Br. J. clin. Pharmac. (1983), **15**, 557–559

DYSTONIC REACTIONS AND THE PHARMACOKINETICS OF METOCLOPRAMIDE IN CHILDREN

D.N. BATEMAN[1], A.W. CRAFT[2], E. NICHOLSON[1] & A.D.J. PEARSON[2]

Departments of Clinical Pharmacology[1] and Paediatrics,[2] The University of Newcastle upon Tyne, Newcastle upon Tyne, NE1 7RU

The pharmacokinetics of metoclopramide have been studied in nine children receiving the drug as prophylaxis for cytotoxic induced vomiting. Plasma concentrations of metoclopramide have also been studied in three children with dystonic reactions to the drug. The pharmacokinetics in children were similar to those reported in healthy adults. There was no difference in the plasma concentration of metoclopramide of children with dystonia when compared to those without this adverse effect. Kinetic differences in childhood do not explain the occurrence of dystonia, which in the individual appears to be related to factors other than plasma drug concentrations.

Introduction

Metoclopramide is a commonly used anti-emetic drug which has been associated with a variety of adverse effects of the central nervous system (Bateman & Davies, 1979; Lavy *et al.*, 1978) and in children in particular with dystonic reactions (Casteels-Van Daele *et al.*, 1970). In adults given standard therapeutic doses, metoclopramide undergoes dose dependent kinetics, and the bioavailability of oral metoclopramide is very variable between 30 and 95% (Bateman *et al.*, 1978; Graffner *et al.*, 1979). In adults the adverse effect of akathisia is related to the peak plasma drug concentration after oral dosing (Bateman *et al.*, 1979).

In order to investigate the possibility that the increased incidence of dystonic reactions in children might be related to alterations in the pharmacokinetics of the drug resulting in higher plasma concentrations, we have investigated the pharmacokinetics of intravenously administered metoclopramide in children, and compared the plasma concentrations obtained with those of three children presenting with acute dystonic reactions.

Methods

Nine children receiving cytotoxic therapy for malignant disease were given intravenous metoclopramide 0.15 – 0.46 mg/kg body weight as a pre-cytotoxic anti-emetic on a total of 11 occasions. The drug was injected slowly over 5 min. Blood samples (5 – 7 ml) were drawn from the cannula used to administer cytotoxic therapy, pre-dose and at 1, 2, 4 and 6 h post dose. Plasma was separated and assayed for metoclopramide by high pressure liquid chromatography (Bateman *et al.*, 1981). Subjective recording of nausea, vomiting and sedation were made using visual analogue scales at the same time as plasma sampling. Three other children were studied who had experienced dystonic reactions. In one child who received metoclopramide 5 mg (0.15 mg/kg body weight) as prophylaxis for cytotoxic induced vomiting a dystonic reaction occurred within 15 min of administration and plasma samples were obtained following this. Plasma was also obtained from two other children who presented at the Royal Victoria Infirmary, Newcastle, with dystonic reactions. These children had been receiving oral metoclopramide prescribed by their general practitioner as treatment for an intercurrent vomiting illness and had received 22.5 and 30 mg respectively in the 24 h prior to presentation. In one of these children the elimination kinetics of metoclopramide was studied. The dystonic reactions were successfully treated in all three children with intravenous anticholinergic therapy.

Pharmacokinetic analysis

In adults the plasma decline of metoclopramide is best described by a bi-exponential equation (Bateman *et al.*, 1978). The alpha (distribution) phase is rapid ($t_{1/2}$ 4.1 ± 2.7 min) and the kinetic parameters derived

0306–5251/83/0500–0557 $02.00

from the β elimination phase are thus an appropriate approximation of the distribution and elimination of the drug. In view of the difficulty in obtaining multiple samples in children, we have therefore used β elimination phase samples and considered the kinetics in terms of a one compartment system. Volume of distribution (V) was derived from:

$$V = \frac{\text{Dose}}{C(0)}$$

where $C(0)$ is the intercept of the plasma drug concentration regression line on the ordinate.
Total body clearance CL was calculated from:

$$\text{CL} = V \times k$$

where k is the apparent elimination rate constant.

Results

The age, dose and derived pharmacokinetic parameters of the nine children receiving metoclopramide for cytotoxic chemotherapy induced vomiting are shown in Table 1. Vomiting occurred within 6 h of administration of the cytotoxic drug during 9 of the 11 treatments. There was no correlation between the frequency of vomiting and the area under the plasma metoclopramide concentration time-curve or the initial plasma concentration of the drug ($C(0)$). Plasma metoclopramide concentrations in two patients presenting with dystonia were 78 and 193 ng/ml respectively and the measured plasma concentration at the time of dystonia in the child who developed dystonia after intravenous metoclopramide for cytotoxic induced vomiting was 143 ng/ml. The plasma half-lives of metoclopramide in two children with dystonia in whom this was measured were 6.9 and 1.3 h and the clearance of metoclopramide in the child with dystonia after intravenous metoclopramide was 0.5 l h^{-1} kg^{-1} body weight. There was no correlation between body weight or age and clearance of metoclopramide.

Discussion

The adverse effect of dystonia is probably secondary to blockade of specific dopamine receptors in the basal ganglia. Dystonic reactions to the neuroleptic butaperazine in adult schizophrenics occurred 23 h or more after a single oral dose (Garver *et al.*, 1978), and the elimination half-life in patients who suffered this effect were reported to be longer than in those who did not (Garver *et al.* (1976). Furthermore, the red blood cell concentrations of butaperazine were significantly higher at the time of dystonia in the patients who suffered this effect than at the same time points in those who did not. Since the red blood cell plasma ratio of metoclopramide is not concentration dependent (Tam *et al.*, 1981) we have measured the plasma concentrations of this drug.

Dystonia with metoclopramide is generally recognised to be more frequent in children (Casteels-Van Daele *et al.*, 1970), but it is not known why only certain of them develop the adverse effect. One possible reason might be that the children affected are in fact receiving an excessive dose of metoclopramide due to increased systemic bioavailability after oral dosing or excess intake in an attempt to alleviate symptoms of nausea. In this study the plasma concentration of metoclopramide taken at the time of dystonic movement in three children was not significantly different to observed plasma concentrations in children receiving metoclopramide for cytotoxic induced vomiting. In addition a reduced rate of elimination of the drug did not appear to be a factor in those children who suffered this effect. These two observations therefore suggest that a change in the pharmacokinetics of metoclopramide in the individual child is not a factor in the production of dystonia. The study was not undertaken on normal children but there was no biochemical evidence of impairment of renal or hepatic function. The difference between our findings with metoclopramide and those reported with butaperazine may be due to the fact that butaperazine has some anticholinergeric activity (Garver *et al.*, 1978).

Although there was no difference in pharmacokinetic variables between children who suffered dystonia and those who did not, there must be other factors that contribute to the occurrence of dystonia and one such factor may be the penetration of metoclopramide into the central nervous system.

In the doses used metoclopramide appeared to be a poor antiemetic in the prophylaxis of cytotoxic induced vomiting.

This work was supported in part by the Cilag Chemie Foundation and Beechams Pharmaceuticals. A.D.J.P. was supported by the Leukaemia Research Fund.

Table 1 Kinetic parameters in children receiving metoclopramide intravenously as an antiemetic

	Age (*years*)	*Dose* (*mg/kg*)	*Half-life* (*h*)	C(0) (*ng/ml*)	V (*l/kg*)	*CL* ($l\,h^{-1}\,kg^{-1}$)
Mean	11.7	0.35	4.4	152	3.0	0.56
± s.e. mean	0.67	0.025	0.56	31	0.38	0.10
Range	7 – 14	0.22 – 0.46	1.7 – 8.3	65 – 395	1.0 – 4.8	0.12 – 1.22

References

BATEMAN, D.N. & DAVIES, D.S. (1979). Pharmacokinetics of metoclopramide. *Lancet*, **ii**, 641.

BATEMAN, D.N., GOKAL, R., DODD, T.R.P. & BLAIN, P.G. (1981). The pharmacokinetics of single doses of metoclopramide in renal failure. *Eur. J. clin. Pharmac.*, **19**, 437–441.

BATEMAN, D.N., KAHN, C. & DAVIES, D.S. (1979). Concentration effect studies with oral metoclopramide. *Br. J. clin. Pharmac.*, **8**, 179–182.

BATEMAN, D.N., KAHN, C., MASHITER, K. & DAVIES, D.S. (1978). Pharmacokinetic and concentration-effect studies with intravenous metoclopramide. *Br. J. clin. Pharmac.*, **6**, 401–407.

CASTEELS-VAN DAELE, M., JAECKEN, J., VAN DER SCHUEREN, P., ZIMMERMAN, A. & VAN DEN BON, P. (1970). Dystonic reactions in children caused by metoclopramide. *Arch. Dis. Child.*, **45**, 130–133.

GARVER, D.L., DAVIS, J.M., DEKIRMENJIAN, H., ERICKSON, S., GOSENFELD, L. & HARASZTI, J. (1978). Dystonic reactions following neuroleptics: Time course and proposed mechanisms. *Psychopharmacology*, **47**, 199–201.

GARVER, D.L., DAVIS, J.M., DEKIRMENJIAN, H., JONES, F.D., CASPER, R. & HARASZTI, J. (1976). Pharmacokinetics of red blood cell phenothiazine and clinical effects. *Arch. gen. Psychiat.*, **33**, 862–866.

GRAFFNER, C., LAGERSTROM, P.O., LUNDBORG, P. & ROHN, O. (1979). Pharmacokinetics of metoclopramide intravenously and orally determined by liquid chromatography. *Br. J. clin. Pharmac.*, **8**, 469–474.

LAVY, S., MELAMED, E. & PENCHAS, S. (1978). Tardive dyskinesia associated with metoclopramide. *Br. med. J.*, **1**, 77–78.

TAM, Y.K., AXELSON, J.E., McERLANE, B., ONGLEY, R. & PRICE, J.D.E. (1981). Dose-dependent pharmacokinetics of metoclopramide in rat: An effect of hemoperfusion? *J. Pharmac. exp. Ther.*, **217**, 764–769.

(Received November 8, 1982, accepted December 20, 1982)