inhibition of reverse transcriptase by foscarnet and zidovudine was once again additive and mutually exclusive (Eriksson & Schinazi 1989; Koshida et al. 1989).

1.4 Viral Resistance to Foscarnet

Resistance did not develop in cytomegalovirus strain Ad169 cultured in human lung fibroblasts for 35 days with foscarnet 500 μmol/L (Wahren & Öberg 1980). However, serial passage of herpes simplex 1 in the presence of foscarnet readily produced drug-resistant mutants (Derse et al. 1982; Eriksson & Öberg 1979). These mutants demonstrated the same growth properties as the susceptible virus. Changes in viral DNA polymerases which conferred resistance were not uniform. Five herpes simplex mutants grown in the presence of foscarnet 1000 μmol/L exhibited 3 distinct types of DNA polymerase (Derse et al. 1982). The enzymes least sensitive to foscarnet had a lower affinity for magnesium, an obligatory cofactor, and a higher affinity for deoxynucleoside triphosphates than the more sensitive wild-type polymerase. Resistance to foscarnet also appeared to be associated with reduced sensitivity to aciclovir and ganciclovir, perhaps arising from shared characteristics of their binding sites.

Clinically, drug resistance of cytomegalovirus did not appear to be the cause of a lack of response to foscarnet in 12 renal transplant or leukaemia patients with cytomegalovirus infections during a mean of 13 or 17 days' therapy (Åkesson-Johansson et al. 1986). The concentration of foscarnet which inhibited cytomegalovirus isolated during treatment from these nonresponders and from 9 responsive patients by 50% were comparable, at 294 and 272 μmol/L, respectively.

1.5 Mechanism of Action

Foscarnet exerts its virustatic effects against cytomegalovirus by selectively inhibiting DNA polymerase induced by the virus in infected cells, and thus preventing elongation of the viral DNA chain (fig. 2). The drug binds directly to a receptor site on the enzyme which differs from that of pyrophosphate, despite sharing some similar kinetic determinants. Cleavage of pyrophosphate from deoxynucleoside triphosphates is blocked, and formation of an inactive foscarnet-DNA polymerase complex prevents the enzyme's release from, or translocation along, the template primer. Foscarnet is also a noncompetitive reversible inhibitor of HIV reverse transcriptase. Unlike the nucleoside analogues aciclovir and ganciclovir, the activity of foscarnet does not depend upon conversion to an active triphosphate by viral thymidine kinase.

Viral replication is therefore inhibited in the presence of foscarnet, but the effect is reversible. Once virus-infected cells are no longer exposed to foscarnet, viral DNA polymerase activity, and therefore replication, resumes.

2. Effects on Host Enzymes and Cells

An ideal antiviral agent should be effective against viruses at concentrations which do not interfere with the cellular processes of the host. Since the target for foscarnet is DNA polymerase, an enzyme system also present in humans, it is crucial that the drug is selective towards the viral enzyme.

The concentration of foscarnet needed to inhibit calf thymus DNA polymerase α was 40 or 50 μmol/L (Eriksson et al. 1982; Helgstrand et al. 1978), compared with 0.3 μmol/L for cytomegalovirus-induced DNA polymerase and 0.1 to 0.5 μmol/L against HIV reverse transcriptase (see sec-

tion 1.1.1). Foscarnet also had 100- to 200-fold higher inhibition constants against human HeLa cell DNA polymerase α compared with the viral enzyme (Sabourin et al. 1978). Other mammalian DNA polymerases were unaffected by foscarnet (see reviews by Öberg 1983, 1989).

Incubation for 18 or 24 hours with foscarnet 1000 μmol/L inhibited DNA synthesis of human embryonic fibroblasts or HeLa cells by 50% (Helgstrand et al. 1978; Stenberg & Larsson 1978), and by 40% in canine kidney cells (Stenberg et al. 1983). Using the same exposure duration and foscarnet concentration, Stenberg et al. (1985) noted, however, that human fibroblast DNA synthesis was reduced by only 10 to 20%, and significant inhibition was only achieved after 72 hours' incubation, despite constant intracellular foscarnet levels being reached within 4 to 8 hours.

The division of human fibroblasts exposed for 24 hours to foscarnet 1000 μmol/L was inhibited by 50%, and completely halted by 10 000 μmol/L (Stenberg & Larsson 1978; Stenberg et al. 1985). Incubation with foscarnet at concentrations below 1000 μmol/L, a level which far exceeds that required for virustatic activity, had no significant effects on HeLa or human fibroblast cell division (Stenberg & Larsson 1978; Stenberg et al. 1983, 1985).

The effects of foscarnet on cell proliferation were reversible, with a recovery of DNA synthesis and cell division once the drug had diffused from the cell (Stenberg & Larsson 1978; Stenberg et al. 1983, 1985).

3. *Pharmacokinetic Properties*

The disposition of foscarnet has been investigated in animal models and in small numbers of patients infected with HIV, usually following intravenous administration, the route used in clinical practice. Foscarnet was detected using a high performance liquid chromatographic (HPLC) system with a sensitivity of 33 μmol/L (Pettersson et al. 1989).

3.1 Plasma Concentrations

After 3 days' oral administration of foscarnet 4000mg every 6 hours as a solution, approximately 17% of the dose was absorbed in 6 HIV-infected patients (Sjövall et al. 1988). Plasma concentrations were routinely below 33 μmol/L, with isolated peaks of up to 50 μmol/L in 2 patients. Saturation of an intestinal sodium/phosphate carrier system, nutrient malabsorption associated with AIDS and foscarnet's slow distribution into cells were suggested as possible reasons for the poor absorption of foscarnet following oral administration. As a consequence, foscarnet cannot be given orally when treating patients with viral disease and only the findings following intravenous administration are of clinical importance.

Foscarnet plasma concentrations ranged from 75 to 500 μmol/L during 3 to 21 days' continuous intravenous infusion of 0.14 to 0.19 mg/kg/min in 2 groups of 6 and 13 HIV-infected patients (Sjövall et al. 1988, 1989). This wide range was due in part to intra- and interindividual variability, and perhaps also to differences in the equilibrium of foscarnet and phosphate deposition in bone (see section 3.2) [Sjövall et al. 1989]. In all patients, plasma concentrations increased rapidly within the first 24 hours of infusion, and then reached a plateau (Sjövall et al. 1988, 1989). However, the greatest concentrations occurred towards the end of a 3-day infusion period of foscarnet 0.16 mg/kg/min (230 mg/kg/day) in 6 patients, suggesting that levels were still gradually increasing and steady-state may not have been achieved within this time (Sjövall et al. 1988).

Mean steady-state plasma concentrations were estimated to be 261 μmol/L in 14 AIDS patients (Gaub et al. 1987) and 228 μmol/L in another 13 (Sjövall et al. 1989) after 6 to 21 days' continuous infusion of foscarnet 0.09 to 0.19 mg/kg/min (table III). Again there were considerable differences between individuals, with values as low as 115 μmol/L and up to 741 μmol/L being recorded (Gaub et al. 1987; Sjövall et al. 1989). Similarly, steady-state concentrations ranging from 140 to 1257 μmol/L were recorded during 73 courses of foscarnet treat-

Table III. Mean pharmacokinetic parameters in HIV-infected patients following intravenous infusion of foscarnet

Reference	No. of pts	Dosage (mg/kg/min) [duration]	C_{ss}[a] (μmol/L)	V_{ss}[b] (L/kg)	$t_{1/2}$ (h)			Clearance (L/h/1.73m^2)[a]			f_e (%)
					λ_1	λ_2	λ_3	CL_s	CL_R	CL_{NR}	
Sjövall et al. (1989)	13	0.14-0.19 [8-21 days]	228 (115-458)	5.1	1.4	6.8	88	9.1 (5.1-16.9)	7.9 (4.4-15.6)	1.2 (0.6-2.5)	87
Sjövall et al. (1988)	6	0.16 [3 days]	(134-202)	1.3	0.5	3.3	18	12.8 (11.1-14.6)	10.6 (8.4-13.4)	2.4 (1.3-3.2)	82

a Mean (range).

b Based on 3-compartment model.

Abbreviations: C_{ss} = plasma concentration at steady-state; V_{ss} = volume of distribution at steady-state; $t_{1/2}$ = mean elimination half-life during phases λ_1, λ_2 and λ_3; CL_s = total plasma clearance; CL_R = renal clearance; CL_{NR} = nonrenal clearance; f_e = fraction of the dose excreted unchanged in the urine at apparent steady-state.

ment in 61 patients (unpublished data on file, Astra). Fanning et al. (1990) reported that although there was significant variability between the mean plasma drug concentrations (range 164 to 529 μmol/L) determined in 13 AIDS patients with cytomegalovirus retinitis during continuous infusion of foscarnet 0.16 mg/kg/min, there was little variation within each individual, with the exception of 2 patients with renal failure. In these patients the increases in plasma foscarnet concentration from 283 to 777 μmol/L and from 59 to 727 μmol/L corresponded to respective rises in serum creatinine from 20 to 210 μmol/L and 75 to 178 μmol/L. In 6 patients receiving maintenance therapy with a 3-hour infusion of foscarnet 75 or 90 mg/kg for 5 days each week, the mean plasma foscarnet concentration ranged from 6 to 61 μmol/L (mean 20 μmol/L) before each infusion, and from 243 to 654 μmol/L (mean 486 μmol/L) following administration (Fanning et al. 1990). There was wide inter- and intrapatient variability in concentration, reflecting in part differences in infusion duration and sampling times.

In 3 renal allograft recipients, mean plasma concentrations of 129, 133 and 208 mg/L were detected following infusion of foscarnet 0.055 mg/kg/min for 5 to 8 days (Klintmalm et al. 1985). The higher concentrations reached with a lower dose in these 3 patients, compared with the AIDS patients, was almost certainly because of reduced clearance due to renal insufficiency.

Administration of an alternative regimen, 2-hour intravenous infusions of foscarnet 60 mg/kg every 8 hours, resulted in mean peak and trough plasma concentrations of 509 and 98 μmol/L, respectively, after 3 days, and 495 and 126 μmol/L after 14 days in 8 patients with AIDS-related cytomegalovirus retinitis (Aweeka et al. 1989).

3.2 Distribution

The mean apparent volume of distribution of foscarnet at steady-state was estimated to be between 0.52 and 0.74 L/kg in patients with HIV infection, following a continuous infusion of 0.14 to 0.19 mg/kg/min for 3 to 21 days or 8-hourly infusions of 60 mg/kg for 14 days (Aweeka et al. 1989; Sjövall et al. 1988, 1989). Based on a 3-compartment model which took into account the long terminal half-life of the drug (see section 3.3), steady-state volume of distribution values of 1.3 and 5.1 L/kg were calculated after 3 days' and 8 to 21 days' treatment, respectively (Sjövall et al. 1988, 1989). Foscarnet therefore appeared to be extensively distributed out of the plasma, although the pattern of distribution in humans has not been studied in detail. A mean foscarnet concentration of 68.5 μmol/L was detected in the CSF of 6 patients with HIV infection, representing 43% of the mean plasma concentration (Sjövall et al. 1989). This relatively high distribution ratio was probably partly due to

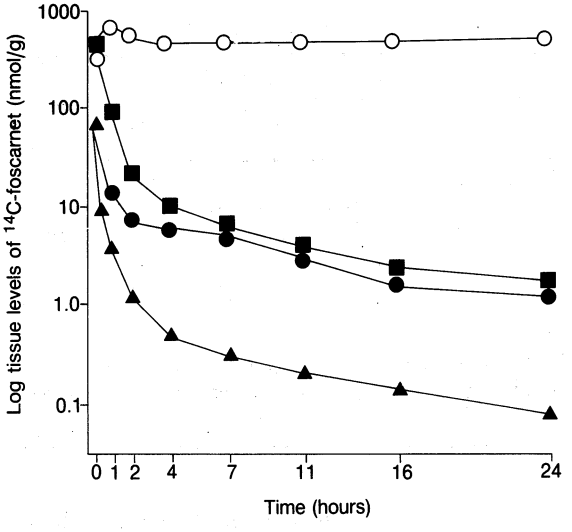

Fig. 3. Tissue concentrations of [^{14}C]foscarnet in bone (○), kidney (■), lung (●) and heart (▲) following a single intravenous dose of 80 μmol/kg in mice (after Helgstrand et al. 1980).

impaired blood-brain barrier integrity in these patients.

Following intravenous administration of [^{14}C]foscarnet to mice, distribution into the CNS was poor (Helgstrand et al. 1980). Around 30% of the administered dose was retained in bone and cartilage, followed by kidney, lung and heart (fig. 3). Foscarnet was deposited in bone tissue, rather than in the marrow, and probably replaced phosphate in the matrix. Conclusive evidence for osteochondral deposition of foscarnet in human subjects is lacking, but it is suggested by the elimination and clearance characteristics of the drug (see section 3.3), and perhaps also by the hyperphosphataemia observed during therapy (see section 5.3).

3.3 Elimination

Foscarnet was not metabolised to any significant extent following intravenous administration and was eliminated principally by the renal route. A mean of 83% of the cumulative dose was detected unchanged in the urine within 36 hours of discontinuing an infusion of foscarnet 0.14 to 0.19 mg/kg/min, and 88% was recovered within a week (Sjövall et al. 1988, 1989). Assuming that foscarnet was excreted entirely via the kidneys, the remainder was probably sequestered into bone and cartilage.

The total body clearance of foscarnet was 9.1 and 12.8 L/h/1.73m^2 after 3 to 21 days' continuous infusion of 0.14 to 0.19 mg/kg/min (Sjövall et al. 1988, 1989), and 0.1 L/h/kg after 14 days' administration of infusions of 60 mg/kg every 8 hours (Aweeka et al. 1989). Mean renal clearance, comprising 44 to 58% glomerular filtration and 42 to 56% tubular secretion, was 7.9 and 10.6 L/h/1.73m^2 after the continuous infusion (Sjövall et al. 1988, 1989), and 0.08 L/h/kg following intermittent administration (Aweeka et al. 1989). Renal clearance thus contributed 82 to 86% of the total plasma clearance of foscarnet. In 6 patients given foscarnet for 3 days, renal clearance was independent of urine flow, suggesting that tubular reabsorption of the drug was negligible (Sjövall et al. 1988). However, in a subsequent study by the same investigators involving 13 patients treated for 8 to 21 days, renal clearance and urine flow increased in parallel, suggesting that tubular reabsorption may occur (Sjövall et al. 1989).

Nonrenal clearance of foscarnet was responsible for around 14 to 18% of the total clearance, and was attributed to uptake into bone (Sjövall et al. 1988, 1989).

The elimination of foscarnet appears to be triphasic, having 2 relatively short periods of elimination of about 0.5 to 1.4 ($t_{½\lambda 1}$) and 3.3 to 6.8 hours ($t_{½\lambda 2}$), followed by a longer terminal phase ($t_{½\lambda 3}$) of 88 hours, ranging between 36 and 196 hours (Aweeka et al. 1989; Sjövall et al. 1988, 1989).

The slow release of accumulated foscarnet from bone was suggested as the likely cause of the long terminal half-life (Sjövall et al. 1989). Consistent with this was the presence of foscarnet 0.64 to 4.3 μmol/L which was detected in a patient's urine using a more sensitive HPLC system over 2 years after therapy ceased (Sjövall et al. 1989).

Although up to about 20% of administered foscarnet was taken up into bone to give a long terminal $t_{½\lambda 3}$, the initial disposition phases were relatively short (about 4 to 8 hours in total),

necessitating continuous or frequent short infusions to maintain adequate plasma drug concentrations.

3.4 Relationship Between Plasma Concentration and Virustatic Effects

In 7 patients with AIDS-related cytomegalovirus retinitis the serum levels of HIV p24 antigen decreased by a mean of 55% during 14 days' treatment with infusions of foscarnet 60 mg/kg every 8 hours (Jacobson et al. 1988). Mean steady-state peak and trough foscarnet concentrations of 557 and 155 μmol/L, respectively, in 5 of these patients correlated poorly with the individual reductions in p24 antigen levels. There was a marginally better correlation with the area under the foscarnet plasma concentration-time curve at steady-state (AUC_{ss}). However, when data from 1 patient with a low pretreatment antigen level of 69 ng/L were excluded, a significant correlation was demonstrated between AUC_{ss} and the decline of p24 antigen.

Such a relationship between foscarnet plasma variables and cytomegalovirus isolation or antigen levels has not been demonstrated, although samples tended to become negative during foscarnet therapy and subsequently yielded cytomegalovirus when treatment was stopped or the dosage reduced during maintenance (see section 4.2).

Generally, most investigators have aimed to maintain foscarnet plasma concentrations between 333 and 500 μmol/L to ensure that effective antiviral levels are sustained (Farthing et al. 1987; Gaub et al. 1987; LeHoang et al. 1989). However, Klintmalm and colleagues (1985) suggested keeping plasma concentrations within the range 100 to 167 μmol/L since these values are virustatic against cytomegalovirus *in vitro* (see section 1.1.2). The risk with the latter approach is that subtherapeutic concentrations may occur more frequently and cytomegalovirus may recur. Indeed, infusions of foscarnet 60 mg/kg every 8 hours gave mean plasma concentrations within the *in vitro* virostatic range, but individual trough levels were below 100 μmol/L in 5 of 8 patients on the third day of treatment and in 3 patients after 2 weeks (Aweeka et al. 1989).

4. Therapeutic Use in Patients with Cytomegalovirus Retinitis

When the T-lymphocyte-mediated immune response is compromised, normally latent cytomegalovirus reactivates causing opportunistic infections such as pneumonitis, colitis, oesophagitis, encephalitis and/or retinitis. Overall, some form of cytomegalovirus infection is common following all types of transplantation and develops in 70 to 90% of cytomegalovirus seropositive bone marrow transplant patients (Klintmalm et al. 1985; Ringdén et al. 1986) and in almost all of those with AIDS (Hirsch 1987). The following discussion deals exclusively with the use of foscarnet in cytomegalovirus retinitis in immunocompromised patients, currently its only approved indication, but it should be recognised that the drug has also been used to treat pneumonitis (Farthing et al. 1987; Ringdén et al. 1986), colitis (Connolly et al. 1989; Weber et al. 1987) and encephalitis (Ringdén et al. 1986) associated with cytomegalovirus infection.

Retinitis is the most prevalent manifestation of cytomegalovirus infection in AIDS patients, occurring in 15 to 46% in the United States, but is relatively uncommon in allograft recipients (Palestine 1988). Diagnosis of AIDS has been made on the basis of cytomegalovirus retinitis in about 9% of cases (Jacobson & Mills 1988). In association with reactivation of latent cytomegalovirus the virus reaches the retina through dissemination in the blood (Bloom & Palestine 1988), and therefore cytomegalovirus is always present systemically in patients with ocular involvement. If untreated, the initial presentation of granular white lesions or fluffy white infiltrate, often with retinal haemorrhages, progresses within about a month and can eventually lead to complete loss of vision from destruction of all layers of the retina (Bloom & Palestine 1988; Jacobson & Mills 1988; Palestine 1988). Cytomegalovirus retinitis is the most common cause of blindness in AIDS patients (Bloom & Palestine 1988). The speed with which vision is impaired depends on the predominant site of retinitis, with optic disc or macular involvement resulting in rapidly failing sight (Bloom & Palestine 1988;

Palestine 1988; Pinching 1989). As active retinitis progresses or is controlled by antiviral therapy, atrophic tissue is formed, which predisposes to retinal detachment and hence blindness (Bloom & Palestine 1988; Jacobson & Mills 1988).

Antiviral therapy therefore aims to arrest the progression of retinitis and forestall or minimise vision impairment. In immunocompromised patients other than those with AIDS, achieving this goal is aided if immunosuppressive measures are modified, enabling some recovery of immune function against the virus (Jeffries 1989). Therapeutic options available to the clinician have generally been limited, but drugs such as foscarnet and ganciclovir have recently been evaluated in this difficult to manage condition. Ganciclovir has been used with varying degrees of success to treat cytomegalovirus retinitis (see review by Faulds & Heel 1990). However, a disadvantage with ganciclovir is that it must be used with extreme caution in some AIDS patients also receiving zidovudine, since each drug produces neutropenia and an additive or synergistic myelosuppression may also occur (see review by Langtry & Campoli-Richards 1989). This may be more of a theoretical than a practical concern, however, since many patients can receive ganciclovir and an effective dose of zidovudine (Pinching, personal communication). The efficacy of foscarnet, and indeed other agents, in the management of patients with ocular cytomegalovirus infection has so far been assessed in preliminary noncomparative studies involving small groups of AIDS patients, and in case reports where it has been administered on a compassionate basis. Presently there are scant data from controlled studies comparing foscarnet with ganciclovir, although a large randomised multicentre trial with this aim is currently underway in the US.

4.1 Case Reports

Case reports describing the use of foscarnet in immunocompromised patients with cytomegalovirus retinitis published to date are summarised in table IV. As can be seen from these individual findings, foscarnet produced a complete or partial response in signs of retinitis in all treated patients. Although caution must be advised in interpreting these encouraging results, they do illustrate some important aspects of foscarnet therapy.

The 2 AIDS patients in whom partial responses occurred are of interest since each had to stop ganciclovir because of neutropenia and thrombocytopenia, and zidovudine therapy, stopped during ganciclovir treatment, was once again possible during administration of foscarnet (Heley 1988; Wood et al. 1989). Maintenance foscarnet therapy was given at home in both patients, via a Hickman central line, aiding independence and self-confidence. Domiciliary treatment is also possible with ganciclovir (Fanning, personal communication; Gazzard, personal communication; Levin et al. 1989).

Progression of cytomegalovirus retinitis was prevented by foscarnet treatment while immune status improved in a patient receiving immunosuppressive therapy to manage graft-versus-host disease following bone marrow transplantation (Ganly et al. 1988). Relapse did not occur after foscarnet was discontinued, suggesting that effective immunity to cytomegalovirus was established once immunological recovery was restored.

4.2 Noncomparative Studies

A number of noncomparative studies have been conducted in small populations with AIDS-related cytomegalovirus retinitis to evaluate the response to induction therapy with foscarnet and prevention of relapse during maintenance (table V). Some of these studies were in abstract form only, making a full analysis of the relative importance of the results difficult.

In one of the earliest clinical trials, an intravenous infusion of foscarnet 230 mg/kg daily for 7 to 28 days resulted in clinical improvement of retinitis in 7 of 9 patients (Michon et al. 1986). Subsequent to this, a foscarnet dosage of 230 mg/kg/day, administered as a continuous intravenous infusion preceded by a bolus dose of 20 or 30 mg/kg, was used as a 2- to 3-week induction regimen in a number of studies (table V). The dosage of foscarnet was reduced by about 30 mg/kg/day for

Table IV. Summary of some case reports of foscarnet in immunocompromised patients with cytomegalovirus retinitis

Reference	Cause of immunosuppression	IV dosage [duration]	Clinical response	Comments
Ganly et al. (1988)	BMT for chronic granulocytic leukaemia; methyl prednisolone	I: [14d] then M: 'one third of full dose' 5/7d[a] [6w]	CR	Improvement in immune status aided response
Heley (1988)	AIDS	I: 230 mg/kg/day [1.5d] then 115 mg/kg/day [2d] then 200 mg/kg/day [14d] then M: 134-144 mg/kg/day [5 mo]	PR	Previously received ganciclovir, discontinued 3 times due to myelosuppression (once with zidovudine); zidovudine recommenced during foscarnet therapy
Singer et al. (1985)	AIDS; renal transplant; prednisolone and azathioprine	I: 600mg bolus then M: 112 mg/kg/day [4w]	CR	Reduction of immunosuppressive therapy and hyperimmune globulin 6g weekly aided response; relapse 3mo later, CR to the same regimen of foscarnet alone. Urine cultures negative by day 24, blood by day 32
Wood et al. (1989)	AIDS	I: 20 mg/kg bolus then 12 g/day [14d] then M: 5g daily [14d] then 5/7d [2mo]	PR	Previous ganciclovir therapy discontinued due to neutropenia, and zidovudine stopped; zidovudine recommenced during foscarnet therapy

a Dosage details not stated.

Abbreviations: PR = partial response (no new lesions and/or no progression of old lesions); CR = complete response (disappearance or decrease in active lesions); I = induction regimen; M = maintenance regimen; BMT = bone marrow transplant; 5/7d = 5 days per week; mo = month; w = week.

every 20 μmol/L increase in serum creatinine above 70 μmol/L and some degree of improvement occurred in over 85% of patients given this induction regimen; retinitis usually resolved completely in 50 to 75% of patients, with partial responses in another 10 to 50% (Fanning et al. 1990; LeHoang et al. 1989; Michon et al. 1986, 1988; Walmsley et al. 1988). Katlama and colleagues (1989a) reported a 100% complete response rate in 26 previously untreated patients.

Generally there was an improvement in the severity of retinitis in the majority of eyes (fig. 4) and only a small proportion demonstrated no improvement or disease progression during induction. However, retinitis recurred within a month of discontinuing foscarnet induction therapy in over two-thirds of surviving patients (LeHoang et al. 1989; Walmsley et al. 1988). Maintenance therapy with a 2- to 3-hour intravenous infusion of foscarnet 90 mg/kg or one-third of the induction dosage (about 77 mg/kg) was then administered daily to patients with adequate renal function for 5 days each week. Almost all patients relapsed, usually within a month of starting maintenance (Walmsley et al. 1988). There tended to be an association between the duration of response and the maintenance dosage; the median time to retinitis recurrence in 2 patients receiving 70 or 75 mg/kg/day was 33 days, compared with 78 days in 5 others receiving 90 mg/kg/day (Fanning et al. 1990). One patient had no evidence of retinitis at death 62 days after beginning treatment, and another continued in remission after 168 days of maintenance therapy. Recurrences of retinitis responded to further foscarnet therapy, but the interval of remission gradually diminished (Walmsley et al. 1988). Interestingly, among 6 patients receiving foscarnet maintenance therapy, relapse was prevented dur-

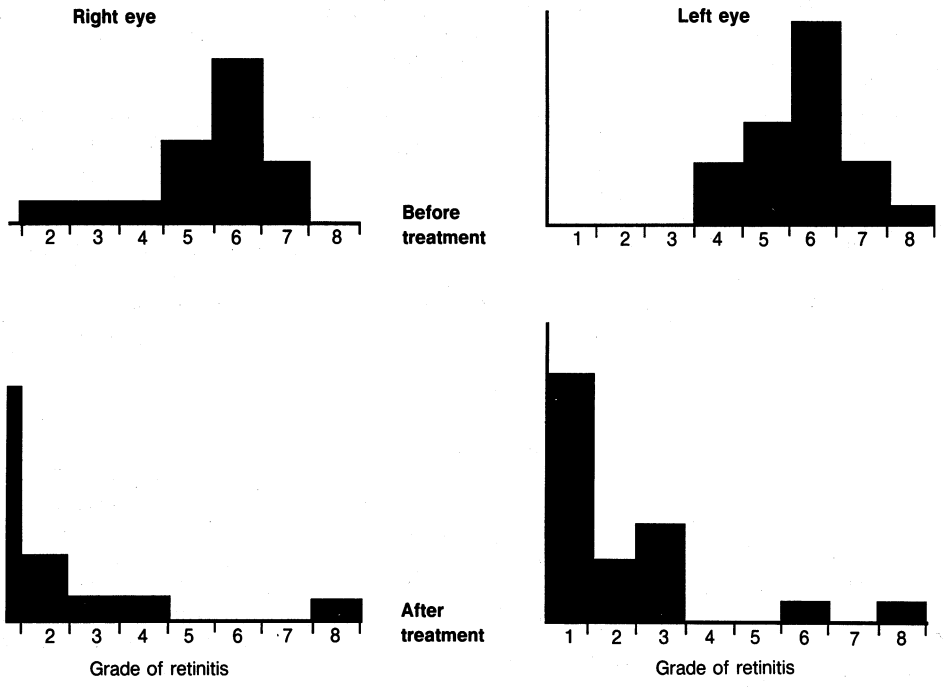

Fig. 4. Grade of cytomegalovirus retinitis in the affected eyes of 31 AIDS patients before and after a mean of 24 days' induction treatment with foscarnet 230 mg/kg/day (after LeHoang et al. 1989]. *Grade of retinitis:* **1** = Residual areas of retinal scarring with changes in retinal pigment epithelium, slight oedema may persist; **2** = < 10 small solitary foci of active retinitis; **3** = > 10 small solitary foci of active retinitis; **4** = < 2 disc diameters of retinitis with confluent active borders; **5** = 2-6 disc diameters of retinitis with confluent active borders; **6** = 6 disc diameters to 1 quadrant of retinitis with confluent active borders; **7** = 1-2 quadrants of retinitis with confluent active borders; **8** = 3-4 quadrants of retinitis with confluent active borders.

ing a 12-week follow-up period only in 3 patients who were also receiving zidovudine (LeHoang et al. 1989). Furthermore, during induction, a complete response was achieved in 9 of 11 patients receiving foscarnet with zidovudine, compared with 10 of 20 receiving foscarnet alone (LeHoang et al. 1989). The results of an ongoing study comparing foscarnet, with or without concomitant zidovudine, to zidovudine alone in 48 AIDS patients with cytomegalovirus retinitis (Polis et al. 1989) are eagerly awaited.

Other investigators used foscarnet 60 mg/kg as a 2-hour intravenous infusion every 8 hours for 2 weeks as induction and then once daily, usually for 5 of 7 days, as maintenance (table V). This intermittent induction regimen is now favoured over the continuous infusion because of better efficacy and tolerability (see section 5.1) [Katlama, personal communication; Mills, personal communication]. The dosage was reduced if creatinine clearance fell below 1.6 ml/min/kg during the induction phase or was less than 1.4 ml/min/kg during maintenance (Jacobson et al. 1989b). Retinitis progressed in only about 10% of patients (Jacobson et al. 1989b; see review by Mills et al. 1988) or 14% of affected eyes (Ussery et al. 1989) during induction, with the majority of the remainder achieving a partial response (Jacobson et al. 1989a,b). A complete response occurred in 42 of 43 patients given 60 mg/kg every 8 hours or 100 mg/kg twice daily for 1 month's induction (Dohin et al. 1990). The halt in disease progression appeared to be related

Table V. Some noncomparative studies of foscarnet in AIDS patients with cytomegalovirus retinitis

Reference	No. of evaluable patients	Dosage [duration]	Clinical response (no. of patients)			Virological response	
			Prog [mean time]	PR	CR	−	+
Dohin et al. (1990)	43	I: 60 mg/kg q8h *or* 100 mg/kg q12h [med 28d]	1[4w]		42	30/30B	
Fanning et al. (1990)	17	I: 20 mg/kg bolus then 230 mg/kg/d [mean 22d] then	1	8	8	8/12U	4/13U
	7	M: 70-75 mg/kg/d (n = 2) *or* 90 mg/kg/d (n = 5) for 5/7d	4 [62d]	1			
Jacobson et al. (1989a)	25	I: 60 mg/kg q8h [14d] then		24			
	16	M: 60 mg/kg/d [≤ 28w]	10 [6-20w]	6			
Jacobson et al. (1898b)	10	I: 60 mg/kg q8h [14d] then	1	7	2	18/18 U ± B	
	6	M: 60 mg/kg/d for 5/7d [3-37 (med 6)w]	6 [24.5d]			9/42 U ± B	
Katlama et al. (1989a)	26	I: 200 mg/kg/d [21-28d]			26	13/16B	3/16B
Katlama et al. (1989b)	21[a]	M: 60 mg/kg/d for 5/7d (n = 11)	10 [28d]	1			
		or 100 mg/kg/d for 6/7 d (n = 10) then	5 [41d]	5			
	19	130 mg/kg/d bolus then	14 [42d]	6			
	8	60 mg/kg bd, prn	7 [24d]	1			
Katlama et al. (1990)	20[a]	M: 100 mg/kg/d [8-95 (mean 23)w]	2 [2w], 6 [9.5w]	12			
LeHoang et al. (1989)	31	I: 20 mg/kg bolus then 230 mg/kg [24d] then	1	10	19	16/16B	
	6	M: 'one third of the daily induction dose' for 5/7d	3 [<5w]				
Michon et al. (1986, 1988)	15[b]	20 mg/kg bolus then 200 or 230 mg/kg/d [14-28d]		1[c]	11[c]	14/15B	
Mills et al. (1988)	44	180 mg/kg/d [18d]		39			
Ussery et al. (1989)	8[d]	I: 60 mg/kg q8h [14d] then M	1[f]	12[f]	1[f]	83% BC	
	12[e]	I: 60 mg/kg q8h [14d]	4 [13d][f]	16[f]	1[f]		
Walmsley et al. (1988)	14	I: 20 mg/kg bolus then 230 mg/kg/d [15d] then		7	7		
	4	M: 'one third of usual total daily dose' for 5/7d	4 [3-4w]				

a All patients had 'successfully completed PFA (foscarnet) induction therapy'.
b 15 patients with cytomegalovirus infection; 11 with retinitis received 13 courses of foscarnet.
c Results presented in terms of the number of courses.
d Previously untreated; details of maintenance regimen not stated.
e Previously treated with ganciclovir; no maintenance therapy administered.
f Results presented in terms of the number of affected eyes.

Abbreviations and symbols: Prog = retinitis progression; PR = partial response (no new lesions and/or no further progression of old lesions); CR = complete response (disappearance or decrease of active lesions); I = induction regimen; M = maintenance regimen; U = urine culture; B = blood culture; BC = buffy coat culture; d = day; w = week; q8h = every 8 hours; 5/7d = 5 days each week; prn = when necessary; − = negative culture; + = positive culture.

to viral elimination since, following the induction course, cytomegalovirus could not be isolated from 83% of buffy coat cultures in one study (Ussery et al. 1989) or from the blood or urine of 7 patients in another (Jacobson et al. 1989b).

Virus was eradicated from the urine (usually within 2 weeks) of 12 patients and from the blood (usually within 1 week) of all 21 recipients of a 21-day induction course with foscarnet 60 mg/kg every 8 hours (Manischewitz et al. 1990). Titres of HIV p24 antigen declined by over 50% in all 10 patients determined as being positive before induction therapy (Polis et al. 1990). Although there was no difference in virustatic response between those patients who began treatment immediately and those in whom it was delayed until a retinitis progression was noted, the latter approach was significantly less effective in delaying further progression (Manischewitz et al. 1990; Polis et al. 1990).

Disease progression in 4 patients during maintenance therapy occurred at the same time as cytomegalovirus reappeared in the blood (Jacobson et al. 1989b). Overall, 21% of cultures became positive and retinitis progressed in over 60% of patients after 2 to 32 weeks of intermittent maintenance therapy with foscarnet 60 mg/kg daily (Jacobson et al. 1989a,b).

The efficacy of higher maintenance doses of foscarnet in preventing progression or recurrence of retinitis was investigated by Katlama and associates (1989b). Relapse occurred in 10 of 11 patients after a mean of 28 days' treatment with foscarnet 60 mg/kg daily for 5 days a week, and after 41 days in only 5 of 10 recipients of 100 mg/kg daily for 6 days a week. 19 patients then went on to receive foscarnet 130 mg/kg as a single daily intravenous infusion, with 14 relapsing after a mean of 42 days. There was a recurrence after 24 days in all except one of 8 patients who subsequently received infusions of 60 mg/kg twice daily. This longer duration of remission achieved with higher doses given daily rather than on 5 days each week has been confirmed in other studies. Katlama's group reported that remission was prevented in 12 of 20 evaluable patients receiving maintenance treatment with foscarnet 100 mg/kg daily as a 2-hour infusion after a follow-up of 8 to 95 (mean 23) weeks (table V) [Katlama et al. 1990]. Of the remaining patients, relapses occurred after 2 weeks' maintenance in 2, and after 6 to 17 (mean 9.5) weeks in 6. Similarly, the median time to retinitis progression in 16 recipients of foscarnet 120 mg/kg daily maintenance therapy was over 17 weeks, significantly longer than the 90- to 95-day remission period obtained with 60 or 90 mg/kg/day in 29 others (Jacobson et al. 1990). The dose of 120 mg/kg/day was not associated with increased nephrotoxicity or anaemia compared with 90 mg/kg/day.

Thus, for maintenance therapy, daily 2-hour infusions of 100 or 120 mg/kg/day now appear to delay the progression of retinitis for significantly longer than 60 to 90 mg/kg given on 5 days per week, without an increase in renal or haematological toxicity. Intermittent (2 or 3 divided daily doses) rather than continuous intravenous infusion of 180 to 230 mg/kg/day is preferred for induction therapy.

4.3 Foscarnet Compared with Ganciclovir

Ganciclovir is used to manage cytomegalovirus retinitis in AIDS patients, and thus studies comparing the efficacy of foscarnet and ganciclovir are of particular interest.

Currently available data suggest that the 2 drugs are of similar efficacy to induction therapy (table VI), although a longer period of treatment may be necessary with foscarnet to achieve a response (Moyle et al. 1990a). It is difficult, however, to establish the relative relapse rates during maintenance therapy with each drug. After 3 months' follow-up, disease progression was documented in 4 of 12 foscarnet recipients compared with all of 12 other patients receiving ganciclovir in 1 study (LeHoang et al. 1988). In another trial, 4 of 6 ganciclovir-treated patients had stable disease during maintenance, in contrast to only 1 of 6 foscarnet recipients (Newell et al. 1989). However, of the other 5 patients administered foscarnet, 4 died and 1 ceased treatment, thus precluding a clinical assessment.

Table VI. Some comparative studies of foscarnet (F) and ganciclovir (G) in AIDS patients with cytomegalovirus retinitis

Reference	No. of evaluable patients	Treatment [duration]	Clinical response (no.)		Relative efficacy	Comments
			progression	response[a]		
LeHoang et al. (1988)	40	F I: [21d][b]		35	F = G	Reversible renal impairment occurred in 5 F recipients; bone marrow toxicity in 10 G recipients
	12	M: [3mo]	4	8		
	32	G I: [21d][b]		28		
	12	M: [3mo]				
Newell et al. (1989)	8	F I: 200 mg/kg/d [21d]	3	5	F = G	Serum creatinine increased in 2/8 F recipients during I, and in 5/6 during M leading to dosage interruption (n = 2), reduction (1) or cessation (1); neutropenia occurred in 3/6 G recipients during M leading to dosage interruption (1), reduction (1) or change to F (1)
			2	1[c]		
	6	M: 130 mg/kg/d for 5/7d [2-19 (mean 11)w]		6		
				4		
	6	G I: 5 mg/kg bid [21d]				
	6	M: 5 mg/kg/d for 5/7d [4-26 (mean 14)w]				

a Includes complete and partial responses, and improvement in visual acuity.

b Dosage details not stated.

c 4 patients died, treatment was discontinued in another.

Abbreviations: I = induction regimen; M = maintenance regimen; d = days; mo = months; w = weeks; 5/7d = 5 days each week; bid = twice daily.

From these limited comparative results and from data obtained with ganciclovir in noncomparative studies (see review by Faulds & Heel 1990), foscarnet and ganciclovir appear to be of comparable efficacy in inducing and maintaining a clinical response in patients with AIDS-related cytomegalovirus retinitis. In comparative studies, the dose-limiting side effect of foscarnet was reversible renal impairment, and that of ganciclovir was neutropenia (table VI). This difference in the tolerability profile of each drug may be an important consideration in some AIDS patients receiving other myelosuppressive medication such as zidovudine (see section 8), although this consideration may perhaps become less important with the increasing availability of haemopoietic growth factors such as granulocyte-macrophage colony-stimulating factor.

5. Adverse Effects

The significant morbidity of immunocompromised patients, compounded by extensive use of concomitant medications, makes it difficult to attribute with confidence a specific adverse effect solely to foscarnet. Nevertheless, trends suggest that reversible renal dysfunction, anaemia and disturbances in serum calcium and phosphate levels are associated with intravenous foscarnet administration.

5.1 Renal

Impaired renal function, usually reversible, is the most common dose-limiting adverse effect during continuous foscarnet therapy. This was manifested clinically by a 2- to 3-fold rise in serum creatinine levels in between 20 and 60% (mean 46%) of AIDS patients receiving foscarnet 130 to 230 mg/kg/day as a continuous infusion and occasionally by polyuria with associated thirst or, less frequently, oliguria (Cacoub et al. 1988; Gaub et al. 1987; Michon et al. 1986; Sjövall et al. 1989; Walmsley et al. 1988). Polydipsia and polyuria, which began after 2 weeks' induction therapy with foscarnet 60 mg/kg 8-hourly in 1 patient with ret-

initis, were caused by nephrogenic diabetes insipidus induced by the drug (Farese et al. 1990). The mean serum creatinine level of 39 AIDS patients receiving foscarnet 112 mg/kg/day for cytomegalovirus infections increased from 81 to 140 μmol/L; a rise of at least 25% was recorded during 37 of 56 courses (Deray et al. 1989). The degree of renal dysfunction was sufficient to necessitate discontinuation of foscarnet in over half the patients with elevated creatinine levels (Gaub et al. 1987; Walmsley et al. 1988), and sometimes resulted in loin pain (Sjövall et al. 1989). Haemodialysis was occasionally necessary when severe renal impairment developed during foscarnet treatment (Cacoub et al. 1988; Deray et al. 1987, 1989; Fanning et al. 1990).

Renal dysfunction appeared to be more moderate and less prevalent during treatment with foscarnet 60 mg/kg every 8 hours rather than as a continuous infusion. Serum creatinine levels were elevated by about 75% in only 2 of 10 recipients of this intermittent regimen (Jacobson et al. 1989b).

Similarly, renal insufficiency occurred during only 7 of 61 (11%) induction courses with foscarnet 60 mg/kg every 8 hours or 100 mg/kg every 12 hours (Dohin et al. 1990). Furthermore, Jacobson and colleagues recently reported that the degree of renal impairment was not increased during daily maintenance treatment with 120 mg/kg compared with 90 mg/kg (Jacobson et al. 1990).

Underlying disease and concomitant treatment with other drugs capable of causing kidney damage, such as aciclovir, pentamidine, cotrimoxazole and ketoconazole, may have contributed to the acute impairment of renal function in some AIDS patients (Gaub et al. 1987; Michon et al. 1986; Walmsley et al. 1988). However, elevated serum creatinine levels were observed in 15 patients who received foscarnet monotherapy and was therefore the likely cause of acute renal failure (Deray et al. 1989). Normal urinary sediment with low or absent proteinuria (Cacoub et al. 1988), and postmortem examination (Deray et al. 1989) revealed that renal dysfunction was caused by acute tubular necrosis or tubular interstitial nephritis (Nyberg et al. 1990). Furthermore, as well as tubular interstitial lesions, crystals were found in the lumens of the glomerular capillaries in 5 biopsy or postmortem kidney samples from patients who developed renal impairment during foscarnet therapy (Beaufils et al. 1990). The physicochemical properties of the crystals were suggestive of crystalline foscarnet.

Renal impairment in patients with previously adequate kidney function was usually reversible (Cacoub et al. 1988; Farthing et al. 1987; Walmsley et al. 1988), and elevated serum creatinine levels also normalised in 26 renal allograft recipients following foscarnet withdrawal (Ringdén et al. 1986).

Hydration with normal saline 2.5 L/day, starting on the night before initiation of foscarnet infusion and continuing throughout the treatment period, helps prevent renal dysfunction. Indeed, in 27 patients receiving 30 courses of foscarnet therapy, saline hydration minimised the drug-induced increase in serum creatinine compared with 39 nonhydrated patients receiving 56 courses (fig. 5) [Deray et al. 1989]. Similarly, an increase in serum creatinine of over 25% occurred during 10 of 78 (13%) courses of foscarnet in 38 hydrated patients, compared with 36 of 55 (66%) in a nonhydrated control group despite a longer duration of therapy with higher doses (Deray et al. 1990). A peak in serum creatinine greater than 200 μmol/L was recorded in 2 of the hydrated patients and in 29 of the nonhydrated patients, respectively. Adoption of an intermittent dosing schedule in 48 of the 78 courses of foscarnet therapy in the hydrated group may also have contributed to the less severe renal impairment in this group.

Development of renal dysfunction is therefore a common occurrence during foscarnet therapy, but can be minimised by adjusting the dosage according to serum creatinine levels (see section 7), maintaining adequate hydration, using intermittent (every 8 or 12 hours) rather than continuous infusions and, if possible, avoiding other potentially nephrotoxic drugs.

5.2 Haematological

Anaemia is the most frequent haematological effect of foscarnet. Between 20 and 50% of AIDS patients had a decrease in haemoglobin concentra-

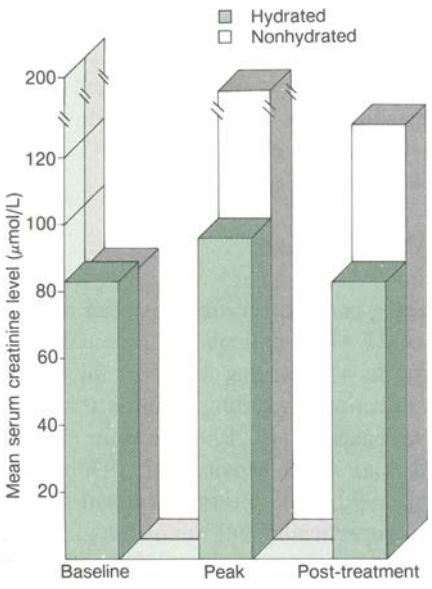

Fig. 5. Mean serum creatinine levels before, during and after 17 to 21 days' continuous infusion of foscarnet 112 mg/kg/day in 35 nonhydrated and in 27 saline-hydrated AIDS patients with cytomegalovirus retinitis (from Deray et al. 1989).

tions of ⩾ 10 g/L (Fanning et al. 1990; Farthing et al. 1987; Jacobson et al. 1989b), and more profound reductions of 20 to 30% have been documented occasionally (Gaub et al. 1987; Walmsley et al. 1988). The nadir in haemoglobin concentration was reached after a mean of 14 days' continuous administration of 230 mg/kg/day (Fanning et al. 1990). Gaub and associates (1987) reported that 6 of 15 AIDS patients developed anaemia during foscarnet therapy which required packed red cell transfusion. However, anaemia in these patients may have been compounded by the relatively large blood volume (0.5L) taken for sampling. Two of 7 patients with cytomegalovirus retinitis had a progressive decline in haemoglobin concentration to below 80 g/L during maintenance with 70 to 90 mg/kg 5 times weekly (Fanning et al. 1990). Haemoglobin concentration decreased after foscarnet administration in 9 of 26 renal transplant recipients, and levels were low before, during and after therapy in 8 bone marrow transplant hosts (Ringdén et al. 1986).

Other haematological adverse effects were infrequent. Thrombocytopenia occurred in 3 of 20 AIDS patients (Fanning et al. 1990) and in 6 of 26 renal graft recipients (Ringdén et al. 1986) who received foscarnet. This was contrary to the overall trend of increased platelet counts, and indeed there was a marked increase from 328 × 10^9/L to 942 × 10^9/L in 1 allograft patient (Ringdén et al. 1986). Although always remaining above 0.8 × 10^9/L, neutrophil counts decreased by less than 20% in 3 patients during intermittent daily treatment with foscarnet 60 mg/kg, and by 50 and 75% in another 2 patients. However, increases of between 20 and 300% were documented in 5 patients who had recently ceased zidovudine therapy (Jacobson et al. 1989b). Similarly, there was a reduction in leucocyte count in 3 renal transplant patients, but overall in bone marrow and renal graft recipients the number of circulating white cells increased (Ringdén et al. 1986). There have been other reports of leucopenia, some of which, however, could not exclusively be attributed to the administration of foscarnet because of concomitant zidovudine therapy (Fanning et al. 1990) or pre-existing myelosuppression (Michon et al. 1986). Seropositive bone marrow transplant recipients who received foscarnet as prophylaxis against cytomegalovirus infection during the pancytopenic phase after transplantation had the same transfusion requirements as untreated patients (Ringdén et al. 1989).

5.3 Metabolic

Serum calcium concentrations increased in over 66% of AIDS patients (Gaub et al. 1987; Jacobson et al. 1989b) and in 20 to 25% of allograft recipients (Ringdén et al. 1986) during foscarnet therapy. Increases were marginally greater than or towards the upper limit of the normal physiological range (2.1 to 2.6 mmol/L) [Jacobson et al. 1989b; Ringdén et al. 1986].

Once again, however, underlying disturbances and concomitant medication must be considered

since hypercalcaemia has been reported in patients with untreated AIDS-related cytomegalovirus infections (Zaloga et al. 1985), and decreases in serum calcium levels have also occurred during foscarnet therapy. Indeed, symptomatic severe hypocalcaemia occurred within 10 days of continued treatment with foscarnet and pentamidine in 4 AIDS patients, and returned to normal in 3 when one or other of the drugs was discontinued (Youle et al. 1988). Since serum calcium did not change in another 5 patients receiving pentamidine and placebo, foscarnet was probably responsible for the disturbance, although an interaction cannot be ruled out. It is worth noting that during foscarnet administration total serum calcium levels may appear normal, yet levels of ionised calcium may be decreased, especially after large doses (Jacobson, personal communication). This would still result in symptoms of hypocalcaemia, and may be a result of foscarnet's ability to chelate with ionised calcium *in vitro* and *in vivo* (unpublished data on file, Astra). However, no changes in serum ionised calcium levels were found in 10 AIDS patients receiving foscarnet 60, 90 or 120 mg/kg/day maintenance therapy, although both parathyroid hormone and calcitriol levels tended to increase (Nauss-Karol et al. 1990).

Hyperphosphataemia occurred in almost all AIDS patients during 2 weeks of foscarnet induction therapy (Gaub et al. 1987; Jacobson et al. 1989b), with markedly elevated phosphate levels above about 1.8 mmol/L in 4 of 10 patients in 1 study (Jacobson et al. 1989b). This may have resulted from foscarnet replacing phosphate in bone, although osteochondral foscarnet deposition has not been demonstrated clinically (Jacobson et al. 1989b; unpublished data on file, Astra). However, foscarnet has also been shown to be a specific competitive inhibitor of sodium and phosphate cotransport across rat and human brush border membranes of proximal renal tubules *in vitro* (Szczepanska-Konkel et al. 1986; Webster et al 1986; Yusufi et al. 1986).

Elevated serum calcium and phosphate levels appeared to be transient and normal physiological values were restored during foscarnet maintenance treatment (Jacobson et al. 1989b). Although no causative association was established, the tremor observed in 3 patients each from 2 groups of 10 and 13 AIDS patients during foscarnet treatment could feasibly have arisen from disturbances in serum calcium levels (Jacobson et al. 1989b; Walmsley et al. 1988).

5.4 Miscellaneous

Recently, penile ulceration has been reported in a total of 27 AIDS patients (with concurrent oral ulceration in 4) receiving foscarnet for cytomegalovirus infection, including retinitis (Connolly et al. 1990; Fégueux et al. 1990; Gilquin et al. 1990; Leonard et al. 1990; Moyle et al. 1990b; Van der Pijl et al. 1990). The ulcers resembled fixed drug eruptions superficially, but not histologically (Connolly et al. 1990; Fégueux et al. 1990; Van der Pijl et al. 1990), and may have been caused by retention of high concentrations of unchanged foscarnet in the subpreputial space, resulting in acute irritant contact dermatitis (Moyle et al. 1990b). Lesions resolved within a month of stopping foscarnet, and reappeared when the drug was reintroduced (Connolly et al. 1990; Fégueux et al. 1990; Gilquin et al. 1990; Moyle et al. 1990b). This local irritation appears to result from repeated exposure of the glans penis to unchanged foscarnet in the urine, the main route of excretion (see section 3.3) [Lernestedt & Chanas 1990]. The current adoption of maintaining adequate hydration to limit renal insufficiency will increase the frequency of urination and may therefore increase the likelihood of penile ulceration (Lernestedt & Chanas 1990). This adverse effect is indeed becoming a significant problem with foscarnet treatment (Gazzard, personal communication), but local personal hygiene may offer relief (Lernestedt & Chanas 1990).

A number of patients experienced phlebitis or thrombophlebitis during continuous peripheral intravenous infusion of foscarnet. Administration of undiluted foscarnet 2.4% (24 mg/ml) solution caused phlebitis in 2 patients, severe enough to warrant discontinuation in one (Farthing et al. 1987; Gaub et al. 1987), but inflammation also occurred

in up to half of the patients when the solution was diluted to 1.2% (12 mg/ml) with normal saline or 5% dextrose (Farthing et al. 1987; Sjövall et al. 1989; Walmsley et al. 1988). This problem can be avoided by infusing foscarnet through a central Hickman line, a route of administration used successfully in the domiciliary treatment of cytomegalovirus retinitis in 2 patients (see section 4.1) [Heley 1988; Wood et al. 1989].

Between 20 and 30% of patients experienced nausea and vomiting during foscarnet treatment (Jacobson et al. 1989b; Ussery et al 1989; Walmsley et al. 1988), and diarrhoea and abdominal pain have also been reported (Sjövall et al. 1989). Dehydration resulting from vomiting and diarrhoea should be prevented, since it could precipitate renal dysfunction (see section 5.1) [Cacoub et al. 1988].

Foscarnet has negligible effects on hepatic function, only occasionally causing slight elevations in serum transaminase levels (Michon et al. 1986; Ringdén et al. 1986). Other adverse effects reported during foscarnet treatment included headache (Sjövall et al. 1989), fatigue or malaise (Sjövall et al. 1989), hallucinations (Ringdén et al. 1986) and transient neurological disturbances (Ussery et al. 1989). It was unclear whether these effects were related to the underlying disease and concomitant medication, rather than foscarnet administration.

6. Drug Interactions

Reversible renal impairment has been reported during concurrent treatment with foscarnet and pentamidine, aciclovir, suramin or cotrimoxazole in some AIDS patients (Gaub et al. 1987; Michon et al. 1986; Walmsley et al. 1988). Although foscarnet appears to cause some degree of renal dysfunction (see section 5.1), the increased serum creatinine levels in these patients may have resulted from an additive effect since many of these agents are potentially nephrotoxic. Consequently, in patients being treated with foscarnet it would seem clinically prudent to avoid concomitant administration of drugs which may also impair renal function, if possible. Coadministration of a drug which inhibits renal tubular secretion may prolong the elimination of foscarnet, since it is entirely renally excreted (see section 3.3).

Table VII. Recommended intravenous dosage of foscarnet depending on renal function (manufacturer's recommendations)

Serum creatinine level (μmol/L)	Foscarnet dose (mg/kg/day)
⩽ 110	200
111-130	130-199
131-150	115-129
151-170	100-114
171-190	86-99
191-210	72-85
211-230	43-71
231-250	21-42
> 250	Not recommended

Severe hypocalcaemia and paraesthesiae developed in 4 patients, with Chvostek's and Trousseau's signs in 3, during 10 days' combined intravenous treatment with foscarnet and pentamidine (Youle et al. 1988). Calcium levels normalised when either of the drugs was withdrawn in 3 patients, and the fourth died with a serum calcium level of 1.42 mmol/L. Foscarnet can cause hypocalcaemia when given alone to patients with AIDS (see section 5.3), and pentamidine appeared to potentiate this effect.

7. Dosage and Administration

In the treatment of immunocompromised patients with cytomegalovirus retinitis, an intravenous bolus of foscarnet 20 to 30 mg/kg is administered over 30 minutes, followed by intravenous infusion initially of 180 to 200 mg/kg daily and adjusted relative to serum creatinine level (table VII). Intermittent infusion, for example 60 mg/kg every 8 hours or 100 mg/kg every 12 hours, is preferred over a continuous infusion on the grounds of a better response rate and reduced toxicity (Katlama, personal communication; Mills, personal communication). This induction phase of treatment is administered for between 1 and 4 (usually 2 or 3) weeks, and there is some evidence that a longer duration of therapy is associated with

more complete responses (Fanning et al. 1990; Katlama, personal communication).

Maintenance therapy, again depending on renal function, follows induction of remission. Daily 2-hour intravenous infusions of foscarnet 100 to 120 mg/kg are more effective in preventing retinitis progression than the original maintenance regimens of 60 to 90 mg/kg given for 5 days each week (Jacobson et al. 1990; Katlama et al. 1990). The higher doses do not appear to be associated with greater toxicity (Jacobson et al. 1990), although this requires further confirmation.

Serum creatinine and both total and ionised calcium levels should be monitored throughout therapy. To reduce the risk of reversible renal insufficiency, adequate hydration, for example with intravenous saline, should be given before and during foscarnet administration, and other potentially nephrotoxic drugs avoided. Foscarnet causes negligible, if any, myelosuppression and therefore may be administered to patients receiving zidovudine, although caution is recommended.

The incidence of penile irritation and ulceration, which is becoming increasingly common, may be minimised by thorough local personal hygiene. Phlebitis can occur during intravenous administration, but this can be minimised by diluting the stock solution of foscarnet (24 mg/ml) by 50% with normal saline or 5% dextrose, or by infusing the drug via a central Hickman line rather than peripherally.

8. Place of Foscarnet in the Management of Cytomegalovirus Retinitis

Cytomegalovirus retinitis is the most common cause of blindness in AIDS patients; it is difficult to treat and has few therapeutic options. Limited clinical data currently available suggest that foscarnet halts the progression of cytomegalovirus retinitis in over 80% of immunocompromised patients. In this respect it appears to be as effective as ganciclovir, and use of the 2 drugs results in similar relapse rates. Given the diversity of patients with cytomegalovirus retinitis, future research should be directed towards clarifying the clinical profiles of foscarnet and ganciclovir so that treatment can be optimised to suit the individual patient's needs. For example, foscarnet has a potential advantage over ganciclovir because it does not appear to potentiate the myelosuppression which often occurs in AIDs patients receiving zidovudine (azidothymidine). Nevertheless in clinical practice, many patients can receive effective doses of ganciclovir and zidovudine together (Pinching, personal communication), and monitoring serum drug concentrations (frequently necessary when potent antivirals are being administered) is currently easier with ganciclovir. A feature of both agents is that they can be administered at home if required. Overall, foscarnet is a welcome alternative to ganciclovir and the results of further comparative trials are awaited with interest.

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