PHARMACOKINETICS OF NOMIFENSINE IN IMPAIRED RENAL FUNCTION

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1 In uremia, an increased frequency of adverse drug reactions is observed at elevated plasma levels of active drug. This is a consequence of decreased renal elimination of unchanged drug or pharmacologically active metabolites.

2 To study the pharmacokinetics of nomifensine in uremia, a single dose of nomifensine maleate 50 mg was given to 10 patients with a glomerular filtration rate between 0 and 61 ml/min. In three additional patients on maintenance haemodialysis, the influence of dialysis on the elimination of nomifensine after single oral doses of 50 mg was studied.

3 Blood samples were obtained before and at regular half-hourly or hourly intervals after administration. Plasma levels of nomifensine were examined using a radioimmunological determination method and pharmacokinetic parameters were calculated by computer program.

4 Whereas in healthy subjects the half-life of nomifensine was found to be 1.8 h, this parameter was found to be prolonged in renal patients. In a patient with a creatinine clearance of 0 ml/min the elimination half-life was 46 hours. Nomifensine is not eliminated by haemodialysis.

5 Our findings suggest that nomifensine should not be administered to renal patients with a glomerular filtration rate below 25 ml/minute.

Introduction

In patients suffering from renal failure an elevated frequency of adverse drug reactions is reported. This is related to unusually high drug plasma concentrations occurring in these patients as a result of several factors: decreased renal elimination of the unchanged drug or its pharmacologically active metabolites, a decreased protein binding of the drug in uremia, a decreased volume of distribution, and impaired rates of drug metabolism (Anderson *et al.*, 1976).

In patients with uraemia, standard doses of diazepam, flurazepam, chlorthalidone, meprobamate, chloral hydrate or short-acting barbiturates can be used, as these drugs are eliminated by extrarenal routes (Schwartz *et al.*, 1965; Koechlin *et al.*, 1965; Douglas *et al.*, 1963; Mark, 1971). Long-acting barbiturates are to be avoided (Cameron *et al.*, 1970). In cases of depression occurring in patients with renal failure, normal doses of phenothiazines and tricyclic compounds can be administered (Carmer *et al.*, 1969; Sjoquist *et al.*, 1971), whereas doses of lithium have to be adjusted.

With these considerations in mind, it seemed logical to study the pharmacokinetics of the new antidepressant nomifensine in patients with renal failure.

Methods

Two studies were carried out, study 1 in 10 patients with renal failure for pharmacokinetics and study 2 in three patients on maintenance dialysis.

Study 1

Patients Table 1 shows the relevant characteristics of the patients.

Protocol

Administration Nomifensine 50 mg orally were given together with breakfast to provide for constant absorption conditions.

Blood samples Samples were obtained before administration, at half-hourly intervals until 4 h after administration of drug continuing at hourly intervals until 8 h, and a final sample was taken at 24 h.

Assessments At the same intervals as the blood samples were taken, blood pressure, pulse rate and side effects were recorded.

Radioimmunoassay All blood samples were handled

Table 1 Characteristics of the 10 patients studied in the first trial

Patient	Diagnosis	Cl _{Cr} (ml/min)
1	Malignant nephroangiosclerosis	9
2	Acute tubular necrosis	3
3	Chronic interstitial nephritis	3
4	Chronic glomerulonephritis	52
5	Acute tubular necrosis	60
6	Chronic pyelonephritis	0
7	Polycystic kidneys	61
8	Chronic pyelonephritis	19
9	Chronic interstitial nephritis	6
10	Chronic glomerulonephritis	25

and plasma levels were assessed as described by Heptner *et al.* (1977).

Study 2

Patients Table 2 shows the characteristics of three patients studied together with the type of membrane used in the dialysis.

Protocol

Administration Nomifensine 50mg orally were given together with breakfast.

Blood samples Samples were obtained before administration and 1, 2 and 3 h afterwards, until the anticipated time of maximum plasma concentrations.

Dialysis was then started and continued for 3 hours. During dialysis blood samples were taken at half-hourly intervals. Finally, at 0, 2, 4 and 6 h after the end of dialysis, blood was taken.

Dialysate samples Dialysate samples were drawn at the beginning, the middle and at the end of dialysis.

Assessments Blood pressure, pulse rate and side-effects were assessed whenever a blood sample was taken.

Radioimmunoassay All blood and dialysate samples were handled and analyzed as described by Heptner *et al.* (1977).

Haemodialysis As shown in Table 2, three different membranes were used. The duration of these routine haemodialysis procedures was approximately 3 hours.

Results

Study 1

Table 3 shows parameters of nomifensine pharmacokinetics, such as time of maximum plasma concentrations (t_{max}), maximum plasma concentrations (C_{max}) and half-life (t_{50}), together with creatinine clearance (Cl_{Cr}) for the 10 patients of this study.

Figure 1 compares the time-plasma concentration curves of the 10 renal patients (arithmetic means and

Table 2 Characteristics of the three patients studied in the second trial

Patient	Cl _{Cr} (ml/min)	Diagnosis	Membrane used (Surface)
1	5	Chronic interstitial nephritis	Cuprophane (1.2 m ²)
2	5	Kimmelstiel-Wilson	Polyacrylonitril (1.0 m ²)
3	5	Polycystic kidneys	Cuprophane (1.5 m ²)

Table 3 Creatinine clearance and pharmacokinetic parameters

Patient	Cl _{Cr} (ml/min)	t_{max} (h after application)	C_{max} (ng/ml)	t_{50}
1	9	2.5	2,326	8.84
2	3	0.5	904	14.68
3	3	4.0	1,330	19.71
4	52	1.5	687	1.15
5	60	2.0	785	1.67
6	0	7.0	545	46.00
7	61	1.5	940	5.00
8	19	3.0	1,407	11.89
9	6	4.0	822	7.67
10	25	1.0	2,417	11.69

Figure 1 Time-plasma concentration for total nomifensine in renal patients (●, mean and extreme values, dose 50 mg) compared with healthy subjects (○, dose 100 mg).

Figure 3 Pharmacokinetics of nomifensine in patient 3 with Cl_{Cr} 3 ml/min (●, dose 50 mg, t_{50} 19.7 h). ○, Healthy subject (dose 100 mg, t_{50} 1.8 h).

Figure 2 Pharmacokinetics of nomifensine in patient 6 with Cl_{Cr} 0 ml/min (●, dose 50 mg, t_{50} 46 h). ○, Healthy subject (dose 100 mg, t_{50} 1.8 h).

Figure 4 Pharmacokinetics of nomifensine in patient 4 with Cl_{Cr} 52 ml/min (●, dose 50 mg, t_{50} 1.2 h). ○, Healthy subject (dose 100 mg, t_{50} 1.8 h).

Figure 5 Pharmacokinetics of nomifensine before, during and after haemodialysis in three patients. Membranes used: ●, cyprophane 1.2 m²; ▲, polyacrylonitril 1.0 m²; ■, cyprophane 1.5 m².

extreme values) compared with the pharmacokinetics in healthy volunteers. It should be noted that the latter had received nomifensine 100 mg, whereas for safety reasons only 50 mg were given to the patients with impaired renal function.

Figures 2, 3 and 4 present the pharmacokinetics of nomifensine as found in three typical patients with different glomerular filtration rates and corresponding half-lives.

Study 2

Figure 5 shows the time-serum concentration curves of the three dialyzed patients before, during and after haemodialysis. (The samples of patient 3 after dialysis were lost.)

In the dialysate of patient 1, dialyzed with a cyprophane membrane of 1.2 m², nomifensine was not detectable. In patient 2, who was dialyzed with a polyacrylonitril membrane of 1.0 m², at the end of the dialysis procedure a nomifensine concentration of 150 ng/ml was found in the dialysate (detection limit of radioimmunoassay 40 ng/ml).

Discussion

The reported results suggest that nomifensine is retained in the plasma of patients with impaired renal function. In this respect nomifensine seems to be different from the tricyclic compounds but similar to lithium.

The drug is probably not eliminated by extrarenal routes.

Nomifensine is not washed out by haemodialysis. The molecular weight of nomifensine is 354 (Hoffmann *et al.*, 1971). Molecules in the range 300–1,500 are less dialysable than smaller molecules such as urea (molecular weight 60) or creatinine (113).

It is noteworthy that some nomifensine was found in the dialysate when the polyacrylonitril membrane was used, whereas there were no detectable concentrations with the small surface area cyprophane dialyzer.

Nomifensine is well tolerated but not accumulated in patients with normal renal function (Rupp *et al.*, 1977; Bergener *et al.*, 1977). To avoid accumulation and adverse reactions we suggest that nomifensine is not given to patients with a glomerular filtration rate of less than 25 ml/min.

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Discussion

PROFESSOR BECKETT (London) remarked that the authors had demonstrated clearly the problems of analyzing drugs and their metabolites in biological fluids. The substantial differences in results obtained from different methods of analysis only emphasized the problems further. He disagreed with Dr Chamberlain who said that a person familiar with a particular type of analysis should use that analysis in his laboratory. This was because two of the methods reported, the ones least likely to suffer from interference (high pressure liquid chromatography and gas chromatography using a nitrogen-specific detector, did not give dissimilar results). The fundamental problem, was getting the drug or metabolite out in a suitable form for application and use in man.

Considering the conjugate, which he believed was highly water soluble, was there relevant accumulation, and would it be important in any biological action? Would the conjugate itself possess an action? Furthermore, was there conjugation on the primary aromatic amine or on the tertiary? This he regarded as important because there were some labile conjugates of tertiary nitrogen which could be hydrolysed under different conditions from normal conjugates.

DR CHAMBERLAIN (Milton-Keynes) suggested that the differences between results had been exaggerated and emphasized that the results were not on the same plasma samples analysed by different methods. Indeed, he was surprised how good the agreement between the methods was.

PROFESSOR BECKETT then asked whether there was any evidence that nomifensine was metabolised directly to metabolites M_2 and M_3 , or

whether metabolite M_1 went to M_2 and M_3 . Was there not a possibility that all three came from the same common intermediates?

DR HEPTNER (Frankfurt) replied that in rat liver slice studies, in which only nomifensine was used as a precursor, all three metabolites appeared according to the same kinetics. He therefore suggested that the metabolites were formed directly from nomifensine. Studies using metabolite M_1 as precursor were underway.

DR MARCEL (Paris) asked Professor Ringoir whether it was advisable to give half-normal doses to patients with diminished creatinine clearance, although exceeding 50 ml/minute.

PROFESSOR RINGOIR (Ghent) replied that one could either do that at normal time intervals, or alternatively give a normal dose at less frequent intervals. It was not possible to dialyze nomifensine, either because the substance was strongly protein bound or because its molecular weight exceeded 300.

ANOTHER SPEAKER asked whether the advice was relevant to treatment with other antidepressives.

PROFESSOR RINGOIR replied that the dose of lithium had to be adjusted when given to depressed patients with renal failure, but that it appeared from the literature that tricyclics could be given at normal dosage. When asked to explain further the relevance of molecular weights because that of nomifensine was not dissimilar from that of the tricyclics, he replied