Epidural and intrathecal narcotics

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Few analgesic methods have met with such rapid and widespread acceptance as centrally administered narcotics. As soon as the effectiveness of intrathecal and epidural narcotics was reported, the technique became immediately popular, because of its low cost, simplicity of administration and long duration of action.

The present review of current literature on narcotic epidural and intrathecal analgesia was undertaken to offer the reader a bird's-eye view on the subject. Conclusions are proposed that should not be regarded as the ultimate state of the art, but as current general guidelines for the rational use of an attractive technique.

Analgesic effects

Chronic pain

Wang was the first to report the clinical use of intrathecal morphine,[1,2] after animal studies had shown the effectiveness of the method.[3] Eight patients suffering from chronic pain were relieved for an average of 20 hours after the intrathecal injection of morphine 0.5 or 1 mg. No adverse effects were reported. The epidural approach was used later for chronic pain relief: morphine 2–5 mg in an adequate volume, usually 10 ml, was found to be effective[4,5] (Table I). Duration was longer with morphine than meperidine or fentanyl and tolerance was slower to appear when morphine was added to a local anaesthetic.

Postoperative pain

Epidural or intrathecal injections of narcotics were later applied to acute pain relief after surgery or trauma. For postoperative comfort, intrathecal[6–8] and more frequently epidural[9–21] narcotics were used without subsequent systemic injections. The intrathecal morphine dosages ranged from 0.2 to 2 mg and epidural morphine, from 2 to 10 mg (Table I). Many types of surgery were tested; intrathecal and epidural morphine was found more effective than placebo,[9] of longer duration than bupivacaine[14] and without the cardiovascular effects[15] of the latter. It appeared important that the drug be injected at the effective spinal level,[22] but the lumbar approach for thoracic pain appeared to produce good analgesia.[23] Dosages needed for relief and type of pain were related.[22] Finally the epidural injection of narcotics was compared to the intramuscular injection and to intercostal local anaesthetic blockade: with regard to duration,[24–27] morphine was found to be superior to the other methods: relief ranging from 12 to 20 hours, varying with the study, the type of surgery and the methods of evaluation used.

Obstetrical pain

The advantage of long-lasting analgesia without vasomotor effects and motor blockade were determining factors in justifying the clinical use of intrathecal and epidural narcotics in obstetrics.[28–43]

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TABLE I Analgesic effects of epidural and intrathecal morphine

	Epidural dose (mg)	*Intrathecal dose (mg)*	*Effectiveness (hours)*
Chronic pain[1–5]	2–5	0.5–1	6–24
Postoperative pain[6–27]	2–10	0.2–2	12–20
Obstetrical pain[28–43]	2–6	1–2	?

TABLE II Respiratory depression after epidural and intrathecal morphine[44–54]

Site	*Dose (mg)*	*Delay (hours)*	*Incidence (%)*
Intrathecal	1–15	4–11	4–7
Epidural	2–20	0.5–12	0.25–0.4

Intrathecal morphine 1 and 2 mg was shown to be effective during labour except during delivery.[29,31] Epidural injections were either ineffective[32,35] or minimally effective[35–42] (Table I). The usual explanation for this lack of effectiveness against obstetrical pain is the increased vascularity of the epidural space with more rapid narcotic absorption. Some believed that adding epinephrine to the analgesic solution would increase effectiveness, but studies have shown that this was not the case.[36,40,43] Thus it is concluded that epidural narcotics have no clinical usefulness in obstetrics.

Adverse effects

Respiratory depression

Shortly after the publication of the first papers on epidural and intrathecal use of narcotics, reports of adverse reactions started to appear. The most important of these was respiratory depression (Table II). Severe respiratory depression and coma were reported to occur from 4 to 11 hours after intrathecal injections, and were characterized by extreme bradypnoea and pin-point pupils.[44–46] Dosages used were in the range of 1 to 15 mg and, in all cases, the depression was reversed by naloxone. Incidence of respiratory depression varied from four to seven per cent, for intrathecal narcotics and from 0.25 to 0.4 per cent for the epidural approach.[47] For lipophilic narcotics like fentanyl (octanol–water distribution 11,220)* methadone (octanol–water distribution 116.33)[64] and meperidine (octanol–water distribution 38.82)[64], the respiratory depression had a tendency to appear soon following the injection (approximately 30 minutes); for less lipophilic narcotics like morphine (octanol–water distribution 1.42)[64] the depression appeared later (from 4–12 hours after the injection). More rapid absorption of lipophilic drugs appears to be the reason for this difference. The severity of respiratory depression was shown to be modified by other factors: dosage, association of intramuscular narcotics,[48] age, association of diseases like sleep apnea,[49] position of patient after the injection[50] and history of drug addiction. CO_2 response-curves and occlusion pressures[51–54] confirmed that doses of epidural morphine of 2 mg or more were enough to cause late respiratory depression even in healthy patients. It was proposed that use of epidural morphine required close surveillance for 12 to 24 hours.

Other adverse effects

Other side-effects of a less dramatic nature also occurred. They included nausea, pruritus and urinary retention and appeared in 15 to 70 per cent of patients.[55,56] In obstetrics it was found necessary to increase the oxytocin dosage for patients who had received intrathecal morphine 2 mg as compared to those who had received 1 mg.[29] The severity of adverse effects were also related in one study to intrathecal morphine dosage: sedation, nausea, urinary retention, respiratory depression being more frequent in patients receiving high doses.[57] Few cardiovascular effects were reported except for those secondary to severe respiratory depression.[58] It was also shown that hypoalgesia spread rostrally and that the trigeminal distribution is reached much later.[59] On the other hand, epidural narcotics did not seem to have any effect on uterine blood flow.[60] One case of catatony was reported after repeated injections of morphine.[61] When used without preservative, it is unlikely that morphine will cause demyelinisation, arachnoiditis or necrosis.[62]

*Personal communication, Janssen Pharmaceutica Inc.

TABLE III Intrathecal and epidural morphine: plasma concentrations

Site	*Dose (mg)*	*Level (ng)*	*Time of sampling (minutes)*
Intrathecal[74]	1–1.75	6	120
Intrathecal[72]	0.2/kg	42	60
Epidural[72]	0.2/kg	67	60
Epidural[70]	0.05/kg	19	12
Epidural[68]	5/70 kg	43	15
Epidural[71]	4	12.5	20

Special considerations

Site of action

Narcotic activity in the epidural space seems to be related to the presence of opiate receptors in laminae 1, 2 and 5 of the dorsal horn of the spinal gray matter.[63] This hypothesis was confirmed by morphine injections into the epidural space in animals[3] and in man.[1,2]

With epidural morphine 10 mg, segmental hypoalgesia was shown to spread cephalad and reached the trigeminal distribution between the sixth and ninth hour.[64,65] This rostral progression was more evident with less liposoluble agents like morphine and may explain such effects as pruritus, respiratory depression, nausea and vomiting by penetration of the nervous centers by opiate drugs. Cerebrospinal fluid assays have shown the rapid transmission of meperidine from the epidural space to CSF.[66,67] Narcotics are bound to specific receptors from which they can be displaced, as shown by the fact that the narcotic antagonist naloxone can reverse adverse effects such as pruritus, urinary retention and respiratory depression. The necessity of injecting additional doses of naloxone to break the recurring adverse effects with time suggests a solid binding of the opiate to the receptor.

Plasma concentrations

After a single injection of epidural morphine, maximal plasma concentration is reached in 20 to 30 minutes[68–71] (Table III). The early respiratory depression seems to be directly related to plasma concentration, while the late depression occurring after 90 minutes is related to rostral spread.[68] It is thought that this fact confirms the direct segmental analgesic properties of epidural opiates. When morphine 0.2 $mg \cdot kg^{-1}$ was administered epidurally, intrathecally and intramuscularly, blood concentrations were highest after the intramuscular injection, followed by epidural and intrathecal injection. There was little difference between the levels after intramuscular and epidural injections.[72]

On the other hand, epidural morphine crosses the placenta rapidly[73,74] and could put the foetus at risk. CSF concentrations after epidural narcotic analgesia reach levels from 40 to 100 times higher than in blood[75] and hypoalgesia is intense and prolonged. In summary, analgesic potency and duration are not related to plasma concentrations of narcotics but to CSF concentrations.[23]

Dose-response curve

Intrathecal and epidural narcotic dosages were first calculated empirically and varied accordingly. As side-effects and severity of complications appeared to be dose-related, dosages were lowered. Epidural narcotic analgesia was specifically studied and different doses of morphine were administered to comparable populations.[76–78]

From these studies, it can be summarized that after abdominal surgery, epidural morphine 4 or 5 mg is as effective and less susceptible to cause complications than higher dosages.[76,77] Dosages of 2 mg or less are less effective. After lower limb surgery, morphine 2 mg is as effective as morphine 4 and 8 mg and causes less side-effects[22,32,78] (Table IV). Weight related dosages do not appear appropriate;[13] for children, after genital surgery, caudal morphine 0.5 $ml \cdot kg^{-1}$ in a solution containing 0.1 $mg \cdot ml^{-1}$ was found to be effective and free of complications.[26]

Choice of agent

Meperidine, fentanyl, morphine, methadone, Beta-endorphin have all been used and compared for

TABLE IV Epidural morphine: dose-response relationship

Study	*Type of surgery*	*Suggested dose (mg)*
Rawal N. *et al.*[22]	Abdominal and Thoracic	4
	Orthopedic	2
Chayen M.S. *et al.*[32]	Orthopedic	2
Martin R. *et al.*[78]	Orthopedic	2
Carmichael F.J.[77]	Abdominal	4
Crawford R.D. *et al.*[76]	Abdominal	5

epidural and intrathecal use.[79–81] Morphine has the longest duration of action and is at least as effective as the other agents. Mixing of narcotics and other drugs has also been examined. Experimentally, droperidol prolongs the duration of action of intrathecal morphine, potentiates its effects and lowers tolerance.[82] Experimentally at least the addition of epinephrine lowers blood concentrations of morphine, shortens onset of action and prolongs its duration[83] but this question is still much debated.[43,71] Mixtures of local anaesthetics and narcotics have also been injected and there is no known interaction between these drugs.[13,43]

Chronic therapy

Epidural and intrathecal morphine have also been studied in cancer and chronic pain patients. Catheters were left in the epidural space for long periods and used for intermittent injections;[84–87] results were satisfactory after the first series of injections but signs of tolerance appeared after approximately ten days and dosages had to be increased. Later, permanent catheters were implanted in the subarachnoid and epidural spaces and connected to reservoirs or perfusion pumps.[88,89] Those implants were found effective but tachyphylaxis, without respiratory depression appeared rapidly; this finding is probably the result of a progressive tolerance to narcotics when constant concentrations of morphine are maintained in the cerebrospinal fluid.[89]

Neurotoxicity after repeated epidural and intrathecal injection of narcotics was also investigated. In two cases, autopsy showed degeneration of the posterior horn; this pathological finding could be caused by prolonged silastic catheter implant,[90,91] repeated injections of opiates or by the underlying pathology.

Conclusions

Administration in acute pain

The effectiveness of epidural and intrathecal narcotic analgesia is well proven. Despite its definite advantages over other methods, adverse effects presently limit its use and consequently it should be used in selected cases.[75,92,93] Certain conditions should be met before the administration of epidural and intrathecal analgesia and its mode of administration should be based on our actual knowledge. The epidural approach appears to be the best with regard to cost–benefit ratio and unless contraindicated should be preferred to the intrathecal approach.[70] Thus this is the approach that we propose (Table V). Obstetrical analgesia, although theoretically interesting[93] has been ruled out during labour, for the time being. Beta-endorphin could eventually be used in obstetrics.[94]

TABLE V Epidural narcotics in acute pain

Prerequisites
1. Intense pain accessible from the epidural space
2. Patients whose respiratory and cardiovascular stability could be compromised by a method of analgesia producing more respiratory depression
3. Availability of close monitoring facilities

Narcotic administration
1. Choice of agent: morphine sulfate without preservative
2. Dosage after lower limb surgery: 2 mg; abdominal and thoracic surgery: 5 mg (adults)
3. If possible, segmental injection in an adequate volume (10 to 20 ml)

Precautions and surveillance
1. Close monitoring of respiratory rate for 24 hours
2. Immediate availability of naloxone
3. Avoid systemic narcotics and CNS depressants except if analgesia is inadequate
4 Position – whenever possible, head up 60 degrees

Use in chronic pain

Intrathecal or epidural narcotic analgesia is not exempt from problems caused by tachyphylaxis and tolerance. This restricts the number of candidates for permanent catheter implants to patients whose life expectancy is very limited. For those patients who are not relieved by conventional means, this technique appears to be a valuable alternative, because the patients already show a marked tolerance and thus are less susceptible to respiratory depression. Before implantation is performed, an effectiveness test should be done.