Pharmacokinetics of naftopidil, a novel anti-hypertensive drug, in patients with hepatic dysfunction

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Summary: The pharmacokinetics of naftopidil, a novel alpha-1 adrenoceptor-blocking anti-hypertensive, were investigated in ten patients (9M/1F) with hepatic dysfunction after oral administration (50 mg, tablet) and after an intravenous infusion of 5.0 mg over 2 minutes. Results were compared to a control group of 12 healthy subjects (6M/6F) of a previous investigation, which was carried out according to the identical study protocol.

The pharmacokinetic parameters obtained for the i.v. administration were comparable in both groups (half life 3.6 ± 3.4 hours in liver-impaired subjects versus 3.3 ± 2.1 hours in controls; clearance 11.9 ± 4.7 ml/minute/kg versus 11.0 ± 1.6 ml/minute/kg).

Following oral administration the plasma levels and half-life times of naftopidil were significantly increased in liver impairment ($t_{1/2}$ 16.6 ± 19.3 hours versus 5.4 ± 3.2 hours in controls; $P = 0.012$). Mean values for the absolute bioavailability in patients with hepatic dysfunction were significantly higher (mean 75%, median 53%, range 13.4–211.0%) compared to healthy subjects (mean 17%, median 16%, range 6.7–29.6%, $P = 0.001$).

Reduction of functional hepatic blood flow in chronic liver disease or, as evidenced in one case as a consequence of shunt surgery, is the probable cause of the observed alteration in naftopidil kinetics. This phenomenon occurred only following the oral 50 mg dose whereas the intravenous 5 mg dose obviously still could be normally handled. Naftopidil demethylation and hydroxylation were both less and non-uniformly affected.

The pharmacokinetic findings suggest that in patients with severe hepatic impairment or evidence for marked changes in hepatic blood flow the dose of naftopidil may require adjustment to the lower end of the therapeutic range and/or may be limited to once daily. However, before definite conclusions can be drawn, further steady-state studies are required. Despite the pharmacokinetic discrepancies no difference in drug tolerability was seen between patients and healthy subjects.

Introduction

Naftopidil is a novel phenylpiperazine vasodilator drug with selective alpha-1 adrenoceptor-blocking activity, which is undergoing clinical evaluation in patients with essential hypertension.¹ Two active metabolites with similar potency to the parent compound are found in the blood and contribute to the therapeutic effects after oral administration.

In general, vasodilatation and the lowering of blood pressure by naftopidil are not accompanied by reflex tachycardia and cause no 'prazosin-like' first-dose phenomenon.² Apart from a peripheral vasodilator effect based upon alpha-1 adrenoceptor blockade, an additional calcium antagonist action^{3,4} as well as a centrally mediated reduction of peripheral sympathetic tone due to the interaction

of naftopidil with central 5-hydroxytryptamine receptors,³ has been suggested. Pharmacokinetic studies in healthy volunteers, elderly and patients with renal impairment exhibited an extensive hepatic metabolism of naftopidil with a total plasma clearance of 9–11 ml/minute/kg, suggesting a close relationship to the liver plasma flow. Therefore, naftopidil pharmacokinetics have now been examined after single intravenous (i.v.) and oral administration to patients with hepatic dysfunction.

Patients and methods

Study design

Both studies (the recent study in subjects with hepatic impairment as well as the previous trial in

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healthy volunteers) were performed according to the same study protocol based on an open-label randomized two-period cross-over design. The clinical part of the investigation in liver-impaired subjects was performed in two centres – St Bartholomew's Hospital, London, UK and LAB GmbH, Neu-Ulm, Germany. All subjects were randomly assigned to receive on two occasions 8 days apart a single oral and intravenous administration of naftopidil. They were fasted from 22.00 hours the previous day, and were instructed to take no alcohol or drugs known to influence drug metabolism throughout the course of the study. Naftopidil was administered between 07.00 and 08.00 hours on an empty stomach. It was given either as an i.v. infusion within 2 minutes, or as a 50 mg tablet with 150 ml tap water. After test drug intake, all subjects remained in a supine position for 4 hours. Blood pressure by mercury sphygmomanometer and pulse rate were measured in a supine position on the right arm after subjects had been rested for at least 3 minutes. Heparinized blood samples were taken from an indwelling venous cannula before drug administration, at the end of the intravenous infusion, and at 5, 10, 15, 30, 45 minutes, and 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 36, 48 and 60 hours post dose. Plasma samples were stored at -20°C until analysed.

Patients

Ten patients (9M, 1F) with hepatic impairment but with no other clinically significant disease were studied. They were 48–69 years old (mean 58 ± 6 years) and their weights ranged from 55 to 92 kg (mean 74 ± 11 kg). Seven had post-alcoholic cirrhosis and one cirrhosis due to chronic active hepatitis. The other two patients suffered either from chronic active hepatitis, or fatty liver together with a history of portal hypertension due to portal vein thrombosis with subsequent palliative spleno-renal shunt surgery. The severity of the liver disease was assessed according to the Child classification into Grades A, B or C.^{5,6} Five patients were treated with other drugs.

All six patients of the German centre were additionally subjected to comprehensive liver function tests including aminopyrine breath test, an indirect measurement of decreased functional hepatic microsomal mass^{7,8} according to Pauwels *et al.*⁹ Caffeine¹⁰ and paracetamol acetaminophen clearance¹¹ were used to investigate the metabolic capacity of phase I and phase II pathway. In addition, fasting bile acids were determined as a parameter mainly reflecting porto-systemic shunting¹² and diminished hepatic clearance of bile acids.¹³

Plasma assay

Plasma naftopidil, desmethyl-naftopidil 2 HCl, and (phenyl)hydroxy-naftopidil 2 HCl concentrations were measured after extraction by reversed-phase high-performance liquid chromatography (HPLC) with fluorimetric detection according to a published internal standard method,¹⁴ starting with 0.5 ml plasma aliquots and attaining a lower limit of quantification of 5 ng/ml for all three compounds. Daily calibration lines from control plasma spiked at 5, 10, 20, 50, 100, 200 ng/ml served for the evaluation of the unknowns.

Pharmacokinetic evaluation

Pharmacokinetic analysis of the data was carried out using the STRIPE computer program.¹⁵

Statistical analysis

Although data are from different trials, explorative statistical tests were performed. Differences in pharmacokinetic measurements between the two groups of subjects were tested using two-sided rank tests (Mann–Whitney–Wilcoxon) for independent observations. $P < 0.05$ was considered statistically significant in an explorative sense as no hypotheses have been formulated in advance.

The protocol and the performance of the study were in accordance with the ethical guidelines of the Helsinki Declaration. All subjects gave their written informed consent to take part, after the protocol had been approved by the Ethics Committees of the General Medical Council of Bavaria and the District Ethics Committee of St Bartholomew's Hospital, London.

Results

Patients and controls from a previous study of identical design¹⁶ were well matched regarding weight, height and laboratory parameters of renal function,* but control subjects were younger than the patients (mean age 27 ± 2.8 versus 58.1 ± 6.2) and additionally the control group had a different sex distribution (patients 9M/1F; healthy subjects 6M/6F). In both cases, experimental data were evaluated compartment-free with a one-exponential terminal decay. In control subjects, for 18 hours onwards, concentrations of naftopidil were often below the lower limit of quantification. The metabolites desmethyl-naftopidil and (phenyl)hydroxy-naftopidil were not detectable after intravenous administration, in patients or in healthy

*For interested readers, detailed case data may be available on request.

subjects. After oral administration measurable plasma concentrations of these metabolites were found in all healthy subjects but only in some of the patients. Concentration–time curves are plotted in Figures 1 and 2, respectively.

The pharmacokinetic parameters obtained for the i.v. administration were comparable in both groups (plasma half-life 3.6 ± 3.4 hours in liver-impaired patients versus 3.3 ± 2.1 hours in controls; plasma clearance 11.9 ± 4.7 ml/minute/kg versus 11.0 ± 1.6 ml/minute/kg), except the maximum plasma concentration (C_{max}).

Following oral administration the plasma levels and half-life times of naftopidil were significantly increased in liver impairment ($t_{1/2}$ 16.6 ± 19.3 hours versus 5.4 ± 3.2 hours in controls; $P = 0.012$). Mean values for the absolute bioavailability in

patients with hepatic dysfunction were significantly higher (mean 75%, median 53%, range 13.4–211.0%) compared to healthy subjects (mean 17%, median 16%, range 6.7–29.6%, $P = 0.001$). In contrast to the i.v. measurements, peak concentrations after oral administration were considerably higher in patients than in controls (Figure 2).

Considering the results of the liver function tests, there was no correlation between the disposition of naftopidil and the results of aminopyrine breath test, caffeine- or paracetamol-clearances, respectively. In contrast a significant decrease in functional hepatic blood flow as evidenced by elevated serum bile acids, was related to a marked increase in naftopidil 'area under the curve' (Figure 3). In addition, the patient in whom a spleno-renal shunt had been fashioned, also exhibited a considerably impairment in his ability to handle naftopidil, comparable to those patients with the largest values for fasted serum bile acids.

Despite the observed significant impact of chronic hepatic disease on naftopidil kinetics, the drug was generally well tolerated by the patients. Orthostatic hypotension or tachycardia were not detected in any case. Physical examination within 8 days of completion of the study showed no pathological findings which could be referred to naftopidil, and no significant changes in laboratory tests of haematological, renal or hepatic function were detected.

Discussion

The analytical performance of the plasma naftopidil assay used in this study was similar to that

Figure 1 Mean plasma level–time courses of naftopidil after i.v. administration of 5 mg. ○ = 10 patients with hepatic impairment; ● = 12 healthy young volunteers.

Figure 2 Mean plasma level–time courses of naftopidil after oral administration of 50 mg (tablet). ○ = 10 patients with hepatic dysfunction; ● = 12 healthy young volunteers.

Figure 3 Fasted serum bile acid concentration, as a parameter of functional hepatic flow, plotted against the area under the curve of naftopidil in six patients with liver disease.

used in previous investigations.¹⁶ Thus, it is permissible to compare the results obtained in these different pharmacokinetic studies. However, it should be noted that the patients with liver impairment were older than the controls. Although some impairment of hepatic drug metabolism may occur on ageing, the pharmacokinetics of naftopidil in the elderly were shown to agree well with those in young healthy volunteers (unpublished results). In the latter population, the absolute bioavailability of orally administered naftopidil (50 mg tablet) has been determined to be about 17%.¹⁵ The mechanism responsible for this low value is presumed to be an extensive first-pass metabolism, since nearly complete ¹⁴C-absorption could be seen following oral [¹⁴C]naftopidil administration (unpublished results). Therefore, naftopidil is obviously a representative of compounds with a high extraction ratio. In general, the influence of liver disease on the clearance of highly extracted drugs is determined predominantly by changes in hepatic blood flow, rather than by other parameters of hepatic drug elimination such as intrinsic hepatic clearance and protein binding.¹⁷ Because hepatic disease often results in reduced hepatic blood flow, sometimes with extensive portosystemic shunting, the clearance of highly extracted drugs is most consistently reduced in this clinical setting. One major effect of portosystemic shunting is a substantial reduction in first-pass metabolism⁶ which may considerably impair the

ability of patients to handle such drugs without them necessarily displaying other marked features of liver disease.¹⁸ This particular clinical constellation was present in one of our patients, with spleno-renal shunt surgery following portal-venous thrombosis without cirrhosis.

In conclusion, our data indicate an impairment of the disposition of naftopidil in patients with chronic liver disease after an oral 50 mg dose and are consistent with high clearance drugs. There was no pharmacokinetic difference following the i.v. administration of 5 mg. Whereas pharmacokinetics after oral dosing with 25, 50 and 100 mg of naftopidil were independent of dose in healthy subjects (unpublished results), the present findings suggest that non-linear pharmacokinetics start at considerable lower doses in patients with reduction in functional hepatic flow in liver disease. However, it is possible that the chosen 5 mg i.v. dose was too low to reflect drug metabolism, rather than distribution.

The pharmacokinetic findings suggest that in patients with severe hepatic impairment or evidence for marked changes in hepatic blood flow the dose of naftopidil may require adjustment to the lower end of the therapeutic range and/or may be limited to once daily. Before definite conclusions can be drawn, further steady-state studies are required. Despite the pharmacokinetic discrepancies, no difference in drug tolerability was seen between patients and healthy subject.

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