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Rostral Spread of Epidural Morphine

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Ten healthy males between 18 and 33 years received 10 mg morphine sulfate intravenously, or by lumbar epidural injection at two sessions 2–4 weeks apart, in random sequence. The following observations were made at intervals for 22 h. (1) Segmental hypalgesia to ice and pin scratch. (2) Cold pressor response test in hand and foot as an index of analgesia. (3) Time of onset and duration of side effects. (4) Serum concentrations of morphine. Few non-respiratory changes were seen after intravenous morphine. Cold pressor response was unchanged in hand and foot, no segmental hypalgesia or itching occurred, and only one subject complained of nausea. Marked changes occurred after epidural morphine. Cutaneous hypalgesia to ice and pin scratch appeared in the thoracolumbar region in all subjects. In six subjects hypalgesia rose to the midthoracic region during the second or third hour and to the trigeminal distribution between the sixth and ninth hour in five subjects. Cold pressor response fell rapidly in the foot during the first 1.5 h after epidural morphine, and a little later cold pressor response also fell in the hand in all subjects, and remained depressed for the duration of the experimental period. Pruritus occurred at three hours in nine of the 10 subjects, nausea at about four hours in six of the subjects, and vomiting at about six hours in five of the subjects. Hypalgesia and side effects were not related to serum concentrations of morphine. These results suggest that lumbar epidural morphine travels cephalad in the cerebrospinal fluid to reach the brain stem and fourth ventricle by the sixth hour. (Key words: Analgesics: morphine. Anatomy: epidural space. Anesthetic techniques: epidural. Complications: nausea; pruritus; vomiting. Pain: postoperative.)

CLINICAL APPLICATION of intraspinal narcotics for pain relief is based on animal work that demonstrated abundant opiate receptors in Rexed's laminae 1, 2, and 5 of the dorsal horn of the spinal gray matter.[1–3] Studies by Yaksh and his colleagues[4] showed that lumbar intrathecal injections of small doses of morphine in cats and rats are followed by prolonged analgesia of the hind limb. In cats, 15 μg of intrathecal morphine produced intense analgesia confined to the hind limb in 90 per cent of animals, but in 10 per cent of the cats analgesia spread to involve the forepaws after 30–45 min. The incidence of spread to the forelimbs increased to more than 50 per cent when the intrathecal dose of morphine was raised to 45 μg, but none of the animals showed any evidence of analgesic involvement of the head and neck. This work has led to the general assumption that intraspinal narcotic analgesia is also predominantly segmental in humans, and rostral spread to cervical and intracranial parts of the neuraxis is a rare, undesirable, and potentially dangerous complication.[5,6]

We present evidence to show that cervical and intracranial spread is the rule rather than the exception, when 10-mg doses of morphine are injected into the lumbar epidural space of humans. We also suggest that the side effects such as pruritus, nausea, and urinary retention are due to alterations of sensory modulation that accompany high rostral spread.

Methods

The effects of preservative-free morphine sulfate were studied in 10 male university students aged 18–33 years. Body weight varied widely, and ranged between 62 and 120 kg (mean weight ± SEM = 82.6 ± 5.1 kg); all were healthy and three were trained competitive athletes. The subjects were fully informed and the protocol received institutional approval by Duke University Medical Center. All subjects received a comprehensive pre-test physical examination, including 5 lead electrocardiogram, urinalysis, and blood chemistry.

Each subject underwent two 26-h periods of study, 2–4 weeks apart in randomized sequence. Ten milligrams of morphine were administered intravenously at one session, and by the lumbar epidural route at the other session. All subjects were fasting from midnight and had consumed no caffeine-containing foods or beverages from 10:00 P.M. the preceding evening.

The studies were carried out on a hospital stretcher bed, in a quiet environment. Between measurements the subjects were allowed to adopt whatever position they found comfortable (to sit, walk about, study or sleep) as they felt inclined. The following measurements were made at each session with the subjects reclining in a 20° head up position.

Serum Morphine Concentrations

Ten milliliters of blood were drawn from a forearm vein for serum morphine assay at the following times: control, before injection of test drug, and then at 0.5, 1, 3, 6, 10, 16 and 22 h after injection. The contralateral arm was used for sampling after intravenous administration. Blood was drawn by a 20-gauge needle into glass

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TABLE 1. Serum Concentrations of Morphine in Nanograms per Milliliter (mean ± SEM) after Intravenous or Lumbar Epidural Administration of 10 mg Morphine Sulfate in 10 Subjects*

Route of Administration	Hours after Injection of 10 mg Morphine			
	0.5	1.0	3.0	6.0
Intravenous	26.2 ± 2.3	15.8 ± 1.6	6.3 ± 1.4	1.5 ± 0.7
Lumbar Epidural	41.5 ± 3.1	20.4 ± 1.6	8.4 ± 0.8	0.6 ± 0.4
P	<0.01	NS	NS	NS

* Limits of accuracy of HPLC assay = 2.5 ng/ml.

syringes, and centrifuged in glass Vacutainers®. The serum was transferred to Teflon® tubes and frozen until assayed for unchanged morphine using high-pressure liquid chromatography and electrochemical detection with nalorphine as an internal standard.[7]

Cold Pressor Response Test (CPRT)

Ice water immersion of an extremity is a powerful noxious stimulus. We used the pressor response to ice water immersion as a quantifiable objective index of hypalgesia in the foot (lumbosacral segments) and the hand (thoracocervical segments), as described previously.[8] Blood pressures were measured by ausculatation with an arm cuff and mercury manometer. The arithmetic mean of four sequential determinations was taken as the control blood pressure before ice-water immersion. The arithmetic mean of the systolic and diastolic pressures measured 60, 90, and 120 s after immersion was calculated, and the pressor response to ice-water immersion was expressed as a percentage change from the resting preimmersion mean. An interval of 15–20 min was allowed to elapse between hand and foot immersions in order to ensure full return of blood pressure to resting levels. CPRT was performed at the following times: one hour before administration of test drug, and at 1.5, 4, and 7 h after intravenous administration, and at 1.5, 4, 7, 11, 16 and 22 h after epidural administration.

Segmental Level of Cutaneous Hyposensitivity

As shown in a previous study,[9] a dermatome level of hyposensitivity to ice and to pin scratch is discernible after epidural narcotic administration. Sensitivity to ice and pin scratch was tested on the skin of thighs, abdomen, chest, neck, and face at the following times: before administration of test drug, and at 10, 20, 30, and 35 min, and 1, 3, 6, 10, 16, and 22 h, or more frequently.

Subjective Impression

The volunteers were encouraged to describe any changes of sensation or bodily functions that they might experience after receiving intravenous and epidural morphine, and they were asked to compare and contrast their feelings during the two experimental sessions.

Serial respiratory measurements also were carried out on the 10 volunteers, and the results of this study will be the subject of a separate communication.

MORPHINE ADMINISTRATION

Sterile, coded ampules containing 10 mg morphine sulfate in 10 ml isotonic saline were prepared by A. H. Robins Company Research Laboratories.

Intravenous Route

Ten milligrams of morphine in 10 ml were injected into a forearm vein over a period of 3 min.

Epidural Route

An epidural catheter with a microbial filter was inserted at the second lumbar interspace, and the subject placed in the supine position. Correct placement of the catheter was confirmed by injection of a trial dose of 10 ml of 2 per cent chloroprocaine, and the catheter and filter were flushed with 1.0–1.5 ml of normal saline. Onset and regression of cutaneous analgesia were determined by ice and pinprick, and a segment-time diagram was constructed for record purposes. Ten milligrams of morphine in 10 ml were injected through the epidural catheter 30 min after complete regression of the chloroprocaine block. The catheter and filter were flushed with 1.0–1.5 ml normal saline and the catheter was withdrawn. Subjects were maintained in a horizontal supine posture for the next 15 min.

MANAGEMENT OF COMPLICATIONS

Side effects were left untreated, except when their continuance might prove injurious to the subjects. Prolonged urinary retention was managed by 5 mg subcutaneous bethanecol (Urecholine®). If this failed to initiate micturition, 0.4 mg intravenous naloxone was given slowly to reverse the effects of the morphine, and the experiment was terminated.

Results of serum morphine and CPRT changes after morphine administration were compared to control resting values before morphine administration, as well as between iv and epidural groups, using Student's *t* test. Parameters are presented as means ± 1 SEM. Values of $P < 0.05$ are considered significant.

Results

Serum Concentrations of Morphine

The rise and fall of serum concentrations of morphine after intravenous and epidural administration are sum-

marized in table 1. Serum concentrations of morphine at the first sampling period (30 min) were significantly higher after epidural than after intravenous administration, but thereafter the levels by the two routes were statistically comparable. Serum concentrations declined exponentially with time, and fell below measurable limits by the sixth hour.

Resting Blood Pressure and Cold Pressor Response Test

The mean resting blood pressure declined slightly during the first four hours after both intravenous and epidural administration. After the fourth hour the trends diverged and the intravenous group returned towards control levels, while the epidural group continued to decline to reach a nadir about 4 mmHg below control level at the seventh hour before returning toward control levels by the eleventh hour. None of these changes was statistically significant.

The serial cold pressor response tests differed markedly in the intravenous and epidural sessions, as shown in figure 1. After intravenous morphine the changes were slight and transient. A small (10 per cent) and brief depression occurred in the hand, but then returned to control levels by the fourth hour. The changes after epidural morphine were strikingly different and involved the foot before the hand. At 1.5 h the CPRT in the foot had fallen steeply to 30 ± 4.2 per cent of control. The hand also became hypalgesic, but at first lagged behind the foot rather unpredictably, as shown by a relatively small fall of CPRT to 66 per cent of control with a large SEM of ± 7.3 per cent at 1.5 h. By the fourth hour the mean depression of CPRT in the hand and foot were indistinguishable, although the behaviour of the hand was still less predictable than the foot, as shown by the larger SEM. From four hours onwards the hand and foot remained comparably and markedly hypalgesic, with the CPRT depressed to approximately 75 per cent of control values in upper and lower extremities. After the eleventh hour the CPRT gradually returned towards normal, but by the 22nd hour it was still 40 per cent below control values in both hand and foot. Subjective sensations were in accord with the objective blood pressure response. All 10 subjects remarked that intravenous morphine did not modify the pain of ice-water immersion, whereas the entire two minutes of immersion became much more tolerable after epidural morphine, especially in the foot.

Dermatome Level of Cutaneous Sensitivity

Preliminary chloroprocaine block was used to verify correct placement and functional effectiveness of the epidural catheter. Chloroprocaine sensory block included

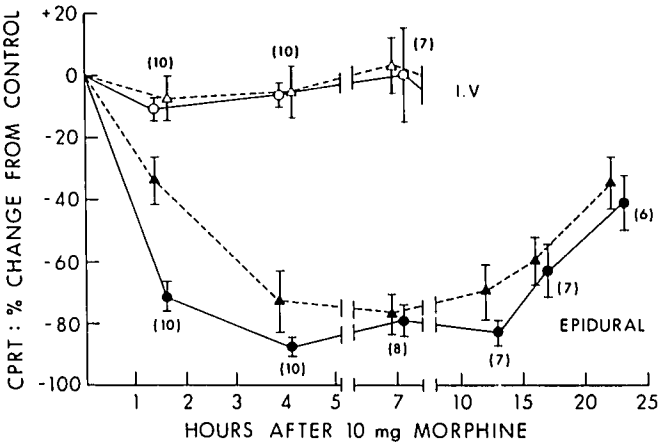

FIG. 1. Serial cold pressor response tests after 10 mg morphine, showing percentage change from control readings in hand and foot after intravenous and epidural administration (Means ± SEM). △ = hand, iv; ▲ = hand, epidural; ○ = foot, iv; ● = foot, epidural. Numbers in parentheses indicate number of subjects observed.

the sacral, lumbar, and lower thoracic segments, but in no case extended above T7, as shown in table 2.

No segmental level of analgesia could be detected after intravenous morphine, and no side effects were encountered except in one subject who experienced transient nausea in the third hour. In contrast, marked and changing segmental effects followed administration of epidural morphine.

A segmental level of cutaneous hypesthesia to cold (ice) and pinprick or pin scratch was discernible within 30 min of epidural morphine injection in eight subjects, and all 10 could appreciate a dermatomal level of sensory change by one hour. In three subjects the sensory level was transient and barely discernible. The initial level of sensory change lay between T9 and L3, as shown in

TABLE 2. Upper Dermatone Limits of Hypalgesia after Lumbar Epidural Local Anesthetic (200 mg Chloroprocaine) and Epidural Morphine (10 mg) in Relation to Time after Injection

	Upper Dermatone Limit and Time after Injection			
	2 Per Cent Chloroprocaine (10 ml)	Morphine Sulfate (10 mg)		
Subject	20 min	1 h	6 h	12 h
1	T11	T9	T5	T4
2	T10	T11	ND	ND
3	T9	T8	V2	ND
4	T10	T11	ND	ND
5	T10	T10	V2	V2
6	T10	T10	ND	ND
7	T9	L3	ND	ND
8	T10	T9	C2	V2
9	T7	T6	V3	V2
10	T9	T9	V2	V2

ND: Not Detectable.

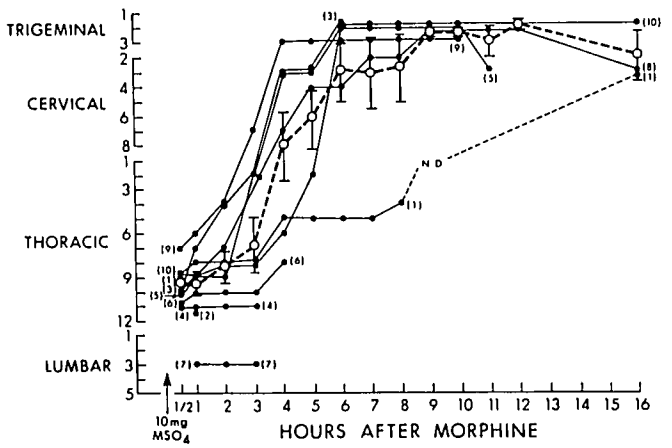

FIG. 2. Segmental spread of cutaneous hypalgesia to ice and pin-scratch after lumbar epidural administration of 10 mg morphine sulfate, showing individual readings and means ± SEM of detectable dermatome levels. Numbers in brackets represent serial numbers of each subject listed in tables 2 and 3. ND = not detectable. O - - - O = mean of detectable dermatomes.

figure 2. As time progressed the level of hypalgesia tended to spread cephalad, and it followed a sigmoid-shaped dermatome-time pattern in the following sequence in six of the 10 subjects. During the second and third hours the level of sensory change gradually rose to the mid-thoracic region. Between the third and sixth hour the rate of spread increased and the sensory level rose rapidly to the upper cervical region in five of the 10 subjects, and by the sixth to ninth hour hypalgesia had spread to the mandibular or maxillary divisions of the trigeminal nerve in each of these five subjects. One subject (#10) could delineate two distinct levels of sensory change, one at the fifth thoracic dermatome and a higher, more subtle level that rose to the maxillary region (V2). The period of most rapid rostral spread occurred between the third and fourth hours. Later, between the twelfth and sixteenth hours, hypalgesia retreated from the trigeminal territory to the upper cervical region, and then faded, so that no discernible level of change to ice of pin scratch could be detected by any of the subjects after the seventeenth hour.

SUBJECTIVE SENSATIONS AND SIDE EFFECTS

All subjects noted that epidural morphine was followed by more intense and prolonged prostration than intravenous morphine. At the intravenous session all subjects were alert, ambulant, and performing intellectual activities by the fifth hour, and nine of the 10 subjects were able to ingest and retain normal amounts of food and fluids. At the epidural session nine of the 10 subjects were less inclined to move about or to perform intellectual tasks and they reported varying degrees of sleepiness and lack of appetite during the first 12–15 h. The degree of indisposition was not related to body weight or habitus. Pruritus, nausea, and vomiting arose sequentially in most of the subjects after epidural morphine. Generalized non-segmental itching occurred with marked punctuality three hours after epidural administration in nine of the 10 subjects at a time when the mean dermatomal level of hypalgesia was still in the mid-thoracic region. About an hour later, when the dermatomal level had reached C8, six of the 10 subjects experienced nausea, and two hours after that, when hypalgesia had reached upper cervical and trigeminal levels, five of them had a brief period of vomiting (see table 3). All of these side effects subsided before the upper level of hypalgesia began to regress in the twelfth hour, except in one subject (#4) in whom pruritus persisted until it was terminated by naloxone administration, in the seventeenth hour.

None of the subjects experienced any urinary dysfunction after intravenous morphine. All 10 subjects had

TABLE 3. Epidural Morphine 10 mg in 10 Male Subjects. Rostral Limits of Cutaneous Hypalgesia and Appearance of Side Effects

Subject	Age (yr)	Weight (kg)	Highest Detectable Level of Cutaneous Hypalgesia	Time from Injection of Epidural Morphine to Onset of Symptoms (hours)		
				Pruritus	Nausea	Vomiting
1	20	72.6	C3	3.0	2.5	4.75
2	20	120.4	T11	3.75	—	—
3	19	70.8	V2	3.0	—	—
4	20	106	T11	3.0*	4.0	7.5
5	18	86.2	V2	3.0	5.0	—
6	21	61.7	T8	3.0	6.0	6.5
7	21	73.5	L3	3.0	2.5	4.0
8	20	72.6	V2	2.5	—	—
9	33	71.2	V3	2.75	4.0	8.75
10	20	91.2	V2	—	—	—
MEAN				3.0	4.0	6.3
SEM				0.11	0.56	0.87

* Mild itching localized to legs at 2 hours, lasting 30 min. Severe generalized itching at 3.9 hours.

varying degrees of urinary dysfunction after epidural morphine. Four subjects voided spontaneously 5.5–15 h after their previous voiding but the urinary volumes were abnormally large. The remaining six subjects had one or more indications for treatment after 15 h. Bethanecol was successful in only two of these subjects. All four of the subjects resistant to bethanecol were given 0.4 mg naloxone, iv, and all four were able to initiate voiding within 10–15 min.

Discussion

Intraspinal narcotics bypass the blood-brain barrier and reach the neuraxis, as it were, by the back door. Epidural meperidine has been shown to penetrate the meninges in humans and to enter the CSF rapidly and in high concentrations.[10] Other narcotics are assumed to enter the CSF at a rate that is dependent on physicochemical characteristics such as pK_a, oil-water solubility ratios, and the pH of the intercellular fluid.[11] Once the narcotic reaches the CSF, penetration from the water phase of the CSF to the lipid phase of the underlying neuraxis occurs at a speed that is determined by the relative aqueous and lipid solubilities of the drug. In rabbits, radioactive morphine has been shown to penetrate to a depth of about 1200 μm within 20 min of intraventricular injection.[12]

Table 4 shows the pK_a and oil-water partition ratios of the narcotics that have been used for clinical relief of pain by the epidural route. It can be seen that morphine is very poorly lipid-soluble compared to meperidine and methadone.[13] Drugs that are poorly lipid soluble, such as morphine, will tend to linger in the water phase of the CSF, to be carried wherever the tides of CSF bulk flow may take them.

Scanning of the cranium after lumbar myelography with radionuclides, or 170 mgI/ml metrizamide[14,15] shows that these markers reach the fourth and lateral ventricles with remarkable regularity by the third hour, and that straining, *e.g.*, by vomiting, accelerates the process of rostral spread in the ventricular pathway.[16] Penetration from the CSF to underlying neuraxial structures will then proceed slowly, and with a delay that is proportional to the low coefficient of oil-water solubility of a narcotic such as morphine.

Our data reflect this general scheme. Our conclusions are based upon the objective criteria of changing CPRT in hand and foot, the sequential appearance of side effects, as well as upon the more subjective observations of cutaneous sensory changes. The latter did not match the temporal spread of analgesia precisely, for cephalad spread beyond T5 could only be detected in 50 per cent of the subjects, and it was sometimes difficult to decide upon the highest dermatomal level of sensory changes.

TABLE 4. pK_a and Oil-water Solubility of Meperidine, Methadone and Morphine*

Drug	pK_a at 37°C	Octanol-water Distribution at pH 7.4 and 37°C
Meperidine	8.50	38.82
Methadone	9.26	116.33
Morphine Sulfate	7.93	1.42

* From data by Kaufman *et al.*[13]

For example, in one subject (#10) two distinct, widely separate and persistent levels could be detected after the fourth hour; one at T6 and the other at the level of the cheek (V2–V3).

The initial segmental distribution of morphine hypalgesia corresponded closely to the spread of analgesia after the preceding local anesthetic injection as shown in table 1. During the first two hours after epidural administration there was little to indicate cephalad spread, and if observation had stopped at the third hour it would have been reasonable to conclude that analgesia was confined to segments supplying the legs and lower trunk, with only slight analgesic effects in the hands and little more intensity than might be attributed to vascular absorption of the narcotic. Also, the dermatomal changes were slight, and not appreciably different from the initial observations at 30 min and one hour. However, after the third hour signs of rapid cephalad spread were unmistakable as dermatomal hypalgesia rose steeply to the cervical and trigeminal distributions, and as diminishing CPRT gave objective evidence of a deepening and an increasingly comparable analgesia in both upper and lower limb segments. At the same time, correlates of disturbed cutaneous and visceral sensation began to appear.

The sequence of events that we observed after the third hour may be explained in terms of morphine action upon spinal or brain stem small-cell systems by one or more of three mechanisms. First, by cephalad spread of morphine in the CSF to the basal cisterns and then penetration from the outer subarachnoid surface of the brain stem. Second, via the ventricular pathway[14,15] by passage from the cisterns into the fourth ventricle and then penetration through the ependymal lining of the ventricular floor. Third, by indirect facilitation or inhibition of deeply placed visceral nuclei following suppression of more shallowly placed nuclei that project upon them. The observed pattern of rostral spread of hypalgesia and the slower sequential appearance of side effects suggest that all three mechanisms were probably involved.

We speculate that the punctual onset of widespread itching at three hours is a manifestation of altered skin sensation due to penetration of morphine to widely projecting modulating centers in the cervical region of the

spinal cord. Similarly, the sequence of ascending hypalgesia from C2 → V3–V2 is probably due to surface penetration of rostral portions of the trigeminal nuclear complex lying close to the surface of the upper cervical cord.

Nausea in the fourth hour and vomiting in the sixth hour may be attributable to one of two mechanisms acting upon medullary centers. Indirect activation of visceral nuclei such as the nucleus solitarius could occur through suppression of inhibitory fibers in the trigemino-solitary tract that travels inward from the caudal end of the superficially placed mandibular lamina of the trigeminal nucleus.[17] Alternatively, nausea and vomiting could be caused by morphine-laden CSF entering the ventricular pathway and reaching structures such as the "chemoreceptor trigger zone" in the area postrema at the caudal end of the fourth ventricle.[18] The pattern of segmental retreat was difficult to follow, for in most cases demarcation of dermatomal hypalgesia became indistinct and then faded by the twelfth hour. However, CPRT remained depressed in arm and leg and did not show any appreciable return to normal until the twentieth hour or so, indicating that a significant degree of hypalgesia existed in the thoraco-cervical segments, even at that late hour.

The sensory changes and adverse effects observed in this series of young, healthy men of widely differing body weight and habitus demonstrate that the analgesic activity and nonrespiratory side effects of 10 mg morphine are negligible by the iv route when compared to the epidural route. They also show that these effects are not related to serum concentrations of morphine, nor are they related to body size over a wide weight range. The precise anatomic pathways and sites of action of epidural morphine within the brain stem remain to be determined, but inductive analysis of our data suggests that ventricular passage may play a significant role in determining the signs of rostral spread that were observed.

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