Eur J Clin Pharmacol (1983) 24: 503–507

European Journal of
Clinical Pharmacology

Pharmacokinetics of Tocainide in Patients with Renal Dysfunction and During Haemodialysis

U. Wiegers[1], P. Hanrath[2], K. H. Kuck[2], A. Pottage[3], C. Graffner[3], J. Augustin[1], and M. Runge[1]

[1]Medical Clinic I and [2]Department of Cardiology, Medical Clinic II Universitäts-Krankenhaus, Eppendorf, Federal Republic of Germany, and [3]AB Hässle Mölndal, Sweden

Summary. The disposition of tocainide was studied in 15 patients with renal dysfunction. In 9 with total renal failure, the plasma half-life ranged from 16.6 to 42.7 h and total plasma clearance from 35 to 94 ml/min. The longest half-lives were found in 1 patient with cirrhosis, 3 taking the enzyme inhibitor allopurinol, and 1 on cimetidine. The mean half-life in the remaining patients was 22.3 ± 4.8 h (± SD). During a 4 h haemodialysis, the half-life in the 9 patients decreased to 8.5 ± 4.6 h, which was calculated to correspond to removal of 25 ± 14% of the drug from the body. In 6 patients with impaired renal function (creatinine clearance 10–55 ml/min) the tocainide half-life ranged from 13.2 to 22.0 h and total plasma clearance from 72 to 122 ml/min. One patient was taking allopurinol and 1 dihydralazine, and the mean half-life in the others was 19.2 ± 4.0 h. The apparent volume of distribution was similar to that found previously in healthy subjects. The results suggest that tocainide elimination is predictably reduced in patients with renal disease.

Key words: tocainide, pharmacokinetics; renal failure, antiarrhythmic drug, haemodialysis, cirrhosis, acetyldigoxin

Tocainide is an analogue of lidocaine with antiarrhythmic effects related to plasma concentration (Winkle et al. 1976). It is rapidly and completely absorbed after oral administration, shows first order kinetic behaviour, and is eliminated by both renal and non-renal routes. The terminal plasma half-life is about 15 h in patients with chronic ventricular arrhythmias and about 13 h in healthy subjects. In individuals with normal renal function about 40% of a dose is excreted unchanged in the urine. (Lalka et al. 1976; Graffner et al. 1980).

As renal excretion is a major route of elimination, tocainide may accumulate in patients with impaired renal function, potentially leading to toxicity. The main aim of the present study was to determine the effects of renal failure on the disposition of tocainide in order to develop dosage guidelines for patients with renal dysfunction. The effect of haemodialysis on the plasma concentration of tocainide was also examined in order to assess the results of this procedure in patients on treatment with this drug.

Patients and Methods

Fifteen patients were included in the study after giving their informed consent to it. Nine (Group A) were undergoing intermittent haemodialysis for end-stage renal failure, and 6 (Group B) had grossly impaired renal function, although they were not on haemodialysis. All patients were hospitalized throughout the study period, and no changes made to their normal activities or drug treatment schedules. Each received 3 400 mg tablets of tocainide hydrochloride (corresponding to 336 mg tocainide base) at intervals of 8 h. Venous blood was taken for tocainide assay at various times during drug administration and 2, 5, 6, 10, 12, 24 and 25 h after the last dose (Group A), or 2, 8, 14, 26, 37 and 51 h after the last dose (Group B). Plasma was separated and stored frozen for assay later by liquid chromatography (Lagerström and Persson 1978). The assay used is specific for unchanged tocainide, even in the presence of high concentrations of metabolites (Persson, personal communication).

Twenty-five h after the last dose of tocainide, patients in Group A started a 4 h period of haemodialy-

Table 1. Tocainide plasma half-life ($t_{½}$), apparent volume of distribution (V) and total plasma clearance (CL) in patients with total (Group A) or partial (Group B) renal failure

Patient No.	Sex	Age [years]	Weight [kg]	Creatinine clearance [ml/min]	$t_{½}$ [h]	C_{3min} [μmol/l]	$C_{\infty min}$ [μmol/l]	V [l]	CL [ml/min]	Concurrent drug therapy[a]
Group A										
1	F	65	49	< 5	20.3	27.3	48.9	114	65	Ad, Ah
2	F	62	49	< 5	37.8	21.6	60.7	183	56	Ad, Ah, Al, I
3	F	66	53	< 5	23.1	26.3	51.2	126	63	Ad, Ah, Ci
4	M	59	59	< 5	42.7	23.4	72.6	174	47	Ad, Ah
5	F	57	97	< 5	37.5	15.9	44.3	248	76	Ad, Al, Cl
6	F	70	67	< 5	27.5	24.5	54.0	145	61	Ad, Ah
7	F	77	51	< 5	24.8	30.7	62.9	111	52	Ad, Ah, Az
8	F	72	45	< 5	16.6	20.7	32.8	135	94	Ad, Cl
9	F	68	51	< 5	36.9	35.6	98.1	110	35	Ad, Ah, Al
Group B										
10	F	85	70	40	21.1	24.3	44.5	131	72	Ad, TH
11	F	26	66	55	13.2	20.1	28.1	120	105	
12	F	84	63	21	20.5	23.5	42.3	133	75	Ad, Co
13	M	51	68	10	22.0	16.0	30.2	202	106	
14	M	66	66	15	21.5	19.9	37.0	161	86	Ad, Al, G, B, Do
15	F	42	69	21	14.5	16.8	24.6	152	122	Ad, Cl, F, Di

[a] Ad = Acetyldigoxin; I = Indomethacin; Az = Azocillin; G = Glibenclamide; F = Frusemide; Ah = Aluminium Hydroxide; Ci = Cimetidine; TH = Triamterene/Hydrochlorothiazide; B = Benzafibrate; Di = Dihydralazine; Al = Allopurinol; Cl = Clonidine; Co = Cotrimoxazole

sis, using a parallel-plate dialyser (ER®-85) with a cellulose membrane (area 1.2 m^2), a blood flow of 150–250 ml/min and a dialysate flow of 500 ml/min. Venous blood for tocainide assay was taken at the end of the dialysis period.

Pharmacokinetic Calculations

The plasma half-life ($t_{½}$) of tocainide was calculated by linear regression analysis using the log concentrations measured 10–25 h (Group A) or 14–51 h (Group B) after the last dose. The half-life during dialysis ($t_{½D}$) was calculated from the pre- and post-dialysis concentrations, assuming first order elimination kinetics. The overall elimination rate constant (k) was derived conventionally from the $t_{½}$, and the fraction of drug in the body removed by haemodialysis (f_D) was calculated using the method of Gwilt and Perrier (1978).

Indirect estimates of the volume of drug distribution (V) and the total plasma clearance (CL) were made as follows: the minimum plasma tocainide concentration at steady state ($C_{\infty min}$) which should have resulted from the administered dose of 336 mg 8 hourly was calculated from the concentration 8 h after the third dose (C_{3min}) using the equation

$$\frac{C_{\infty min}}{C_{3min}} = \frac{1}{(1-e^{-3k\cdot\tau})}$$

where τ is the dosage interval. V was then calculated from

$$C_{\infty min} = \frac{D}{V}\left(\frac{1}{1-e^{k\cdot\tau}}\right) e^{k\cdot\tau}$$

where D is the dose given, and CL derived using the equation $CL = k \cdot V$ (Gibaldi and Perrier 1975). For the patients in Group A, the amount of drug present at the start of dialysis (A) was approximately estimated from the elimination rate constant, assuming complete absorption of each dose, and using the equation

$$A = D\,(e^{-41k} + e^{-33k} + e^{-25k})$$

where 41, 33 and 25 are the h between dosing and the start of dialysis. The amount of drug removed by dialysis (A_D) was then calculated from f_D, the fraction removed by dialysis. The above calculations assume one compartment model behaviour, first order kinetics and rapid and complete absorption. To test the validity of these assumptions, the change in plasma concentration resulting from dialysis of Group A was predicted in the following manner: with one compartment behaviour and first order kinetics the change in concentration should equal the amount removed by dialysis (A_D) divided by the volume of distribution (V). The additional contribution of non-dialysis elimination to the total change can be calculated as

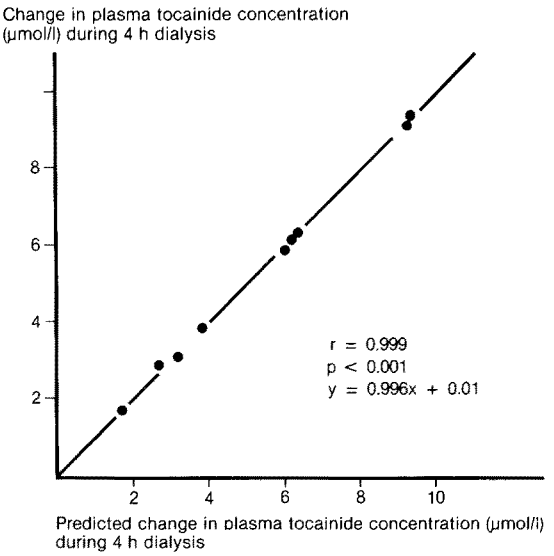

Fig. 1. Comparison of the measured and predicted changes in plasma tocainide resulting from 4 h of haemodialysis. See text for methods used to calculate the predicted values

Table 2. Tocainide plasma half-life ($t_{½D}$) and fraction (f_D) and amount (A_D) of drug removed during a 4 h haemodialysis in patients with end-stage renal failure

Patient No.	$t_{½D}$ [h]	f_D	A_D [mg]
1	2.9	0.53	177
2	5.7	0.33	180
3	11.1	0.12	44
4	6.4	0.30	177
5	16.2	0.09	49
6	15.2	0.07	33
7	7.0	0.24	96
8	5.9	0.24	64
9	6.2	0.30	163
Mean ± SD	8.5 ± 4.6	0.25 ± 0.14	109 ± 64

$$\text{Change in plasma concentration} = \frac{CL \cdot C_D \cdot t_D}{V}$$

where C_D is the mean concentration during dialysis, and t_D the duration of dialysis. The sum of the predicted changes was then compared to the change measured during the period of haemodialysis.

Results

Details of the patients are given in Table 1. All 9 patients in Group A had been undergoing intermittent haemodialysis for periods of up to 4 years. None of the 6 patients in Group B were undergoing haemodialysis, but all had severe renal dysfunction (creatinine clearance 10–55 ml/min) of up to 15 years duration. In addition to renal disease, other conditions included from which they suffered diabetes mellitus (Patients 1, 14), hypertension (Patients 3, 11, 13, 15), and cirrhosis (Patient 4). All 9 patients in Group A were taking acetyldigoxin and 7 aluminium hydroxide; four of the 6 patients in Group B were also taking acetyldigoxin. Amongst other drugs being administered were allopurinol (4 patients), cimetidine (1 patient) and the vasodilator dihydralazine (1 patient).

The mean plasma half-life of tocainide ranged from 16.6 to 42.7 h in patients in Group A and from 13.2 to 22.0 h in those in Group B; individual pharmacokinetic values given in Table 1. In Group A the longest half-life (42.7 h) was found in the patient with hepatic cirrhosis in addition to endstage renal failure. Three other patients in Group A had a half-life greater than 30 h and all were taking allopurinol. The patient in Group B taking allopurinol had a half-life of 21.5 h.

Estimates of the total plasma clearance (CL) ranged from 35 to 94 ml/min in Group A and 72 to 122 ml/min in Group B. In the latter, the lowest clearance values were found in the 2 elderly patients and in the patient on allopurinol. Estimates of the apparent volume of distribution (V) were similar in the groups, 110 to 2481 in Group A and 120 to 2021 in Group B.

The measured and predicted changes in plasma tocainide concentration resulting from dialysis are compared in Fig. 1. In all patients the measured concentration during dialysis, fell from 1.7–9.4 μmol/l (mean 5.4 ± 2.7 μmol/l); the pharmacokinetic parameters calculated from these data are given in Table 2. The mean half-life of tocainide during dialysis was 8.5 ± 4.6 h, and dialysis was calculated to have removed 25 ± 14% of the drug present in the body at the start of the dialysis period. Estimates of the amount of drug removed ranged from 33–180 mg (mean 109 ± 64 mg).

Discussion

In patients with chronic ventricular arrhythmias and presumed normal renal function, the mean half-life of tocainide is approximately 15 h (Winkle et al. 1976; McDevitt et al. 1976; Woosley et al. 1977). Shorter half-lives have been reported in healthy subjects – mean 11.3 h (Lalka et al. 1976) and mean 13.5 h (Graffner et al. 1980), corresponding to mean total plasma clearance values of 166 ± 14 (± SD) and 194 ± 33 ml/min, respectively. In patients with acute

myocardial infarction, the mean half-life was 14.3 h and the mean total plasma clearance was 205 ± 64 ml/min (Graffner et al. 1980).

In the patients with renal failure reported here, the half-life of tocainide was generally longer and the total plasma clearance was less than has been previously reported in subjects with normal renal function. Although this finding would be consistent with loss of the 40% renal contribution to elimination which has been described in healthy subjects (Lalka et al. 1976; Graffner et al. 1980), other explanations require consideration in view of the heterogenity of the patients studied. In Group A the longest half-life and 1 of the lowest clearance values was found in the patient (No. 4) with cirrhosis in addition to renal failure. Three other patients in Group A (Nos. 2, 5 and 9) had half-lives longer than 30 h, and all 3 were taking the enzyme inhibitor allopurinol. As these increases in half-life are greater than would be predicted on the basis of loss of renal elimination alone, the findings suggest that non-renal elimination of tocainide was also reduced in the patients. In view of this possibility, the patient with cirrhosis, all patients taking allopurinol, and 1 patient (No. 3) taking cimetidine have been excluded from further consideration of the effects of renal dysfunction on tocainide disposition. One other patient (No. 15), with the highest clearance value in Group B, has also been excluded because of the possibility that the vasodilator dihydralazine increased the clearance of tocainide.

In the remaining patients in Group A, the half-life of tocainide ranged from 16.6 to 27.5 h (mean 22.3 ± 4.8 h) and total plasma clearance from 52 to 94 ml/min (mean 68 ± 18 ml/min). Although the increase in half-life was consistent with the loss of a 40% renal contribution to elimination, the total plasma clearance was less than expected. This finding appeared to result from the reduced weight of the patients with total renal failure, as the total plasma clearance corrected for weight (1.34 ± 0.53 ml/min/kg) was similar to values for the non-renal clearance of tocainide reported in healthy subjects (1.31 ± 0.25 ml/min/kg, Lalka et al. 1976; 1.60 ± 0.33 ml/min/kg, Graffner et al. 1980). In Group B, the half-life of tocainide ranged from 13.2 to 22.0 h (mean 19.2 ± 4.0 h) and the total plasma clearance from 72 to 106 ml/min (mean 90 ± 19 ml/min/kg; 1.34 ± 0.28 ml/min/kg), the lowest clearance values being found in the 2 patients more than 80 years old. Estimates of the apparent volume of tocainide distribution were 126 ± 16 l (2.42 ± 0.40 l/kg) in Group A and 147 ± 37 l (2.19 ± 0.53 l/kg) in Group B, findings similar to those reported in healthy subjects (1.62 ± 0.22 l/kg, Lalka et al. 1976; 2.9 ± 0.2 l/kg Graffner et al. 1980). The distribution volume of lidocaine, an analogue of tocainide, is also unchanged in patients with uraemia (Thomson et al. 1973).

The results of the present study suggest that tocainide clearance falls and its half-life increases in patients with renal failure. This is presumably due to a reduction in the renal clearance of tocainide proportional to the degree of renal dysfunction. However, in view of the additional drug therapy given to most of the patients reported here, alternative explanations require consideration. Acetyldigoxin, taken by all patients in Group A, and the majority in Group B, could have produced a uniform reduction in tocainide clearance and this possibility cannot be excluded by the data available, although interactions of this type have not been previously reported with acetyldigoxin. In addition, aluminium hydroxide was taken by 7 of the 9 patients in Group A, but none in Group B. Antacids are known to influence the absorption of a number of drugs, and by altering the bioavailability of tocainide could have systematically affected the calculation of values in Group A. However, the possibility of reduced absorption of tocainide with antacids seems unlikely, as this would have resulted in an overestimate of clearance. In fact, the clearance values in patients given antacids were invariably less than in the patients not so treated.

The bioavailability of tocainide is virtually complete in healthy subjects (Lalka et al. 1976; Graffner et al. 1980) and this was assumed to be the case for the purpose of the calculation made here. If increased absorption of tocainide occurred with antacids, this assumption is even more likely to have been valid.

During haemodialysis, the mean half-life of tocainide fell to 8.5 ± 4.6 h, a change which was calculated to correspond to removal of 25 ± 14% of the quantity present at the start of the procedure. The half-life during dialysis was less than that reported in healthy subjects, and was directly related to patient weight ($p < 0.05$; Kendall's Rank Correlation test). Although the calculation of half-life during dialysis was based on only 2 data points, the predicted change in plasma tocainide during dialysis derived from this data showed a good correlation with the change actually measured. This would suggest that the assumptions made for the pharmacokinetic calculations were valid, and that during repeated oral administration and dialysis, tocainide shows one compartment model behaviour, first order kinetics and rapid and complete absorption. In view of the change in half-life during dialysis, and the fraction of the body content removed, haemodialysis may be useful in the management of patient's suffering over-

dosage with tocainide, and patients on haemodialysis may need drug replacement following the procedure.

From the findings it is concluded that the elimination of tocainide is impaired in patients with renal dysfunction. In patients with total renal failure, the dose of tocainide should be reduced by 50% by increasing the dosage interval. A reduction in dose may also be necessary in patients with partial renal dysfunction, and plasma level monitoring at steady state is recommended, as factors other than renal function such as liver disease and concurrent drug therapy, may influence the dosage required.

Haemodialysis increases the rate of elimination of tocainide and may remove an appreciable amount of it from the body. In fact, haemodialysis appears to clear the drug as effectively as normal mechanisms of elimination.

Acknowledgements. We wish to acknowledge the help of Ms. B. Månsson and P. Hindshaw who typed the manuscript.

References

Gibaldi M, Perrier D (1975) Pharmacokinetics. Marcel Dekker, New York

Graffner C, Conradson T-B, Hofvendahl S, Rydén L (1980) Pharmacokinetics of tocainide following intravenous and oral administration in healthy subjects and in patients with acute myocardial infarction. Clin Pharmacol Ther 27: 64–71

Gwilt PR, Perrier D (1978) Plasma protein binding and distribution characteristics of drugs as indices of their hemodialyzability. Clin Pharmacol Ther 24: 154–161

Laderström P-O, Persson BA (1978) Liquid chromatography in the monitoring of plasma levels of antiarrhythmic drugs. J Chromatogr 149: 331–340

Lalka D, Meyer MB, Duce BR, Elvin AT (1976) Kinetics of the oral antiarrhythmic lidocaine congener, tocainide. Clin Pharmacol Ther 19: 757–766

McDevitt DG, Nies AS, Wilkinson GR, Smith RF, Woosley RL, Oates JA (1976) Antiarrhythmic effects of the lidocaine congener, tocainide, 2-amino-2′, 6′-propionoxylidide, in man. Clin Pharmacol Ther 19: 396–402

Thomson PD, Melmon KL, Richardson JA, Cohn K, Steinbrunn W, Cudihee MD, Rowland M (1973) Lidocaine pharmacokinetics in advanced heart failure, liver disease and renal failure in humans. Ann Intern Med 78: 499–508

Winkle RA, Meffin PJ, Fitzgerald JW, Harrison DC (1976) Clinical efficacy and pharmacokinetics of a new orally effective antiarrhythmic tocainide. Circulation 54: 884–889

Woosley RL, McDevitt DG, Nies AS, Smith RF, Wilkinson GR, Oates JA (1977) Suppression of ventricular ectopic depolarisations by tocainide. Circulation 56: 980–984

Received: July 13, 1982
accepted in revised form: December 13, 1982

Prof. Dr. P. Hanrath
Department of Cardiology
Medical Clinic II
Martinistraße 52
D-2000 Hamburg 20
Federal Republic of Germany