Effect of haemodialysis on metoclopramide kinetics in patients with severe renal failure

M. R. WRIGHT¹, J. E. AXELSON^{1,2,6}, D. W. RURAK^{4,6}, B. McERLANE¹, G. H. McMORLAND^{2,6}, R. C. ONGLEY^{3,6}, Y. K. TAM⁷, & J. D. E. PRICE^{5,6}

¹Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, ²Department of Anaesthesiology, ³Division of Dermatology, ⁴Department of Obstetrics and Gynaecology, ⁵Division of Nephrology, ⁶Faculty of Medicine, The University of British Columbia, Vancouver and ⁷Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta

The kinetics of metoclopramide and the effects of haemodialysis on metoclopramide kinetics were examined in eight uraemic subjects 1 h and 24 h prior to the onset of dialysis. In spite of the relatively minor contribution of renal clearance to total body clearance in normals, metoclopramide kinetics were substantially altered in uraemia. The total body clearance was decreased by 2–4 fold, terminal elimination half-life proportionately increased, while the volume of distribution appeared to be unaffected compared with that previously demonstrated in normal healthy subjects. Haemodialysis does not appear to be effective in removing metoclopramide from the body and metoclopramide clearance subsequent to dialysis is unaltered. The kinetic parameters in the uraemic subjects are not significantly different between drug administrations 1 or 24 h prior to the time of onset of haemodialysis. Following kidney transplantation, in one subject, there appeared to be a rapid return to apparently normal kinetics from the uraemic state.

Keywords metoclopramide uraemia haemodialysis kidney transplantation

Introduction

Metoclopramide is effective in controlling the nausea and vomiting often associated with uraemia (Jones, 1968) and is widely used for this purpose. The observation has been made that the total clearance of metoclopramide in uraemic patients is much less than that seen in normal individuals despite the fact that renal clearance in normals is small (Bateman & Davies, 1979; Caralps, 1979; Bateman & Gokal, 1980). A subsequent investigation in our laboratory has shown a similar decrease in total body clearance in normals is small (Bateman & Tam *et al.*, 1981a). The mechanism(s) for this observed change has not been elucidated. One possibility may be that an unidentified substance which accumulates in uraemic plasma is capable of inhibiting metoclopramide metabolism. Such

a process has been demonstrated for (–)-propranolol in rats (Terao & Shen, 1985) and for racemic propranolol in uraemic humans (Bianchetti *et al.*, 1976). Furthermore, both studies suggest that this 'inhibitor' is dialysable. If such a process occurs for metoclopramide, then the pharmacokinetics of the drug could be expected to differ depending on the time of drug administration, relative to the initiation of dialysis.

The objectives of this investigation, therefore, were to examine the pharmacokinetics of metoclopramide in patients with severe renal disease, during and subsequent to haemodialysis and, in one patient, before and after a kidney transplant.

Correspondence and reprint requests: Professor J. E. Axelson, Division of Pharmaceutics and Biopharmaceutics, 2146 East Mall, Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, B.C., Canada V6T 1W5

Methods

Eight patients, seven males and one female, with severe renal impairment (creatinine clearance $< 10 \text{ ml min}^{-1}$) and on maintenance haemodialysis were studied. The protocol received the approval of the Human Ethics Committee of the University of British Columbia. All patients gave informed, written consent. Haematological and biochemical laboratory values were recorded from the patients' medical charts. All patients were requested to fast for 12 h before the study and to minimize food intake until at least 4 h following drug administration. All subjects were dialyzed using the Travenol® CF 1200 or 1211 capillary dialyzer at a blood flow rate of 200 ml min^{-1} for 3.5 to 5 h, depending upon their medical needs. The patients continued to take required medications during the study; these included multivitamins, aluminium hydroxide, laxatives and antihypertensive drugs. No analytical interference was noted due to any of these substances, their metabolites or the metabolites of metoclopramide, during measurement of metoclopramide.

The dialysis patients received a 10 mg i.v. dose of metoclopramide on two separate occasions. The first drug administration occurred 24 h prior to a dialysis session. Blood samples (1 ml) were taken from an indwelling cannula (Butterfly® 19-INT, Venisystems, Abbott Ireland Ltd) into a glass 1 ml tuberculin syringe (Glaspak®, Becton and Dickson, Rutherford, N.J.), centrifuged and the plasma then stored in clean Pyrex® culture tubes with screw-on PTFE-lined caps. Blood samples were drawn at -15, 5, 15, 30, 45, and 60 min, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 h following drug administration and at half-hourly intervals from the arterial and venous lines of the dialyser for the duration of the patients' haemodialysis. Following a period of at least 1 week, the patients were given a second 10 mg i.v. dose of metoclopramide 1 h prior to dialysis. Blood samples were taken at -15, 5, 15, 30, 45, and 60 min, then half-hourly from the dialyser arterial and venous lines during dialysis, and then at 5, 6, 8, 10, 12, and 24 h.

One patient received a kidney transplant before the second drug administration occurred. This allowed us to examine the pharmacokinetics of metoclopramide in this subject on three occasions, *viz.*, before transplantation, 16 days following renal transplantation and again 3 months following surgery. The protocol followed was the same as that used for the first drug administration to the renal patients. Relevant laboratory indices are shown in Table 2.

All samples were analysed by the gas-

chromatographic method of Riggs *et al.* (1983). Following analysis of biological samples for metoclopramide content, the data were plotted manually to yield initial kinetic estimates. The concentration *vs* time data were then fitted by AUTOAN (Sedman & Wagner, 1976) to give computer generated estimates of the kinetic parameters and assignment of a kinetic model. These initial estimates were then used by the computer program NONLIN (Metzler *et al.*, 1974) to yield final estimates of the kinetic parameters. Area under the plasma concentration *vs* time curve (AUC) values were estimated by the trapezoidal approximation. All kinetic calculations were based on the NONLIN generated parameters and the determined AUC values.

Statistical evaluations were performed using the paired *t*-test (significance of $P < 0.05$, two-tailed).

The values of clearance, volume of distribution and bioavailability were derived using standard equations (Gibaldi & Perrier, 1982). The dialysis parameters, extraction efficiency and dialyser clearance were calculated by the A-V difference method of Lee & Marbury (1984).

Results

The mean ($\pm$ s.d.) kinetic data derived from the uraemic subjects are tabulated in Table 1. In the individual subjects, there were no significant differences in the kinetic parameters for metoclopramide, when the 24 and 1 h predialysis studies were compared. Total body clearance was markedly decreased in uraemics ($0.16 \pm 0.06 \text{ l h}^{-1} \text{ kg}^{-1}$; $0.30 \pm 0.17 \text{ l h}^{-1} \text{ kg}^{-1}$) from the

Table 1 Metoclopramide pharmacokinetic parameters in uraemic volunteers

	24 h prior to haemodialysis	1 h prior to haemodialysis
λ_1 (h^{-1})	7.29 ± 5.53	6.10 ± 5.98
λ_2 (h^{-1})	0.058 ± 0.04	0.078 ± 0.05
AUC ($\mu\text{g l}^{-1} \text{ h}$)	1345.6 ± 1148.2	997.4 ± 1063.3
CL ^a ($\text{l h}^{-1} \text{ kg}^{-1}$)	0.16 ± 0.06	0.30 ± 0.17
V _{area} (l kg^{-1})	3.34 ± 1.23	4.44 ± 1.9
E ^b (%)	15.5 ± 12.5	20.1 ± 8.4
CL _D ^c (l h^{-1})	1.22 ± 1.11	1.84 ± 0.8

a. CL is the total body clearance.

b. E is the dialyser extraction efficiency.

c. CL_D is the dialyser clearance.

Paired *t*-testing showed no significant differences in the values of the calculated kinetic parameters with respect to the time of onset of dialysis relative to the time of dosing.

values seen in normal volunteers reported by our laboratory (Wright *et al.*, 1988) (0.370 ± 0.084 l $\text{h}^{-1} \text{kg}^{-1}$), while the terminal elimination half-life was proportionately increased in uraemia. In contrast, the volume of distribution (3.34 ± 1.23 l kg^{-1} ; 4.44 ± 1.91 l kg^{-1}) was relatively unchanged in the uraemics (V_{area} normals = 3.30 ± 1.30 l kg^{-1}). The extraction efficiency of the dialyser ranged from 2–38% and the dialyser clearance from 0.18–3.47 l h^{-1} , and accounted for less than 30% of total body clearance in all patients.

The data from the renal transplant recipient

are shown in Table 2. During uraemia, the typical pattern of greatly decreased total body clearance and increased elimination $t_{1/2}$ was seen. However, following transplantation, at both 16 days and 3 months, the kinetic parameters were in the range observed for normal volunteers.

There was no evidence of major side effects, including akathisia or dystonia, in any of the uraemic subjects. Some volunteers did experience transient drowsiness and mild irritability, which occurred very soon after intravenous drug administration.

Table 2 Metoclopramide pharmacokinetic and clinical parameters for uraemic volunteer BM before and after kidney transplantation.

Parameter	Before	16 days after	3 months after
Date	November 20/83	September 10/85	December 6/85
Weight (kg)	77.3	73.5	84.5
Serum creatinine ($\mu\text{mol l}^{-1}$)	1202	159	150
Blood urea nitrogen (mmol l^{-1})	38	13	10
λ_1 (h^{-1})	6.08	8.70	6.19
λ_2 (h^{-1})	0.11	0.21	0.21
AUC ($\mu\text{g l}^{-1} \text{h}$)	713.8	316.9	145.9
V_{area} (l kg^{-1})	1.52	2.10	3.74
CL^{a} (l $\text{h}^{-1} \text{kg}^{-1}$)	0.18	0.43	0.81
$\text{CL}_{\text{R}}^{\text{b}}$ (l $\text{h}^{-1} \text{kg}^{-1}$)	—	0.06	0.08
$\text{CL}_{\text{NR}}^{\text{c}}$ (l $\text{h}^{-1} \text{kg}^{-1}$)	0.18	0.37	0.73
% dose excreted intact	—	14	10

a. CL, is total body clearance

b. CL_{R} , is renal clearance

c. CL_{NR} , is nonrenal drug clearance.

Discussion

The finding in normal volunteers that renal elimination accounts for only about 25% of total body clearance (Wright *et al.*, 1988; Bateman, 1983), suggests that renal failure should have relatively little effect on metoclopramide kinetics. Metoclopramide has low protein binding (~40%), the extent of which is unchanged in uraemia (Webb *et al.*, 1986). Hence, it would be expected that metoclopramide kinetics in uraemia should be relatively similar to those of the normal volunteers. However, clinical experience (Bateman, 1979; Caralps, 1979) and subsequent pharmacokinetic investigation (Bateman *et al.*, 1981; Lehmann *et al.*, 1985) suggests that this is not the case. From our present results, it appears that there is at least a two-fold decrease in total clearance. This is accompanied by a proportionate increase in terminal elimination half-life without any significant change in the volume of distribution. In addition, haemodialysis is inefficient at clear-

ing metoclopramide from the body. This would be expected from the large volume of distribution of this drug. Therefore, our results and those of Lehmann *et al.* (1985) suggest that dosage supplementation subsequent to dialysis is unnecessary.

Although previous investigators (Bateman *et al.*, 1981; Lehmann *et al.*, 1985) have examined the basic pharmacokinetics and removal of drug by haemodialysis, the present investigations focussed on a somewhat different aspect of metoclopramide pharmacokinetics in renal failure. When a patient is haemodialysed, the blood is 'cleansed' of end-products of metabolism many of which could be potential inhibitors of drug metabolism (Terao & Shen, 1985). By examining each patient on two separate occasions, it was anticipated that a change in the elimination kinetics of metoclopramide might be demonstrated, mediated by the removal of a plasma 'inhibitory substance' as suggested for propranolol (Bianchetti *et al.*, 1976; Terao & Shen, 1985). The lack of a demonstrated effect

of haemodialysis on metoclopramide kinetics suggests that either there is no such 'inhibitor' of metoclopramide metabolism accumulating in the plasma of the uraemic subjects or, alternatively, that if there is such a substance it is not removable by haemodialysis. The latter view may be supported by the apparently rapid change in metoclopramide kinetics following kidney transplantation. This rapid reversion of kinetics to apparently normal values may suggest that there is no irreversible deficit in metoclopramide metabolism induced by renal failure. Our observations are in apparent contrast with those of Terao & Shen (1985) and Bianchetti *et al.* (1976), who have postulated such a dialysable inhibitory substance in similar studies of propranolol disposition.

In spite of a relatively minor contribution of renal clearance to total clearance in normals, kidney failure substantially alters metoclopra-

mid pharmacokinetics. This change is manifested by a large decrease in total body clearance accompanied by a large increase in terminal half-life but no change in volume of distribution. The mechanism of the unexpected alteration of metoclopramide pharmacokinetics in kidney disease remains unclear and warrants further investigation.

The authors are grateful to the Medical Research Council of Canada (MRC), The Kidney Foundation of Canada and the Vancouver Foundation for their support of this research. The authors also wish to thank the MRC for the MRC Studentship Award to Mr M. R. Wright. Thanks are offered to A. H. Robins Canada, Inc. and Nordic Laboratories, Inc. for the supply of authentic metoclopramide reference standards and the clinical supplies used in this drug metabolism study. Finally, the dedication and effort offered by Ms Nora Wong, R.N., during the experimentation with the dialysis patients is warmly recognized.

References

- Bateman, D. N. (1983). Clinical pharmacokinetics of metoclopramide. *Clin. Pharmacokin.*, **8**, 523-529.
- Bateman, D. N. & Davies, D. S. (1979). Pharmacokinetics of metoclopramide. *Lancet*, **i**, 166.
- Bateman, D. N. & Gokal, R. (1980). Metoclopramide in renal failure. *Lancet*, **i**, 982.
- Bateman, D. N., Gokal, R., Dodd, T. R. P. & Blain, P. G. (1981). The pharmacokinetics of single dose metoclopramide in renal failure. *Eur. J. clin. Pharmac.*, **19**, 437-441.
- Bateman, D. N., Kahn, C. & Davies, D. S. (1980). The pharmacokinetics of metoclopramide in man with observations in the dog. *Br. J. clin. Pharmac.*, **9**, 371-377.
- Bianchetti, G., Graziani, G., Brancoccio, D., Morganti, A., Leonetti, G., Manfrin, M., Sega, R., Gomeni, R., Ponticelli, C. & Morselli, P. L. (1976). Pharmacokinetics and effects of propranolol on terminal uremic patients undergoing regular dialysis treatment. *Clin. Pharmacokin.*, **1**, 373-384.
- Caralps, A. (1979). Metoclopramide and renal failure. *Lancet*, **i**, 554.
- Gibaldi, M. & Perrier, D. (1982). *Pharmacokinetics*, 2nd Edition, pp. 83-84. New York: Marcel Dekker Inc.
- Jones, C. T. (1968). Metoclopramide in the treatment of nausea. A double blind trial. *N.Z. med. J.*, **68**, 388-393.
- Lee, C. C. & Marbury, T. C. (1984). Drug therapy in patients undergoing haemodialysis: Clinical pharmacokinetic considerations. *Clin. Pharmacokin.*, **9**, 42-66.
- Lehmann, C. R., Heironimus, J. D., Collins, C. B., O'Neil, T. J., Pierson, W. P., Crowe, J. T., Melikian, A. P. & Wright, G. J. (1985). Metoclopramide kinetics in patients with impaired renal function and clearance by haemodialysis. *Clin. Pharmac. Ther.*, **37**, 284-289.
- Metzler, C. M., Elfring, G. L., & McEwen, A. J. (1974). A package of computer programs for pharmacokinetic modelling. *Biometrics*, **30**, 562-563.
- Riggs, K. W., Axelson, J. E., Rurak, D. W., Hasman, D. A., McErlane, B., Bylsma-Howell, M., McMorland, G. H. & Price, J. D. E. (1983). Electron-capture determination of metoclopramide in biological fluids using fused silica capillary columns: Application to placental transport studies in sheep and humans. *J. Chromatogr.*, **276**, 319-328.
- Sedman, A. & Wagner, J. G. (1976). *AUTOAN. A decision-making pharmacokinetic computer program*. Publication distribution service. Ann Arbor, Michigan.
- Tam, Y. K., Axelson, J. E., McErlane, B., Kapil, R. P., Riggs, K. W., Ongley, R. & Price, J. D. E. (1981). The pharmacokinetics of metoclopramide in rats with experimental renal and hepatic dysfunction. *J. Pharmac. exp. Ther.*, **219**, 141-146.
- Terao, N. & Shen, D. D. (1985). Reduced extraction of *l*-propranolol by perfused rat liver in the presence of uremic blood. *J. Pharmac. exp. Ther.*, **233**, 277-284.
- Webb, D., Buss, D. C., Fifield, R., Bateman, D. N. & Routledge, P. A. (1986). The plasma protein binding of metoclopramide in health and renal disease. *Br. J. clin. Pharmac.*, **21**, 334-336.
- Wright, M. R., Axelson, J. E., Rurak, D. W., McErlane, B., McMorland, G. H., Ongley, R., Tam, Y. K. & Price J. D. E., (1988). Linearity of metoclopramide kinetics at doses of 5-20 mg. *Br. J. clin. Pharmac.*, **26**, 471-475.

(Received 14 January 1988,
accepted 14 June 1988)