Placental transport of metoclopramide: Assessment of maternal and neonatal effects

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Twenty-three patients undergoing general anaesthesia for Caesarian section for healthy term pregnancies were entered into a double blind study using metoclopramide (MCP) and a normal saline placebo. Of these patients, eight received intravenous metoclopramide, 12 a normal saline placebo and three were lost to clinical follow-up. The maternal gastric volumes were measured and maternal and foetal MCP plasma concentrations were determined by gas–liquid chromatography. The Neurological and Adaptive Capacity Score tests of Amiel, Barrier and Schnider (NACS) were used to attempt evaluation of neonatal responses to MCP. Maternal gastric volume was significantly lower ($p < 0.05$) in the treated patients. There were no marked differences in Apgar scores, cardiovascular parameters or neurobehavioural scores between the treated and untreated groups of neonates. At no time were the foetal metoclopramide plasma concentrations observed to exceed maternal values.

Key words

PREMEDICATION: metoclopramide, placental transport, foetal effects.

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Aspiration of stomach contents during obstetrical anaesthesia is still the most common cause of maternal mortality due to anaesthesia; it is the fourth overall cause of maternal death after haemorrhage, toxaemia and sepsis.[1] Ever since Mendelson[2] in 1946 first described the syndrome of pulmonary aspiration in obstetric patients undergoing general anaesthesia, there have been studies to elucidate mechanisms involved. Gastric volume and pH are important contributing factors and it is generally well accepted that gastric contents with a volume of less than 0.4 $ml \cdot kg^{-1}$ and a hydrogen ion concentration $[H^+]$ of less than 3.16×10^{-3} milliequivalents per litre ($mEq \cdot l^{-1}$) are probably not hazardous.

Some of the commonly employed preventative measures aimed at reducing the incidence of pulmonary aspiration consist of fasting patients during labour and prior to elective Caesarian section, rapid sequence induction with cricoid pressure and the use of antacids.

Foulkes and Jenkins[3] have shown that both the oral non-particulate antacid, sodium citrate (0.3M) and the histamine H_2-receptor antagonist, cimetidine, effectively raise the pH above 2.5, the deemed critical value.[4] It should be considered, however, that the administration of 30 ml of sodium citrate may raise the gastric volume appreciably, further contributing to the risk of gastric aspiration. The use of antacid therapy to raise maternal gastric pH is also not considered to be invariably reliable.[5]

A more recent method of reducing aspiration risk involves the use of the potent antiemetic and gastric motility modifier metoclopramide (MCP). Metoclopramide has been shown to significantly diminish the frequency of vomiting during labour,[6] as well as to increase the gastric emptying rate[7] and

tone of the lower oesophageal sphincter,[8] both of which are reduced in labour. These positive actions of MCP have led to its more frequent use in obstetrical anaesthesia in Canada as well as in Europe and Japan.[9]

In view of MCP's potential to reduce maternal mortality due to pulmonary aspiration it is used increasingly in parturient women undergoing general anaesthesia. Unfortunately, little is known of the potential for MCP placental transport and its possible effects upon the neonate.[6,7] It is recognized, however, that there are reports of an increased incidence of side effects (agitation, irritability, extra-pyramidal dystonia) with MCP in infants and young children, although in most cases the recommended dose of MCP had been exceeded.[10,11]

The present report describes the results of a placental transport study conducted in a double-blind fashion in parturient women undergoing elective Caesarian section. Maternal and foetal plasma concentrations of MCP have been measured using an electron-capture gas-liquid chromatography assay method recently developed in our laboratory for use in placental transport studies in humans and sheep.[12] Maternal drug effects of MCP have been assessed through measurement of gastric volumes and neonatal drug effects determined using Apgar and the NACS neurobehavioural tests.[13]

Materials and methods

This study received the approval of the Ethics Committee on Human Experimentation which decided specific consent was not required. Patient selection was limited to ASA (American Society of Anaesthesiologists) Physical Status Class I individuals who wished to have general anaesthesia for delivery of full-term gestation where there was no evidence of foetal distress. All patients were comparable as regards to age, weight and gestational age, while none of the patients experienced dyspeptic symptoms other than the oesophageal refluxing commonly encountered in late pregnancy. Twenty-three patients were fasted overnight and were given 30 ml 0.3 M sodium citrate p.o., one hour prior to induction of anaesthesia. Metoclopramide ($\bar{x}$ = 0.14 ± 0.02 $mg \cdot kg^{-1}$) or an equivalent volume of placebo normal saline was administered intravenously in a randomized double blind manner approximately 30 minutes preoperatively ($\bar{x}$ = 30.60 ± 10.34 min; range, 12–51 min.).

Anaesthesia was induced in all patients using standard techniques of rapid sequence induction and cricoid pressure. Thiopental 4.0 $mg \cdot kg^{-1}$ (± 1.4 mg) was used for induction. All patients were subsequently maintained with $N_2O:O_2$::50:50 and halothane 0.5 per cent prior to delivery of the infant. Following delivery a Salem gastric tube (14 gauge) was inserted orally by an independent observer and maternal stomach contents were aspirated until dry. These results were recorded and filed in a sealed envelope until completion of the study. A maternal venous (MV) blood sample was taken after induction of anaesthesia prior to the delivery of the infant. Both umbilical venous (UV) and arterial (UA) blood samples were obtained at delivery from a doubly clamped section of the umbilical cord. The samples were then placed in heparinized tubes, centrifuged and the plasma removed and frozen (−20° C) for later analysis using an assay method recently established in our laboratory capable of metoclopramide measurement with an average coefficient of variation of 5–6 per cent.[12]

Apgar scores were assessed by the attending paediatric intensive care nursery team at one and five minutes. Neonatal heart rate and blood pressure (systolic) (by Arteriosonde*) were recorded one hour after birth. One examiner, blind to the gastric volume aspiration data, scored and evaluated the infants at two, four, six and 24 hours of age using the NACS Neurobehavioural test. This examiner was a resident in anaesthesia with special training in neonatal care.

Analysis of the accumulated data on each of the following parameters: gestational age, birth weight, heart rate, blood pressure, maternal gastric volume, maternal age and weight, dose of MCP and administration times was completed using the Students' t-test subprogramme of the Statistical Package for the Social Sciences version 9 (SPSS:9).[14] Significance was determined at the 0.05 level.

Results

Three infants developed respiratory difficulties at delivery and were subsequently transferred to the intensive care nursery (ICN). Since these babies

*Roche Model 1010 Arteriosonde, Roche Medical Electronics, Cranbury, N.J. 08512.

TABLE I Plasma analysis data

Patient code	Maternal Age (yrs)	Wt (kg)	I.V. Dose ($mg \cdot kg^{-1}$)	Sample elapsed time (min) MV[1]	UMB[2]	Maternal gastric volume (ml)	Plasma MCP concentrations ($ng \cdot ml^{-1}$)[3] MV	UV	UA
MCP treated									
2S	28	68	0.15	29	32	35	61.16 ± 0.22	18.82 ± 0.13	18.28[4]
5S	24	70	0.10	34	42	35	57.22 ± 1.97	38.64 ± 2.43	38.06[4]
9S	23	80	0.15	21	30	8	63.01 ± 3.12	38.75 ± 3.27	32.78[4]
12S	27	84	0.14	50	53	4	49.06 ± 3.51	45.57 ± 3.64	43.02 ± 1.05
19S	20	68	0.15	31	30	9	85.03 ± 2.05	48.57 ± 0.78	48.14[4]
22S	23	63	0.14	15	19	12	57.72 ± 2.02	35.71 ± 0.53	24.79 ± 1.10
29S	31	90	0.15	32	36	14	42.19 ± 0.49	25.87 ± 0.15	30.53 ± 2.31
34S	33	75	0.15	30	34	35	74.34 ± 2.50	37.05 ± 0.62	34.80 ± 1.95
$\bar{X}$	26.13	74.75	0.14	30.25	34.50	19.00[5]	61.22	36.12	33.80
SD	±4.42	±9.24	±0.02	±10.19	±9.91	±13.57	±13.53	±9.73	±9.59
Placebo									
1S	31	60	0.15	34	37	165	—	—	—
3S	22	62	0.15	51	59	190	—	—	—
7S	29	82	0.12	27	35	20	—	—	—
8S	33	64	0.14	24	28	63	—	—	—
10S	27	55	0.10	12	20	52	—	—	—
16S	28	75	0.15	45	56	48	—	—	—
26S	31	86	0.14	28	36	15	—	—	—
28S	30	70	0.14	21	22	5	—	—	—
30S	37	90	0.15	30	31	27	—	—	—
32S	34	86	0.14	25	36	5	—	—	—
33S	30	62	0.15	40	46	30	—	—	—
42S	27	63	0.14	26	30	95	—	—	—
$\bar{X}$	29.92	71.25	0.14	30.25	36.33	59.58[5]			
SD	±3.85	±12.06	±0.02	±10.77	±12.09	±61.07			

[1]MCP administration time – MV sample time.
[2]Umbilical samples (UV, UA); MCP administration time – delivery time.
[3]Mean ($\bar{X}$) of two separate determinations ± one standard deviation (SD).
[4]Single determination.
[5]Significantly different at $p < 0.05$, Students' t-test (SPSS-9)[14].

were lost to neurological follow-up, *viz.*, Apgar and NACS assessment, they, along with their mothers, were excluded from the study thus reducing the number of participants to 20.

Eight out of the 20 patients who were involved in the double-blind study received MCP while the remaining 12 were given sodium chloride for injection, as evidenced by the lack of a chromatographic peak for MCP. The results of the plasma determinations were in agreement with the coded treatments when the code was broken following completion of the plasma analyses. Plasma MCP concentrations (MV, UV, UA) are presented in Table I illustrating that MCP does undergo placental transfer. In no instance did foetal cord plasma MCP concentrations (UV, UA) exceed maternal values over the period of study (12–53 min. following MCP administration).

The results of MCP's effect on maternal gastric volume are also shown in Table I. There is a significant difference (Students' t-test, $p < 0.05$) between the volumes of treated and untreated patients ($\bar{x} = 19.0 \pm 13.5$ ml *vs* $\bar{x} = 59.5 \pm 61.0$ ml) confirming the observation of others.[7] It can also be observed that there is a wide variation in the gastric volumes within the untreated group.

TABLE II Infant data

Patient Code	Gestational age (weeks)	Sex (M, F)	Birth Weight (g)	Apgar[1] Score	HR bpm	BP (systolic) (mm·Hg)
MCP treated						
2S	40	M	3800	8, 9	148	55
5S	40	M	3060	8, 9	122	65
9S	40	F	4060	9, 10	140	58
12S	39	F	3540	9, 9	160	56
19S	39	F	2690	9, 9	150	58
22S	40	M	3070	8, 9	148	56
29S	39	F	3670	9, 9	150	50
34S	39	F	4760	9, 10	160	68
$\bar{X}$	39.5		3581		147	58
SD	±0.5		±6.55		±12	±8
Placebo						
1S	40	F	3340	9, 9	150	55
3S	40	F	3900	3, 9*	169	74
7S	38	F	3910	8, 9	145	54
8S	38	F	3240	8, 9	152	68
10S	38	F	2960	8, 10	145	62
16S	39	F	3380	8, 9	160	46
26S	40	M	3050	7, 9	140	58
28S	40	F	3220	8, 9	176	52
30S	40	F	3858	8, 9	150	58
32S	40	M	4680	8, 9	148	60
33S	38	M	3040	8, 9	160	56
42S	40	M	2840	9, 10	140	50
$\bar{X}$	39.3		3451.5		153	58
SD	±0.1		±154		±11	±8

[1]Apgar scores determined at one and five minutes post delivery (,).
*Unanticipated problems at delivery likely contributed to low 1 min Apgar score.

Roberts and Shirley[4] have also shown that there is a large range in gastric volumes in patients fasted for 8–12 hours prior to delivery by Caesarian section.

Application of the Students' t-test to the analysis of gestational age, sex distribution, birth weight and cardiovascular parameters (HR, BP) demonstrated no significant differences between the treated and untreated groups (Table II). Although the BPs appear low, this may be a measurement artifact associated with the use of the Arteriosonde. All babies were pink and well perfused at birth, with good peripheral pulses.

The results of one and five minute Apgar assessments are presented in Table II. Except for baby 3S (in the untreated group) who had a low Apgar score because of unexpected problems at delivery, all of the one minute Apgar scores and all five minute scores were ≥7. These findings are in agreement with previous Apgar score measurements where maternal administration of MCP occurred.[7]

The summarized findings of the NACS tests are presented in Table III. At two, four and six hours a considerable number of the infants in both groups were mildly depressed (NACS scores <33; range, 24–32) while at 24 hours all had scores of 33 or more (range 33–39). The raw scores were subjected to a 2 × 4 repeated measures analysis of variance using the ANOVAR subroutine of SPSS:9[14] which showed no significant differences between the treated and untreated groups. The charts of the infants were also carefully reviewed for records of abnormal movements, restlessness, undue drowsiness or difficulty in feeding; none of the infants in either the test or control group experienced any identifiable problems.

One patient (19S) experienced transient dys-

TABLE III Percentage of neurological and adaptive capacity scores (NACS) less than 33

Infant post-delivery assessment times (hours)	*2*	*4*	*6*	*24*
Treated	50	50	38	0
Placebo	75	42	50	0

phoric restlessness 10–15 min. following MCP injection; however, this mother's baby showed no marked difference in either Apgar or NACS scores.

Discussion

Pinder *et al.*[10] discussed the toxic reactions encountered with MCP administration in children and infants. Such adverse reactions have included agitation, irritability and the usual manifestations of extrapyramidal dystonia. In view of the increased incidence of side effects encountered in the young, it seemed appropriate to assess MCP placental transport and to perform neurological evaluation of the infant.

Metoclopramide with its low molecular weight and high lipid solubility has been postulated to be transferred across the placenta subsequent to maternal administration;[9,15] however, there are no reports on this topic in the literature.[9,15] Our study demonstrates that metoclopramide does cross the placenta resulting in measurable concentrations in cord blood (Table I).

In a recent review, Waddell and Marlowe[16] noted that only a limited interpretation could be made on the basis of such a single-point determination in human studies of placental transport. While these studies do demonstrate drug transfer, comparisons of maternal and foetal (cord) levels must be made cautiously since a distribution equilibrium state between mother and foetus may or may not have been attained at the time of delivery and sampling. Since ethical considerations preclude *in utero* foetal blood sampling in humans, the present investigators have initiated a comprehensive study of MCP placental transfer in a chronically catheterized pregnant sheep preparation.[17] Preliminary findings indicate that the transfer of MCP across the placenta is rapid (<1 min.) and that foetal concentrations exceed maternal at 90 minutes after administration.

Controversy[18] surrounds the neurobehavioural tests. We accept that this examination may not be sensitive to the subtle effects of drugs. However, as Tronick[18] points out, it systematizes observations and provides the framework for close examination over the 24-hour period during which we decided to study these infants. We have chosen to use the Neurological and Adaptive Capacity Score (NACS) of Amiel-Tison, Barrier and Shnider[13] because it avoids noxious stimuli and can be performed quickly. Depressed or abnormal babies would have been readily noted. Our results show that there are no apparent differences between the treated and untreated groups.

From Table I it can be concluded that the gastric volumes in the untreated group are highly variable and that treatment results in a significant increase in gastric emptying ($p < 0.05$). Furthermore, this study confirms the findings of Roberts and Shirley[4] that there is a large range in gastric volumes in patients tested for 8–12 hours prior to delivery by Caesarian section. Both studies demonstrate that there is no safe time interval between the last meal and delivery which guarantees an empty stomach.

In conclusion, we have documented for the first time that metoclopramide crosses the placenta after therapeutic preoperative IV doses to parturient women undergoing elective Caesarian section. Furthermore, we have not observed any adverse effects on the neonate while we have been able to confirm differences in maternal gastric volumes between treated and untreated patients.

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Résumé

Vingt-trois patientes subissant une césarienne sous anesthésie générale pour grossesse non compliquée ont été soumises à une étude à double insu. Huit patientes ont reçu du métoclopramide intraveineux, douze ont reçu du salin 0.9 pour cent, trois n'ont pu être suivies en post-opératoire. Les volumes gastriques maternels ont été mesurés et le métoclopramide maternel et foetal a été dosé par chromatographie gaz–liquide. Le score au test d'Amiel, Barrier et Schnider (neurological and adaptive capacity score 'NCAS') a été utilisé pour l'évaluation de la réponse du nouveau-né au métoclopramide. Les volumes gastriques maternels étaient significativement plus petits ($p < 0.05$) dans le groupe traité. Il n'y a pas eu de différence marquée des scores d'Apgar, des paramètres cardiovasculaires ou des scores neurobehavioraux entre les nouveaux-nés des deux groupes. En aucun temps le taux plasmatique du métoclopramide foetal a excédé celui de sa mère.