A COMPARISON OF THE EFFICACY OF CYCLIZINE AND PERPHENAZINE IN REDUCING THE EMETIC EFFECTS OF MORPHINE AND PETHIDINE

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- 1 The ability of cyclizine (50 mg) and perphenazine (2.5 and 5.0 mg) to counteract the emetic effects of pethidine (100 mg) and morphine (10 and 15 mg) was compared in women undergoing a standard minor operation with a standard anaesthetic.
- 2 Perphenazine (5.0 mg) was as effective an anti-emetic as cyclizine (50 mg) and both were more effective than perphenazine (2.5 mg).
- 3 The reduction in vomiting and nausea by cyclizine (50 mg) and perphenazine (5 mg) was approximately the same following pethidine (100 mg) and morphine (10 mg) but much less against the larger dose of morphine.
- 4 Both anti-emetics had a rapid onset of action but their anti-emetic activity did not last as long as the emetic effect of morphine.
- 5 Perphenazine (5 mg) was accompanied by an unacceptably high incidence of restlessness.
- 6 In clinical practice cyclizine (50 mg) is preferred to perphenazine (5 mg) as an anti-emetic.

Introduction

Cyclizine and perphenazine are among the most popular anti-emetics in current use and the efficacy of each has undoubtedly been proven in a variety of circumstances. Despite their popularity, there has been no controlled study of their comparative anti-emetic potencies under standard conditions. A major problem in such a study is to obtain a constant emetic effect in man against which to evaluate the anti-emetic activity. This paper reports a controlled comparison of the effects of clinical doses of cyclizine and perphenazine against the emetic effects of morphine and pethidine in which all drugs were given intramuscularly. These opiates were chosen because of the different time course of their action with pethidine having an earlier onset and shorter effect as compared with morphine (Dundee, Clarke & Loan, 1965). It was carried out in patients having a single minor operation with a standard anaesthetic in which the environment and observations were also constant. The method has been used for studying a large number of premedicant drugs (Clarke, Dundee & Loan, 1970), and its reliability has been evaluated by Morrison, Hill & Dundee (1968).

Cyclizine hydrochloride (Marzine, Valoid) is an anti-histamine which has been used widely in

the prevention and treatment of travel sickness (Chinn, Handforth, Smith, Cone, Redmond, Maloney & Smith, 1952) and radiation sickness (Stoll, 1957). In anaesthetic practice it has also been used for its anti-emetic effect (Dent, Ramachandra & Stephen, 1955; Moore, Bridenbaugh, Piccioni, Adams & Lindstrom, 1956; Dundee, Halliday, Nicholl & Moore, 1966) while Dundee & Jones (1968) have demonstrated its efficacy in preventing analgesic-induced nausea and vomiting in ambulant patients. Until comparatively recently cyclizine (50 mg) was commercially available in compounds mixed with morphine (10 mg) (Cyclimorph 10) and (15 mg) (Cyclimorph 15).

Perphenazine (Fentazin, Trilafon) is a phenothiazine with a piperazine side chain. Its anti-emetic use is largely limited to the immediate peri-operative period (Moore, Bridenbaugh, van Acheren & Cole, 1958; Dobkin, 1959; Lind & Breivik, 1970). When given alone to adults in 5 mg doses, Ayd (1961) and Dundee, Moore, Love, Nicholl & Clarke (1965) found a high incidence of extrapyramidal side effects including oculogyric crises. When used as pre-anaesthetic medication combined with pethidine (100 mg), Dundee, Nicholl, Clarke, Moore & Love (1965) found perphenazine (5 mg) resulted

in a greater reduction in sickness than promazine (25 or 50 mg), triflupromazine (10 mg), propiomazine (20 or 40 mg), thiethylperazine (10 mg) or promethazine (10, 25, or 50 mg) and this prompted the present comparison despite the reportedly high incidence of side effects with perphenazine. It was also considered worthwhile to study the effect of a smaller (2.5 mg) dose of perphenazine to see if this would have a useful anti-emetic effect with lesser toxicity.

Methods

Identical ampoules were prepared containing either pethidine (100 mg), or morphine (10 or 15 mg) alone or combined with cyclizine (50 mg), or perphenazine (5.0 and 2.5 mg) (Table 1). The stability of the mixtures was tested by their manufacturers. The drugs were given as preanaesthetic medication to fit women undergoing minor morning gynaecological operations in one hospital. A double blind design was followed throughout. Initially the drugs were numerically labelled and given in random order. In this experimental population it is important to eliminate the bias due to the powerful emetic effect of cervical dilatation *per se*, therefore towards the end of the trial the drugs were ordered openly to balance the numbers in each group who had and who had not dilatation of the cervix uteri. However, the blind conditions were maintained by having the drugs ordered by colleagues not directly involved in the study so that the observers still did not know the identity of the drug given.

The drugs were given by deep intramuscular injection by the nursing staff about 1.5 h before the scheduled operating time. Half of the patients were seen 20, 40, 60 and 90 min after injection and the remainder were visited once during the 60-90 min period. All observations were made by the authors. At each visit a subjective assessment was made of the degree of drowsiness, anxiety and restlessness or excitement, and the occurrence and severity of side

effects (injection pain, dizziness, tachycardia, hypotension, nausea and vomiting) were recorded. When both nausea and vomiting occurred in one patient this was recorded as vomiting which also included retching. At each visit the efficacy of the drug as a premedicant was graded on a five point scale:

Patient asleep	5
Patient sleepy	4
Slight benefit	3
No sedation but patient calm	2
No sedation, patient agitated	1

At the end of each preoperative study the desired effects of the drug noted between 60-90 min after injection and the side effects occurring up to that time were recorded.

Anaesthesia was with methohexitone, nitrous oxide-oxygen and no volatile agents were given. All patients had regained consciousness within 5 min of the end of the operations, which lasted between 5-10 min, and they were returned directly to the ward and frequently visited by one of the observers. No postoperative analgesics or nourishment were given to any patient during the first 6 postoperative hours. The occurrence of vomiting or nausea was noted at the end of the first, and also at the end of the sixth, postoperative hour and recorded with the above-mentioned standardization. From this the total incidence of emetic effects during the first 6 h after operation and the total pre- and postoperative incidence were calculated.

Table 1 gives the number of patients in each study group. It was initially intended that each should consist of 100 patients but because of the high incidence of restlessness associated with perphenazine 5 mg this drug was withdrawn from the trial after only 50 patients had received it. Each of the groups was broadly comparable with respect to average age and weight and duration of operation and in an analysis reported in detail elsewhere it has been shown that these are not important sources of bias in this experimental design (Morrison *et al.*, 1968). The preoperative findings are not reported in full except in as far

Table 1 Numbers of patients in the different series studied.

Opiate	Anti-emetic			
	Nil	Cyclizine (50 mg)	Perphenazine (5 mg)	Perphenazine (2.5 mg)
Morphine (10 mg)	200	100	50	100
Morphine (15 mg)	100	100	50	100
Pethidine (100 mg)	300	100	100	100

as they relate to undesirable effects of the combinations studied. The anaesthetic technique was exactly the same in each group, so that the emetic effect of this, if any, can be discounted in the comparison of the groups. A full description of the methodology used in this long continuing series of clinical trials has been given by Dundee, Nicholl & Moore (1962).

Results

Table 2 gives the percentage incidence of emetic sequelae in the pre- and postoperative period in the twelve groups of patients. For the sake of clarity the incidence of vomiting and nausea in the different postoperative periods is pooled and the only occasion where there is a marked difference in the figures for these two is referred to specifically below.

Preoperative sickness was much more common after pethidine 100 mg than following either dose of morphine. Both anti-emetics markedly reduced sickness after pethidine to a significant degree ($P < 0.0001$) but the reduction in vomiting was less with cyclizine. In contrast cyclizine (50 mg) reduced the preoperative emetic effects of morphine (10 and 15 mg) to a greater degree than either dose of perphenazine, but the incidence of both vomiting and nausea was too low after this opiate for any statistical differences to be detected.

Both cyclizine (50 mg) and perphenazine (5 mg) very significantly ($P < 0.001$) reduced postoperative vomiting and nausea in patients premedicated with morphine (10 mg). Both appeared to be equally effective and their protective action was most marked in the first hour after operation. Perphenazine (2.5 mg) was not nearly as effective as the 5 mg dose in reducing the emetic sequelae in the first 6 h after operation ($\chi^2 = 16.36$; $P < 0.0005$) but nevertheless it had an appreciable anti-emetic action ($\chi^2 = 4.94$; $P < 0.05$).

As expected morphine (15 mg) was followed by more postoperative vomiting and nausea than the 10 mg dose ($\chi^2 = 11.315$; $P < 0.001$), this effect being most marked in the 1-6 h period after operation when there was a great increase in the incidence of vomiting (63% as compared with 36% following the 10 mg dose). All three preparations studied appeared to be equally effective as anti-emetics and while the reduction in nausea and vomiting was highly significant ($\chi^2 = 15.064$; $P < 0.0005$), over half the patients still had some emetic sequelae after the larger dose of morphine.

Both doses of perphenazine caused a highly

Table 2 Percentage incidence of vomiting (V) and nausea (N) in the patients premedicated with a narcotic analgesic, with or without cyclizine (C) or perphenazine (P).

		Morphine (10 mg)			Morphine (15 mg)			Pethidine (100 mg)		
		C	P	P	C	P	P	C	P	P
Pre-op.	V	3	2	0	0	6	2	13	5	1
	N	9	2	6	5	11	14	31	11	16
	Nil	88	96	94	86	83	84	56	84	83
Post-op.	0-1 h V and N	35	3	6	19	36	18	31	16	10
	1-6 h V and N	53	23	18	43	77	50	38	15	13
	0-6 h V	44	9	16	34	65	34	31	13	8
	N	17	14	4	13	14	18	18	12	11
	Nil	39	77	80	53	21	48	51	75	81
	Pre- and post-op.	46	11	16	34	65	34	34	16	13
Pre- and post-op.	V	15	13	10	17	15	22	25	16	21
	Nil	39	76	74	49	20	44	41	68	66

significant reduction in postoperative sickness after pethidine (100 mg) ($\chi^2 = 49.340$; $P < 0.0001$): both appeared to be equally effective in this respect and slightly more effective than cyclizine (50 mg).

When the overall incidence of pre- and postoperative vomiting and nausea is studied the above conclusions still apply, except that perphenazine (5 mg) was slightly more effective than the 2.5 mg dose in reducing emetic sequelae after pethidine (100 mg) but the difference was not significant ($t = 1.903$; $0.20 > P > 0.10$).

In the doses used neither of the anti-emetics markedly affected the soporific action of the narcotic analgesics. However, the addition of perphenazine, particularly the 5 mg dose, decreased the anxiolytic effect of the opiates in the 60-90 min period after administration. Table 3 gives the appropriate data for the series of patients having morphine (10 mg), the data for the morphine (15 mg) and pethidine (100 mg) series being qualitatively similar.

Perphenazine was associated with a high incidence of restlessness, particularly in the 5 mg dosage (Table 4). This occurred about 45-60 min after drug administration and was not observed with cyclizine.

Discussion

Under the conditions of this study both cyclizine (50 mg) and perphenazine (2.5 and 5.0 mg) were useful in countering the emetic sequelae following morphine (10 and 15 mg) and pethidine

Figure 1 The percentage incidence of good (black), fair (stippled) and poor (open) sedation with the various premedicants studied, based on the distribution of efficacy scores, together with the average scores. C cyclizine; P perphenazine.

Table 3 Percentage incidence of varying degrees of apprehension noted at 60-90 min after morphine (10 mg) given alone or with cyclizine (C) or perphenazine (P).

Degree of apprehension	Nil	C (50 mg)	P (5.0 mg)	P (2.5 mg)
Nil	72	75	42	68
Slight	23	19	46	27
Moderate-marked	5	6	12	5

Table 4 Percentage incidence of varying degrees of apprehension noted at 60-90 min after morphine (10 mg) and pethidine (100 mg) given alone and with cyclizine (C) or perphenazine (P).

Opiates	Restlessness	Nil	C (50 mg)	P (5.0 mg)	P (2.5 mg)
Morphine (10 mg)	Slight	2	1	16	8
	Marked	1	1	6	0
Morphine (15 mg)	Slight	0	3	18	15
	Marked	1	0	2	0
Pethidine (100 mg)	Slight	2	1	7	1
	Marked	0	0	6	0

(100 mg). They appeared to act quickly as judged by the reduction in preoperative vomiting and nausea after pethidine. However, their anti-emetic effects appeared to be of much shorter duration than the emetic effect of either opiate.

Taking all the results together cyclizine (50 mg) was as effective as perphenazine (5 mg) and both were more effective than perphenazine (2.5 mg). However, they were limited in their ability to counteract the more powerful emetic stimulus of morphine (15 mg).

When other effects of these anti-emetics are considered there is little doubt that under the conditions of this study, cyclizine (50 mg) was much less toxic than perphenazine (5 mg) and

the incidence of restlessness following the latter was unacceptably high. While akathisia (motor restlessness) is a recognized complication of perphenazine therapy (Ayd, 1961; Dundee *et al.*, 1965), it was surprising to find such a high incidence when the phenothiazine was given with an opiate. When the overall effect of each drug or drug combination is assessed as to usefulness as a premedicant (Fig. 1), the mixture of an opiate with cyclizine is preferable to the opiate-perphenazine combination.

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