ORIGINAL ARTICLE

A Comparison of Antiemetic Efficacy of Droperidol Alone and in Combination with Metoclopramide in Day Surgery Anaesthesia

C C Loo, FRCA, E Thomas, FFARACS, H M Tan, MMed, T H Sia, MMed, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899

Summary

We have studied the antiemetic efficacy of droperidol alone, and in combination with metoclopramide in first trimester termination of pregnancy in day surgery. The aim was to determine whether the addition of metoclopramide could further reduce the incidence of postoperative nausea and vomiting (PONV) but avoid excessive sedation. Group I (control, n=40) received i.v. droperidol 0.625 mg at induction. Group II (study, n=40) received i.v. droperidol 0.625 mg and i.v. metoclopramide 10 mg at induction. The incidence of nausea at 1 and 2 hours postoperatively was 23% and 10% in group I, and 5% and nil in group II respectively. The difference in the incidence of nausea was significant at $p<0.05$ at one hour but not at two hours postoperatively. No patients vomited. There was no difference in the sedation and pain score between them. We did not observe any significant side effects attributable to either drug. All patients were discharged home within 3 hours. We conclude that in the prevention of PONV, the combination of metoclopramide and droperidol is superior to the use of droperidol alone at one hour but not at two hours postoperatively.

Key Words: Ambulatory surgery, Postoperative, Nausea, Vomiting, Droperidol, Metoclopramide

Introduction

Postoperative nausea and vomiting (PONV) is one of the most common side effect in gynaecological operations and had been reported to be as high as 65% when antiemetics were omitted[1]. Droperidol and metoclopramide are commonly used as antiemetics but their efficacies vary amongst the studies conducted thus far. Studies combining both drugs were also done but with conflicting results[1,2]. The optimal dose for droperidol is still uncertain but higher doses (2.5mg) are associated with greater degree of sedation which is not desirable in day surgery[3]. This study was designed to compare the antiemetic efficacy of droperidol alone and in combination with metoclopramide. The aim is to determine whether the addition of metoclopramide could further reduce the PONV but avoid excessive sedation. We have decided against a placebo group as previous studies had already shown that antiemetics did reduce PONV and thus may not be necessary to subject patients to such discomfort.

Materials and Methods

We studied a total of 80 Chinese, female patients who were ASA 1 undergoing first trimester termination of pregnancy in day surgery. This study was approved by the ethics committee of our hospital. The patients were divided randomly into 2 groups using sealed envelope technique. The control group (group I, n=40) was administered i.v. droperidol 0.625 mg, and the study group (group II, n=40) was administered i.v. droperidol 0.625 mg + i.v. metoclopramide 10 mg at induction. The anaesthetic management for both groups was identical except for the addition of metoclopramide in group II. Patients who complained of nausea/vomiting

preoperatively or received prostaglandin pessary were excluded.

The anaesthetic management was as follows: No premedication was prescribed. At induction, i.v. fentanyl 1μg.kg^{-1}, i.v. droperidol 0.625 mg and i.v. propofol 2 mg.kg^{-1} were given. In addition, i.v. metoclopramide 10 mg was given to group II. Anaesthesia was maintained with N_2O:O_2 at 4:2 L.min^{-1} respectively and isoflurane 0.5% via a face mask with the patient breathing spontaneously. No patients required assisted ventilation. Patients were allowed to regain consciousness in the operating theatre (eyes opening) before being transported to the recovery room. Patients were assessed for nausea vomiting, sedation and pain at 1 and 2 hours postoperatively and upon discharge by the same nurse blinded to the study. The sedation score was as follows: 0=alert, 1=mild, occasionally drowsy, 2=moderate, frequently drowsy but easily arousable, 3=severe, difficult to arouse. The pain score was as follows: 0=no pain, l=mild, not limiting activity, 2=moderate, limiting activity, 3=severe, needs immediate analgesia. Patients were discharged only if they were completely asymptomatic, able to walk without assistance and having an adult to accompany home.

Data were analysed by *t* test, Fisher's exact test and Wilcoxon rank sum (unpaired) test. A p value of < 0.05 was taken as statistically significant.

Results

The 2 groups were comparable with regard to age, weight, gestational age and duration of operation (Table I). The incidence of nausea in group I (droperidol) was 23% and 10% at one and two hours postoperatively respectively (Table II). Group II (droperidol and metoclopramide) was 5% and nil respectively. The difference in the incidence of nausea was significant at $p<0.05$ at one hour but not at two hours postoperatively. Although patients had nausea postoperatively, none of the patients in either group vomited. None of the patients required treatment for their nausea.

Sedation scores at one and two hours postoperatively were analysed by Wilcoxon rank sum (unpaired) test which showed no difference between the groups ($p=0.494$ and >0.5 respectively). Pain scores at one and two hours postoperatively were analysed by Wilcoxon rank sum (unpaired) test which showed no difference between the groups ($p>0.5$). In group I (droperidol),

Table I
Patient characteristics on Droperidol as Droperidol + Metoclopramide

Characteristics	Treatment group		p value
	Droperidol (n=40)	Droperidol + Metoclopramide (n=40)	
Age (yrs) mean ± SD	33.7 ± 8.5	33.6 ± 8.8	0.9589
Weight (kg) mean ± SD	57.5 ± 11.2	59.3 ± 11.7	0.4842
Duration of operation (min) mean ± SD	6.6 ± 2.4	6.0 ± 2.0	0.2282
Gestational age (weeks) mean ± SD	7.45 ± 1.14	7.55 ± 1.05	0.6844

t test for 2 independent samples showed no difference between the groups

Table II
Incidence of nausea and vomiting

Groups	1st hour		2nd hour	
	nausea	vomiting	nausea	vomiting
1	9 (23%)	0 (0%)	4 (10%)	0 (0%)
2	2 (5%)	0 (0%)	0 (0%)	0 (0%)

Fisher's Exact test showed the difference in the incidence of nausea was significant at one hour (p=0.0238) but not at two hours (p=0.0578) postoperatively

47.5% and 77% of patients were fully alert at one and two hours postoperatively respectively. In group II (droperidol + metoclopramide), it was 45% and 80% respectively. In group I, 28% (91% mild pain) and 13% (80% mild pain) experienced pain at one and two hours postoperatively respectively. In group II, it was 18% (58% mild pain) and 5% (50% mild pain) respectively. 68% of patients in group I and 78% in group II were completely asymptomatic (fully alert, no pain, and no nausea or vomiting) at 2 hours postoperatively and discharged home. All patients were completely asymptomatic and discharged home by 3 hours postoperatively.

Discussion

Droperidol and metoclopramide are two of the most commonly employed antiemetics for PONV. The efficacy of droperidol is well established although Cohen *et al* found that i.v. droperidol 1.25 mg was ineffective in minor gynaecological operation[4]. Metoclopramide is a controversial drug and about 50% of all studies found it to be ineffective[5].

The cause of PONV is multifactorial. The background factors which may modify PONV are age, sex, motion sickness, phase of menstrual cycle, type and duration of surgery, anaesthetic drugs and postoperative pain. We have managed in our study to control these confounding variables. About 50% of pregnancies are associated with nausea and vomiting, usually begin by the 6th week and cease by the 12th week. We have excluded those patients who complained of preoperative nausea and vomiting, and there was no difference in the gestational age between the 2 groups.

Doze *et al*[2] found that combination of droperidol and metoclopramide was superior to droperidol alone in midtrimester abortion. They administered i.v. droperidol 0.5-1 mg with and without i.v. metoclopramide 10-20 mg, and their incidence of nausea ± vomiting was 39% and 19% respectively. However Pandit *et al*[1] did not find any difference. They compared i.v. droperidol 10 and 20 $\mu g.kg^{-1}$ with i.v. metoclopramide 10 mg plus i.v. droperidol 10 $\mu g.kg^{-1}$ in outpatient gynaecological laparoscopy. Their incidence of PONV was 25%, 20% and 25% respectively. They also found that i.v. droperidol 5 $\mu g.kg^{-1}$ to be ineffective. The results of our study concur with that of Doze. None of our patients vomited, whereas 5%-10% of patients vomited in Pandit *et al's* study. The difference is probably because thiopentone was used by Pandit *et al* whereas propofol was used in ours[6]. Our incidence of nausea at one hour (control group=5%) is lower than that of Doze (39%, 19%). The difference is also probably because thiopentone and methohexitone were used by Doze instead of propofol. Droperidol belongs to the butyrophenone group and its antiemetic effect is due to its anti-dopaminergic effect. After i.v. administration its distribution $T_{1/2}\alpha$ is 10 min and elimination $T_{1/2}\beta$ is 2 hours[7]. The optimal dose for droperidol is still uncertain. Effective doses range from ultralow of 0.25 mg[8,9] to 5 mg[3]. Pandit *et al*[1] found the optimal dose to be 20 $\mu g.kg^{-1}$. 10 $\mu g.kg^{-1}$ was also effective but not 5 $\mu g.kg^{-1}$. Higher doses (>1.25 mg) may be used but the greater degree of sedation and delayed recovery[4,8] may not be desirable in day surgery. Doses of 1.25 mg or less was found by most investigators to be effective and did not prolong discharge times[1,10].

Droperidol could cause extrapyramidal side effects in both high and low doses. This was reported by Dupre *et al*[11], 0.1-0.17 mg.kg^{-1} in children and Melnick *et al*[12], 0.625 mg in adults. Droperidol has adrenergic blocking properties and may cause hypotension. No extrapyramidal side effects or hypotension occurred in our study.

Metoclopramide also reduces the incidence of PONV via the anti-dopaminergic mechanism. In addition, it increases gastric emptying. Doze *et al*[2] attributed the reduction of nausea and vomiting in the droperidol plus metoclopramide group to the supplementary gastrokinetic action of metoclopramide. An oral dose of metoclopramide is absorbed rapidly and the mean time to peak concentration is 0.9 hours[13] and the elimination $T_{1/2}\beta$ is 4 hours. After i.v. administration, there is rapid redistribution, $T_{1/2}\alpha$ is 4.9 min[14]. Is it an effective antiemetic? If it is, what is the best route of administration and optimal dose? As mentioned above, 50% of all studies found it to be ineffective. Bone *et al*[15] found i.v. 10 mg to be effective but not Cohen *et al*[4]. Oral administration may be more effective than the i.v. route because of the rapid redistribution. Miller *et al*[16] found an oral dose of 10mg to be effective but not Pandit *et al*[1]. The recommended dose of metoclopramide for PONV is 10 mg[17] but 20 mg may be more effective[5]. There is no consensus on its efficacy, optimal dose or route of administration. Metoclopramide at the recommended dose for PONV is devoid of sedative side effects which makes it suitable for day surgery. Its gastrokinetic action is certainly desirable in spontaneously breathing patient under general anaesthesia. However the extrapyramidal side effects must not be forgotten and the incidence is about 28.6 per million[18]. It can be treated with i.m. or i.v. benztropine 1-2 mg. The other possible side effects include hypotension, supraventricular tachycardia and paradoxically, bradycardia. We did not observe these side effects in our study.

Droperidol is an effective antiemetic but may cause excessive sedation in higher doses in day surgery anaesthesia. Our study aims to determine if its efficacy could be further improve by the addition of metoclopramide but avoid excessive sedation. Our results show that the addition of i.v. metoclopramide l0 mg to i.v. droperidol 0.625 mg was superior to the use of droperidol alone in respect to PONV at one hour postoperatively. The reason could be because of the fact that both drugs act on the same dopaminergic receptors. A dose of 0.625 mg of droperidol may not have been the optimal dose and the addition of another dopaminergic antagonist did improve the outcome. As mentioned previously, Pandit *et al*[1] found the optimal dose of droperidol to be 20 μg.kg^{-1}. A dose of 0.625 mg works out to be about 10 μg.kg-l in our sample. Thus a dose of 1-1.25 mg may have been the optimal dose. The other reason could be the gastrokinetic action of metoclopramide. Studies have shown that gut distension is a cause of PONV and by increasing gastric emptying, metoclopramide may have decreased the incidence of PONV via this mechanism. There was no difference in the incidence of nausea/vomiting between the 2 groups at 2 h postoperatively. The reason could be the short duration of action of the anaesthetic drugs employed. Isoflurane at 0.5% and N_2O at 66% for a mean exposure duration of 6-7 min during the operation is unlikely to have any significant residual emetogenic at 2 h postoperatively. The duration of action of 50 μg of fentanyl is about 30 min and thus also may not have any significant residual emetogenic at 2 h postoperatively. However it should be noted that the $T_{1/2}\beta$ of fentanyl is about 2-4 h and there is always a possibility of sequestration of fentanyl in the stomach, with subsequent reabsorption from the small intestine causing systemic effects. Thus although it is unlikely for 50 μg fentanyl to have any residual effect at 2 h postoperatively, there is still a distinct albeit remote possibility. The other reason could be due to type II error, i.e. the insignificant result at 2 h could be due to lack of power of the test. Indeed the power in our test to detect a difference at 2 h postoperatively was 0.33, which was below the recommended 0.8.

Shall the anaesthetists combine both droperidol and metoclopramide in future anaesthetics in day surgery routinely? The difference in the incidence of nausea was only significant at one hour but not at two hours postoperatively and no patients vomited. None of the patients required treatment for their nausea and all were asymptomatic at three hours postoperatively. Therefore, the authors feel that there is no justification to recommend the routine use of both drugs in

combination in day surgery for termination of pregnancy. However in patients with known history of severe postoperative nausea and vomiting, the use of both drugs may be beneficial and justifiable.

Conclusion

In conclusion, in the prevention of PONV, the combination of metoclopramide and droperidol was found to be superior to the use of droperidol alone at one hour but not at two hours postoperatively.

References

1. Pandit SJ, Kothary SP, Pandit UA, Randel G, Levy L. Dose response study of droperidol and metoclopramide as antiemetics for outpatient anaesthesia. Anesth Analg 1989;68 : 798-802.
2. Van A. Doze, Audrey Shafer, Paul F. White, Nausea and vomiting after outpatient anaesthesia- Effectiveness of droperidol alone and in combination with metoclopramide. Anesth Analg 1987;66 : S41.
3. Mortensen PT. Droperidol(Dehydrobenzperidol): Postoperative anti-emetic effect when given intravenously to gynaecological patients. Acta Anaesthesiol Scand 1982;26 : 48-52.
4. Cohen SE, Woods WA, Wyner J. Anti-emetic efficacy of droperidol and metoclopramide. Anesthesiology 1984;60 : 67-9.
5. DJ Rowbotham. Current management of postoperative nausea and vomiting. Br J Anaesth 1992;69(Suppl.1) : 46S-59S.
6. Korttila K, Ostman P, Faure E, Apfelbaum JL, Prunskis J, Ekdawi M, Roizen MF. Randomised comparison of recovery after propofol-nitrous oxide versus thiopentoneisoflurane-nitrous oxide anaesthesia in patients undergoing ambulatory surgery. Acta Anaesthesiol Scand 1990;34 : 400-3.
7. Cressman WA, Plostnieks J, Johnson PC. Absorption, metabolism and excretion of droperidol by human subjects following intramuscular and intravenous administration. Anesthesiology 1973;38 : 363-9.
8. O'Donovan N, Shaw J. Nausea and vomiting in day case dental surgery. Anaesthesia 1984;39 : 1172-6.
9. Shelley ES, Brown HA. Antiemetic effect of ultra low dose droperidol. Abstract, American Society of Anaesthesiologists Annual Meeting, Chicago 1978 : 633-4.
10. Korttila, Kauste A, Auvinen J. Comparison of domperidone, droperidol and metoclopramide in prevention and treatment of nausea and vomiting after balanced anaesthesia. Anesth Analg 1979;58 : 396-400.
11. Dupre LJ, Stieglitz P. Extrapyramidal syndromes after premedication with droperidol in children. Br J Anaesth 1980;52 : 831-3.
12. Melnick BM. Extrapyramidal reactions to low dose droperidol. Anesthesiology 1988;69 : 424-6.
13. Ross-Lee LM, Hooper WD, Bochner F. single-dose pharmacokinetics of metoclopramide. Eur J Clin Pharmacol 1981;20 : 465-71.
14. Bateman DN, Kahn C, Mashiter K, Davies DS. Pharmacokinetic and concentration-effect studies with intravenous metoclopramide. Br J Clin Pharmacol 1978;6 : 401-7.
15. Bone ME, Wilkinson DJ, Young JR, Charlton S. Ginger root- a new antiemetic; The effect of ginger root on postoperative nausea and vomiting after major gynaecological surgery. Anaesthesia 1990;45 : 669-71.
16. Miller CD. Silent regurgitation in day case gynaecological patients. Anaesthesia 1988;43 : 321-3.
17. Association of the British Pharmaceutical Industry. Data Sheet Compendium 1991-92. London: Datapharm Publications Limited, 1991;148.
18. Bateman DN, Rawlins MD, Simpson JM. Extrapyramidal reactions with metoclopramide. .BMJ 1985;291 : 930-2.