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Intrathecal medication delivery

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In the 20 years since its introduction, intrathecal medications delivered by drug pump have become a standard treatment for chronic pain. The key technical advance that made this possible was the development of an implantable pump for slow continuous infusion. Originally designed for insulin infusion, the pump systems were readily adapted for intrathecal delivery by simply adding a suitable catheter system. Although the use for diabetes has been delayed because of the lack of a stable insulin preparation that would not block the pump system, morphine was a natural drug to use because of high water solubility and long stability in the pump reservoir.

The key conceptual scientific breakthrough that made the application possible was the demonstration of opiate receptors in the spinal cord. As the physiology of the dorsal horn neurons has been slowly revealed by numerous investigators, it has become clear that this region has a major role in the regulation and processing of sensory input [1]. Pain signals from small myelinated fibers and C-fibers are summed, strengthened, or inhibited by a complex array of interneurons of feed forward and feedback circuits. Even a type of neuronal "learning" on the spinal cord level affects pain signal transmission. The opioid agonists exert their spinal effects primarily on receptors in the dorsal horn. The receptors are localized presynaptically on small-diameter pain fibers (capsaicin-positive) and act by inhibiting the influx of calcium through voltage-gated channels. This, in turn, reduces the transmitter release at the axon terminal. Other opiate receptors are located at the postsynaptic membrane and cause inhibition by activating outward potassium flow.

When morphine was first used intrathecally, many of the details of dorsal horn circuitry and pharmacology were unknown, and many remain unknown to this day. The striking clinical effect was evident, however. A bolus dose of morphine provided many hours of pain relief and did not cause the central side effects of drowsiness and respiratory depression to the same degree as seen with systemic dosing. The extension of this observation was to deliver morphine through implanted drug pumps for chronic pain. This jump from acute pain, usually postoperative pain, to chronic pain syndromes like failed back syndrome was taken at a time before the physiologic differences in the nature of these two pain states were delineated. Fortunately, many chronic pain conditions are modified by opiate agonists, so the delivery of morphine is useful. Nevertheless, it is still important to remember that the patient with chronic pain has a differently programmed dorsal horn than an acute pain patient and that what works intrathecally with one group may not work with the other.

The unusual pharmacodynamics of intrathecal drug delivery

Putting medications into the cerebrospinal fluid (CSF) is an old technique, but the peculiarities of drug distribution using this method are not usually presented in medical training. When a water-soluble substance is introduced into the lumbar subarachnoid space, it has only two ways to be distributed: diffusion and convection. Diffusion is

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a physically slow process dependent on random movements of molecules and based on a concentration difference. The speed of diffusion is related to the size of the concentration gradient. In practical terms, it takes many minutes to hours for diffusion to redistribute medicines in the CSF and tissue. (Think of the time it takes a lump of sugar to distribute in a cup of coffee if the coffee is not stirred). Convective flow is entirely different. The high kinetic energy from the pulsations of the arteries around the brain results in large pulsatile movements of CSF back and forth in the subarachnoid space. The result is substantial and rapid mixing of CSF. Any molecules in the different areas of concentration mix quickly. Furthermore, a bulk CSF turnover, approximately five times a day in human beings, distributes medications throughout the nervous system. The effect of this bulk flow and pulsatile mixing is to spread medications placed into the lumbar area through the spinal region and then over the brain convexities. The half-life of most water-soluble medicines in the lumbar area is about 90 minutes because of these factors [2].

Distribution of molecules through the brain or spinal tissue is much different. Molecules must make their way through the extracellular space, which is torturous and narrow. The extracellular space is 20% or less of the tissue mass. Experiments have shown that the movement of ions through brain tissue is 10 times slower than through plain agar [3]. This means that once a molecule is carried to the edge of the spinal cord, a long time is required for it to diffuse down its concentration gradient into the tissue. Tissue provides other barriers. Lipid-soluble molecules go into the cell body or cross into capillaries and are eliminated. Proteins may be degraded or bound to receptors before they reach the intended site of action. Morphine and baclofen, the two most commonly used intrathecal medications, work well precisely because they are water soluble and not subject to rapid metabolic breakdown.

The distribution process of convection and diffusion has important practical implications for drug delivery. First and foremost, drug delivery is slow. It takes up to an hour or more for morphine introduced into the lumbar area to reach the receptor sites in the dorsal horn of the lumbar spinal cord; most of this time is taken by diffusion through cord tissue. When testing with an intrathecal bolus dose, the optimum clinical response cannot be assessed for 1 to 3 hours. Slow diffusion in also means slow diffusion out. That is why a single bolus of morphine, which has a half-life of 90 minutes in CSF, can have a lasting clinical effect for up to 12 to 18 hours. The consequence is that changes in intrathecal dosing should be done once or, at most, twice per day to assess effects. Another corollary is that a bolus dose is a poor way to help breakthrough pain. It does not work because of the long delay in clinical effect. Adjusting flow rates to give more pain medication at certain times during the day must be done several hours before the increased pain relief is desired. Most important, if an overdose is given, nothing can be done to remove the morphine rapidly from the tissue. With a large overdose, the high levels in tissue may take a day or more to be dissipated into the CSF and blood. Supportive care is necessary until the drug is slowly released from the tissue.

The slow onset and slow wearing off of effects of intrathecal delivery are particularly useful for pain. Intrathecal delivery can be thought of as analogous to slow-release oral morphine preparations. The pharmacokinetics smooth transitions when the infusion rate is changed.

One of the key advantages of lumbar infusion is a steady-state gradient of medication from the lumbar to cervical area [2]. This has been studied for a number of large and small water-soluble molecules, including morphine, and the ratio of cervical to lumbar concentration is about 1:4. The constant production of new CSF flowing out of the fourth ventricle dilutes the CSF from the lumbar region, and the mixing in the spinal canal results in distribution along the cord. It should be noted that variability from patient to patient is the rule and that ratios from 1:2 to 1:9 are seen. This variability means that finding the right dose for a given patient is empiric, and doses may vary considerably to provide the same morphine concentration at receptor sites in the dorsal horn. In spite of variability, the always higher levels in the lumbar level compared with the cervical region reduce central/brain side effects, increasing the effective therapeutic ratio for morphine.

Catheter placement affects distribution along the spinal cord. This has not been well studied in patients but would be expected from models of CSF flow and empiric observations. Central side effects are increased when the catheter tip is placed in the cervical area. Pain control of arm and even facial pain can be achieved with high catheter placements but at the price of more drowsiness. Some physicians try to place the catheter tip at the spinal cord dermatomal level of pain. This may maximize local drug concentration, but drug

distribution may not be as even, and the higher the catheter, the lower the side effect ratio becomes.

Response to intrathecal morphine, clinical studies

One does not have to be a brain surgeon to recognize that delivery of morphine via drug pump to the spinal cord is an excellent way to relieve pain. Morphine goes directly to an effective site of action, brain sites that produce side effects are avoided, and consistent stable levels of relief can be achieved for most patients. Because these advantages were known from postoperative intrathecal delivery use and a suitable intrathecal preparation of the morphine was available, approval of intrathecal delivery of morphine by an implanted drug pump was obtained without formal randomized blind studies of efficacy. Initially, the main group of patients selected for implantation had severe cancer pain, so there were good reasons to approve the pump rapidly.

The result has been that until recently, the only investigations of chronic intrathecal morphine have been retrospective or prospective uncontrolled observational studies [4,5]. These have been useful to establish what types of patients respond, the duration of response, and side effects, but skeptical physicians have wondered if a surgical procedure to relieve pain is really better than optimal medical treatment. Because pain management specialists only suggest implantation of a pump after medical management has failed, not having class I information about the technique was not as much of a concern to many clinicians.

Fortunately, an excellent prospective randomized study on cancer patients has just been published [6]. It deserves to be discussed in some detail because it answers many important questions not addressed by the purely observational studies previously available. A total of 202 cancer patients were entered into the trial comparing comprehensive medical management with intrathecal drug delivery via an implanted pump. Cancer patients were selected who had visual analogue scale (VAS) ratings of 5 or greater on 200 mg/d of oral morphine (or equivalent) or lower if doses caused medically intractable side effects. Patients had to be expected to continue to have pain throughout life, to have an expected life span of at least 3 months, and to be suitable for the surgical implantation of the drug delivery system. All the sites in the study had a "structured approach" to pain management and experience in implanting and managing pumps.

The patients were randomized to further medical treatment or pump implantation and were followed biweekly for 12 weeks and then monthly for 6 months. The two outcome measures were VAS score and a standardized drug toxicity score. Clinical success, the primary outcome measure, was a 20% or better reduction in VAS score or equal VAS score with a 20% or more reduction in toxicity, and this was measured at 4 weeks. A crossover to pump implantation was allowed if medical therapy failed, which happened in five patients.

The results for clinical success are shown in Table 1. Both the medically treated and drug pump–treated patients improved significantly (70.8% and 84.5%, respectively), with the drug pump patients making a greater gain (statistically significant at the 0.05 level). Conversely, only 1 of 10 implant patients failed to have pain or toxicity reduced by 20%, whereas 1 of 4 medically treated patients failed. A table of side effects (Fig. 1) showed that the implant patients had significantly less fatigue or depressed level of consciousness, as would be expected with the intrathecal drugs. The severe adverse effects were equal in the two groups, but, obviously, all the pump and catheter problems were in the implant group. Whether analyzed by intent-to-treat or by actual treatment (eg, receiving a pump), the results were still significant.

The results clearly demonstrate that drug pump therapy is superior to medical treatment and that the surgery is not associated with more serious adverse effects than medical treatment. They also point out how poor "maximum medical treatment" is for most patients. By becoming study patients at a pain center, 70% of patients who were

Table 1
Results for clinical success

	Pump	Medical	*P*
VAS pain reduced 20% or same VAS but reduced toxicity 20% or more	87.5%	70.8%	0.5
Both pain and toxicity reduced 20% or more	57.7%	37.5%	0.2
Neither pain nor toxicity reduced	11.3%	23.6%	0.5

Abbreviation: VAS, visual analogue scale.

Adapted from Smith TJ, Staats PS, Deer T, et al. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity and survival. J Clin Oncol 2002; 20:4040–9.

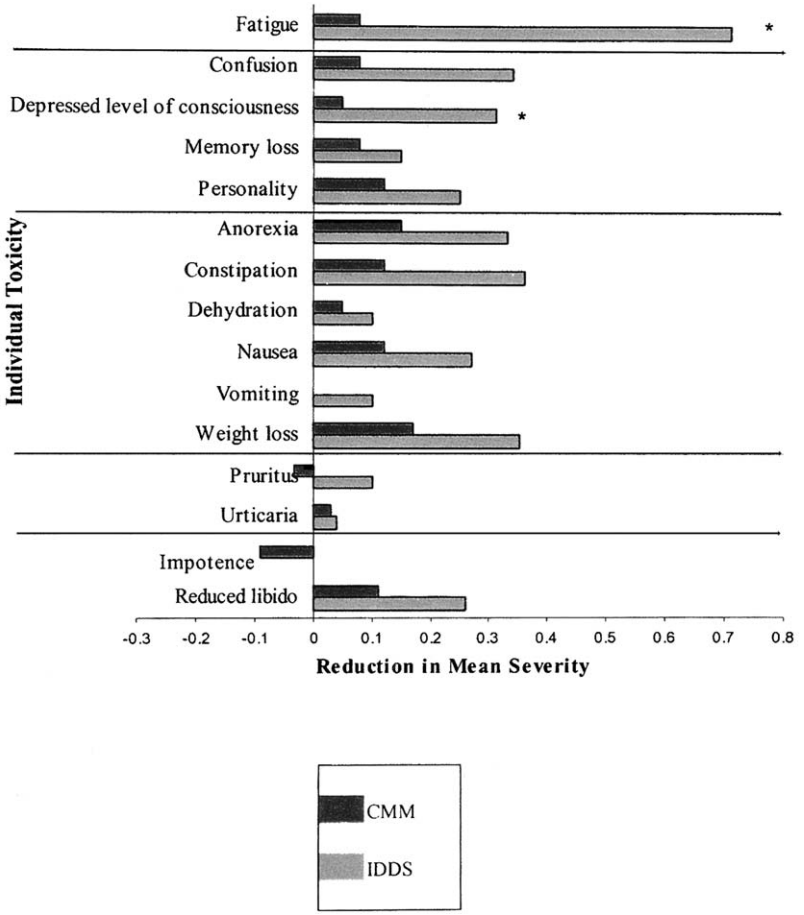

Fig. 1. Side effects of medical treatment (comprehensive medical management [CMM]) versus drug pump implant (implantable drug delivery system [IDDS]). $*P = 0.05$. Note marked decrease in fatigue and depressed level of consciousness. (*From* Smith TJ, Staats PS, Deer T, et al. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity and survival. J Clin Oncol 2002;20:4040–9; with permission).

already supposedly getting maximum medical treatment were improved on further medical therapy. Clearly, the cancer patients being treated for pain were not getting adequate care. Added attention to and expert care for pain work. Many studies have shown that cancer patients are undertreated for pain, and that is by far the most important lack in care for these patients.

An unexpected finding of the study is that those patients who had a drug pump implanted lived longer (Fig. 2). Because this was a secondary end point and was added to make sure surgery did not increase mortality, its significance is not clear. If increased longevity is truly a treatment effect, it might be speculated that better pain control with the pump should be considered a therapeutic indication. Certainly, this question needs to be examined in future studies.

Although it is clear from this well-executed study that cancer pain can be effectively treated with intrathecal morphine, only observational studies have been done on chronic noncancer patients. In the largest review of cancer and noncancer patients to date, both groups had the same efficacy with intrathecal drug treatment [7]. Patients with neuropathic pain or nociceptive pain responded equally well. This is in spite of the expectation that morphine would not work for neurogenetic pain. In practice, morphine is most frequently used to initiate treatment and maintain it. Other opiates, such as the more potent hydromorphone, have been used, and the local anesthetic

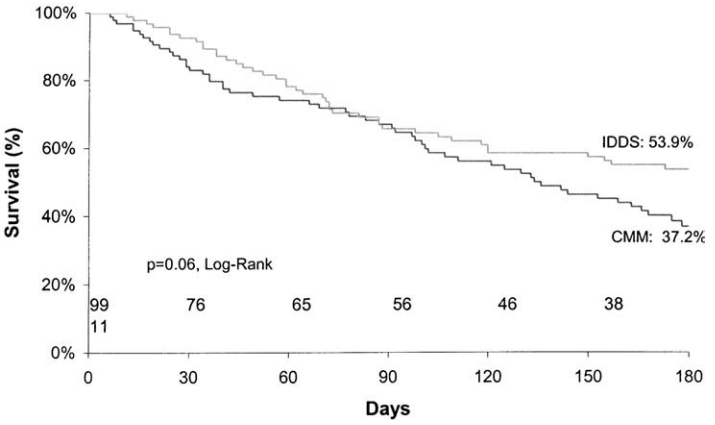

Fig. 2. Survival in the medical treatment group (comprehensive medical management [CMM]) versus drug pump implant group (implantable drug delivery system [IDDS]). The survival is greater at 180 days in the drug pump–treated patients.

bupivacaine is often added to morphine or hydromorphone. There are no randomized or blind studies that prove bupivacaine is of value, but many pain physicians use it as a supplement. Clonidine, an α_2 agonist, has been used for many years intrathecally for neurogenic pain. Unfortunately, controlled studies on its effectiveness are not available. Because clonidine may lower blood pressure, it must be used carefully, and stopping it can cause rebound hypertension. (For a complete review of what drugs might be used for intrathecal administration, the reader is referred to the article by Dougherty and Staats [1]. For a clinical review, the reader is referred to the article by Bennett et al [8]). Polypharmacy has been the rule rather than the exception for oral analgesics, so it should not be a surprise that polypharmacy is widely used intrathecally. The major difference is that aside from morphine, none of these drugs have been approved for intrathecal use, and few long-term toxicologic studies have been done. The alternative or supplementary drugs can be readily formulated in appropriate concentrations for intrathecal use but are not currently approved by the US Food and Drug Administration (FDA). Any physician using them must balance the unknown risks of off-label medications against the needs of the patient. The physicians who have the largest pain practices, in general, use the most combinations of medications.

Little is known about the long-term efficacy of intrathecal medications for pain. Observation tallies of successful treatment use various outcome measures and follow patients over relatively short periods [9]. One gets the sense from the literature that about 60% to 70% of chronic pain patients respond well (> 50% decrease in VAS) for at least 6 to 12 months (see Table 1 in the article by Winkelmüller et al [4] and Table 3 in the article by Bennett et al [5]). Longer term data are generally lacking, but in the large series followed by Winkelmüller and Winkelmüller [10], efficacy was maintained for up to 5 years in most of these initially responsive patients, although medications other than morphine alone were often necessary.

Side effects of intrathecal morphine

The same adverse effects of oral or systemic morphine can occur with intrathecal use. Nausea, vomiting, and drowsiness are not uncommon with bolus doses or initial titration of the intrathecal infusion. These effects are most often dose related and can be managed by decreasing the dose. As long-term tolerance develops, the effects usually decrease on their own. Pruritus is also common at the beginning of therapy and dissipates in 24 to 48 hours, except in rare individuals. Long-term diaphoresis, weakness, and weight gain can occur but do not usually stop therapy. Neuroendocrine effects are induced by long-term intrathecal morphine, loss of libido and impotence in men, and amenorrhea in women. Hormone replacement may be useful [11].

Two serious side effects that may require cessation of treatment are myoclonus and peripheral edema. The myoclonus can be severe, continuous, and painful. Substituting hydromorphone may be helpful. Edema can vary but, on occasion, may be so severe that it is necessary to stop

intrathecal morphine. Diuretics, interestingly, do not improve the situation, and the pathophysiology of the edema is unknown.

The special problem of an inflammatory mass

As with any new technique, rare side effects did not become known until large numbers of patients were treated. The occurrence of an inflammatory mass or granuloma at the tip of the infusion catheter is one such problem that only recently has been documented in detail, although an individual case report was published 10 years ago. In a recent publication, 41 cases were assembled: 16 from the medical literature and 25 from FDA adverse effects reports [12]. In all cases, the inflammatory mass was found to be at the level of the catheter tip. On average, the mass took 2 years to become clinically evident, and as would be expected from its position, it produced signs and symptoms of spinal cord injury. In a third of cases, a complete cord injury occurred. In a few cases, only loss of drug effect was noted. MRI accurately pinpointed the problem; in most cases, surgery was done to relieve the compression and remove the catheter system. In only 16 of 41 patients was a complete recovery obtained.

Paraplegia is a high price to pay for pain treatment. The true incidence of mass formation is not known, because MRI surveys are not available and the number of cases may well be underreported. A risk of approximately 1 in 1000 is a reasonable guess as to incidence, but this could be off by an order of magnitude.

A number of factors seem to be associated with the mass formation. First of all, it is not found in any intrathecal baclofen patients, so it is not caused by the silastic catheter but by the infused opiate. Most often, it occurred with thoracic placement of the catheter tip and with high concentrations and high daily doses of morphine or hydromorphone infusion. Pathologic examination of the mass reveals a fibrous, tough, usually rounded ball of material with an embedded catheter. Cultures have been negative in almost all cases. This leads to the hypothesis that the mass forms because of the high concentration of an opiate at the catheter tip in a low CSF flow region. The small amount of scarring around the silastic catheter in some patients possibly sequesters the opiate; then, a process of scarring increases the concentration more. In some but not all cases, unapproved drugs were used or morphine at higher than normal concentrations was given. The problem may be compounded by polypharmacy and drug interactions.

Regardless of the cause, anyone using chronic intrathecal pain medications must be alert to the potential complication and warn patients of the risk and what signs and symptoms might occur. The lack of pain control with increased dosage and complaints suggesting nerve root or cord compression provide the best clinical clues to catch the problem early. The data also suggest that placement of the catheter tip below the conus, where there is better CSF circulation, and avoiding high concentrations or dosages of morphine, should help avoid the problem.

The best solution would be to have new pain medications that do not cause inflammation. Many intrathecal pain medicines could work [1], but it will be years before they are available in an approved form. For the present, clinical awareness of the possibility of granuloma formation and MRI to make a diagnosis are the best we can do to detect this rare but serious complication.

Summary

This brief review of intrathecal pain medication delivery has emphasized the unusual but useful pharmacology of CSF drug delivery, the new study definitely showing that the method is helpful in cancer pain, and the rare complication of mass formation at the catheter tip. As new medications are developed for intrathecal delivery, this field is likely to expand, especially if a wider range of dorsal horn receptor mechanisms underlying pain processing can be modified. The changes in spinal cord signaling that are induced by chronic pain states are being investigated, and new possibilities for intervention are likely. The availability of a reliable well-understood way of delivering such new therapies by implanted drug pumps will speed the process. Intrathecal morphine for chronic pain has an important role in helping many patients with a wide variety of pain conditions and, as with all pain treatment, is woefully underused.

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