The bioavailability and disposition of 1-(β-D-arabinofuranosyl)-5-(1-propynyl)uracil (882C87), a potent, new anti-varicella zoster virus agent

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1 The bioavailability and disposition of 882C87, an anti-varicella zoster virus (VZV) agent, have been investigated in healthy young and elderly volunteers.

2 The mean bioavailability of a 200 mg tablet was 21.1% in the young (range 13.3–33.0%, n = 10) and 24.6% in the elderly (range 14.4–38.4%, n = 8), which is sufficient to achieve plasma concentrations well above the IC50 for anti-VZV activity.

3 Plasma concentrations of 882C87 after 50 mg i.v. were higher in the elderly than in the young, associated with a significantly longer half-life (13.7 vs 11.8 h) and decreased renal clearance (0.11 vs 0.14 ml min⁻¹ kg⁻¹) and total clearance (0.15 vs 0.17 ml min⁻¹ kg⁻¹).

4 After intravenous administration, the main route of elimination of 882C87 was renal with 81.6% recovered unchanged in urine in the young and 71.2% in the elderly. The pyrimidine base, 5-propynyluracil (5-PU) was unquantifiable in plasma and only present in trace amounts in urine.

5 After oral administration to four healthy volunteers, only 17% of a dose of [¹⁴C]-882C87 was recovered unchanged in urine and 58% as 5-PU, with total recovery in urine accounting for 86% of the dose. There was a lag of 4–12 h before the appearance of 5-PU in plasma, peak concentrations were one-third to a half those of 882C87. The data suggest that 5-PU is formed from unabsorbed 882C87 in the gut lumen and then absorbed and excreted in urine.

6 882C87 is a potential once daily treatment for shingles.

Keywords bioavailability pharmacokinetics varicella zoster virus 882C87

Introduction

882C87, (1-(β-D-arabinofuranosyl)-5-(1-propynyl)uracil, molecular weight 282.25), is a nucleoside analogue with potent and specific anti-varicella zoster virus (VZV) activity. It has an IC50 of 1–2 μM against a range of VZV clinical isolates and laboratory strains, and is approximately 7 fold more potent than acyclovir [1]. Shingles, caused by reactivation of latent VZV infection in dorsal root ganglia, is increasingly common with advancing age [2]. Post-herpetic neuralgia (PHN), which occurs in more than 50% of older adults after an attack of shingles [3] is the most common and difficult to treat long-term consequence of shingles and there is undoubtedly a need for more effective treatments of acute attacks of shingles to try and reduce the incidence of PHN as well as to enhance recovery from the acute rash.

Peak plasma concentrations of acyclovir after 800 mg are only about 7.5 μM [4], somewhat less than its

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IC₅₀ for VZV; its poor bioavailability, together with a short half-life, necessitate five times a day dosing in the treatment of shingles [4–6]. Even famciclovir, which has recently been approved for the treatment of shingles requires three times a day dosing [7]. In contrast, studies of single oral doses of 50–1600 mg 882C87 in young adults and 50–100 mg in healthy elderly volunteers have shown that peak concentrations of the drug are substantially above the IC₅₀ after all doses and, at doses above 100 mg in the young and 50 mg in the elderly, concentrations remain above the in vitro IC₅₀ for more than 24 h after dosing [8, 9]. After oral doses of 882C87 up to 100 mg plasma concentrations are higher in the elderly than the young, associated with an increase in half-life from 12 h to 15 h in the elderly and a decrease in renal clearance related to lower creatinine clearance in the elderly [9]. The pyrimidine base 5-(1-propynyl)uracil (5-PU, Wellcome code number 248U88), which has no antiviral activity, is the main metabolite of 882C87 in rat and dog but is not detected in plasma in man for at least 5 h after single doses of 882C87 suggesting that it may be formed from unabsorbed 882C87 within the gastrointestinal tract, possibly by bacterial action in the large intestine [8–10].

This paper describes two studies undertaken to characterise further the pharmacokinetics and oral bioavailability of 882C87 and to investigate the site, extent and route of its metabolism in young adults and the elderly.

Methods

Design of studies

Study 1: Absolute bioavailability of 882C87 Initially a test dose of 25 mg 882C87 was given as a 1 h i.v. infusion to two healthy young adult volunteers and the plasma concentrations were compared with those previously obtained after oral doses. Subsequently, 10 healthy adult male volunteers (age 21–39 years, weight 55.6–94.7 kg, estimated creatinine clearance, using the Cockcroft & Gault equation [11] 54–112 ml min⁻¹) and eight healthy elderly volunteers (two men, six women, age 66–80 years, weight 48.0–79.2 kg, estimated creatinine clearance 44–88 ml min⁻¹) received a 200 mg oral dose and a 1 h i.v. infusion of 50 mg 882C87 in a randomised, crossover study with at least a week between occasions. The i.v. dose of 50 mg was chosen to give similar concentrations to those after the 200 mg oral dose. Subjects abstained from alcohol for 24 h before and after dosing but caffeine containing drinks were not restricted. All doses were given after an overnight fast. After the oral dose, blood samples were taken pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 15, 18, 24, 32, 48, 72 and 96 h post dose and urine collected for 96 h, additional samples were taken at 15 and 45 min after the start of the intravenous infusion. Pulse and blood pressure were measured pre-dose, every 15 min during the i.v. infusion and 1, 2, 4, 8, 12 and 24 h post dose and the ECG (lead II) was monitored for 4 h after the start of the infusion. Subjects were asked if they felt unwell or different from usual in any way at the end of the infusion and 4, 8, 12 and 24 h post-dose. Full blood counts and biochemical profiles were determined pre- and 48 h post-dose.

Study 2: Disposition of radiolabelled 882C87 Four healthy male volunteers (age 30–43 years, weight 77.6–105.5 kg) received a 200 mg (50 μCi) capsule of 14C-labelled 882C87. Labelling was at the 2 position on the pyrimidine ring and radiochemical purity was > 98%. The estimated total body exposure was 72 μSv, within the WHO limits for a category I study. Subjects abstained from alcohol containing drinks for 36 h before and 24 h after dosing and caffeine containing drinks were not permitted on the study day. Dosing was after an overnight fast. Blood samples were taken pre-dose and at 1, 2, 4, 6, 8, 10, 12, 24, 32, 48, 96 and 168 h afterwards and all urine and faeces collected for 168 h after dosing. Pulse and blood pressure were measured at intervals and adverse experiences recorded for the duration of sampling. Full blood counts and biochemical profiles were determined pre-dose and on the eighth day after dosing.

Both studies were approved by the Wellcome independent Protocol Review Committee and the Camberwell Health Authority Ethics Review Committee and all volunteers gave written informed consent. Young adult volunteers were recruited from the Wellcome Employee Healthy Volunteer Panel and elderly volunteers from the Wellcome Healthy Elderly Volunteer Panel and the Clinical Age Research Unit Elderly Volunteer Panel at King’s College Hospital. All volunteers were required to be in good general health, taking no regular medication and with no relevant past medical history or abnormal findings on physical examination, ECG, full blood count, biochemical profile or urinalysis.

Sample handling

In study 2, a 1 ml aliquot of each blood sample was added to 4 ml water to form a haemolsate which was then frozen. All blood samples in study 1 and the remaining blood from each sample in study 2 were centrifuged for 10 min at 3,000 rev min⁻¹, within 30 min of collection and the plasma separated and frozen at −20°C for subsequent assay. All urine collections were tested for blood and protein, the volume was recorded and an aliquot taken and frozen for subsequent assay. The date, time and weight of each faecal collection was recorded. The whole collection was then homogenised in water to provide samples for analysis.

Plasma drug assay

Plasma and urine samples were stored at −20°C until assay by h.p.l.c., with u.v. detection at 290 nm, for both 882C87 and 5-PU [12]. Plasma samples were pretreated using an Automated Sequential Trace En-
enrichment of Dialysates (ASTED) procedure to remove macromolecules by dialysis and to concentrate and clean up the sample. The plasma sample was injected into the donor channel of the dialyser and held static while 950 μl of 2 mmol 1⁻¹ monochloroacetic acid was transported through the recipient channel to the trace enrichment cartridge. The volume of recipient through the dialyser was divided into 1.46 pulses of 650 μl and after each pulse the recipient solution was held static for 2 min 6 s. The enrichment cartridge was then eluted for 8 min with the h.p.l.c. mobile phase to bring the analytes onto a 150 × 4.6 mm column packed with 5 μm particle diameter Spherisorb ODS2. The mobile phase of the h.p.l.c. consisted of 4% v/v acetonitrile in 0.004 M aqueous ammonium acetate adjusted to pH 5 with acetic acid and the column was eluted for 9 min. Calibration standards of a suitable range of concentrations of 882C87 and 5-PU were placed at the beginning and end of each sample run. Inter- and intra-assay coefficients of variation were less than 3% in the range 1–25 μM and less than 5% at concentrations of 0.2 and 0.4 μM for both components. The assay had a lower limit of quantification of 0.2 μM for 882C87 and 0.4 μM for 5-PU.

Urine drug assay

Urine assays were performed using a modification of the ASTED-h.p.l.c. procedure with u.v. detection at 290 nm [13]. The time that the ASTED prelude cartridge was in-line with the h.p.l.c. mobile phase was reduced, which effectively performed ‘heart-cutting’ to remove unwanted late eluting peaks and reduce the chromatographic analysis time. The mobile phase consisted of tetrahydrofuran:dimethylammonium hydrogen orthophosphate (100 mmol l⁻¹, pH 7.0):water in the ratio 1.3:0.01:98.69 v/v/v at a flow rate of 1.4 ml min⁻¹. Calibration standards were run at the beginning and end of each sample run and the mean inter- and intra-assay coefficients of variation were 1.6–3.6% across the range of concentrations assayed. The lower limit of quantification was 2.5 μM for 882C87 and 5-PU.

Assay of radioactivity

Plasma and urine total radioactivity was determined by liquid scintillation counting of duplicate 500 μl aliquots. For haemolysates and faecal homogenates, 3 × 500 μl aliquots were combusted to provide samples for liquid scintillation counting. The lower limit of detection for radioactivity was twice background activity.

Metabolite profiling

The metabolite profile of [¹⁴C]-882C87 was determined in urine samples containing more than 10% of the administered radioactivity using reverse phase h.p.l.c. with simultaneous u.v./radiochemical detection. A 250 × 4.6 mm Lichrosorb RP8 10 μ column was used and elution performed over a 10 min period with 2% tetrahydrofuran in 2 mM ammonium acetate. Column recovery was > 90% of injected radioactivity. The same urine samples were analysed by t.l.c. (Silica Gel 60 F-254 plates with ethylacetate:isopropanol:water, 45:5:2 as mobile phase) as a check that all drug related components were detected by h.p.l.c. To confirm the identity of the h.p.l.c. peaks a urine sample was spiked with authentic [¹⁴C]-882C87 and 5-PU and subjected to the same h.p.l.c. method.

Pharmacokinetic analysis

Model-independent plasma pharmacokinetic parameters for 882C87 and plasma radioactivity were determined from the data using SIPHAR, a PC-based pharmacokinetic analysis package [14]. Values of t_max and C_max were obtained directly from the concentration-time profiles and the terminal rate constant λ was obtained by peeling the logarithm of the concentration-time profile from 12 h to the last measurable concentration. AUC was calculated using the linear trapezoidal rule up to the last measured concentration, C_t, and extrapolated to infinity from C_t/λ. The terminal half-life (t½) was calculated as 0.693/λ, total clearance as (F × Dose)/AUC and volume of distribution (V_d/F) as (CL/F)/λ. Renal clearance was calculated as urinary recovery/AUC and mean residence time and steady state volume of distribution after i.v. dosing (Vss) were calculated using statistical moments [15].

Model-independent parameters for 5-PU were determined using similar methods to those for 882C87 except that CL/F and V_d/F were not determined. In all cases the number of points (at least 3) on the logarithm of the plasma concentration-time profile used to obtain the terminal rate constant λ was decided by inspection. In addition a minimum estimate of the lag time (t lag), the time of the last undetectable concentration after dosing was obtained directly from the plasma concentrations.

The concentration of radioactivity in red blood cells at each time-point was calculated from

\[ C_t = \frac{C_b - C (1 - H)}{H} \]

where C_t is the concentration in red blood cells, C_b is the blood concentration, C the plasma concentration and H the haematocrit (determined as the mean of the values on day 1 and 8 for each subject).

Statistical analysis

In study 1, the effect of age on pharmacokinetic parameters of 882C87 and 5-PU was investigated by analysis of variance. AUC, C_max, t½, V_sst, V/F, CL, CL/F, CL_R and MRT, but not urinary recoveries, were log transformed prior to analysis and the mean and 95% confidence interval (CI) determined for the ratio of each parameter in the elderly compared with the young. For t_max and t lag the non-parametric 95% CI was calculated for the difference in median values (elderly–young) for each parameter.
Results

All subjects completed the two studies according to the protocol. There were no clinically significant changes in pulse, blood pressure, full blood counts, plasma biochemistry or urinalysis in either study. One young subject was a migraineur and suffered an attack 2 days after dosing. There were eight other reports of mild headaches and one of mild abdominal pain the day after dosing. None of these was considered likely to be attributable to 882C87 administration.

Study I

After an i.v. dose of 25 mg 882C87 in two young volunteers, $C_{\text{max}}$ was 8.0 and 9.6 µM and AUC was 128.2 and 134.4 µM h. After 50 mg i.v., plasma concentrations of 882C87 were slightly higher in the elderly than in the young (Figure 1, Table 1), but the differences in $C_{\text{max}}$ and AUC were not statistically significant.

![Figure 1](image.png)

**Figure 1** Mean plasma concentrations of 882C87 (■ 200 mg oral in young, □ 200 mg oral in elderly, ● 50 mg i.v. in young, ○ 50 mg i.v. in elderly) and 5-PU (▲ 200 mg oral in young, △ 200 mg oral in elderly) in young adult and elderly volunteers after single 882C87 doses of 200 mg orally and 50 mg i.v.

Table 1  Geometric mean (range) pharmacokinetic parameters of 882C87 in young ($n = 10$) and elderly ($n = 8$) volunteers after a 50 mg 1 h i.v. infusion and a 200 mg oral dose

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Young</th>
<th>50 mg i.v.</th>
<th>95% CI (E/Y)</th>
<th>Young</th>
<th>200 mg oral</th>
<th>95% CI (E/Y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$F$ (%)*</td>
<td>18.4</td>
<td>(12.6-21.9)</td>
<td></td>
<td>21.1</td>
<td>(13.3-33.0)</td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (µM)</td>
<td>19.3</td>
<td>(15.9-26.8)</td>
<td>0.82-1.33</td>
<td>10.2</td>
<td>(6.4-17.7)</td>
<td></td>
</tr>
<tr>
<td>AUC (µM h)</td>
<td>251.1</td>
<td>(167.0-304.3)</td>
<td>0.98-1.57</td>
<td>199.1</td>
<td>(128.2-338.9)</td>
<td>288.6</td>
</tr>
<tr>
<td>$t_{\frac{1}{2}}$ (h)</td>
<td>11.8</td>
<td>(10.5-13.5)</td>
<td>1.09-1.25</td>
<td>12.2</td>
<td>(10.7-14.4)</td>
<td>14.1</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (h)**</td>
<td>4.0</td>
<td>(4.0-6.0)</td>
<td></td>
<td>4.5</td>
<td>(3.0-8.0)</td>
<td></td>
</tr>
<tr>
<td>CL (ml min⁻¹ kg⁻¹)</td>
<td>0.17</td>
<td>(0.14-0.21)</td>
<td>0.74-0.98</td>
<td>0.15</td>
<td>(0.11-0.19)</td>
<td></td>
</tr>
<tr>
<td>CL/F (ml min⁻¹ kg⁻¹)</td>
<td>0.14</td>
<td>(0.10-0.19)</td>
<td></td>
<td>0.15</td>
<td>(0.11-0.19)</td>
<td></td>
</tr>
<tr>
<td>CLR (ml min⁻¹ kg⁻¹)</td>
<td>0.11</td>
<td>(0.08-0.15)</td>
<td>0.65-0.91</td>
<td>0.14</td>
<td>(0.09-0.14)</td>
<td></td>
</tr>
<tr>
<td>$V_{ss}$ (l kg⁻¹)</td>
<td>0.17</td>
<td>(0.14-0.22)</td>
<td>0.91-1.16</td>
<td>0.16</td>
<td>(0.14-0.21)</td>
<td></td>
</tr>
<tr>
<td>$V_f/F$ (l kg⁻¹)</td>
<td>0.88</td>
<td>(0.67-1.28)</td>
<td></td>
<td>0.76</td>
<td>(0.53-0.99)</td>
<td></td>
</tr>
<tr>
<td>MRT (h)</td>
<td>16.1</td>
<td>(14.3-18.2)</td>
<td>1.12-1.29</td>
<td>18.8</td>
<td>(17.7-21.5)</td>
<td>22.3</td>
</tr>
<tr>
<td>Urinary recovery (%)*</td>
<td>81.6</td>
<td>(70.4-91.7)</td>
<td>-20.3-0.6</td>
<td>17.1</td>
<td>(10.8-30.8)</td>
<td>17.3</td>
</tr>
</tbody>
</table>

*Arithmetic mean and 95% CI for difference.
**Median and 95% CI for median difference.
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Table 2  Geometric mean (range) pharmacokinetic parameters of 5-PU in young (n = 10) and elderly (n = 8) volunteers after 200 mg oral dose of 882C87

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Young</th>
<th>Elderly</th>
<th>95% CI (E/Y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (μM)</td>
<td>2.8 (1.2–5.5)</td>
<td>3.7 (2.5–4.7)</td>
<td>0.88–2.09</td>
</tr>
<tr>
<td>AUC (μM h)</td>
<td>76.7 (34.7–144.6)</td>
<td>140.1 (106.0–193.5)</td>
<td>1.11–3.00</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>10.6 (7.3–16.2)</td>
<td>12.4 (7.5–14.9)</td>
<td>0.86–1.58</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (h)**</td>
<td>22.4 (12.0–31.9)</td>
<td>31.6 (24.0–53.0)</td>
<td>0.14</td>
</tr>
<tr>
<td>$t_{\text{lag}}$ (h)**</td>
<td>6.8 (4.0–12.0)</td>
<td>8.8 (5.0–12.0)</td>
<td>-1.6</td>
</tr>
<tr>
<td>$CL_d$ (ml min$^{-1}$ kg$^{-1}$)</td>
<td>0.71 (0.46–1.14)</td>
<td>0.52 (0.38–0.68)</td>
<td>0.56–0.94</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>29.6 (23.0–43.0)</td>
<td>37.2 (25.7–53.0)</td>
<td>0.98–1.62</td>
</tr>
<tr>
<td>Urinary recovery (%)*</td>
<td>34.4 (14.3–59.3)</td>
<td>38.9 (21.2–53.5)</td>
<td>-9.2, 17.9</td>
</tr>
</tbody>
</table>

*Arithmetic mean and 95% CI for difference.

**Median and 95% CI for median difference.

Table 3  Arithmetic mean ± s.d. pharmacokinetic parameters of 882C87, 5-PU and plasma radioactivity after a 200 mg oral dose of $[^{14}C]882C87$ (n = 4)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>882C87</th>
<th>5-PU</th>
<th>$^{14}$C</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (μM)</td>
<td>7.7 ± 2.2</td>
<td>3.4 ± 0.9</td>
<td>8.1 ± 1.9</td>
</tr>
<tr>
<td>AUC (μM h)</td>
<td>175.9 ± 53.8</td>
<td>113.3 ± 38.6</td>
<td>322.3 ± 82.0</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>12.3 ± 0.9</td>
<td>13.6 ± 2.3</td>
<td>11.0 ± 2.3</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>6.5 ± 1.9</td>
<td>30.0 ± 4.0</td>
<td>7.0 ± 3.8</td>
</tr>
<tr>
<td>$CL/F$ (ml min$^{-1}$ kg$^{-1}$)</td>
<td>0.79 ± 0.24</td>
<td>0.78 ± 0.07</td>
<td></td>
</tr>
<tr>
<td>$CL_d$ (ml min$^{-1}$ kg$^{-1}$)</td>
<td>0.13 ± 0.01</td>
<td>0.83 ± 0.20</td>
<td></td>
</tr>
<tr>
<td>$V/F$ (l kg$^{-1}$)</td>
<td>1.98 ± 1.3</td>
<td>39.2 ± 6.6</td>
<td></td>
</tr>
</tbody>
</table>

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significant. However, $t_{1/2}$ was 2 h longer in the elderly than the young associated with a significant decrease in total systemic clearance; there were no differences in volume of distribution. Renal clearance which accounted for between 70 and 80% of total clearance was significantly lower in the elderly. Eighty-two percent of the dose was recovered unchanged in urine in the young and 71% in the elderly. The absolute bioavailability of a 200 mg oral dose of 882C87 tended to be higher in the elderly than in the young with mean values of 24.6 and 21.1% respectively. After oral dosing, values of $C_{\text{max}}$ and AUC were significantly higher in the elderly than in the young. Pharmacokinetic parameters were similar to those after i.v. dosing (Table 1) except that urinary recovery of unchanged drug was only 17% in both groups.

After i.v. dosing with 882C87, 5-PU was undetectable in plasma at all timepoints and urinary recovery only accounted for 0–3.7% of the dose in the young and 0–64% of the dose in the elderly. By contrast, after oral dosing, 34.4% of the dose was recovered as urinary 5-PU in the young and 38.9% in the elderly (Table 2). There was a lag time ($t_{\text{lag}}$) of at least 4 h, and up to 12 h, after oral administration of 882C87 before 5-PU was detected in plasma after which concentrations rose to peak at 12–54 h, tending to be later in the elderly. The AUC for 5-PU was approximately one-third that of 882C87 and was significantly higher in the elderly than in the young associated with a significant decrease in $CL_R$ (Table 2).

![Figure 2](image-url)  Mean plasma concentrations of 882C87 (■), 5-PU (▲), summed 882C87 and 5-PU (○) and radioactivity (●) after a single, 200 mg, oral dose of $[^{14}C]882C87$.

Study 2

After a 200 mg oral dose of $[^{14}C]882C87$, plasma concentrations and pharmacokinetic parameters of 882C87 and 5-PU were similar to those in study 1 (Table 3, Figure 2). In all subjects, at all timepoints, plasma concentrations of radioactivity were slightly greater than the sum of the concentrations of 882C87 and 5-PU but $t_{1/2}$ for plasma radioactivity was similar to that of 882C87 and 5-PU. Whole blood (haemo-
lysat) radioactivity was lower than that in plasma at all timepoints. Calculated red blood cell radioactivity increased gradually up to a peak of 2.5–3.0 μm equivalents 32 h post-dose, approximately two-fifths of plasma radioactivity at the same time-point; later calculations were not possible as plasma radioactivity fell below the detection limit.

One subject admitted to an incomplete urine collection with only 53.6% of the administered radioactivity recovered in urine and 9.4% in faeces. In the three subjects with complete collections, mean urinary recovery of the administered radioactivity was 86.3% with 8.7% in faeces. Urinary 882C87 accounted for 17% of the administered dose and 5-PU for 58.3% in the subjects with complete collections; hence about 11% of the dose was recovered in urine as unidentified radioactivity. Radio-h.p.l.c. and t.l.c. profiles confirmed that most of the radioactivity was 5-PU or 882C87 with a small peak eluting at the solvent front. In the subject with an incomplete urine collection, urinary 5-PU accounted for 29% of the administered radioactivity and 882C87 for 14.4%; 9.4% was recovered in faeces.

Discussion

Single i.v. and oral doses of 882C87 were well tolerated in this study. The relationship between plasma concentrations of anti-herpes agents and optimal anti-VZV therapy is poorly understood. However, maintaining plasma concentrations above the in vitro IC<sub>50</sub> is likely to be required although what multiple above the IC<sub>50</sub> may be needed is unknown. The long half-life of 882C87, which seems to be unique among nucleoside analogues, will give plasma concentrations substantially above IC<sub>50</sub> throughout a 12–24 h dosing interval suggesting that effective antiviral treatment might be achieved with once daily dosing.

The oral bioavailability of a 200 mg tablet of 882C87 was 21.1% in the young and 24.6% in the elderly. This modest bioavailability was nevertheless associated with plasma concentrations substantially above the in vitro IC<sub>50</sub> for VZV [1]. In addition, other studies have shown that plasma concentrations of 882C87 are proportional to dose up to and including 400 mg and continue to rise substantially, although less than dose-proportional, at doses up to at least 1600 mg [2, 4].

After oral administration of [14C]-882C87, most of the dose was recovered in urine as 5-PU and unchanged 882C87. Only 10–11% of the administered radioactivity was recovered as unidentified metabolite(s). Plasma radioactivity exceeded the sum of the concentrations of 882C87 and 5-PU at all timepoints but the difference was always less than 1 μM. This suggests the presence of one or more unidentified metabolites in plasma and urine after oral dosing with 882C87 but that they are present in low concentrations relative to the parent drug and pyrimidine base. As the elimination half-life of plasma radioactivity is similar to those of 882C87 and 5-PU the elimination of the additional, minor metabolites may be formation-rate dependent.

After intravenous dosing with 882C87, 82% of the administered drug was recovered unchanged in the urine in the young and 71% in the elderly and renal clearance accounts for most of the total clearance. Given a mean bioavailability of 21.1% in the young and 24.6% in the elderly, the recovery of about 17% of the administered dose of 882C87 in urine after oral dosing also represents a recovery of 80% of the bioavailable drug in the young and 70% in the elderly. Renal clearance therefore represents the main route of elimination of 882C87 from plasma.

After intravenous dosing only trace amounts of 5-PU, the pyrimidine base, are detectable in urine but after oral dosing, more of the dose is recovered in urine as 5-PU than as unchanged 882C87. Urinary recovery of 5-PU accounts for 35–40% of the administered dose while the oral bioavailability of 882C87 is only 20–25%. First pass metabolism of 882C87 to 5-PU cannot account for these findings due to the lag time of several hours before 5-PU is detected in plasma after oral dosing and the complete absence of 5-PU in plasma after intravenous dosing with only very low recoveries in urine. An alternative explanation is that 5-PU is formed by the breakdown of unabsorbed 882C87 within the gut lumen, probably the large intestine in view of the lag time, from where it is then absorbed and subsequently eliminated unchanged in urine. Thus, its pharmacokinetics are totally independent of those of 882C87. Significant amounts of 5-PU are detected in faeces after incubation with 882C87 for 12 h or more (M. Dickins, Wellcome Foundation, personal communication). The ‘elimination’ half-life of 5-PU describes the rate at which its plasma concentration falls, however, as the breakdown of 882C87 is a slow process in vitro it is likely that the kinetics of 5-PU are formation-rate limited. Metabolism of drugs by gastrointestinal flora is an unusual route of elimination, however, another thymidine analogue, BVaUa (sorivudine, 1-β-D-arabinofuranosyl-E-5-(2-bromovinyl)uracil has recently been shown to undergo similar breakdown to the pyrimidine base E-5-(2-bromovinyl)uracil (BVU) [16] and there is some conversion of AZT (zidovudine, 3'-azido-3'-deoxythymidine) to AMT (3'-amino-3'-deoxythymidine) by various intestinal bacteria [17].

As in a previous study [3] plasma concentrations of 882C87 and 5-PU were higher in the elderly than in the young adults. There was little difference in mean weight between the groups (66.2 kg in the elderly, 71.0 kg in the young) and no difference in volume of distribution but there was a trend to higher bioavailability in the elderly. Although the 3.5% absolute difference in mean bioavailability was not statistically significant, a retrospective power calculation showed that the study could only have detected a significant (P < 0.05) difference in absolute bioavailability of at least 8.2% (with 80% power). The differences in plasma concentrations, and the increase in elimination half-life in the elderly, were also related to reduced renal function. In this study, renal clearance of 882C87 was 12% of estimated creatinine clearance in
the elderly and 11% in the young. Since 882C87 is 88% protein bound across the concentration range 1–100 μM, its renal elimination may be solely attributable to passive filtration of unbound drug without tubular secretion. However, after oral doses of 800 and 1600 mg there is a small but significant fall in renal clearance, without a change in protein binding, suggesting that active, saturable processes are involved in the renal elimination of 882C87 at much higher concentrations than in this study [4].

Volume of distribution was unaffected by age. The calculated concentration of radioactivity in red blood cells was lower than that in plasma at the same timepoints suggesting that there is limited distribution of [14C] into red blood cells. For the first 24 h after dosing, when most of the radioactivity is [14C]-882C87, red cell concentrations are 0.5–2 μM and they increase slightly at later timepoints suggesting that [14C]-5-PU may enter cells more freely.

In conclusion, the oral bioavailability of 200 mg 882C87 is 20–25%, sufficient to achieve plasma concentrations substantially above the in vitro IC50 for VZV. Most of an intravenous dose is excreted unchanged in urine. This is also true of the fraction of 882C87 absorbed after an oral dose but unabsorbed drug is broken down to the pyrimidine base 5-PU in the large intestine with consequent absorption and elimination in urine. The small amount of drug unaccounted for may be due to other unidentified metabolites present in very low concentrations relative to the parent drug and pyrimidine base. Plasma concentrations of 882C87 are higher in the elderly, related to a decrease in renal clearance and a trend to higher bioavailability, and showing that predictions of plasma concentrations after repeated doses of 882C87 in the, mostly elderly, patient population are likely to be underestimates if based on data only from young adult volunteers.

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