ORIGINAL ARTICLE

Monitoring plasma levels of ganciclovir in AIDS patients receiving oral ganciclovir as maintenance therapy for CMV retinitis

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Objective To investigate whether low ganciclovir serum levels in patients on maintenance oral ganciclovir therapy are associated with recurrence of CMV retinitis.

Methods A prospective study of the plasma concentration of ganciclovir after initiation of maintenance oral ganciclovir therapy in 14 AIDS patients who had recovered from acute cytomegalovirus (CMV) retinitis.

Results Five of the 14 patients exhibited a mean time to recurrence of 37 days. The mean trough plasma concentration of ganciclovir in these patients after 1 month of oral ganciclovir therapy, was 0.40 ± 0.30 mg/L. Nine patients had a mean time of progression of 263 days. The mean trough plasma concentration of ganciclovir in the latter patients was 0.80 ± 0.60 mg/L.

Conclusions Patients exhibiting trough plasma levels of ganciclovir below 0.6 mg/L may be at higher risk of progression than patients who exhibited levels above 0.6 mg/L.

Keywords Cytomegalovirus, oral ganciclovir, ganciclovir plasma levels

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INTRODUCTION

Retinitis is the major manifestation of acute cytomegalovirus (CMV) disease in AIDS [1,2]. Although the prevalence of CMV infections in patients with advanced HIV disease has decreased with recent advances in antiretroviral therapy, CMV retinitis remains associated with substantial morbidity, mortality and impaired quality of life.

Intravenously administered ganciclovir has been proved to be beneficial in AIDS patients with CMV retinitis, both as induction therapy and maintenance treatment of CMV retinitis [3]. Oral ganciclovir at 3000 mg/day has also been shown to be effective in preventing the recurrence of CMV retinitis in AIDS [4,5], and one study has suggested that oral ganciclovir may be effective as primary prophylaxis of acute CMV disease in patients with AIDS [6]. However, CMV retinitis usually recurs within 86 ± 5 days despite maintenance therapy [5].

The response to treatment with ganciclovir is influenced by pharmacokinetic variability between subjects. Thus, during induction treatment, low plasma concentrations of ganciclovir have been shown to be associated with failure of therapy [7].

Oral ganciclovir has a low bioavailability ranging between 3 and 9%. With intakes of 1000 mg every 8 h, the mean trough levels of ganciclovir in serum have been reported to be between 0.3 and 0.5 mg/L [8,9]. The present study was designed to investigate whether trough plasma levels of ganciclovir may be of value in monitoring AIDS patients on maintenance therapy with this drug.

PATIENTS AND METHODS

Study population

Plasma levels of ganciclovir were measured prospectively in 14 randomly selected patients with AIDS from January 1995 to October 1996. All patients had had acute CMV retinitis without evidence of other end-organ disease and had been treated with intravenous ganciclovir, 5 mg/kg twice daily for 21 days, before being started on maintenance oral ganciclovir at 1000 mg every 8 h. Oral ganciclovir was supplied in 250 mg hard gelatin capsules. All patients had normal renal function. The patients were evaluated weekly by fundus examination during induction therapy and then twice a month by the same ophthalmologist.

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Failure of treatment was defined as the progression of the limits of the initial lesion or the appearance of a new lesion in a previously uninvolved area. All the patients were maintained on antiretroviral therapy during the study. During oral ganciclovir maintenance therapy, a protease inhibitor was added to current antiretroviral treatment for five out of the 14 patients.

Sample collection and analytical method

Blood samples were drawn at steady-state just before intake of the drug (trough level) once during the first month after initiation of maintenance treatment. Considering the short elimination half-life of oral ganciclovir of 4.4 h [10], this steady state was achieved in all patients after 1 day of therapy. In six patients, several samples were available after the first month of therapy and did not exhibit a significant variability. All samples were processed using an original method combining ion-pair high performance liquid chromatography (HPLC) and spectrophotometric UV detection at 254 nm [11]. Five hundred microlitres of plasma were deproteinized using 6% perchloric acid, and aciclovir (2.5 μg) was added as an internal standard. Samples were mixed, centrifuged, and the supernatant neutralized with 22% sodium acetate. Aliquots of 50 μL were then injected onto a 15-cm × 4.6 mm (internal diameter) Lichrospher 100 C-18 column (Merck, Darmstadt, Germany). The column was eluted at a constant flow rate of 1 mL/min with 0.005 M sodium 1-heptane sulphonate and 0.02 M potassium dihydrogen phosphate adjusted to pH 2.6 with phosphoric acid-acetonitrile (98 : 1, v/v). The threshold of sensitivity of the assay was 0.1 mg/L ganciclovir.

Statistical analysis

Time to recurrence of retinitis was measured from the date of initiation of maintenance therapy. We first compared mean trough levels of patients with a short interval before recurrence (less than 90 days) and with those with an interval to recurrence over 90 days. The period of 90 days was selected because it corresponds to the mean time to progression with oral maintenance ganciclovir as reported previously by the European and Australian cooperative study group [5]. Statistical analysis was carried out using Student's *t*-test.

We then assessed the time to progression in relation to trough levels of ganciclovir by separating the patients on the basis of trough plasma concentrations of ganciclovir below or over 0.6 mg/L, using Kaplan–Meier plots and log-rank tests. This cut-off was chosen since residual plasma concentrations above 0.6 mg/L have been found to correlate with successful treatment of acute CMV infection with intravenously administered ganciclovir [7,12,13]. If a patient did not progress within the period of the study, time to progression was taken as the date of the last ophtalmologic examination before study termination.

RESULTS

The patients were 13 males and one female aged between 30 and 51 (mean age 39 ± 6 years). The mean CD4 cell count at diagnosis of CMV retinitis and at the end of follow-up on ganciclovir oral therapy were $14 \pm 10 \times 10^6$/L (ranging between 1 and 60) and 29 ± 42 (1–158), respectively. The mean plasma HIV-RNA levels at diagnosis of CMV retinitis and at the end of follow-up on ganciclovir oral therapy were 5.2 ± 0.4 Log/mL (ranging between 4.6 and 5.6) and 3.5 ± 0.92 (2.7–5.15), respectively.

The mean trough plasma concentrations of ganciclovir were 0.63 ± 0.54 mg/L, ranging between 0.15 and 1.90 mg/L (Figure 1). The mean time of progression was 172 ± 124 days with a median of 115 days, ranging between 23 and 441 days.

In five of the 14 patients the time to recurrence was less than 90 days. The mean time to progression was 37 ± 9 days and the mean trough plasma concentration of ganciclovir in these patients was 0.40 ± 0.30 mg/L. Two of these five patients were receiving combined antiretroviral therapy including a protease inhibitor. In the other nine patients their time period to recurrence was longer (over 90 days). Their mean time to progression was 263 ± 102 days (ranging between 110 and 441 days) and the mean trough plasma concentration of ganciclovir was 0.80 ± 0.60 mg/L. Three of these nine patients were receiving a protease inhibitor. Thus, low trough plasma concentrations were associated with earlier recurrence of retinitis, although the difference did not reach statistical significance.

Nine patients had plasma trough levels of ganciclovir below 0.6 mg/L and five had levels above 0.6 mg/L. The risk of progression was higher in the group of patients with low residual concentrations of the drug, although, as above, no significant statistical difference was reached (Figure 2).

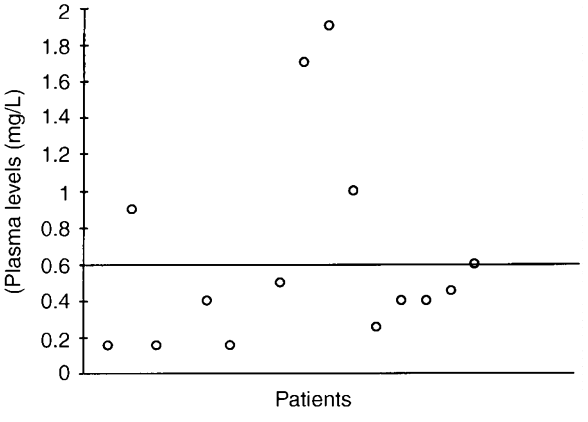

Figure 1 Distribution of trough ganciclovir plasma levels at steady state in 14 patients treated with oral ganciclovir 1000 mg three times daily.

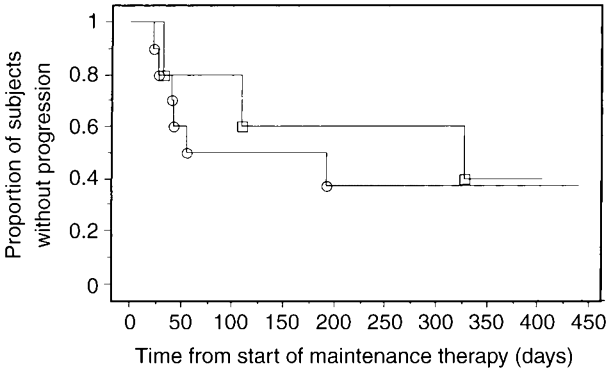

Figure 2 Proportion of patients remaining free of progression on maintenance therapy with oral ganciclovir as determined by fundoscopy assessments (Kaplan–Meier estimates). (○) Patients exhibiting trough plasma levels of ganciclovir <0.6 mg/L ($n=9$); (□) patients exhibiting trough plasma levels of ganciclovir $\geqslant 0.6$ mg/L ($n=5$); $P=0.58$ using a log-rank comparison test.

DISCUSSION

Few pharmacokinetic studies are available for oral ganciclovir. Low bioavailability of oral ganciclovir is a limitation on treatment of CMV infection [8–10]. Differences in ganciclovir pharmacokinetics have been observed between different populations of patients [14]. Ganciclovir is metabolized intracellularly into an active triphosphated form by kinases and the intracellular levels of the active ganciclovir triphosphate are the real determinant of drug efficacy. Nevertheless, serum levels of the prodrug may serve as a surrogate marker for intracellular levels of ganciclovir [7,12].

Two previous studies have reported mean trough plasma levels of 0.54 ± 0.32 and 0.23 ± 0.07 mg/L, and mean peak plasma levels of 1.11 ± 0.56 mg/L and 1.18 ± 0.36 mg/L after an oral regimen of 1000 mg every 8 h in HIV-infected patients [8,9]. The mean plasma ganciclovir concentrations were thus within the range known to inhibit 50% of most clinical CMV isolates [15–18]. In the present study, we observed mean trough levels of 0.63 ± 0.54 mg/L in 14 patients, with low intersubject variability. There was no statistically significant relationship between trough levels of ganciclovir and time to progression of CMV retinitis, which may be dependent on the small number of patients in the study since there was a clear trend towards more rapid progression in patients exhibiting lower trough levels of the drug. In addition, we had previously shown that plasma concentrations of ganciclovir below 0.6 mg/L were associated with failure of therapy during induction treatment of CMV retinitis with intravenously administered ganciclovir [7]. A plasma ganciclovir concentration of 1.0 mg/L is associated with efficacy of oral ganciclovir for prophylaxis against CMV after renal transplantation [19]. In the present study, we have not measured resistance to ganciclovir that could override the significance of blood levels of ganciclovir. However, viral resistance has been observed with a frequency of 6.5%, in patients having received a prolonged treatment with oral ganciclovir [20].

We suggest that studies designed for predicting the outcome of ganciclovir therapy in CMV retinitis should use both virological markers such as plasma levels of viral DNA and pharmacokinetic parameters, in order to optimize the care of patients.

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