Dependence of the Dose-Response Curve on Incision Site for Intrathecal Morphine

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(Key words: intrathecal morphine, incision site, dose-response curve)

Many clinical reports have demonstrated the effectiveness of intrathecal morphine for postoperative analgesia[1]. However, intrathecal morphine has been administered with a wide range of doses and the optimal dose has not been decided[2-4].

This study was undertaken to determine the minimum effective dose of intrathecal morphine analgesia at the sites of different surgical incisions. We have also investigated the duration of analgesia and determined the incidence of side effects.

Methods

This study consisted of 204 patients of ASA class I or II. The patients were divided into 3 groups according to the sites of surgical incisions:

Group I : the upper end of the incision was between Th6 and Th9 dermatomes;
Group II : between Th10 and Th12 dermatomes; and
Group III : S dermatome.

The types of surgery in each group were:

Group I : gastrectomy and cholecystectomy (n = 106);
Group II : hysterectomy (n = 53); and
Group III : TUR-P and TUR-Bt (n = 45).

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J Anesth 1:115–118, 1987

These 3 groups were then subdivided according to the dose of morphine. The dose of morphine was increased from one subgroup to another in stepwise increments of 10- 30 μg within each group. The range of morphine dose was from 10 μg to 150 μg.

Morphine was mixed with 6–16 mg of tetracaine and diluted with 2.0–2.5 ml of 10% dextrose. We injected it intrathecally at the L2–3 interspace in the lateral position before surgery. As for Group I, we used nitrous oxide, oxygen and a low concentration of enflurane (less than 0.8%) and we supplemented analgesia by epidural lidocaine in case of prolongation of surgery.

In Group II and III, we administered 5–10 mg of diazepam intravenously for sedation during surgery.

The duration of analgesia was determined as the time from injection of morphine until the patient requested an additional analgesic during a 24-hour period.

Effectiveness was defined as the percentage of patients with analgesia over 24 hours. ED_{50} was determined as a dose of morphine which produced analgesia over 24 hours in 50% of the patients.

We placed a catheter in the radial artery of the patients in Group I to monitor blood pressure, this allowed us to make arterial blood gas studies at the end of surgery and at 6 and 12 hours after the injection of intrathecal morphine.

Respiratory depression was defined as a decrease in respiratory rate to 10 times/min or less and/or an increase of CO_2 pressure of

Table 1. Patient data

Group	Morphine (μg)	Patients (n)	Age (yr)	Sex (Male/Female)	Height (cm)	Weight (kg)	Duration of Surgery (hr)
I	0	19	56.7 ± 13.0	10 / 9	155.5 ± 8.0	54.3 ± 11.1	2.2 ± 1.2
	60	11	53.9 ± 13.5	4 / 7	154.0 ± 6.0	50.3 ± 8.6	2.3 ± 1.7
	80	9	55.0 ± 13.3	4 / 5	158.5 ± 7.3	59.3 ± 9.8	3.4 ± 2.4
	100	16	55.1 ± 10.7	8 / 8	160.4 ± 9.0	59.1 ± 11.3	2.5 ± 1.1
	120	27	60.6 ± 11.4	20 / 7	160.7 ± 7.0	56.7 ± 10.9	3.0 ± 1.7
	150	24	58.3 ± 11.7	13 / 11	155.3 ± 8.3	55.0 ± 11.2	2.4 ± 1.1
II	0	9	42.6 ± 6.0	0 / 9	153.9 ± 4.5	53.9 ± 8.3	1.3 ± 0.4
	30	8	49.4 ± 5.6	0 / 8	149.2 ± 8.1	56.7 ± 12.1	1.3 ± 0.2
	40	13	41.7 ± 5.7	0 / 13	151.2 ± 5.6	52.7 ± 7.6	1.0 ± 0.2
	60	12	46.3 ± 7.5	0 / 12	151.4 ± 4.5	54.8 ± 4.3	1.2 ± 0.4
	80	11	44.9 ± 4.5	0 / 11	152.6 ± 6.2	52.3 ± 7.9	1.4 ± 0.4
III	0	11	73.6 ± 8.1	11 / 0	157.8 ± 6.3	52.0 ± 13.7	1.1 ± 0.4
	10	11	70.5 ± 10.6	11 / 0	159.4 ± 8.6	55.5 ± 8.4	1.2 ± 0.5
	20	15	69.9 ± 17.0	12 / 3	156.9 ± 6.4	52.4 ± 7.8	0.9 ± 0.4
	40	8	69.6 ± 11.0	6 / 2	154.3 ± 5.1	46.4 ± 6.7	1.2 ± 0.4

Mean ± SD
Not significant between subgroups in Group I, II and III

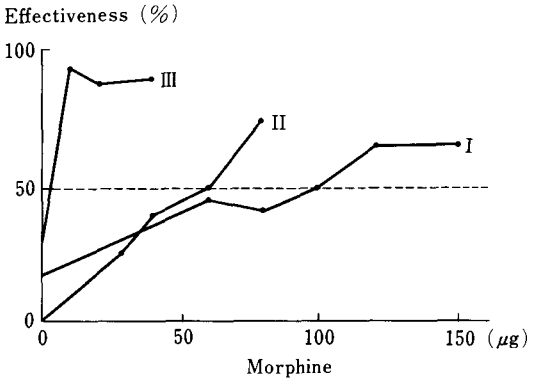

Fig. 1. The relationship between the dose of intrathecal morphine and effectiveness in Group I, II and III

more than 50 mmHg.

Statistical analysis was performed using Student's t-test, Wilcoxon analysis or Fisher's exact test. A value of $P<0.05$ was considered statistically significant.

Results

There were no significant differences with regard to age, sex, height, weight and duration of surgery among the subdivided groups in each group (table 1).

Duration of analgesia

In Group I, the duration of analgesia became significantly longer in morphine subgroups of 80 μg or more in comparison with the subgroup of 0 μg (table 2). Similarly, significantly longer analgesia was observed morphine subgroups of 40 μg or more in Group II, and 10 μg or more in Group III. Duration of analgesia increased dose-dependently in Groups I and II.

Table 2. Duration of analgesia

Group	Morphine (μg)	Duration of analgesia (hr)
I	0	9.4 ± 7.5
	60	15.2 ± 9.3
	80	16.8 ± 8.1 *
	100	18.0 ± 8.5 *
	120	18.1 ± 8.5 *
	150	20.6 ± 6.4 *
II	0	6.8 ± 5.9
	30	12.6 ± 8.7
	40	14.9 ± 8.3 *
	60	16.1 ± 8.9 *
	80	20.4 ± 7.2 *
III	0	12.7 ± 7.6
	10	20.3 ± 2.3 *
	20	22.1 ± 5.2 *
	40	22.6 ± 3.9 *

Mean ± SD
* Significant difference from 0 μg ($P < 0.05$)

Effectiveness

Effectiveness increased dose-dependently in

Table 3. Side effects

Group	Morphine (μg)	Nausea・Vomiting (%)	Respiratory deperession (%)
I	0	21	0
	60	9	0
	80	22	0
	100	25	0
	120	15	0
	150	21	29 *
II	0	50	0
	30	50	0
	40	23	0
	60	25	0
	80	45	0
III	0	0	0
	10	18	0
	20	16	0
	40	13	0

* Significant difference from 120 μg ($P < 0.05$)

Groups I and II (fig. 1). The value of ED_{50} in Group I, II and III was 100 μg, 60 μg and 5 μg respectively.

Side effects

Nausea and vomiting occurred in about 20% of the patients in Group I, about 40% in Group II and about 10% in Group III (table 3). There were no significant differences with regard to nausea and vomiting among the subdivided groups in each group. However, the indicence of nausea and vomiting was significantly higher in female patients.

Respiratory depression occurred significantly in 29% of the patients who received 150 μg of morphine.

Discussion

We would like to discuss the effectiveness of intrathecal morphine in terms of opiate receptors. Opiate receptors in the spinal cord are found at high density in dorsal horn laminae I and II[5]. An opiate drug injected within the CSF is placed very near to its sites of action. If the pharmacodynamic effect of the opiate is directly proportional to receptor occupancy[6], the analgesic effect will not increase by giving a dose of the opiate that exceeds the amount of the receptor occupancy.

Gregory et al. measured tritium-labeled morphine concentration in the brain and the spinal cord after intrathecal morphine injection in baboons[7]. They demonstrated that morphine ascends in the subarachnoid space and is absorbed into the spinal cord and the medulla oblongata in a time-dependent fashion.

Consequently, excessive dose of intrathecal morphine will increase the incidence of side effects rather than enhance the analgesic effect. Therefore, it is necessary to determine the optimal dose, that is, the minimum effective dose of intrathecal morphine.

We administered intrathecal morphine in extremely low dose ranges and observed that the duration of analgesia increased dose-dependently in each subgroup.

The optimal dose of intrathecal morphine, in terms of ED_{50} in our study, is 100 μg to produce analgesia in the patients who underwent upper abdominal surgery, 60 μg for lower abdominal surgery, and 5 μg for perineal surgery respectively.

Effectiveness of intrathecal morphine was also found to vary in a dose-dependent fashion according to the site of incision.

We should pay attention to the possibility of respiratory depression when we inject 150 μg

or more morphine intrathecally.

(Received Nov. 28, 1986, accepted for publication Nov. 28, 1986)

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