Atazanavir: a novel inhibitor of HIV-protease in haemodialysis

Sir,

Atazanavir is a novel azapeptide protease inhibitor with high specificity for, and activity against, HIV-1 protease. Atazanavir has a pharmacokinetic profile that allows for once-daily oral administration. It is a moderate inhibitor of hepatic cytochrome P450 enzymes and interacts with several drugs [1]. However, it has been shown that even drugs whose elimination is predominantly hepatic may have altered pharmacokinetics in patients with renal impairment [2]. Furthermore, both currently available protease inhibitors and renal insufficiency may potentially cause serious metabolic complications, significantly, elevation of lipids and triglycerides [3–5] and increase in cardiovascular risk. Moreover, since significantly fewer lipid changes have been reported with atazanavir [6], its use may be of interest in patients with renal insufficiency. However, no atazanavir pharmacokinetic data are available for patients with renal failure.

We report a pharmacokinetic study of atazanavir in one patient with renal insufficiency requiring haemodialysis. A 48-year-old antiretroviral-experienced HIV-infected African man with history of stable chronic renal insufficiency as defined by a serum creatinine of 200 μmol/l and creatinine clearance of 40 ml/min was admitted for severe acute renal failure according to HIV-associated nephropathy on kidney biopsy (focal segmental glomerulosclerosis with collapsed glomerular tuft, microcystic dilatation of tubules and interstitial inflammatory infiltrate). Despite previous antiretroviral therapy (didanosine 250 mg/day, lamivudine 100 mg/day and nevirapine 100 mg/day), he became anuric and needed haemodialysis. His antiretroviral treatment was modified for atazanavir 400 mg/day, lopinavir/ritonavir 4 capsules (532/132 mg)/day and efavirenz 600 mg/day. Atazanavir pharmacokinetics was performed after multiple (2 weeks) oral administration of a two-capsule single daily dose with patient consent. Blood samples were collected just before and 1, 2, 3, 4, 5, 6, 12, 18 and 24 h after oral administration. The study was performed between and during dialysis sessions. Paired arterial and venous blood samples were also performed simultaneously 2 h after the start of haemodialysis. Haemodialysis was performed for 4 h using a F60 polysulphone dialyser (surface area 2 m²) every 2 days with a double-needle access to a radial

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1Niigata University Graduate School of Medical and Dental Sciences
2Clinical Nephrology and Rheumatology
Niigata
Japan
Email: jjkaz@med.niigata-u.ac.jp


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**Fig. 1.** A 62-year-old female who had been undergoing haemodialysis therapy for 15 years. Ectopic calcified tissue was extracted from the right wrist joint during surgical therapy for carpal tunnel syndrome. (A) Calcified tissue is indicated by the von Kossa staining (arrows). (B) The immunoreaction for AHSG can be seen surrounding the calcified tissue.
arteriovenous fistula with a constant dialysate flow rate of 500 ml/min and blood flow rate between 250 and 300 ml/min. Pharmacokinetic parameters obtained for our patient were then compared with those of subjects with normal renal function [1]. Influence of haemodialysis was also studied with calculation of the extraction ratio $E$ and the haemodialysis clearance $CL_{HD}$. Moreover, we determined the significance of haemodialysis clearance as compared with total body clearance:

$$F_{HD}(CL_{HD}/(CL_{HD} + CL_{ER}))$$

where $CL_{ER}$ is ‘extra-renal’ clearance [7].

Neither clinical (nausea, rash, diarrhoea, abdominal pain or vomiting) nor biological [hyperlipidaemia, elevation of serum transaminases (ASAT: 30 and 32 IU/l; ALAT: 25 and 21 IU/l, respectively) and unconjugated hyperbilirubinaemia] side effects were observed.

Our pharmacokinetic parameters are summarized in Table 1.

### Table 1. Pharmacokinetic parameters of atazanavir in a haemodialysed HIV$_1$-infected patient

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Our patient (off-dialysis day)</th>
<th>Reference values at steady state [1]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg)</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>Dosing interval (h)</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>4855</td>
<td>2918–5867</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>4</td>
<td>2–4</td>
</tr>
<tr>
<td>$C_{\text{min}}$ (ng/ml)</td>
<td>375</td>
<td>149–219</td>
</tr>
<tr>
<td>AUC (ng h/l)</td>
<td>49 800</td>
<td>18 590–33 500</td>
</tr>
<tr>
<td>$T_{1/2}$ (h)</td>
<td>7.19</td>
<td>5.28</td>
</tr>
<tr>
<td>$CL/F$ (ml/min)</td>
<td>134</td>
<td>420</td>
</tr>
<tr>
<td>$V_d/F$ (l)</td>
<td>83.4</td>
<td>109–187</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$E$ (%)</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>$CL_{HD}$ (ml/min)</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>$F_{HD}$ (%)</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>

Dosing interval day values of maximum plasma concentration $C_{\text{max}}$, minimum plasma concentration $C_{\text{min}}$ (at 24 h) and area under concentration–time curve (AUC) were 4855 ng/ml, 375 ng/ml and 49 800 ng h/l, respectively. In addition, values of time to reach maximum plasma concentration $T_{\text{max}}$, apparent elimination half-life $T_{1/2}$, apparent total body clearance $CL/F$ and apparent volume of distribution $V_d/F$ were 4 h, 7.19 h, 134 ml/min and 83.41, respectively.

Atazanavir concentrations were 2198 and 1807 ng/ml before and after haemodialysis, respectively. Two hours after the start of haemodialysis, arterial and venous concentrations were 2183 and 1881 ng/ml, respectively. Values of $E$ and $CL_{HD}$ of atazanavir were 14% and 40 ml/min, respectively. $F_{HD}$ was 23%, i.e. below the 25% limit value above which haemodialysis clearance should be considered clinically significant.

Our results showed that atazanavir pharmacokinetics differed in our haemodialysis patient as compared with reference values in patients with normal renal function. However, in this case, atazanavir was associated with both efavirenz and ritonavir. Such an association has been reported to induce a 40% increase in atazanavir AUC in patients with normal renal function (http://www.retroconference.org/2003/abstract/). Indeed, the AUC increase observed in our patient was most likely due to the coadministration of efavirenz and ritonavir rather than secondary to renal failure-induced pharmacokinetic alterations. This increased AUC, thus, resulted in a decreased $CL/F$ and an increased $T_{1/2}$.

From these data, we suggest that atazanavir should be administered at its normal dosage in patients with renal insufficiency undergoing haemodialysis. Furthermore, atazanavir seems not to be significantly dialysable and administration may, thus, be performed anytime before or after the session on haemodialysis days. However, further studies would be needed to confirm these preliminary results.

Conflict of interest statement. None declared.

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Gemella morbillorum peritonitis in a patient being treated with continuous ambulatory peritoneal dialysis

Sir,

Peritonitis is a serious problem for peritoneal dialysis (PD) patients, and is a major cause of hospitalization, catheter loss and transfer to haemodialysis [1]. We present a peritonitis episode caused by an unusual pathogen, Gemella morbillorum. A 55-year-old man was admitted to hospital after noticing that his dialysis effluent was slightly cloudy. He received three exchanges of 1.36% and one exchange of 2.27% 2000 ml of