The effect of renal impairment on the pharmacokinetics and metabolism of bopindolol

N. J. MACDONALD, A. C. GRANT¹, R. S. C. RODGER¹, P. A. MEREDITH & H. L. ELLIOTT

University Department of Medicine and Therapeutics and ¹Renal Unit, Stobhill General Hospital, Glasgow G21 3UW

The pharmacokinetics of the non-selective β -adrenoceptor antagonist, bopindolol, have been studied in 18 hypertensive patients with varying degrees of renal impairment following single and multiple oral dosing. Bopindolol, which undergoes extensive hepatic metabolism, was found to accumulate in patients with chronic renal failure but the disposition in patients on regular haemodialysis did not differ significantly from patients with normal renal function. The mechanism underlying these changes in pharmacokinetics is not clear but suggests the presence of metabolic inhibitors in uraemic plasma which are removed by regular haemodialysis.

Keywords bopindolol chronic renal failure pharmacokinetics

Introduction

Patients with renal impairment frequently have concomitant hypertension which requires drug treatment. Since renal perfusion may be altered by antihypertensive drugs, particularly in the short-term, there is the possibility of reduced renal function and aggravation of existing renal impairment. With β -adrenoceptor antagonist drugs, short-term studies have shown falls in glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) with most β -adrenoceptor blockers (Swainson *et al.*, 1980; Zech *et al.*, 1977) while, in the long-term, a reduction in GFR has been attributed to the non-selective β -adrenoceptor blocker propranolol (Wilkinson *et al.*, 1980).

The choice and dose of antihypertensive therapy in chronic renal failure (CRF) is also influenced by considerations of drug disposition. In general, drugs which undergo predominantly hepatic metabolism (without the production of active or toxic metabolites) are preferred and are administered in standard doses. However, even with drugs which undergo significant presystemic elimination, variable pharmacokinetic results have been reported in renal impairment. For example there have been reports of altered drug metabolism for the β -adrenoceptor blocker propranolol (Bianchetti *et al.*, 1976) and for the dihydropyridine calcium antagonists, nitrendipine (Ankermann *et al.*, 1989), nifedipine (Kleinbloesem *et al.*, 1985) and nicardipine (Ahmed *et al.*, 1991).

Therefore, prediction of drug disposition in renal impairment on the basis of conventional pharmacological principles may be an oversimplification and with any new antihypertensive drug, there is a specific need to assess both the effects on renal function and the

pharmacokinetics in patients with renal failure. Bopindolol, a racemic mixture of R and S isomers, is a non-selective β -adrenoceptor antagonist with a long duration of action (Aellig, 1985) and some intrinsic sympathomimetic activity (Berthold *et al.*, 1981). It is a prodrug which undergoes extensive first pass hepatic metabolism to a single active metabolite, with no parent drug appearing in the systemic circulation, and is further metabolised to numerous inactive metabolites which are eventually eliminated by the kidney (Aellig *et al.*, 1986; Platzer *et al.*, 1984).

The principal aim of this study was to investigate the influence of renal impairment on the pharmacokinetics of bopindolol.

Methods

Eighteen patients, eight males and 10 females, aged 51 ± 8 years, either newly diagnosed hypertensives or patients in whom current treatment was poorly tolerated or ineffective, participated in an open, pharmacokinetic study which involved a 3 week placebo phase and 4 week active treatment period. Written, informed consent was obtained from all patients and the study was approved by the local Research and Ethics committee. Previous antihypertensive treatment was withdrawn not less than 2 weeks before the placebo phase and at entry into the active treatment phase diastolic blood pressure, as measured by semiautomatic sphygmomanometer (Sentrion, Bard Biomedical), was greater than 90 mm Hg but less than 120 mm Hg.

Patients were enrolled into one of three groups on the basis of timed 24 h urine collections for creatinine clearance (average of two).

Group 1: Normal renal function. Creatinine clearance $> 80 \text{ ml min}^{-1}$; 2M, 4F; aged 50 ± 9 years, $\text{CL}_{\text{Cr}} 97 \pm 13 \text{ ml min}^{-1}$.

Group 2: Moderate renal clearance. Creatinine clearance $10\text{--}80 \text{ ml min}^{-1}$; 2M, 4F; aged 53 ± 9 years, $\text{CL}_{\text{Cr}} 38 \pm 28 \text{ ml min}^{-1}$.

Group 3: Severe renal impairment. Creatinine clearance $< 10 \text{ ml min}^{-1}$; 4M, 2F; aged 53 ± 4 years, on regular haemodialysis treatment.

Patients attended the Clinical Pharmacology Research Unit (CPRU) following a 12 h fast for a pharmacokinetic study of the first dose of 0.5 mg oral bopindolol (racemic mixture). Plasma concentrations of hydrolysed bopindolol were determined by a radioreceptor binding assay (Rosenthaler, 1982) from blood samples taken frequently until 24 h after the dose. This assay measures the active hydrolysed moiety in both its R and S forms. There is no evidence in man of stereoselective metabolism of either bopindolol itself or of the hydrolysed metabolites (Sandoz, Basel: data on file). Patients in Groups 1 and 2 thereafter took 0.5 mg bopindolol daily and re-attended the CPRU after 4 weeks for an identical pharmacokinetic study. Haemodialysis patients (Group 3) received only the single administration of bopindolol which in all cases occurred on the day preceding dialysis. Blood pressure and heart rate were measured at intervals throughout each study day and renal function (GFR and ERPF) was assessed in groups 1 and 2 by standard clearance techniques using $[^{51}\text{Cr}]$ -EDTA and $[^{125}\text{I}]$ -hippuran which were simultaneously administered by bolus intravenous injection at 2 h after drug administration.

Data analysis

The pharmacokinetics of bopindolol (as its active hydrolysed metabolite) were assessed using model dependent and model independent means. Model independent analysis was undertaken by application of the trapezoidal rule to 24 h. For the acute data, the AUC to infinity was determined by adding the residual area from 24 h to infinity by dividing the plasma concentration at 24 h by k . Model dependent kinetic analysis was undertaken by fitting a hierarchy of different models to the concentra-

Figure 1 Mean plasma drug concentration-time profiles following a single oral dose of bopindolol. (group 1 ●; group 2 □, group 3 △).

tion data. Appropriateness of models was assessed from a number of standard criteria of goodness of fit. In all subjects the most appropriate model was a two compartment model with first order input. The pharmacokinetic parameters were compared by analysis of variance and linear regression analysis was performed to correlate creatinine clearance with kinetic parameters.

The indices of renal function, GFR and ERPF, were expressed as $\text{ml min}^{-1} 1.73 \text{ m}^{-2}$ body surface area and compared following acute and chronic drug administration by paired Student's t -test.

Results

Mean drug concentration-time profiles following the first dose of bopindolol are shown in Figure 1 and the pharmacokinetic parameters are summarised in Table 1. There was good agreement between the parameters derived from the model dependent and independent approaches. For group 2, the AUC and maximum concentration (C_{max}) after the single dose were significantly ($P < 0.05$) greater for the renal impairment group (Group 2) than for either groups 1 and 3. There were no significant differences among the three groups in the elimination half life ($t_{1/2,z}$), although the longest half-life was found in the dialysis patients (Group 3). During steady state treatment, in Groups 1 and 2, there were

Table 1 Pharmacokinetic parameters after single and multiple doses of bopindolol

	Pharmacokinetic parameters					Derived model dependent	
	C_{max} (ng ml ⁻¹)	Model independent	$t_{1/2,z}$ (h)	t_{max} (h)	AUC (ng ml ⁻¹ h)	$t_{1/2,z}$ (h)	
		AUC (ng ml ⁻¹ h)					
<i>Acute</i>							
Group 1	2.3 ± 0.9	17.8 ± 7.8	6.2 ± 1.6	1.3 ± 0.3	17.7 ± 7.6	6.6 ± 1.5	
Group 2	3.5 ± 0.6*	32.7 ± 15.6*	6.6 ± 1.6	1.3 ± 0.6	33.1 ± 13.4	8.8 ± 1.1	
Group 3	2.4 ± 1.6	19.9 ± 8.0	7.6 ± 3.2	1.1 ± 0.4	17.4 ± 7.9	8.9 ± 5.5	
<i>Chronic</i>							
Group 1	2.8 ± 1.0	22.4 ± 10.0†	7.3 ± 1.5†	1.6 ± 0.9	22.2 ± 9.5	10.2 ± 3.6	
Group 2	4.3 ± 1.3*	42.2 ± 13.8*†	9.9 ± 3.2†	1.4 ± 0.4	42.1 ± 13.0	11.4 ± 3.4	

AUC(0,∞) (acute); AUC(0,24) (chronic).

* group 2 vs group 1/group 3; $P < 0.05$

† group 1/group 2 acute vs chronic; $P < 0.05$.

significant increases in both AUC and $t_{1/2,z}$ ($P < 0.05$). There were no significant correlations between creatinine clearance and kinetic parameters either on the basis of all three groups or on subgroup analysis.

Bopindolol was well tolerated by all patients after single and multiple doses. There were small reductions from baseline in blood pressure but the blood pressure profile was similar in all three groups over the acute study day. After 1 month of therapy, baseline diastolic blood pressure was < 90 mm Hg in five patients in group 1 and four patients in group 2 but this was an open, uncontrolled study in which efficacy was not a primary aim.

There were no significant changes in renal function (GRR and ERPF) after single and multiple doses of bopindolol. In group 1 the mean values for GFR were 101 ± 24 and 106 ± 23 for acute and chronic dosing respectively, compared with 42 ± 28 and 44 ± 28 $\text{ml min}^{-1} 1.73 \text{ m}^{-2}$ in group 2. Corresponding values for ERPF were 480 ± 154 and 550 ± 186 in group 1 and 106 ± 158 and 219 ± 166 $\text{ml min}^{-1} 1.73 \text{ m}^{-2}$ in group 2.

Discussion

Renal function (GFR) was stable during single and multiple dosing with bopindolol. In particular there was no deterioration after 4 weeks chronic administration across a range of renal function. This extends similar findings in hypertensive patients with normal renal function (Fabre *et al.*, 1986) and suggests that bopindolol does not have the adverse effects on renal function reported with some other β -adrenoceptor blockers (Zech *et al.*, 1980).

From the pharmacokinetic data there is evidence that renal impairment may have had significant effects upon the disposition of hydrolysed bopindolol. In the subgroup of patients with moderate renal impairment (group 2) the results are consistent with reduced renal drug clearance. However, in the dialysis patients, by contrast, the

pharmacokinetics do not differ significantly from 'normal' patients. Thus, the altered pharmacokinetics cannot be attributed solely to renal functional impairment since, on that basis, the lowest drug clearance should have occurred in group 3.

Similar changes in disposition have been reported with propranolol and nicardipine, both of which, like bopindolol, undergo mainly hepatic metabolism without formation of renally eliminated active metabolites. Changes in the volume of distribution, reduction of hepatic blood flow leading to reduced hepatic extraction, or accumulation of inactive metabolites have been suggested in explanation. In this study, the increase in peak drug concentration (i.e. of the hydrolysed active metabolite) after acute administration to the patients with moderate renal failure (group 2) makes it unlikely that the accumulation of inactive metabolites was responsible for inhibiting further drug metabolism. In addition, in a similar study with nicardipine there was no evidence of significant changes in volume of distribution or of hepatic blood flow (Ahmed *et al.*, 1991).

Reports in the literature disagree on the influence of CRF on the pharmacokinetics of drugs undergoing significant hepatic metabolism. This may be attributable to the heterogeneous nature of the patients studied both in the extent of their renal impairment and whether or not they are receiving regular dialysis. The mechanism of the differences in drug disposition in patients with uraemia short of dialysis compared with those on regular dialysis is not clear. Studies, including this present study, suggest that 'metabolic inhibitors' are present in uraemic plasma but are removed by regular haemodialysis.

In conclusion, the influence of renal disease on drug disposition cannot always be predicted from general clinical pharmacological principles and there may be no alternative to undertaking studies with individual drugs in patients with a range of renal impairment.

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