Pharmacokinetics of pantoprazole in patients with end-stage renal failure

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Abstract

Background. Pantoprazole is a selective inhibitor of the gastric H⁺/K⁺-ATPase with a low potential to interact with the cytochrome P450 enzyme system. Since pantoprazole is metabolized in the liver to metabolites which are mainly cleared by the renal route, it was the aim of this study to investigate its pharmacokinetics in patients with end-stage renal failure undergoing regular haemodialysis.

Methods. Eight patients with end-stage renal failure (creatinine clearance < 5 ml/min, age 45–65 years) on regular haemodialysis (duration of haemodialysis 4–5 h, cuprophan-dialyser Hemoflow E3, surface 1.3 m²) were given single i.v. doses of 40 mg pantoprazole one day before haemodialysis (A) and on a haemodialysis day immediately before the start of the haemodialysis (B). Concentrations of pantoprazole and metabolite M2 were determined in plasma and urine over 24 h and in timed samples of the dialysis fluid by HPLC. The protein binding was determined using equilibrium dialysis.

Results. The pharmacokinetic characteristics of pantoprazole AUC; t½, CL and Vd area (geometric means) were 2.4 mgxh/l, 0.63 h, 0.227 l/h/kg and 0.206 l/kg on day A (without dialysis) and 2.3 mgxh/l, 0.8 h, 0.237 l/h/kg and 0.273 l/kg on day B (with dialysis), respectively.

The protein binding was 96%. Pantoprazole was found in small amounts in the dialysis fluid (max. 2.1% of the dose) but not in the urine. Pantoprazole was well tolerated. In particular, there were no clinically relevant changes in blood count, electrolytes or liver enzymes.

Conclusions. Haemodialysis has no influence on the pharmacokinetic characteristics of pantoprazole. Thus, pantoprazole is not dialysed to any relevant degree, and therefore no dose-adjustment is required for patients with end-stage renal failure undergoing regular haemodialysis treatment.

Key words: pantoprazole; renal impairment; haemodialysis; proton-pump inhibitor

Introduction

Pantoprazole is a proton-pump inhibitor of the class of substituted benzimidazoles, characterized by its favourable pharmacokinetic properties [1] and its low potential to interact with other drugs in man [2]. The latter is probably due to its unique metabolism as compared with other proton-pump inhibitors (PPI). Apparently, all PPIs share the same initial step of phase I metabolism, but only pantoprazole is further conjugated by a non-saturable phase II system [3]. Pantoprazole accumulates in the acidic compartment of the parietal cell, where it is protonated and chemically rearranged to the active inhibitor which then covalently binds to the H⁺/K⁺-ATPase. This results in a long duration of action.

As to pharmacokinetics, pantoprazole is extensively metabolized in the liver, has a total serum clearance of 0.11 l/h/kg, a serum elimination half-life of about 1.1 h and an apparent volume of distribution of 0.151/l/kg; 98% of pantoprazole is bound to serum proteins [1]. Elimination half-life, clearance and volume of distribution are independent of the dose [4]. The main serum metabolite M2 (pharmacologically inactive) of pantoprazole is formed by demethylation at the 4-position of the pyridine ring, followed by conjugation with sulphate. Its serum elimination half-life is about 1.5 h. Almost 80% of an oral or intravenous dose is excreted as metabolites in the urine; the remainder is found in faeces and originates from biliary secretion [1].

For another proton-pump inhibitor of the same class of compounds, e.g. omeprazole, its disposition characteristics were unchanged in renal impairment. The elimination of metabolites, however, was decreased [5]. Haemodialysis had no influence on its pharmacokinetics [6].

Owing to its extensive metabolism in the liver, it...
could be expected that renal impairment would also not influence the pharmacokinetics of pantoprazole to a clinically relevant degree. Due to the high protein binding of pantoprazole no relevant influence of haemodialysis on its pharmacokinetics was anticipated, but the metabolites might behave differently. Therefore, it was the aim of this study to investigate the pharmacokinetics of pantoprazole and its main metabolite M2 in patients with end-stage renal failure undergoing regular haemodialysis.

Subjects and methods

Ethics

The study protocol was approved by an independent ethics committee and all subjects gave their written informed consent prior to the start of the study.

Subjects

Eight subjects (5 m/3 f) with end-stage renal failure and normal findings associated with stable renal impairment who had been on regular dialysis for at least 3 months and treated with constant medication entered the study (see Table 1). Exclusion criteria were infectious diseases, hypertension, encephalopathy, bilirubin >2 mg/dl, haemoglobin <8 g/dl, serum albumin <30 g/l, Quick <50%, thrombocytes <50 000/μl, and treatment with antilucre drugs, cyclosporine or anti-inflammatory drugs within 2 weeks prior to the start of the study.

All subjects received water-soluble vitamins after the haemodialysis and calcium-containing phosphate binders, four of them additionally needed aluminium-containing phosphate binders (subjects 2, 4, 5 and 7). Erythropoietin was injected s.c. after the haemodialysis in a weekly dosage between 2000 and 6000 IE (except subjects 5 and 8), oral iron salts were given to subjects 1 and 6. Subjects 2 and 5 were treated with calcitriol (0.25 and 0.5 μg/day, respectively) as well as with acetylsalicylic acid (100 mg/day). All subjects except patient 6 received frusemide 160–375 mg/day. The daily antihypertensive medication was the following: subjects 1 and 8, captopril (12.5 mg each); subject 3, nifedipine (5 mg); subject 6, nifedipine (60 mg), clonidine (450 μg), and captopril (25 mg); subject 7, enalapril (2.5 mg).

Study design and medication

The study was conducted as a randomized two-period crossover. Each subject was given two single i.v. doses (2-min injection) of 40 mg pantoprazole (Byk Gulden, Konstanz, Germany), one dose on the day before a regular haemodialysis (Study day A, during a short dialysis free interval of 24 h) and one dose on a haemodialysis day (day B, following a dialysis-free interval of 48 h). All subjects received immediately before initiation of haemodialysis 3000 IE heparin and during the haemodialysis procedure 1000 IE heparin per hour. The wash-out period between the two i.v. doses was at least 5 days, but not more than 14 days.

Venous blood was withdrawn from the arm opposite to the arm with the shunt. During haemodialysis, blood was taken from the inflow line to the dialyser (Fresenius A 2008 Ethik and a capillary dialyser cuprophan 1.3 m² surface area). Three millilitres of blood were withdrawn before and at 0.25, 0.5, 1, 2, 3, 4 h, and at the end of haemodialysis before reinfusion (day B only) and at 6, 8, 10, 12 and 24 h using NH₄-heparinized syringes. The blood was centrifuged to provide plasma which was stored immediately at −20°C.

Twenty-four-hour urine was collected on both study days. In order to avoid degradation of pantoprazole or metabolite M2, the urine was stabilized with 10 ml each of 8.4% NaHCO₃ solution which was placed in the bottles before collection. During the 24-h urine collection the urine bottles had been on regular dialysis for at least 3 months and treated with antilucre drugs, cyclosporine or anti-inflammatory drugs within 2 weeks prior to the start of the study.

Table 1. Demographic and anthropometric data

<table>
<thead>
<tr>
<th>Subj. no.</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>Creatinine clearance (ml/min) pre-study</th>
<th>On regular dialysis since (months)</th>
<th>Reason for renal impairment</th>
</tr>
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<tr>
<td>1</td>
<td>F</td>
<td>51</td>
<td>65</td>
<td>160</td>
<td>4.9</td>
<td>7</td>
<td>CGN</td>
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<tr>
<td>2</td>
<td>F</td>
<td>59</td>
<td>72</td>
<td>161</td>
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</tr>
<tr>
<td>3</td>
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<td>81</td>
<td>183</td>
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<td>6</td>
<td>APKD</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>61</td>
<td>72</td>
<td>185</td>
<td>0.8</td>
<td>57</td>
<td>APKD</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>45</td>
<td>77</td>
<td>178</td>
<td>1.8</td>
<td>34</td>
<td>APKD</td>
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<tr>
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<td>M</td>
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<td>77</td>
<td>186</td>
<td>0.7</td>
<td>29</td>
<td>APKD</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>57</td>
<td>81</td>
<td>170</td>
<td>4.7</td>
<td>30</td>
<td>CGN</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>64</td>
<td>72</td>
<td>165</td>
<td>3.9</td>
<td>5</td>
<td>NSc</td>
</tr>
</tbody>
</table>

APKD, adult polycystic kidney disease; CGN, chronic glomerulonephritis; NSc, nephrosclerosis.

Pantoprazole and metabolite M2 concentrations in plasma, urine, and dialysate

Determination of plasma concentrations of pantoprazole and its main metabolite M2 was performed using a reversed-phase HPLC-method which was validated for pantoprazole [7]. Serum concentrations of pantoprazole were expressed as its Na salt. The limits of quantitation in plasma were 0.03 mg/l for pantoprazole-Na or 0.03 mg Eq/l for its main
metabolite M2, respectively. M2 was quantified in relative concentration units of pantoprazole only since no synthetic reference compound was available for full validation. Analysis of urine or dialysis fluid samples was done analogously, however, with direct injection of the samples onto the HPLC column. The respective limits of quantitation in urine were 0.1 mg/l for pantoprazole-Na or 0.1 mg Eq/l for M2. Corresponding values for dialysis fluid were 0.3 mg/l (pantoprazole) or 0.3 mg Eq/l (M2).

**Protein binding**

The protein binding of pantoprazole was determined in samples taken at 15 min or 3 h post-dose on day 1 (without dialysis) by spiking each sample with 0.5 mg/l 14C-labelled pantoprazole-Na, followed by equilibrium dialysis for 5 h. Concentrations were measured using liquid scintillation counting.

**Pharmacokinetic evaluation**

For pantoprazole-Na in plasma, area under the concentration vs time curve, AUC, total plasma clearance, CL, volume of distribution, Vd, area, and elimination half-life, t1/2, were calculated using standard methods [8]. For the plasma metabolite M2, AUC, t1/2, maximum plasma concentrations, Cmax, and the time of its occurrence, tmax, were calculated or directly taken from the measured data. For pantoprazole in the dialysis fluid AUC(0–5 h) and t1/2 were calculated as described above. Estimation of the total amount of dialysed pantoprazole-Na was done by multiplication of AUC(0–5 h) with the flow of the dialysate (30 l/h).

**Statistics**

For pantoprazole-Na, the results of day A (without haemodialysis) were compared with day B (with haemodialysis) by means of distribution free ratio analysis. Point estimates and 90% confidence limits are given for the ratio of the population medians day B/day A. As metabolite M2 is quantified on a relative scale only, no ratio analysis was performed for this compound. All other data are presented descriptively.

**Results**

**Plasma concentrations of pantoprazole-Na and metabolite M2**

Following intravenous 2-min injection, maximum plasma concentrations of pantoprazole were observed at the first measured timepoint (0.25 h). Plasma concentrations decreased monoexponentially with elimination half-lives of 0.63 h (without haemodialysis) or 0.80 h (with haemodialysis) respectively (Table 2). Ten hours after injection, pantoprazole plasma concentrations were below the limit of quantitation on both study days. For the metabolite M2, maximum plasma concentrations of 1.40 mg Eq/l (without haemodialysis) or 1.36 mg Eq/l (with haemodialysis) were observed 0.75 h or 1.0 h after injection (Table 3). M2 was eliminated with half-lives of 2.7 or 3.0 h respectively. Twenty-four hours after dosing, M2 plasma concentrations were near or below the limit of quantitation. From Figure 1 it follows that plasma concentrations of both pantoprazole and M2 were similar on the two study days. Consistently, the pharmacokinetic characteristics derived thereof showed no relevant changes between the two study days for either compound. Intra- and interindividual variation of AUC of pantoprazole was small.

**Pantoprazole-Na and metabolite M2 in urine**

Pantoprazole-Na concentrations in urine were below the limit of quantitation in all subjects on both study days. The amounts of excreted metabolite M2 were low, the maximum being 2.3% of the dose.

**Pantoprazole-Na and metabolite M2 in dialysis fluid**

Only small amounts of pantoprazole-Na were found in the dialysate, the maximum amount being 2.1% of the dose. The median half-life of pantoprazole-Na in the dialysis fluid was 1.06 h. Metabolite M2 could not be analysed in the dialysis fluid due to interferences.

**Protein binding**

The mean plasma protein binding of pantoprazole at 15 min or 3 h post-dose on day A (without dialysis) was 96% as determined by equilibrium dialysis.

**Safety and tolerability**

Pantoprazole was well tolerated. There were no relevant changes in clinical laboratory parameters (in particular plasma electrolytes or liver enzymes) nor in blood pressure or heart rate.

**Discussion**

Haemodialysis does not influence the plasma pharmacokinetics of pantoprazole or its main metabolite M2. Due to its comparable plasma concentrations and pharmacokinetic characteristics on the day with or without haemodialysis, only small amounts could be expected in the dialysis fluid. Consistently, only negligible amounts of pantoprazole were found in the dialysis fluid. Thus pantoprazole is virtually not dialysable. Therefore, dialysis will not be helpful in case of an overdose which, however, has not yet been experienced. Even at a dose of 240 mg injected once daily over 7 days [9] or a bolus injection of 80 mg followed by a long-term infusion of 8 mg/h over 3 days [10] pantoprazole was well tolerated.

A comparison of the pharmacokinetic characteristics of pantoprazole in this patient population with end-stage renal failure and healthy volunteers from a previous study [4] shows lower AUC values and shorter elimination half-lives for this patient group. The shorter elimination half-life in patients with end-stage renal failure could be caused by the slightly lower protein-binding in this subpopulation (96%) as compared to healthy volunteers (98%). This could also contribute to the slightly higher volume of distribution.
Table 2. Pharmacokinetic characteristics (geometric mean, geom. 68% range) for pantoprazole-Na and ratio analysis (point estimate, 90% confidence interval)

<table>
<thead>
<tr>
<th>Pantoprazole Na</th>
<th>AUC (0–inf) (mgxh/l)</th>
<th>t_{1/2} (h)</th>
<th>Cl (l/h/kg)</th>
<th>V_{d area} (l/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day A, without haemodialysis</td>
<td>2.40 (1.58, 3.66)</td>
<td>0.63 (0.52, 0.76)</td>
<td>0.227 (0.157, 0.329)</td>
<td>0.206 (0.161, 0.264)</td>
</tr>
<tr>
<td>Day B, with haemodialysis</td>
<td>2.30 (1.42, 3.73)</td>
<td>0.80 (0.55, 1.15)</td>
<td>0.237 (0.153, 0.367)</td>
<td>0.273 (0.215, 0.348)</td>
</tr>
<tr>
<td>Ratio analysis</td>
<td>0.96</td>
<td>1.27</td>
<td>1.04</td>
<td>1.32</td>
</tr>
<tr>
<td>Day B/day A</td>
<td>(0.90, 1.02)</td>
<td>(1.03, 1.56)</td>
<td>(0.98, 1.11)</td>
<td>(1.10, 1.59)</td>
</tr>
</tbody>
</table>

Table 3. Pharmacokinetic characteristics (geometric mean, geom. 68% range) for metabolite M2. For t_{max}, median (min, max) is given

<table>
<thead>
<tr>
<th>Metabolite M2</th>
<th>AUC (0–inf) (mg Eq.xh/l)</th>
<th>C_{max} (mg Eq/l)</th>
<th>t_{1/2} (h)</th>
<th>t_{max} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day A, without haemodialysis</td>
<td>6.65 (4.36, 10.14)</td>
<td>1.40 (1.06, 1.85)</td>
<td>2.7 (2.1, 3.5)</td>
<td>0.75 (0.5, 2.0)</td>
</tr>
<tr>
<td>Day B, with haemodialysis</td>
<td>7.40 (4.92, 11.13)</td>
<td>1.36 (1.13, 1.65)</td>
<td>3.0 (1.91, 4.8)</td>
<td>1.0 (1.0, 2.0)</td>
</tr>
</tbody>
</table>

Fig. 1. Mean (SEM) pantoprazole and metabolite M2 plasma concentrations with and without haemodialysis. Plasma concentrations are given as mg/l for pantoprazole and mg Eq/l for M2, respectively.

in patients with renal failure in comparison to normals but in both the range overlaps considerably. Heparin during haemodialysis might additionally lead to a displacement of pantoprazole from protein binding. The AUC of the metabolite M2 was higher in the patients with renal failure probably due to its decreased renal elimination. Nevertheless, no accumulation has to be expected since plasma concentrations of M2 after 24 h were near or below the limit of quantitation in all patients (LOQ = 0.03 mg Eq/l).

The comparison of both studies in the different groups has to take into account that they were not matched for age, sex, weight etc. Actually, an oral study in patients with severe renal impairment (creatinine clearance < 20 ml/min) showed no relevant difference in the pharmacokinetic characteristics of pantoprazole and metabolite M2 in comparison to a matched group of healthy controls [11]. As pantoprazole has a low potential to interact with other drugs in man [2], no influence of the current comedinations on the pharmacokinetics of pantoprazole is to be expected.

As the pharmacokinetic characteristics of pantoprazole and its metabolite M2 are comparable without and with haemodialysis (using a low-flux dialysis membrane), and taking into account the safety and tolerability of pantoprazole in these patients, no dose adjustment is required for patients with end-stage renal failure undergoing regular haemodialysis treatment.
Pantoprazole in end-stage renal failure

References


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