Optimum Dose of Epidural Morphine for Postsurgical Analgesia

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To determine the optimum dose of epidural morphine for postoperative pain control, 0.5 – 4.0 mg of morphine was administered to 198 patients who had undergone operations on lower abdomen or lower extremities under continuous epidural anesthesia. Analgesic effect of morphine and incidence of nausea or vomiting were studied using linear discriminant analysis. As explanatory variables, age and dose of morphine were statistically significant in discriminating analgesic effect of morphine. Among indices for physique of patients, height was the most useful for predicting the analgesic effect. The dose which made the discriminant function zero corresponded to the minimum effective dose (MED) of morphine and it was expressed as follows; MED ($mg \cdot meter^{-1}$) = $-0.0107 \times$ age $+ 1.85$. Predicting the incidence of nausea or vomiting in relation to the dose of morphine did not reach a level of statistical significance. (Key words: epidural morphine, postsurgical pain, nausea and vomiting, minimum effective dose, linear discriminant analysis)

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Epidural administration of morphine hydrochloride is widely used to relieve acute and chronic pain of various origins. This method is quite effective, but is not free from side effects. In order to minimize adverse reactions, the drug should be administered with minimum effective dose. We conducted this study to determine optimum dose of epidural morphine for postsurgical analgesia. We applied linear discriminant analysis, a method of multivariable analysis, to analyze analgesic effect and incidence of nausea or vomiting complicated by morphine treatment. The results of this study will be compared with that of buprenorphine which we did before[1].

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Methods

We studied 198 postoperative patients who had undergone elective operations on lower abdomen or lower extremities under continuous epidural anesthesia. Following patients were excluded from the study: those younger than 20 years old, with psychotic or digestive diseases, with ASA risk score 3 or more, and those suffering from nausea or vomiting before and during operation. Oral consent for the study was obtained preoperatively.

Hydroxyzine 50 mg or diazepam 10 mg with atropine 0.3 – 0.5 mg was administered intramuscularly 30 – 45 min before induction of anesthesia. Hydroxyzine and diazepam were omitted in the patients scheduled for C-section and those over 70 years old. An epidural catheter was inserted through a 17-gauge Tuohy needle placed at L_{1-2} or $_{2-3}$ interspace and passed about 5 cm cephalad. Analgesia was obtained with 12 – 15 ml of 2% lidocaine and with additional doses of

Table 1. The subjects and the operations performed

departments	operations	number (male)	age mean (SD)
gynecology	total hysterectomy	76	45.4
	resection of ovarian tumor	(0)	(10.9)
obstetrics	abdominal C-section	44	28.9
		(0)	(5.1)
urology	resection of ureteral stone	33	70.9
	or hypertrophied prostate	(30)	(13.4)
orthopedics	repair of fractures on the	32	66.4
	lower extremities	(15)	(16.2)
general surgery	herniotomy of inguinal	13	64.2
	or femoral hernia	(5)	(9.4)
total		198	50.6
		(50)	(19.1)

(Transurethral and vaginal operations were excluded.)

0.5% bupivacaine. In certain cases, 5 – 10 mg of diazepam or 7.5 – 30 mg of pentazocine was given intravenously, or 50 – 67% nitrous oxide was administered with face mask as a supplement.

At the end of operation, a dose of morphine chosen randomly in the range of 0.5 – 4.0 mg (10 – 70 $\mu g \cdot kg^{-1}$) was administered via epidural catheter with 4 ml of 0.25% bupivacaine. Additional analgesics were administered in the wards with the request of patients. The treatment was considered successful when a patient required no analgesics for the first 8 hours after administration of morphine. When a patient complained of nausea or vomiting within 12 hours of administration, it was considered caused by epidural morphine.

Statistical analysis was performed in the following way. At first, the patients were divided into groups according to sex, age and dose of morphine. Chi-square test was applied to compare analgesic effect and incidence of nausea or vomiting between these groups.

Secondly, linear discriminant analysis was performed. In the analysis, the outside criteria were analgesic effect of morphine and incidence of nausea or vomiting. The explanatory variables were age and sex of patients, and dose of morphine. Dose of morphine was calculated in three manners: dose per weight ($\mu g \cdot kg^{-1}$), dose per body surface area (BSA, $mg \cdot m^{-2}$) and dose per height ($mg \cdot meter^{-1}$). Statistical significance of each explanatory variable was accepted with $P < 0.05$ in the analysis of discriminant coefficients. A discriminant function (Z) to predict analgesic effect was calculated using the explanatory variables of statistical significance. A dose of morphine which made the function zero was defined as the minimum effective dose (MED) of morphine.

This discriminant function was applied again to determine the effectiveness of discrimination. When analgesic treatment was successful with $Z \geq 0$ and when unsuccessful with $Z < 0$, the discrimination by the function was correct. The rate of correct discrimination (%) was calculated by dividing the number of subjects correctly discriminated by the total number. Three different ways of calculating dose of morphine were compared from the view of effectiveness of discrimination.

Results

The surgical operations performed, and the characteristics of patient groups are shown in table 1 and 2. The success rate of epidural epidural morphine treatment was 70.7% in all 198 cases. The success rate in the patients who

Table 2. Characteristics of the groups, success rate of epidural morphine analgesia and incidence of nausea or vomiting

Group	n	age mean (SD)	dose mean (SD)	success rate (%)	nausea (%)
Sex –male	50	69.2 (14.2)	37.8 (17.7)	64.0	12.0*
–female	148	44.3 (16.3)	42.2 (16.7)	73.0	27.0
Age –1 (20–39)	66	29.5 (5.5)	40.6 (17.1)	65.2	18.2
–2 (40–59)	66	48.5 (5.4)	41.0 (16.8)	71.2	33.3**
–3 (60–) (years old)	66	73.8 (7.1)	41.7 (17.2)	75.7	18.2
Dose –1 (10–29)	66	51.1 (18.9)	21.1 (5.1)	51.5***	21.2
–2 (30–49)	66	50.3 (19.2)	41.2 (5.1)	78.8	19.7
–3 (50–70) ($\mu g \cdot Kg^{-1}$)	66	50.4 (19.2)	60.9 (5.2)	81.8	28.8
total	198	50.6 (19.1)	41.1 (17.1)	70.7	23.2

*$P < 0.05$ between male and female
**$P < 0.05$ between Age–1 and 2, Age–2 and 3
***$P < 0.01$ between Dose–1 and 2, Dose–1 and 3

Table 3. Results of discriminant analysis

outside criteria	index of body size	F-value of discriminant coefficients			rate of correct discrimination (%)
		age	sex	dose	
analgesic effect	height	9.5**	3.4	28.4**	70.2
	BSA	7.1*	2.9	26.5**	68.7
	weight	5.0*	2.8	22.6**	66.7
nausea or vomiting	height	2.4	11.6**	0.2	57.1
	BSA	2.5	11.4**	0.0	59.1
	weight	2.4	11.0**	0.1	60.6

(**$P < 0.01$, *$P < 0.05$)

received morphine less than 30 $\mu g \cdot kg^{-1}$ was lower compared with the others. Differences in the rate were not observed between the sexes and between the age groups (table 2).

In the first discriminant analysis, age and dose of morphine were effective in discriminating analgesic effect of morphine. Among three indices for dose, dose per height was the most effective in predicting analgesic effect (table 3). Using age and dose per height as explanatory variables, another discriminant analysis could be performed. By this analysis, we obtained the discriminant function (Z); $Z = 0.0192 \times$ age (years) $+ 1.79 \times$ dose ($mg \cdot meter^{-1}$) $- 3.31$. In 113 patients for whom the analgesic treatment was expected to be successful ($Z \geq 0$), the success rate was 85.0%. In 85 patients for whom the treatment was expected to be unsuccessful ($Z < 0$), the success rate was 51.8%. The rate of correct discrimination was 69.2% over all. A scattered graph (fig. 1) shows the relations between age, dose and analgesic effect of morphine. The straight line in the figure corresponds to the dose which made the discriminant function zero. The minimum effective dose (MED) of morphine was expressed as follows; MED ($mg \cdot meter^{-1}$) =

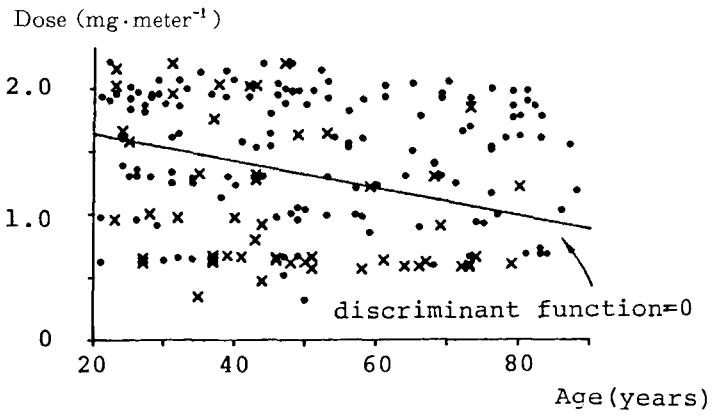

Fig. 1. Scattered graph for age and dose of morphine.
Closed circle indicates that analgesic treatment with epidural morphine was successful, and (×) indicates that it was unsuccessful.

$-0.0107 \times$ age $+ 1.85$. Using body weight (Kg) and body surface area (m^2), the discriminant functions were calculated in the same way. Here MED ($\mu g \cdot kg^{-1}$) $= -0.195 \times$ age $+ 48.06$, MED ($mg \cdot m^{-2}$) $= -0.0090 \times$ age $+ 1.80$.

The overall incidence of nausea or vomiting was 23.2% in all 198 patients. The incidence was higher in female than in male and was also higher in the patients 40 – 59 years old (table 2). In the discriminant analysis, none of the variables except sex was effective in predicting the incidence of nausea or vomiting (table 3).

Discussion

Pain control during postoperative period is of invaluable importance because postsurgical pain brings about various adverse reactions such as respiratory depression, difficulty in coughing, hypertension and tachycardia[2]. Epidural administration of morphine or other analgesics is one of the most effective methods for relieving postsurgical pain. However, this method is not free from side effects, respiratory depression, nausea or vomiting, pruritis, and difficulty in urination. Large dose of morphine is not recommended because the incidence of side effects is considered dose-dependent[3,4]. We conducted this study to determine the MED of morphine and to know whether incidence of side effects was really lower with MED. We focused on nausea and vomiting because these were most frequently observed symptoms among side effects of epidural morphine.

In order to evaluate analgesic effect and incidence of nausea or vomiting appropriately, various factors which may have had influences on these parameters had to be taken into consideration; original diseases which needed operations, sites and techniques of operations, methods of anesthesia, age, sex, and physique of patients. As for operations, they were limited to those on lower abdomen or lower extremities, and methods of anesthesia were also limited to continuous epidural anesthesia. We assumed that patients were suffering from postsurgical pain with equal severity and consistency. The influences of age, sex and physique were analized by linear discriminant analysis, a method for predicting or classifying data with linear functions of multiple parameters[5]. In this analysis, we computed discriminant functions which could most accurately predict the appearance of analgesic effect and side effects. We defined the dose which made the discriminant function zero as the minimum effective dose (MED), arriving at the formula: MED ($mg \cdot meter^{-1}$) $= -0.0107 \times$ age $+ 1.85$. This is the borderline dose above which most patients are expected to be successfully treated.

As with buprenorphine on which we reported previously[1], age was a factor of statistical significance in predicting the outcome of epidural morphine treatment. It is known that older patients are particularly sensitive to systemically administered morphine[6]. Our

results suggest that epidural morphine analgesia is also age-dependent. Our MED was expressed as a linear function of age, and it indicated that an increase in age from 20 to 70 years reduced morphine requirement to two thirds. The rate of correct discrimination using our discriminant function was not remarkably high. If we had analyzed with logarithmic or quadratic function of age, more efficient discrimination might have been possible. In that case, however, resulting MED would have become too complex for clinical application.

Little is known about the correlation between requirement of epidural morphine and physique of patient. Drugs administered intravenously or intramuscularly are usually calculated with dose per body weight. The dose requirement of local anesthetic for nerve blocks, such as epidural block[7] or brachial plexus block[8], are often determined by height. Our data revealed that requirement of epidural morphine could also be calculated as a function of height. Analgesic effect of epidural buprenorphine, in contrast to morphine, is more predictive with dose per body weight than with dose per height. We speculate that epidural morphine manifests its analgesic effect mainly through direct spinal action, while the action of buprenorphine may depend more on the systemic action due to its rapid vascular uptake. This might be the reason why the dose of epidural buprenorphine needs to be as much as intravenous or intramuscular administration.

Nausea and vomiting are not life-threatening but are quite unpleasant complications associated with epidural morphine. Some reports suggest that the incidence is high when large doses of morphine are administered[4] and also high in females[9,10]. If we can predict the patients who are liable to suffer from nausea or vomiting, we may prevent it by decreasing the dose or by administering antiemetics together with morphine[11]. However, we could not find any linear correlations between dose and the incidence of nausea or vomiting. This indicates that reducing dose of morphine does not necessarily decrease the incidence. Further analysis on side effects other than nausea or vomiting may be required to determine optimum dose of morphine treatment.

In concluding, we could express minimum effective dose of epidural morphine as a function of age, however, further studies are required to determine the safety margin by analyzing the incidence of side effects.

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