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(*Accepted 6 February 1985*)

Comparison of the antiemetics metoclopramide and promethazine in labour

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Abstract

A double blind trial was conducted in 477 mothers in labour to compare the antiemetics metoclopramide 10 mg and promethazine 25 mg and placebo when added to the first dose of pethidine. Metoclopramide and promethazine were equally effective, and both better than placebo, in reducing the incidence of nausea and vomiting after the administration of pethidine. Seventy seven per cent of mothers were drowsy, and 8% slept in the hour after the pethidine injection, with no difference between the groups. The sedative effect was more persistent in the promethazine group, 66% of whom were still drowsy after delivery. One third of the mothers in each group needed further analgesia, with 77% of these ultimately requesting an epidural. The reduction in pain half an hour and one hour after pethidine, assessed by a visual analogue scale, were, respectively, 22% and 22% for placebo; 26% and 23% for metoclopramide; 13% and 9% for promethazine.

Analgesia after metoclopramide was significantly better than that after promethazine in terms of pain score, duration of first injection, and need for Entonox. Metoclopramide is therefore to be preferred to promethazine as an antiemetic in labour.

Introduction

Mothers being delivered at St Thomas's Hospital are offered a choice of analgesia, and although over 40% receive an epidural, 40% initially choose pethidine. In centres where epidurals are not available round the clock pethidine is used more extensively, often combined with a phenothiazine derivative to counteract emesis. A combination of promethazine and pethidine has been popular for many years as a premedicant[1] and in labour.[2 3] Trials in other types of patients, however, have shown promethazine to be a profound and long acting sedative[4 5] with an antianalgesic effect.[6] Metoclopramide has been used as a postoperative antiemetic since the 1960s.[7] Many clinical trials in labour have investigated its effects on gastric emptying,[8-10] but only one formally studied its antiemetic effect in comparison with perphenazine, with no investigation of its antinauseant properties.[11] We examined the incidence of nausea and vomiting, sedation, and analgesia after metoclopramide, promethazine, and placebo given intramuscularly with the first dose of pethidine in a double blind trial in labour.

Methods

Patients requiring pethidine in labour, who gave their verbal consent, were included in the trial. Those with severe fetal abnormalities or intrauterine death diagnosed before delivery were excluded. With the first dose of pethidine (100-150 mg) each patient was given a randomly coded ampoule containing either metoclopramide 10 mg, promethazine 25 mg, or saline (2 ml) intramuscularly. This was termed the first injection. Any patient who needed further analgesia was given either pethidine alone or an epidural, as requested (the second injection). The occurrence of nausea, vomiting, and drowsiness or sleep was recorded by the midwife in the hour preceding the injection and in each subsequent hour until delivery or the next injection. Pain relief was assessed using the visual analogue pain score before and half an hour and one hour after the injection. The need for nitrous oxide plus oxygen (Entonox), oxytocin, or a further injection of antiemetic was also recorded.

A questionnaire relating to analgesia, sedation, and emesis was presented to the patient shortly after delivery.

The results were examined using χ^2 test for numerical data; the standard error of each proportion was calculated from the formula:

$$\mathrm{SE}\left(\frac{r}{n}\right)=\sqrt{\frac{1}{n}\left[\frac{r}{n}\times\left(1-\frac{r}{n}\right)\right]}$$

the significance of the difference between proportions was calculated using the formula:

$$\left(\frac{r_1}{n_1}-\frac{r_2}{n_2}\right)\Big/\sqrt{\frac{r_1+r_2}{n_1+n_2}\left(1-\frac{r_1+r_2}{n_1+n_2}\right)\left(\frac{1}{n_1}+\frac{1}{n_2}\right)}$$

where r = number of positive responders. Student's t test was used to compare pain score.

Results

A total of 600 coded ampoules were used, but because of the mistaken inclusion of mothers who had already received antiemetics, delivery within an hour of the injection, or shortcomings in data collection, only 477 patients took part in the trial (metoclopramide 157, placebo 161, promethazine 159).

There was no significant difference between the groups in age,

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parity, length of labour after the first injection, type of delivery, need for oxytocin, or severity of pain before analgesia (table I). The numbers of patients observed in each successive hour fell because of the onset of the second stage, the need for further analgesia, or human failing, until by four hours fewer than 70 patients remained in each group.

Nausea and vomiting—Both antiemetics prevented the increase in nausea and vomiting (fig 1) associated with pethidine and placebo, and by four hours promethazine produced a significant reduction in nausea from the level before pethidine administration ($p < 0.05$). There was no significant difference between the groups in the number of mothers given further antiemetic agents.

TABLE I—*Clinical data*

	Placebo	Metoclopramide	Promethazine
Total number of patients	161	157	159
Parity:			
0	90	96	99
⩾1	71	61	60
No given oxytocin during labour	104	116	106
Mean (SEM) pain score at first injection	7·17 (1·51)	7·36 (1·40)	7·09 (1·56)
Mean (SEM) interval between first injection and delivery (h)	4·71 (0·30)	5·50 (0·36)	5·02 (0·29)
Delivery (No of patients):			
Spontaneous	125	124	124
Instrumental	24	23	26
Operative	12	10	9

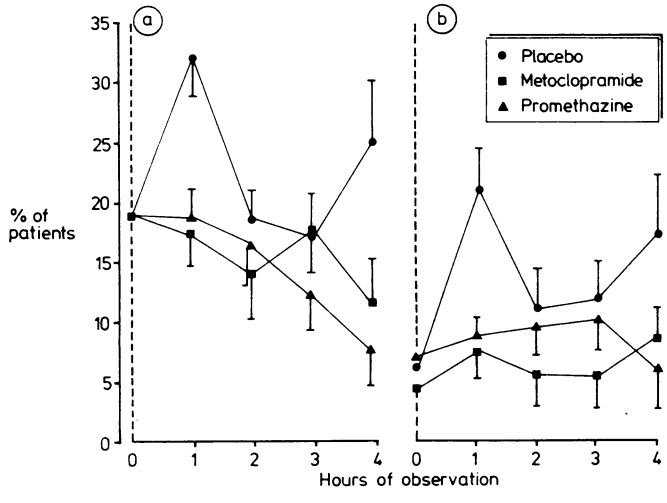

FIG 1—Percentage of patients with (*a*) nausea and (*b*) vomiting before (0) and in the four hours after injection of placebo, metoclopramide, and promethazine. Vertical bars represent standard errors of the proportions. Significantly more patients in the placebo group had nausea than in each other group in the first and fourth hours ($p < 0.001$). The proportion vomiting in the placebo group was significantly different from that in the promethazine group in the first and fourth hours ($p < 0.001$), and from that in the metoclopramide group in the first ($p < 0.001$), second, third, and fourth hours ($p < 0.01$).

Sedation—During the first hour after the pethidine injection drowsiness increased from 9·7% to 77% with 8% actually sleeping, but with no difference between the groups (fig 2). During the second, third, and fourth hours significantly more drowsiness and sleep occurred after promethazine ($p < 0.001$), with no significant difference between metoclopramide and placebo.

Analgesia—The pain relief from pethidine was significantly less good with promethazine than with metoclopramide or placebo (fig 3). Moreover, significantly fewer mothers in the metoclopramide group required Entonox in the hours after injection than in the other groups ($p < 0.01$; table II). A similar number of women in each group asked for further analgesia, either epidural (68%) or pethidine (32%), but more in the promethazine group chose epidural analgesia second time round ($p < 0.05$). Fifteen patients (eight taking metoclopramide) having opted for a second injection of pethidine, which was given alone, ultimately requested epidural analgesia. Thus of the patients who needed more than one dose of pethidine to take them through labour, 77% required epidural analgesia sooner or later. The duration of analgesia, measured as the time between the first and second injections, was longest with metoclopramide, and the difference between the metoclopramide and promethazine groups was significant ($p < 0.05$).

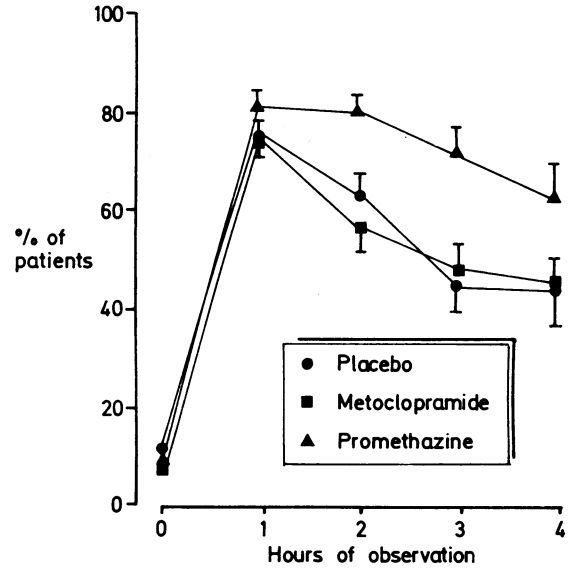

FIG 2—Percentage of patients who were sedated in the hour before (0) and in the four hours after injection of pethidine plus placebo, metoclopramide, and promethazine. Vertical bars represent standard errors of the proportions.

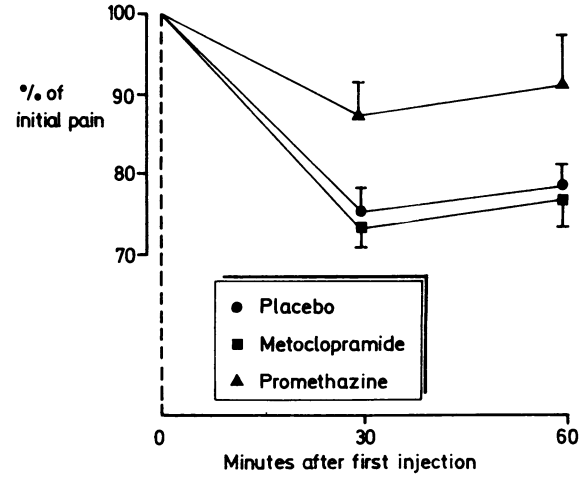

FIG 3—Pain score 30 and 60 minutes after injection of pethidine plus placebo, metoclopramide, or promethazine, presented as a percentage of the pain score at time 0. The difference between promethazine and metoclopramide was significant at 30 minutes ($p < 0.01$).

TABLE II—*Details of analgesia*

	Placebo	Metoclopramide	Promethazine
No of patients requiring Entonox	74 (46%)	45 (29%)	67 (42%)
No of patients requiring a second injection	54 (34%)	52 (33%)	57 (36%)
Primiparas	38	38	41
Multiparas	16	14	16
No who had pethidine	19	21	12
No who had epidural	35	31	45
No requiring epidural as 3rd injection	4	8	3
Mean (SEM) duration of first injection (h)	4·39 (0·16)	4·52 (0·09)	3·60 (0·07)

Outcome—All babies were born alive, with no significant difference in Apgar scores between the groups (table III).

Patient questionnaire—Ninety seven per cent of subjects responded to the questionnaire, with no significant difference between the groups (table IV).

TABLE III—*Mean Apgar scores in babies born to women in the three groups*

	Placebo	Metoclopramide	Promethazine
1 minute	7·56	7·73	7·68
5 minutes	8·92	9·09	9·07

TABLE IV—*Results of patients' questionnaire*

	% Of positive responses		
	Placebo	Metoclopramide	Promethazine
Pain relief in labour			
Satisfactory	30·4	35·8	32·7
Fair	38·6	43·0	42·3
Unsatisfactory	31·0	21·2	25·0
Pain relief during delivery			
Satisfactory	39·2	43·9	49·3
Fair	26·5	28·05	29·6
Unsatisfactory	34·3	28·05	21·1
During labour:			
Did you feel sick?	54·1**	38·7	38·8
Did you vomit?	35·2**	23·3	21·1
During or after delivery:			
Did you feel sick?	25·7	30·5	23·8
Did you vomit?	18·2	18·9	17·9
During labour:			
Were you sleepy?	79·1	78·5	86·7
Did you sleep?	23·6	26·0	35·9*
Do you feel drowsy now?	49·0	41·1	65·8**
Woud you have liked another form of pain relief?	37·2	40·7	40·7

*p = 0·05; **p = 0·01.

Discussion

The inclusion of a control period of observation allowed some assessment of the performance of pethidine itself, which appeared in this study to be more effective in inducing sedation, nausea, and vomiting than in relieving pain.

Nausea and vomiting—Conner *et al* found that promethazine did not protect against nausea associated with morphine.[5] In our present trial both metoclopramide and promethazine prevented the increase in nausea and vomiting associated with pethidine administration, with promethazine having a more sustained effect. The patients' memories of nausea and vomiting during labour were consistent with the midwives' findings—that the two antiemetics were equally effective and better than placebo. In a similar trial which showed the antiemetic and sedative effects of promazine, the mothers' memories neither correlated with the midwives' findings nor distinguished between promazine and placebo.[12] In our study the overall incidence of both nausea and vomiting was higher when assessed in the patients' questionnaire because it covered a longer time span than the period studied by the midwives. The incidence of vomiting at delivery was related to the fact that all patients, except those delivered by caesarean section, received ergometrine in the form of Syntometrine at delivery. While metoclopramide is a selective dopaminergic (D_2) blocker in the chemoreceptor trigger zone, promethazine acts principally as a histamine (H_1) antagonist and anticholinergic in the vomiting centre complex.[13] It has been suggested that a combined dopaminergic and H_1-cholinergic blocker might be the most effective antiemetic.[14] Perphenazine, however, a phenothiazine which possesses both these actions, was no more effective than metoclopramide in reducing vomiting in labour,[11] though the incidence of nausea was not investigated.

Sedation—Pethidine itself caused significant drowsiness in the first hour. The well recognised sedative effect of promethazine[4 5] borne out by both the midwives' and patients' questionnaires, only became apparent in subsequent hours, and indeed persisted after delivery (table IV). Pethidine is much shorter acting than promethazine. It is clearly disadvantageous if a mother who receives promethazine in early labour and later opts for epidural analgesia loses the benefit of alertness. Metoclopramide was free from sedative effect.

Analgesia—That two thirds of the patients required only a single analgesic injection suggests that in many patients labour was progressing rapidly and therefore becoming increasingly painful. Nevertheless, the reduction in pain score at 30 minutes of only 24%, even with the exclusion of the promethazine group, is in stark distinction to the 80-90% reduction in pain reported after epidural blockade using the same technique of assessment.[15-17] When promethazine was added to pethidine pain relief was barely perceptible. Despite the wide use of promethazine, this is the first demonstration of its antianalgesic effect in labour, no earlier workers having used the visual analogue scale to measure pain. The reduced apparent duration of pethidine "analgesia" in the promethazine group and the larger number of patients choosing an epidural analgesic as the second injection are further confirmation of the antianalgesic effect of promethazine. Our results suggest that, by contrast, metoclopramide may have slightly potentiated pethidine analgesia, in the improved pain score at 30 minutes, the increased apparent duration of effect of pethidine, and the smaller number of patients requiring Entonox or opting for epidural analgesia second time round. The mothers' opinion of the analgesia did not differ significantly between the groups, most being either satisfied or fairly satisfied. Nature's amnesia is well recognised in parturition. The increased number who were satisfied at delivery reflects the fact that 78% of these had by then received an epidural.

Our results suggest that metoclopramide is to be preferred to promethazine for combination with pethidine in labour for the sake of improved analgesia and less sedation. Both are effective in counteracting nausea and vomiting, and while a combination of dopamine and H_1 antagonist might be more so, it would, of course, possess the sedative effect common to the latter group.

We thank the conscientious midwives at St Thomas's Hospital, who completed the forms; Mr A Swan for statistical advice, the statisticians of the community medicine department for help with computing, the pharmacists for preparing coded ampoules, and the obstetricians for permission to carry out this trial on their patients.

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(Accepted 8 February 1985)