OBSERVATIONS ON EXTRADURAL MORPHINE ANALGESIA IN VARIOUS PAIN CONDITIONS

F. MAGORA, D. OLSHWANG, D. EIMERL, J. SHORR, R. KATZENELSON, S. COTEV AND J. T. DAVIDSON

SUMMARY

We report the extradural administration of low-dose morphine in 10 ml of 10% dextrose (2–3 mg) to 98 adult patients with various types of acute and chronic pain. Extradural morphine injections were given either via a Tuohy needle (single or repeat injection) or via an extradural catheter. Pain relief was evaluated by subjective scoring and by the subsequent need for systemic analgesics. In 56% of patients, pain relief was considered good or excellent, in 24% it was fair, and in 20%, poor. The best results were after surgery and trauma and in patients with advanced peripheral vascular disease. The analgesia of each dose of extradural morphine lasted for 8 h (mean range 4–36 h). There was no motor, sensory or sympathetic blockade and no respiratory or haemodynamic complications. Dizziness and vomiting occurred in two patients, and urinary retention for about 12 h in three.

Recent reports have indicated that effective and prolonged pain relief can be obtained in man by the injection of small doses of morphine or pethidine into either the subarachnoid (Wang, 1978; Samii et al., 1979; Wang, Nauss and Thomas, 1979) or the extradural space (Behar et al., 1979; Cousins et al., 1979). This clinical application is based on the work of Snyder (1977a, b) and Yaksh and Rudy (1977, 1978) in animals, who attributed pain relief to a selective spinal analgesia caused by the direct action of the narcotics on specific opiate receptors that are richly distributed in the posterior horn of the spinal cord. Such an action is supported by (a) the small dose needed to abolish pain in both animals (Yaksh and Rudy, 1977) and man (Behar et al., 1979; Wang, Nauss and Thomas, 1979); (b) neurological examination which failed to demonstrate sympathetic, sensory or motor loss after narcotic treatment; (c) pharmacokinetic studies which proved that, after extradural injection of pethidine in man, the drug reached the spinal cord; (d) following adequate pain relief, the blood concentration of pethidine was much less than that found after i.v. injection of commonly used doses of this drug (Cousins et al., 1979).

The majority of clinical trials with both spinal and extradural opiate analgesia have been limited to small numbers of patients, mainly suffering from intractable pain associated with malignancy (Behar et al., 1979; Cousins et al., 1979; Wang, Nauss and Thomas, 1979). The present study reports our observations on the effect of extradural morphine in 98 patients suffering from pain of various types, with special emphasis on ischaemic and low back pain, labour pain and pain after multiple trauma or surgery, or both, accompanied by respiratory dysfunction.

PATIENTS AND METHODS

Extradural morphine was administered to 98 patients (60 women and 38 men, age range 22–82 yr), suffering from severe pain of differing origin and duration (table I). Thirty patients attended the outpatient clinic and 68 were in hospital at the time of treatment.

Of the 21 patients with low back pain, three were treated during an acute attack of radiculitis superimposed on the chronic pain, and the others had continuous uniform complaints for long periods, attributable to osteoarthritic changes, previous discectomy and similar conditions.

Among the patients afflicted with cancer, nine had diffuse intractable pain because of primary invasion of inoperable carcinoma of the cervix, bladder or colon, and seven suffered localized pain from bone metastases in the ribs, lumbar vertebrae or sacrum.

Thirty patients were women in labour: 14 at term and 16 after induced abortion with intra-amniotic prostaglandins in the second trimester of gestation.

Fifteen subjects were in acute pain from multiple trauma or surgery, or both. Three of the patients with post-traumatic pain had multiple rib fractures; one had sustained anterior fractures with consequent...
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<th>(100%)</th>
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flail chest, severe dyspnoea and $P_{A_1}$ less than 9.3 kPa while breathing oxygen by mask ($Fi_{O_2} > 0.5$). Eight of the surgical patients were elderly, presenting with various degrees of chronic obstructive lung disease: three had undergone repair of a high incisional hernia, two had aorto-femoral bypass, one had undergone cholecystectomy, and two repair of a fractured neck of femur. Five patients were given general anaesthesia, an extradural catheter being introduced after operation to permit continuous administration of morphine. This route of administration was necessary because of respiratory distress which was related, at least in part, to pain after operation. The other three patients were operated on under extradural anaesthesia. As they were known to have severe pulmonary disease, the catheter was left in place for postoperative morphine administration. The two remaining surgical patients complained of severe pain after operation in spite of large doses of narcotics.

Five patients had ischaemic pain because of peripheral vascular disease; three of these had undergone lumbar sympathectomy and vascular graft procedures 1–3 yr previously. The two other patients were undergoing aorto-femoral bypass; both had ischaemic heart disease and pre-gangrene of one or both legs. Because of excruciating pain, not relieved by large doses of narcotics and sedatives even when at rest, extradural morphine was commenced on the day of admission in both patients and was reinstated after operation in one. The other patient developed pulmonary embolism; surgery had to be postponed and extradural morphine administration was continued for 8 days.

No systemic analgesia or sedation was given for at least 6 h before treatment with extradural morphine. Except for the women in labour, none of the patients fasted. The mode of treatment was explained, and informed consent was obtained in each instance. Clinical examination lay special emphasis on localization of pain and tenderness, and limitation of movement. Each dose of morphine consisted of 2–3 ml of a 0.1% morphine·HCl solution in 10% glucose (i.e. 2–3 mg of morphine·HCl). The solution, free from preservatives, was prepared under aseptic condition in our hospital pharmacy and stored in
EXTRADURAL MORPHINE IN PAIN

5-ml amber, rubber-capped vials, each containing 2-5 ml. The vials were kept in a dark place and were used within 1 month of preparation. Each dose of morphine was mixed with 8 ml of normal saline. Every effort was made to perform the extradural puncture at the level closest to the sensory innervation from the pain focus, which in most patients was in the lumbar region. In the cases of rib fractures and in patients with abdominal wounds, extradural injection was at the high and low thoracic extradural space, respectively.

Thirty patients were injected with single or repeated doses of morphine via a Tuohy extradural needle. In 68 patients, the drug was administered via an indwelling extradural catheter, one or two times daily for up to 8 days. In 10 of the obstetric patients, one dose of morphine did not suffice, and a subsequent amount of 2 mg was given 10-20 min later.

Arterial pressure, heart rate, respiratory rate and the behaviour of the patients were monitored for 1 h following the morphine injection, special attention being paid to signs of central nervous system impairment. All patients were seen again at least once in the next 24 h.

In two patients, c.s.f. morphine concentration was measured repeatedly by radioimmunoassay technique during 6 h after injection of morphine 2 mg into the extradural space. The radioimmunoassay technique used antibodies for morphine which were obtained from rabbits according to the method of Spector and Parker (1970).

The intensity of pain after treatment was evaluated by the patient: good when there was either complete or marked pain relief obviating the need for further analgesics for at least 4 h following the administration of morphine; fair when pain was diminished, function was partially improved and use of systemic analgesic drugs was considerably reduced; and poor when there was little or no alleviation.

RESULTS

The overall results were good in 56.1% of patients, fair in 23.5%, and poor in 20.4% (table I). The analgesic effects were noted 8-10 min following the injection of extradural morphine, became maximal at 15-20 min, and persisted for a mean duration of 8 h (range 4-36 h).

The most favourable results were obtained in the surgical group, in the patients with multiple rib fractures and in those suffering from ischaemic pain associated with advanced peripheral vascular disease. Pain after surgery was diminished not only during absolute rest but also when associated with movement. Deep breathing became considerably more comfortable and chest breathing exercises were tolerated well. Peripheral vasoconstriction decreased, skin colour improved, and repeated blood-gas examinations showed consistent, although statistically insignificant, increases in PaO₂, as compared with the pre-morphine values. The extradural catheter could be removed after 2 days of morphine treatment.

In two of the patients with ischaemic pain, morphine was discontinued after 2 days, but had to be reinstated a few hours later because of severe pain, and was subsequently maintained for 8 days. This period was the longest in our series. One to two doses of morphine daily proved to be sufficient to keep the patient free of pain, and only occasionally were sedatives necessary.

The analgesic action of extradural morphine in the patients suffering from intractable pain as a result of malignancy, and in the chronic low back pain group, reflected the overall results as presented in table I. In more than half of these two groups of patients, analgesic drugs could be either withdrawn or considerably reduced, the patient's mood and motor function improved, and a better response to various forms of conventional therapy became apparent. An exception was two patients with acute low back pain, who arrived at the clinic in distress, unable to move or lie down. Extradural morphine 2 mg failed to exert any influence, but the addition of 0.5% bupivacaine 3 ml with methylprednisolone, injected to the fourth lumbar interspace 15 min later, suppressed the pain immediately.

In 10 of the 16 patients who underwent induced abortion, extradural morphine abolished labour pain 10-20 min after commencement of treatment. The pain did not recur until the abortion process had started, sometimes many hours later. In the other six women, the morphine had no appreciable effect; addition of 0.5% bupivacaine 4 ml into the extradural space, however, proved successful and complete pain relief was obtained for as long as 6-9 h.

The effect on full-term labour pain was disappointing. A second dose of morphine 2 mg, given 10 min after the initial administration, also failed to reduce the pain. Bupivacaine 0.5% 8 ml had to be added to obtain pain relief, which sometimes lasted for up to 6 h.

None of the patients in the present series showed any signs of sympathetic denervation, loss of temperature-, touch- or pinprick sensation, or motor loss;
nor were there any adverse respiratory or haemodynamic effects.

Complications were encountered in five cases: one woman with causalgia and one man with chronic low back pain complained of dizziness, and vomited intermittently for a few hours following the morphine injection. In another patient, the dura was inadvertently punctured; the extradural needle was withdrawn and reinserted at a higher interspace. This patient, and two others, developed urinary retention over the next 12 h. One of them, an elderly male suffering from benign prostatic hypertrophy and severe ischaemic heart disease, required bladder catheterization. In all three patients, bladder function returned to normal the following day.

The radioimmunoassay tests showed clearly that the opiate was present in the cerebrospinal fluid 10–20 min after extradural injection of morphine 2 mg and that it reached peak values of 28 ng ml\(^{-1}\) after about 35 min.

**DISCUSSION**

Opiate drugs are known to exert a direct anti-nociceptive influence on the spinal cord (Yaksh and Rudy, 1977, 1978). This is supported by the *good* pain relief obtained in 56.1\(^*\) of our heterogeneous group of pain patients with only small doses of extradural morphine, and with the encouraging results of our preliminary study (Behar et al., 1979) and those reported by Cousins and others (1979) with extradural pethidine.

The morphine injected into the extradural space reached the spinal cord as demonstrated by its presence in the cerebrospinal fluid in two of our patients. Similar conclusions were drawn by Cousins and others (1979) using extradural pethidine.

The degree of pain relief in the present study was similar within each group of patients with similar pain disorders, but differed widely between groups. The patients who benefited most were those with acute, large areas of diffuse pain such as after abdominal surgery (*good* results in all 10 patients), with multiple rib fractures (*good* in four out of five patients) and in association with ischaemic pain (*good* in four out of five patients). Although evaluation of the effect is based on the patient's subjective report and no control study was attempted, it was confirmed objectively by the marked clinical improvement in breathing and an increase in \(P_aO_2\) and by the auspicious change in behaviour and mood of the patients, and their willingness and ability to function within the limits of their basic disorder. Hypoventilation and failure to take periodic deep breaths because of pain after operation and chest trauma may result in decreased FRC and intrapulmonary shunting with hypoxaemia. Pain relief often restores respiratory function and corrects the hypoxaemia (Spence and Smith, 1971; Spence and Logan, 1975). The facts that extradural morphine improved respiratory function in the surgical patients with obstructive lung disease without haemodynamic disturbances and, furthermore, succeeded in augmenting ventilation in the patient with anterior flail chest, obviating the need for mechanical ventilatory assistance, make this mode of treatment highly appropriate in such patients. An important aspect of this therapeutic modality is that it obviates systemic narcotic administration in these patients and those with ischaemic pain.

The least effect was seen in acute, localized pain such as radiculitis or causalgia. It is conceivable that in these conditions pain is caused by direct local nerve irritation accompanied by abnormal reflex activity consisting of secondary muscular spasm, which does not respond to extradural morphine. In these cases, nerve blocks with local anaesthetics known to interrupt pain transmission while producing decreased motor tone and sympathetic transmission are indicated. Therefore, whenever treatment with extradural morphine was of no avail, local anaesthetic drugs were immediately administered.

In full term labour pain also the results were poor, and even an additional extradural injection of 2 mg of morphine in 10 of the women failed to abolish pain. The failure of extradural morphine to act on the motor and sympathetic fibres may explain the lack of effect on pain in childbirth.

The results obtained in the chronic pain patients suffering from cancer and those with low back pain syndrome are comparable to the figures reported when using other forms of treatment such as physical therapy, extradural block and nerve block with anaesthetic agents and steroids (Hannington-Kiff, 1971; Defalque, 1974; Breivik et al., 1976; Ferrert, 1978) and electrical stimulation (Swerdlow, 1968; Long and Hagfors, 1975; Magora et al., 1978).

It seems that, in the disease processes where pain is the sole, or major, manifestation of the pathological disorder, extradural morphine exerts considerable influences. If, on the other hand, pain is accompanied—or caused—by secondary muscular spasm (defensive muscular contraction), sympathetic hyperexcitation or vasoconstriction, or both, the effect of extradural morphine is negligible. The mode of action of
extradural morphine is most probably related to the analgesic effect of the opiate, without affecting the motor or sympathetic systems.

The results presented here are based on the effects of extradural injections of morphine, administered in doses of 2 mg. Comparable results, as reported by other investigators, were achieved while using much larger doses of extradural pethidine (100 mg) (Cousins et al., 1979) or intrathecal morphine (20 mg) (Samü et al., 1979). It is reasonable that the analgesia induced by morphine is related not only to the drug's concentration in the c.s.f. per se, but also to a direct endogenous inhibitory effect upon the spinal cord neurons (Cannon, Liebeskind and Frenk, 1978). If this is indeed the case, it follows that minute quantities of the morphine bind to the opiate receptors, thereby triggering secretion of endorphins. In support of this assumption are the findings of Sjölund, Terenius and Erikssson (1977) who reported low endorphin concentrations in patients suffering from chronic pain and which returned towards normal by centrally applied analgesics (Cannon, Liebeskind and Frenk, 1978).

Very high doses of regionally applied narcotics may have an additional effect upon the nerve root, or even on the peripheral nerve but, except for experimental work in the axon preparation of the squid (Simon and Rosenberg, 1970), this hypothesis still belongs in the realm of the laboratory. Evidently, large regional concentrations of morphine risk systemic effects and their use is certainly unwarranted.

A most promising feature of the treatment with low-dose extradural morphine was the lack of any adverse side-effect, thus making close and continuous patient supervision unnecessary and rendering administration of morphine through an indwelling extradural catheter most suitable for home care of patients with intractable pain (Chayen, 1979, personal communication). Furthermore, as the effect of extradural morphine is prolonged (up to 36 h) and is not associated with tachyphylaxis, neither the dose nor the frequency of therapy need to be increased for long periods of time.

From the technical point of view, if opiate analgesia indeed affects the neurons early in the ascending pain pathways, the site of injection in relation to the pain dermatone is crucial, and the drug should therefore be applied at the level innervating the pain focus. On the other hand, since extradural administration of morphine is not associated with sympathetic block, extensive extradural analgesia (thoracic or cervical) may be achieved by injecting increased amounts of the drug at a site distant from the origin of pain without the danger of consequent haemodynamic disturbance. Samü and others (1979), for instance, obtained upper thoracic analgesia in their patients, without central depression after injection of morphine 20 mg to the lumbar intrathecal space. However, until more precise and detailed studies have been conducted, injection of small doses of the opiate is advocated, given as near as possible to the pain dermatome.

Although sensory or motor loss, or postural hypotension do not appear after extradural morphine, it is advisable to keep the ambulatory patient under observation for at least 1 h after treatment since dizziness and vomiting may occur. We encountered transient urinary retention in three patients, which may be explained by the fact that morphine increases the tone of the detrusor muscle and of the vesical sphincter, thus impeding micturition (Lee and Atkinson, 1973).

As with other pain remedies, the current treatment with extradural morphine is but a battle won in the war against pain. Its beneficial features include the lack of significant side-effects as compared with other modalities utilized in pain relief and—most plausible—it's setting in motion the natural defence resources of the body.

REFERENCES


OBSERVATIONS SUR L’ANALGESIE EXTRADURALE A LA MORPHINE POUR LE SOULAGEMENT DE DIVERSES DOULEURS

RESUIME

Ce rapport concerne l’administration extradurale de faibles doses de morphine dans 10 ml de dextrose à 10% (2-3 mg) à 98 malades adultes souffrant de divers types de douleurs aiguës et chroniques. Les injections extradurales de morphine ont été faites soit à l’aide d’une aiguille de Tuohy (une seule injection ou injection répétée), soit à l’aide d’un cathéter extradural. Le soulagement de la douleur a été évalué par cotation subjective et par le besoin de recevoir ultérieurement d’autres agents analgésiques systémiques. Dans 56% des cas, le soulagement de la douleur a été jugé bon ou excellent, dans 24%, des cas acceptables, et dans les 20%, restant, médiocres. Les meilleurs résultats obtenus sont ceux qui ont suivi les interventions chirurgicales et les traumatismes de même que ceux constatés sur les patients ayant une maladie vasculaire périphérique avancée. L’analgesie provoquée par chaque dose de morphine extradurale a duré 8 h (plage moyenne 4-36 h). Il n’y a eu aucun blocage moteur, sensitif ou sympathique ni aucune complication respiratoire ou hémodynamique. Deux malades ont souffert de vertiges et de vomissements, et trois autres ont eu une rétention d’urine pendant environ 12 h.

RESUMEN

Este informe se ocupa del tratamiento extradural de pequeñas dosis de morfina en 10 ml de dextrosa al 10% (2-3 mg) a 98 pacientes adultos que padecían de distintos tipos de dolores crónicos y agudos. Se practicó la inyección de morfina extradural ya sea mediante una aguja Tuohy (inyección única o inyecciones repetidas) ya sea mediante una sonda extradural. Se hizo una evaluación del alivio del dolor por marcación subjetiva y necesidad consecuente de analgésicos sistémicos. En un 56% de los pacientes, el alivio del dolor se consideró como bueno o excelente, en un 24%, fue regular y en un 20% malo. Los mejores resultados se obtuvieron después de cirugía y trauma y en pacientes con enfermedad vascular periférica avanzada. La analgesia de cada dosis de morfina extradural duró durante 8 h (duración media 4-36 h). No hubo bloqueo motor, sensorial o simpático ni tampoco complicaciones respiratorias o hemodinámicas. Dos pacientes sufrieron vómitos y vértigos y tres más tuvieron una retención urinaria durante 12 h aproximadamente.