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Analgesic Effect of a Small Dose of Intrathecally Administrated Morphine for the Relief of Postoperative Pain

(morphine/spinal cord/pain relief)

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Intrathecal injections of 0.05 to 0.625 mg morphine were given to 60 Japanese patients ranging in age from 16 to 76 years scheduled to undergo surgery of the lower abdomen or the lower extremities.

Each patient experienced a considerable amelioration of the postoperative pain and duration of the effect was for 7 to more than 48 hours. Twenty-eight of fifty-three patients given over 0.1 mg of morphine requested no analgesics, postoperatively.

In cases of less than 0.4 mg of morphine, there were no apparent side effects but two patients, given over 0.5 mg of morphine (women aged 51 and 61 years) experienced decreased respiratory rate or carbon dioxide retention. These techniques of alleviating postoperative pain should be considered for application only in the presence of experts.

In recent animal experiments, morphine administrated directly into the spinal subarachnoid space of the rat produced potent analgesia (1). Subsequent studies confirmed this finding and showed that repeated intrathecal injections of morphine did not cause adverse tissue reactions in the spinal cord (2, 3). Since these first reports, clinical reports have also been made (4–8).

However, recent studies have shown that a large dose of morphine given intrathecally may depress respiration (5–8). Further studies are needed to establish the clinical applicability of intrathecal injection of morphine, particularly with regard to the optimal dosage or even route of administration (9).

We presents our results of the relief of the postoperative pain by small doses of morphine injected into the spinal subarachnoid space, during the postoperative period.

MATERIALS AND METHODS

Sixty Jananese patients ranging in age from 16–76 years were scheduled to undergo surgery of the lower abdomen or the lower extremities. Forty-five patients were premedicated with diazepam, pentazocine and atropine before surgical procedures. As assessed from early experiments, we prepared a

solution which included 0.4 mg of morphine in 4 ml of 7.5% glucose with 20 mg of tetracaine and 5 mg of phenylephrine. This solution was injected into the lumbar subarachnoid space and as a result, the total dose of morphine was 0.05 to 0.625 mg. Anesthetic management was according to usual procedures. Postoperatively, duration of effects of anesthesia, duration of postoperative analgesia and untoward effects were investigated.

RESULTS

All patients experienced a considerable amelioration of postoperative pain and the duration of the effect was for 7 to over 48 hours (Fig. 1). Thirty

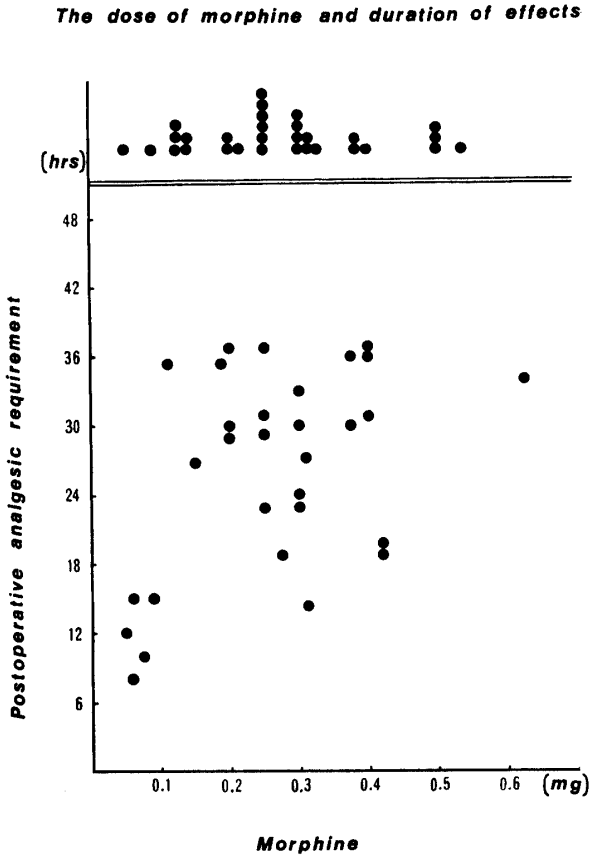

Fig. 1. Relationship between a dose of morphine and the duration of the analgesic effect. In the cases pointed above the double line, analgesics were not given during the postoperative period.

patients were given no analgesics during the postoperative period. Eight patients were prescribed analgesics for back pain, three for headache and two for pain due to a Foley catheter left *in situ* in the urinary bladder.

The duration of the analgesic effect of intrathecal tetracaine with phenylephrine was 9.5 hours, on an average. Three of the seven patients given less than 0.1 mg of morphine requested analgesics immediately after disappearance of anesthetic effects.

Twenty-eight of fifty-three patients given over 0.1 mg of morphine did not

request any analgesics during the postoperative period (Table I). The effect

TABLE I. *Postoperative Analgesic Effect of Intrathecally Administrated Morphine*

Dose of morphine	Total	No. of patients	
		Analgesics (−)	Analgesics (+)
<0.1 mg	7	2	5
0.1 mg>	53	28	25

Three of the seven patients given less than 0.1 mg of morphine requested analgesics immediately after disappearance of the effects of anesthesia. Twenty-eight of fifty-three patients who were given over 0.1 mg of morphine requested no analgesics during the postoperative period.

of amelioration of pain in the other patients was 14 to 36 hours. Eight to ten hours after intrathecal administration of morphine, two patients (women aged 51 and 61 years) experienced a slight decrease in respiratory rate and there was evidence of carbon dioxide retention. According to the postoperative arterial blood gas findings in the recovery room, there was no apparent rela-

TABLE II. *Postoperative Arterial Blood Gas Findings in Recovery Room**

	With morphine	Without morphine
No. of patients	13	80
Age	44.3±17.5	55.4±17.1
pH	7.34±0.04	7.35±0.04
PCO_2	41.9±4.54	42.0±5.65
PO_2	219±34	177±46
BE	−3.03±2.57	−2.84±2.92

*Values are means±1 SD (t-test, $p<0.005$). All patients were given oxygen 3 liters per min. (Ohio face mask), in the recovery room. The dose of morphine was 0.24 mg on an average. There was no apparent relationship between those given morphine and those not given morphine, intrathecally.

tionship between those given morphine and those not given morphine, intrathecally (Table II).

DISCUSSION

Kitahata *et al.* reported the concept of opiate action at the spinal cord cells as well as at the supraspinal level (10). Yaksh *et al.* clearly demonstrated that injection of minute doses of narcotic analgesics into the spinal subarachnoid space produces potent analgesia, painful stimuli being blocked by an action taking place exclusively in the cord (1). Opiate receptors were identified microelectronically in the substantia gelatinosa of the spinal cord (11). Since,

Wang (2) reported the clinical analgesic effects of intrathecally administrated morphine, a number of workers have reported the clinical effects of epidurally (12—16) or intrathecally administrated morphine (4—7).

In the original report of Wang (2), eight patients given 0.5 to 1 mg of morphine in physiologic saline had 12 to 24 hours of relief of pain due to malignancy with no signs of respiratory depression. Similarly, Samii *et al.* administrated 20 mg of morphine to 10 patients and there were no signs of respiratory depression (4).

On the other hand, more recent reporters (5—9) suggested the intrathecal administration of a large dose of morphine causes respiratory depression that may progress to the point of apnea. Liolios and Anderson discussed a patient who was given morphine, 15 mg in 1.5 ml 10% dextrose in water intrathecally. This patient remained in a 40° upright incline for four hours, and then three hours after resuming a supine position was found to have suffered a cardio-respiratory arrest (5).

Althougth cerebrospinal fluid circulation is poorly understood, there is evidence that the ascent of cerebrospinal fluid from the lumbar intrathecal space to the cisterna magna occurs within one to two hours, and then through the Sylvian foramina into the fourth ventricle within an additional four to eight hours (17). Liolios and Anderson suggested that cause of these complications was the reflux of morphine from the spinal subarachnoid space to the ventricle system with a direct depression of the respiratory and cardiac centers of the fourth ventricle (5). This period of the time coincides with the onset of respiratory depression in large number of reported patients (8, 6). Glynn *et al.* suggest that opiate elimination occurs by absorption via the choroid plexus and therefore especially after large doses, opiates may pass into the fourth ventricle before absorption (6).

Clearly, in clinical practice if intrathecal opiates were to became a commonly accepted modality to prevent postoperative pain, respiratory depression or apnea would likely occur after the patient has left the recovery room. In our early cases, we found a deep sedation and respiratory depression in the case of administration of over 0.5 mg but, with less than 0.4 mg, we found no respiratory depression. However, in the report of Winnie, it was stated that sophisticated methodology and experimental techniques that led to the discovery of this previously unknown physiologic response to pain and the imaginative biochemical studies that led to the identification of both the specific opiate receptor and ligands, led to clinical studies in man that were totally uncontrolled, unscientific and in some cases, downright dangerous (9). Davis *et al.* have demonstrated that even as little as 1 mg morphine is not a safe dose when injected into the subarachnoid space (7).

While specific data are just as sketchy in reports relating to epidural opiates, it appears that agents given by this route may be critically important. There are a few reports (12—14) concerning epidural morphine in cumulative total of approximately 200 patients without a single case of sedation or respiratory depression. However, in recent papers concerning the use of epidural

meperidine (2, 10, 11), some patients reportedly developed respiratory depression. These workers found that higher doses given epidurally as well as intrathecally depress the respiratory function.

The advantage of this method would be to provide relief from pain without an attendant loss of motor or sensory function (4, 13). It is tempting to speculate that this technique may be used for analgesia and/or postoperative pain in the field of obstetrics. We found that small doses of intrathecal morphine are useful for the relief of postoperative pain. In agreement with Glynn *et al.* (6) and Winnie (9) care must be taken if larger dose of opiates are to be used and these techniques should only be considered in specialized institutions where there is a surveillance.

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