—Regular Articles—

Evaluation of the Effective Drugs for the Prevention of Nausea and Vomiting Induced by Morphine Used for Postoperative Pain: A Quantitative Systematic Review

Takeshi HIRAYAMA,*[,a] Fumiyoshi ISHII,[b] Kazuo YAGO,[a] and Hiroyasu OGATA[b]

Department of Hospital Pharmacy, Kitasato University East Hospital,[a] 2–1–1 Asamizodai, Sagamihara 228–8520, Japan and Department of Biopharmaceutics, Meiji Pharmaceutical University[b] 2–522–1 Nosio, Kiyose-shi, Tokyo, 204–8588, Japan

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Postoperative nausea and vomiting (PONV) with morphine therapy develops in more than 60% of patients after surgery, markedly reducing patient QOL. The prophylactic effect of several antiemetics has already been studied, but evaluations, and even those using the same drug, are not uniform. The present research involved a meta-analysis of randomized controlled trials on prophylactic drug therapy for PONV in patients receiving morphine for the treatment of postoperative pain. The efficacy of the prophylactic administration of the drugs was examined.

As a result, meta-analysis of five drugs was possible and the evidence of efficacy was shown for three drugs ranked in order of an increasing odds ratio (OR) and confidence interval (CI): dexamethasone (OR: 0.23, 95% CI: 0.15—0.35, $p<0.00001$), droperidol (OR: 0.27, 95% CI: 0.21—0.34, $p<0.00001$), and metoclopramide (OR: 0.48, 95% CI: 0.30—0.75, $p<0.001$). These results suggest that the three drugs are effective in prophylactic treatment for PONV. Of them, dexamethasone used as a prophylactic drug for PONV provided the best results. Dexamethasone was shown to reduce the incidence of PONV from 66—80% to 16—50% with a dose of 1.25 to 10 mg and to be suitable as a first drug of choice.

Key words——morphine; antiemetics; meta-analysis; PONV (Postoperative nausea and vomiting); dexamethasone; metoclopramide; droperidol; ondansetron

INTRODUCTION

Various analgesics are currently used to treat postoperative pain. Morphine, a narcotic analgesic, is used frequently and administered intravenously,[1] epidurally,[2] subarachnoidally,[3] subcutaneously,[4] and intramuscularly.[5] Continuous intravenous injection of morphine by patient-controlled analgesia (PCA) is often used in many countries and rated favorably.[6] Morphine is used to obtain a favorable analgesic effect for any dosing method, but it may increase the incidence of Postoperative nausea and vomiting (PONV) or make food intake difficult, which leads to the discontinuance of its administration. Such a PONV is a significant problem for patients after surgery since it decreases the patient's quality of life (QOL) and satisfaction with the treatment as a whole.

To prevent PONV, several drugs have already been given and various reports on the efficacy have been published. Horta *et al*. reported that droperidol had no prophylactic effect on PONV in cesarean section patients.[7] In contrast, Sanansilp *et al*. reported that droperidol reduced the incidence of PONV in cesarean section patients.[8] Pitkanen *et al*. reported that metoclopramide had no prophylactic effect on PONV in patients who underwent orthopaedic prosthesis surgery.[9] Walder *et al*. reported that metoclopramide reduces the incidence of moderate to severe nausea in patients undergoing gynaecological surgery.[10] Davies *et al*. reported that ondansetron has no prophylactic effect on PONV for patients undergoing a hysterectomy.[11] Alexander *et al*. reported that 72% of patients that underwent orthopaedic surgery and received ondansetron developed no PONV.[12] Thus, evaluation of the same drug varies with the study.

The current research concerned a meta-analysis of randomized controlled trials that studied prophylactic drug therapy for PONV for patients given morphine for the treatment of postoperative pain. The evidence of the prophylactic effect of droperidol, metoclopramide, dexamethasone, propofol and ondansetron were examined. Of the effective drugs, the drug with the best evidence of a prophylactic effect was evaluated and examined in detail.

METHODS

The studies reported were searched from The

MEDLINE-Database (1966 to February 2000) and Cochrane Library (2000, issue 1) using the following criteria:

1) MeSH-NAUSEA
2) MeSH-VOMITING.explode
3) #1 or #2
4) MeSH-MORPHINE.explode
5) #3 and #4
6) MeSH-RANDOM ALLOCATION.explode
7) MeSH-CLINICAL CONTROLLED TRIALS.explode
8) MeSH-RANDOMISED CONTROLLED TRIALS.explode
9) #6 or #7or #8
10) #5 and #9
11) MeSH-HUMAN
12) #10 and #11

From the data retrieved, studies to be examined were selected according to the following criteria:

(1) Written in English;
(2) Parallel design study;
(3) The subjects were patients who were over 18 years of age and given morphine to control postoperative pain;
(4) The drug is intravenously given for the purpose of preventing PONV;
(5) A placebo is used as the control;
(6) The endpoint is ''the presence or absence of nausea and/or vomiting'';
(7) The observation period was 24 hours postoperatively, in principle. In the absence of an evaluation during this 24-hour period, assessment within 20 to 48 hours was acceptable.

In addition, the quality of the study was evaluated as described below. Jadad's scoring system[13] was used and 5 points were given to the highest score on the three items of randomization, blinding, and withdrawals in terms of evaluation. A study in which only ''randomized'' testing was described was given one point. Two points were given to a study in which ''randomized'' testing was performed and a method of randomization was described; the method also had to be an appropriate because of the use of a table of random numbers or of a computer-generated table. The score for a study was regarded as 0 points if there was no description of ''randomized'' testing or if the method of randomization was inappropriate because patients were allocated alternately, or according to date of birth, date of admission, hospital number, etc. A study in which only ''double-blind'' testing was described was given one point. A study was given two points if ''double-blind'' testing was described and its method was appropriate (use of an identical placebo, active placebo, dummy, etc.). A study in which there was no description of ''double-blind'' testing or the double-blind method was inappropriate was given 0 points. Finally, a study in which the number of withdrawals and their reasons were described was given one point. This methodology was used to select only quality studies with 3 or more points for analysis.

Using the above methodology, two of the authors selected the studies to be analyzed and ascertained whether their selection was the same. When the selection differed between the two researchers, whether to select the study was decided through discussion. Only test drugs each for which three studies were selected were included in the meta-analysis.

For statistical analysis, the number of patients assigned and the number of patients who experienced at least one episode of nausea or vomiting during the observation period were calculated based on the data collected for each prophylactic agent. In addition, the odds ratio (OR) and its 95% confidence interval (CI) with respect to the incidence of nausea and vomiting for each study were calculated and pooled using a method of meta-analysis. Prior to the pooling, the lack of homogeneity in the study results was tested using a Q-test with a level of significance of 10%. When a lack of homogeneity was not noted for the test drugs, the Peto's fixed effect model (Peto method)[14] was used to calculate the pooled OR and its 95% CI. When a lack of homogeneity was noted and it was possible to pool, a random effect model was used for calculation.

These methods were used to statistically evaluate the efficacy of each prophylactic antiemetic agent with respect to nausea and vomiting induced by morphine administered for postoperative pain. Statistical analysis was performed using the software program Review Manager 4.0.4 (Update Software 1999).

RESULTS

From the MEDLINE Database and Cochran Library, 166 and 164 RCT reports were retrieved, respectively. Of these, studies on any of five drugs that met the inclusion criteria and were subjected to the meta-analysis are summarized in Table 1. Evaluation by Jadad's scoring system, operation (setting), number of subjects, dosing regimen of morphine, dosing regimen of the test drug, number of patients who developed nausea and/or vomiting, and effectiveness are shown in this table. The test drug was

Table 1. Details of RCT Reports that Were Retrieved from the MEDLINE Database and Cochran Library and Met the Inclusion Criteria

Reference No.			Random	Blind	Dropout	Setting	patients study arm	control	Opioid (morphine) medication	Program	Dose Means	Active Drug
Doroperidor												
8	Sanansilp V	1998	1	2	1	caesarean section	32	33	epidural		5 mg	droperidol
7	Horta ML	1993	1	2	1	caesarean section	54	53	epidural		2 mg	droperidol
15	Pueyo FJ	1996	1	2	1	abdominal surgery	25	25	PCA	60 mg/60 ml	32±18 mg 48 h	droperidol
12	Alexander R	1995	1	2	1	orthopaedic surgery	43	41	PCA	60 mg/60 ml	66.8 mg 24 h	droperidol
16	Kaufmann MA	1994	1	2	1	elective surgical	70	67	PCA	120 mg/60 ml	40.4±2.9 mg 24 h	droperidol
17	Gon TJ	1994	1	2	1	orthopaedic procedures	20	20	PCA	30 mg/60 ml	0.67 mg/kg 24 h	droperidol
17	Gon TJ	1994	1	2	1	orthopaedic procedures	20	20	PCA	30 mg/60 ml	0.7 mg/kg 24 h	droperidol
17	Gon TJ	1994	1	2	1	orthopaedic procedures	20	20	PCA	30 mg/60 ml	0.67 mg/kg 24 h	droperidol
18	Russell D	1996	1	2	1	caesarean section	20	20	PCA	60 mg/60 ml	53 mg 20 h	droperidol
19	Grebenik C.R	1996	1	2	1	cardiac surgery	200	198	PCA	60 mg/60 ml	28.6 mg 24 h	droperidol
20	Sharma SK	1993	1	2	1	abdominal hysterectomy	21	21	PCA	60 mg/60 ml	63.5 mg 24 h	droperidol
Metoclopramide												
10	Walder AD	1994	1	2	1	gynaecological surgery	25	25	PCA	60 mg/60 ml	37.5 mg 24 h	metoclopramide
16	Kaufmann MA	1994	1	2	1	elective surgical	71	67	PCA	120 mg/60 ml	46.8±3.3 mg 24 h	metoclopramide
21	Ellis FR	1970	2	2	1	gynaecological surgery	18	24	intramuscular		10 mg	metoclopramide
21	Ellis FR	1970	2	2	1	gynaecological surgery	20	24	intramuscular		10 mg	metoclopramide
9	Pitkanen MT	1997	1	2	1	orthopaedic prosthesis surgery	23	25	intrathecal		0.3 mg	metoclopramide
Dexamethasone												
22	Lopez OL	1996	1	2	1	gynaecological surgery	25	25	PCA	60 mg/60 ml	39±22.4 mg 48 h	dexamethasone
23	Liu K	1999	1	2	1	gynaecological surgery	30	30	PCA	60 mg/60 ml	16.9±4.7 mg 24 h	dexamethasone
23	Liu K	1999	1	2	1	gynaecological surgery	30	30	PCA	60 mg/60 ml	15.5±7.2 mg 24 h	dexamethasone
23	Liu K	1999	1	2	1	gynaecological surgery	30	30	PCA	60 mg/60 ml	15.5±7.2 mg 24 h	dexamethasone
23	Liu K	1999	1	2	1	gynaecological surgery	30	30	PCA	60 mg/60 ml	13.7±6.9 mg 24 h	dexamethasone
24	Wang JJ	1999	1	2	1	abdominal total hysterectomy	38	36	epidural		3 mg	dexamethasone
Propofol												
25	Bree SE	1998	1	2	1	gynaecological surgery	25	24	PCA	100 mg/50 ml	47 24 h	propofol
26	Grattidge P	1998	1	2	1	hip or knee replacement surgery	40	41	intrathecal		0.2—0.3 mg	propofol
27	Montgomery JE	1996	1	2	1	gynaecological surgery	24	23	PCA		39.1 24 h	propofol
28	Torn K	1994	1	2	1	arthoplasty surgery	20	20	intrathecal		0.3 mg	propofol
Ondansetron												
15	Pueyo FJ	1996	1	2	1	abdominal surgery	25	25	PCA	60 mg/60 ml	34±19 mg 48 h	ondansetron
12	Alexander R	1995	1	2	1	orthopaedic surgery	43	41	PCA	60 mg/60 ml	73.7 mg 24 h	ondansetron
22	Lopez OL	1996	1	2	1	gynaecological surgery	25	25	PCA	60 mg/60 ml	39±22.4 mg 24 h	ondansetron
9	Pitkanen NT	1997	1	2	1	orthopaedic prosthesis surgery	25	25	intrathecal		0.3 mg	ondansetron
11	Davies P.R.F.	1996	2	2	1	abdominal hysterectomy surgery	33	33	PCA	60 mg/60 ml	55 mg 24 h	ondansetron

Reference No.	Dose initial	maintenance	Control Drug	Observation period	experimental event patient(h)	control event patient(h)	patients with end point/total patients	
							Response %(Active)	Response %(Control)
Doroperidor								
8	2.5 mg iv: just after delivery		placebo(saline)	24 h	4	15	88	55
7	2.5 mg iv: just after delivery		placebo(saline)	24 h	8	7	85	87
15	2.5 mg iv: end of surgery	1.25 mg iv: 12 h later	placebo(saline)	24 h	8	18	68	28
12	1.25 mg iv: end of surgery	5 mg/60 ml: PCA	placebo(saline)	24 h	23	33	47	20
16	2.5 mg iv: end of surgery	7.5 mg/60 ml: PCA	placebo(saline)	36 h	12	36	83	46
17	1.25 mg iv: end of surgery	5 mg/60 ml: PCA	placebo(saline)	24 h	6	16	70	20
17	1.25 mg iv: end of surgery		placebo(saline)	24 h	7	16	65	20
17		5 mg/60 ml: PCA	placebo(saline)	24 h	5	16	75	20
18	0.87 mg iv: end of surgery	10 mg/60 ml: PCA	placebo(saline)	20 h	7	16	65	20
19		10 mg/60 ml: PCA	placebo(saline)	24 h	46	92	77	54
20		3 mg/60 ml: PCA	placebo(saline)	24 h	10	20	52	5
Metoclopramide								
10		30 mg/60 ml: PCA	placebo(saline)	24 h	3	10	88	60
16	20 mg iv: end of surgery	60 mg/60 ml: PCA	placebo(saline)	36 h	28	36	60	46
21	10 mg iv: end of surgery		placebo(saline)	24 h	8	15	56	37
21	20 mg iv: end of surgery		placebo(saline)	24 h	9	16	55	33
9		20 mg×3 at 6 h	placebo(saline)	24 h	12	15	48	40
Dexamethasone								
22	8 mg iv: befor the induction anesthesia		placebo(saline)	48 h	10	20	60	20
23	1.25 mg iv: befor the induction anesthesia		placebo(saline)	24 h	15	19	50	37
23	2.5 mg iv: befor the induction anesthesia		placebo(saline)	24 h	8	19	73	37
23	5 mg iv: befor the induction anesthesia		placebo(saline)	24 h	6	19	80	37
23	10 mg iv: befor the induction anesthesia		placebo(saline)	24 h	6	19	80	37
24	8 mg iv: end of surgery		placebo(saline)	24 h	6	20	84	44
Propofol								
25		5 mg/50 ml: PCA	placebo(iverip)	24 h	17	16	32	33
26	end of surgery	30 mg/h/20 h: div	placebo(intralipid)	24 h	10	6	75	85
27		1 mg/kg/h/24 h: div	placebo(intralipid)	24 h	14	15	42	35
28	10 mg iv: befor the induction anesthesia	30 mg/24 h: div	placebo(intralipid)	24 h	12	13	40	35
Ondansetron								
15	4 mg iv: end of surgery		placebo(saline)	24 h	11	18	56	28
12	4 mg iv: befor the induction anesthesia	8 mg/60 ml: PCA	placebo(saline)	24 h	12	33	72	20
22	4 mg iv: befor the induction anesthesia		placebo(saline)	48 h	12	20	52	20
9		8 mg×2 at 12 h	placebo(saline)	24 h	13	15	48	40
11	4 mg iv: befor the induction anesthesia	4 mg at 8 h later	placebo(saline)	24 h	28	23	15	30

droperidol in 11 studies,[7,8,12,16—21] metoclopramide in 5 studies,[9,10,16,21] dexamethasone in 6 studies,[22—24] propofol in 4 studies,[25—28] and ondansetron in 5 studies.[9,12,15,22]

The results of testing the lack of homogeneity the results of studies for each of the four test drugs are shown. Droperidol: Q=15.77 (df=10), p=0.15; Metoclopramide: Q=2.63 (df=4), p=0.15; Dexamethasone: Q=4.23 (df=5), p=0.65; and Propofol: Q=1.62 (df=3), p=0.81. With these four drugs, the Peto method was used for meta-analysis. Since a lack of homogeneity was noted for ondansetron (Q=18.30 (df=4), $p<0.01$), on the contrary, the random effect model was used for meta-analysis for ondansetron.

The results of the meta-analysis for the test drugs, droperidol, metoclopramide, dexamethasone, propofol, and ondansetron, are shown in Figs. 1, 2, 3, 4 and 5, respectively. Figures for meta-analysis indicate the absence of any significant difference between the test drug group and the placebo group when the range of 95% CI contains an odds ratio (Peto OR) of 1. The range of the 95% CI not containing the central odds ratio of 1 and that is lower than 1 indicates a significant decrease in the incidence of nausea and vomiting due to the test drug. A range greater than 1 indicates an increase in the OR.

The results of the meta-analysis of 11 studies with droperidol in Fig. 1 indicate an OR of 0.27, a 95% CI of 0.21—0.34, $p<0.00001$, and a highly significant decrease in the incidence of nausea and vomiting when compared to the placebo group. The results with metoclopramide in Fig. 2 indicate an OR of 0.48, a 95% CI of 0.30—0.75, and p=0.001, and those with dexamethasone in Fig. 3 indicate an OR of 0.23, a 95% CI of 0.15—0.35, and $p<0.00001$. The results with propofol in Fig. 4 indicate an OR of 1.09, a 95% CI of 0.61—1.95, and p=0.8, with no significant decrease in the incidence of nausea and vomiting. The results with ondansetron in Fig. 5 indicate an OR of 0.40, a 95% CI of 0.13—1.22, and $p<$ 0.00001, with a decreasing tendency but no significant difference in the incidence of nausea and vomiting in the ondansetron group in comparison to the placebo group.

DISCUSSION

For the present research, the incidence of nausea and vomiting in 1035 control patients (placebo groups) in the studies was 60.9%. There is great necessity for prophylactic treatment given such a high incidence of nausea and vomiting that is directly as-

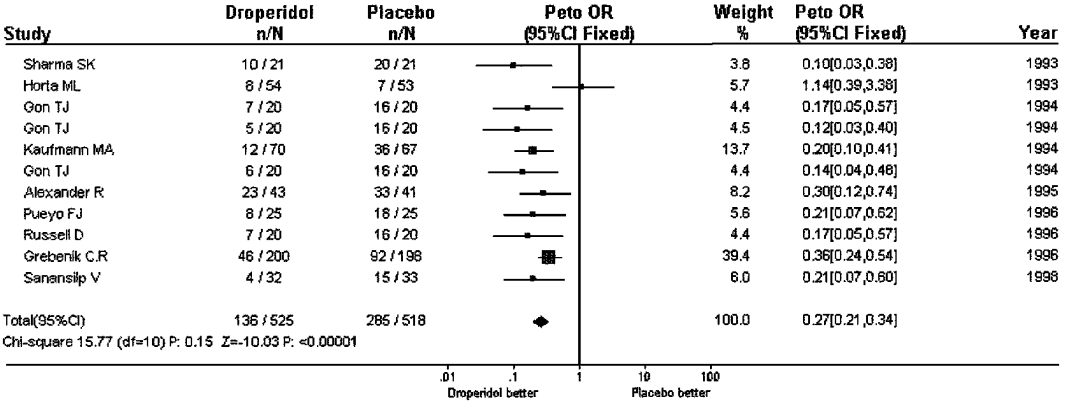

Fig. 1. Effect of Droperidol on PONV: Droperidol VS Placebo

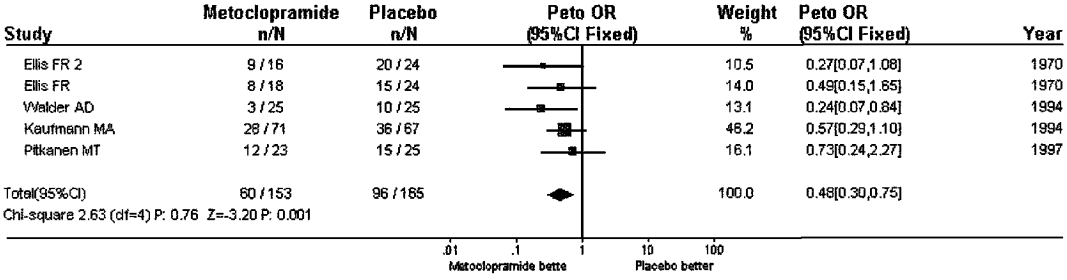

Fig. 2. Effect of Metoclopramide on PONV: Metoclopramide VS Placebo

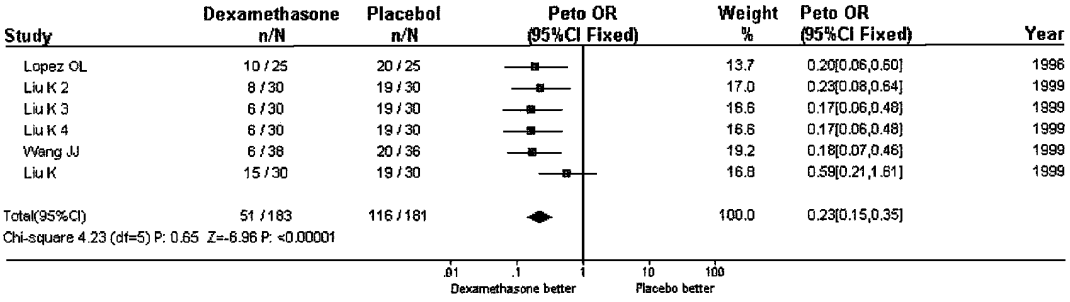

Fig. 3. Effect of Dexamethasone on PONV: Dexamethasone VS Placebo

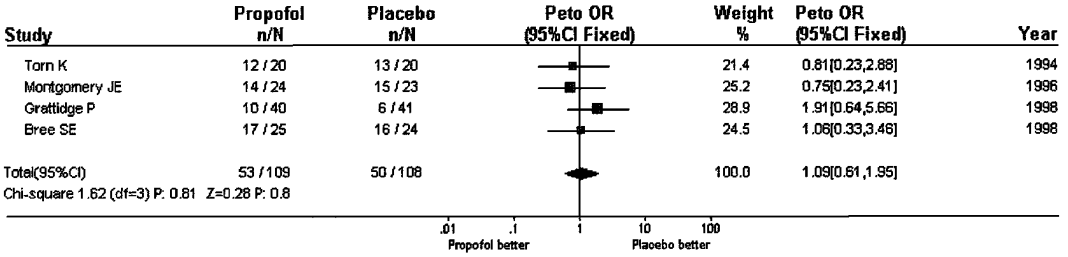

Fig. 4. Effect of Propofol on PONV: Propofol VS Placebo

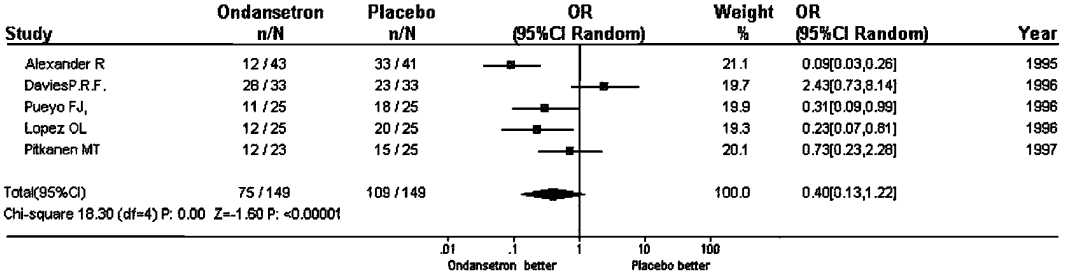

Fig. 5. Effect of Ondansetron on PONV: Ondansetron VS Placebo

sociated with a decrease in patient QOL.

The present research involved a meta-analysis of the prophylactic effect of antiemetics given for the prevention of nausea and vomiting and evaluated their efficacy. In 1999, Martin *et al*. studied the effects of and adverse reactions related to prophylactic antiemetics given to the patients who used morphine as PCA.[29] They reported that of droperidol, hyoscine TTS, ondansetron, tropisetron, propofol, metoclopramide, clonidine, and promethazine, meta-analysis of multiple reports demonstrated the efficacy of droperidol alone, with no correlation between the effect and dose. The incidence of adverse reactions such as sleepiness were found to be related to the dose given.

In the present research, meta-analysis of five drugs was performed under the following conditions: 1) the subjects are ''patients who received morphine for the purpose of treating postoperative pain,'' and are not restricted to patients who used PCA; 2) ''the final retrieval date must be February 22, 2000,'' etc. As a result, greater efficacy for droperidol, which is similar to that reported by Martin *et al*., was noted. Greater efficacy was also shown for dexamethasone. The efficacy of metoclopramide was noted, but the efficacy of propofol was not noted.

Of the five drugs studied, three were shown to be effective. These drugs were dexamethasone, droperidol, metoclopramide in order of a higher odds ratio. These results suggest that, in order of decreasing efficacy, dexamethasone, droperidol, metoclopramide should be used for the effectiveness of prophylactic drug therapy for PONV in patients given morphine for the treatment of postoperative pain.

The dose/24 h was 1.25 mg at the lowest and 10 mg at the highest, with an average of 5.8 mg for dex-

amethasone. The initial dose of droperidol was 1.25 mg to 2.5 mg and its maximal maintenance dose was 10 mg/60 ml (PCA), with an average of 5.6 mg. The dose of metoclopramide was 10 mg at the lowest and 80 mg at the highest, with an average of 40 mg.

Morphine induces nausea and vomiting mainly by:

(1) directly acting on the chemoreceptor trigger zone (CTZ) in the area postrema of the medulla, with the action conveyed to the vomiting center (VC);

(2) increasing the sensitivity of vestibular function and indirectly stimulating the CTZ, with the action conveyed to the VC; and

(3) decreasing the stomach motility, prolonging the gastric emptying time, and increasing the possibility of esophageal reflux.

Droperidol shows an antiemetic action by competitively antagonizing dopamine in D2 receptors in the CTZ. Metoclopramide is an antiemetic that has both a dopamine-blocking action and a gastrointestinal motility-activating action. These two agents are effective pharmacologically since they antagonize the above nausea and vomiting action induced by morphine.

Ondansetron exhibits an antiemetic action by antagonizing vomiting signals in the afferent path from the stomach or small intestine, CTZ and solitary tract nucleus, and a transmitter substance 5-HT_3. This is partly different from the above antiemetic action. Despite no significant difference ondansetron gave a relatively good result with an odds ratio of 0.40, and therefore needs to be further studied using an increased number of patients, etc. since release of 5-HT_3 may be partly associated with PONV.

Dexamethasone was the most effective agent although its reasonable mechanism of antiemetic action was unknown. Thus, the meta-analysis of previously published studies suggested that three drugs were effective for prophylaxis with respect to PONV. The evidence was higher with dexamethasone (odds ratio: 0.23), droperidol (odds ration: 0.27), and metoclopramide (odds ration: 0.48) in order. This means that either dexamethasone or droperidol should be given for prophylaxis with respect to PONV in view of the odds ratio. Of them, dexamethasone was shown to be the agent with the best evidence and able to decrease the incidence of PONV from 56—80% to 16—50% (odds ratio: 0.23) with a dose of 1.25—10 mg.

In addition to the results of this research, contemplation of the adverse events brought by each antiemetic, such as delayed postoperative wound healing or infection due to a steroid dexamethasone, oversedation due to droperidol, and parkinsonism due to metoclopramide, enabled the selection of prophylactic agents with respect to PONV that suit individual patients.

REFERENCES

1) Mann C., Pouzeratte Y., Boccara G., Peccoux C., Vergne C., Brunat G., Domergue J., Millat B., Colson P., *Anesthesiology*, **92**, 433–441 (2000).
2) Suwanchinda V., Suksompong S., Prakanrattana U., Udompunthurak S., *Med. Assoc. Thai.*, **83**, 358–363 (2000).
3) Joshi W., Reuben S. S., Kilaru P. R., Sklar J., Maciolek H., *Anesth. Analg.*, **90**, 1102–1106 (2000).
4) Chan W. H., Lin C. J., Sun W. Z., Tsai S. P., Tsai S. K., Hsieh C. Y., Kao Hsiung. I., Hsueh Ko. Hsueh., *Tsa. Chih.*, **15**, 419–427 (1999).
5) Bourke M., Hayes A., Doyle M., McCarroll M., *Anesth. Analg.*, **90**, 427–430 (2000).
6) Choi Y. K., Brolin R. E., Wagner B. K., Chou S., Etesham S., Pollak P., *Obes. Surg.*, **10**, 154–159 (2000).
7) Horta M. L., Horta B. L., *Reg. Anesth.*, **18**, 118–20 (1993).
8) Sanansilp V., Areewatana S., Tonsukchai N., *Anesth. Analg.*, **86**, 532–537 (1998).
9) Pitkanen M. T., Numminen M. K., Tuominen M. K., Rosenberg P. H., *Eur. J. Anaesthesiol.*, **14**, 172–177 (1997).
10) Walder A. D., Aitkenhead A. R., *Anaesthesia*, **49**, 804–806 (1994).
11) Davies P. R., Warwick P., O'Connor M., *Anaesthesia*, **51**, 880–882 (1996).
12) Alexander R., Lovell A. T., Seingry D., Jones R. M., *Anaesthesia*, **50**, 1086–1088 (1995).
13) Jadad A. R., Moore R. A., Carroll D., Jenkinson C., Reynolds D. J. M., Gavaghan D. J., McQuay H. J., *Controlled Clin. Trials*, **17**, 1–12 (1996).
14) Yusuf S., Peto R., Lewis J., Collins R., Sleight P., *Prog. Cardiovasc. Dis.*, **27**, 335–371 (1985).
15) Pueyo F. J., Carrascosa F., Lopez L., Iribarren M. J., Garcia-Pedrajas F., Saez A., *Anesth. Analg.*, **83**, 117–122 (1996).
16) Kaufmann M. A., Rosow C., Schnieper P., Schneider M., *Anesth. Analg.*, **78**, 988–994 (1994).
17) Gan T. J., Alexander R., Fennelly M., Rubin

A. P., *Anesth. Analg.*, **80**, 81–85 (1995).
18) Russell D., Duncan L. A., Frame W. T., Higgins S. P., Asbury A. J., *Acta. Anaesthesiol. Scand.*, **40**, 600–605 (1996).
19) Grebenik C. R., Allman C., *Br. J. Anaesth.*, **77**, 356–359 (1996).
20) Sharma S. K., Davies M. W., *Br. J. Anaesth.*, **71**, 435–436 (1993).
21) Ellis F. R., Spence A. A., *Anaesthesia*, **25**, 368–371 (1970).
22) Lopez-Olaondo L., Carrascosa F., Pueyo F. J., Monedero P., Busto N., Saez A., *Br. J. Anaesth.*, **76**, 835–840 (1996).
23) Liu K., Hsu C. C., Chia Y. Y., *Anesth. Analg.*, **89**, 1316–1318 (1999).
24) Wang J. J., Ho S. T., Liu Y. H., Ho CM., Liu K., Chia Y. Y., *Anesth. Analg.*, **89**, 117–120 (1999).
25) Bree S. E., West M. J., Taylor P. A., Kestin I. G., *Br. J. Anaesth.*, **80**, 152–154 (1998).
26) Grattidge P., *Acta. Anaesthesiol. Scand.*, **42**, 124–127 (1998).
27) Montgomery J. E., Sutherland C. J., Kestin I. G., Sneyd J. R., *Anaesthesia*, **51**, 554–557 (1996).
28) Torn K., Tuominen M., Tarkkila P., Lindgren L., *Br. J. Anaesth.*, **73**, 411–412 (1994).
29) Martin R., Tramer M. D., Dphil., Walder M. D., *Anesth. Analg.*, **88**, 1354–1361 (1999).