Intrathecal drug delivery systems

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Key points

Intrathecal drug delivery (ITDD) systems comprise an IT catheter connected to a drug reservoir, which may be externalized and connected to a pump, or fully implanted.

Two groups of patients may benefit from ITDD: those with spasticity (baclofen) and those with refractory pain.

The purpose of an ITDD system is to deliver drug(s) close to target receptor sites in the dorsal horn of the spinal cord.

Ziconotide is a relatively new drug that may offer some therapeutic advantages over opioids, although it has significant side-effects of its own.

IT drug delivery is an evolving therapy, and current drugs and practice may change in the light of new information.

Anaesthetists have made use of the intrathecal (IT) space to provide optimum anaesthesia and analgesia for decades. Most commonly to tide the patient through the operative period, but also for postoperative pain relief. The advantages of the techniques and the comparative effectiveness of the drugs compared with other methods of administration are well known.

Those of us who work in the field of chronic pain management are faced with providing relative analgesia over days and weeks for terminal cancer patients, months and years for those with progressive cancer-related pain and over decades for those with intractable pain of either malignant or non-malignant aetiology.

We can do this to a great extent with the intrathecal drug delivery (ITDD) systems currently available. There are, of course, many treatment options available for patients with chronic pain and ITDD systems are by no means a first-line treatment, but in selected patients both can relieve pain and restore the quality of life in the short and long terms. It should be possible to relieve pain below the diaphragm with relative ease. Above the diaphragm, the effects of drugs on the cardio-vascular system may limit the use of effective doses of drugs. ITDD is an evolving therapy, and current drugs and practice may change in the light of new information.[1]

What ITDD systems are available?

In its simplest form, an ITDD system consists of a catheter connected to a pump. The pump can be an external device or a fully implanted system with a reservoir that can be refilled percutaneously. There are two types of fully implantable pumps: fixed rate or programmable. Various infusion options are possible: simple continuous or more complex variable rates. The pump can be programmed for the patient to self-administer boluses. The physician can set the bolus dose, the duration of infusion, the lock-out interval, and the maximum number of activations allowed per day; the patient activates the bolus facility.

The major advantage of such 'as required' dosing regimens is that they give the flexibility necessary for unstable, unpredictable, or complex pain problems such as progressive cancer-related pain. There is a suggestion that using a low-dose background infusion with a required bolusing regime may reduce the incidence of granuloma formation. It certainly reduces the development of the tolerance and tachyphylaxis to bupivacaine and opioid infusions that occurs over time. The disadvantages are reduction in time between refills and the increase in use that inevitably shortens the life of the battery. The technology involved at the patient interface is relatively simple, but some degree of understanding and dexterity is still required.

Each system has its own advantages, disadvantages, and limitations. Systems with external reservoirs and pumps have the major advantages of simplicity and cost. It is relatively easy and cheap to implant a catheter and start an infusion. External reservoirs are easy to change and dose alterations are simple. The use of relatively high volumes for example, of dilute local anaesthetics, is possible. Physician administered boluses are possible. The problem is then in having trained professionals to manage the patient thereafter. Trained staff need to be available to deal with any problems and to refill and adjust the pump. Place of care may be limited to hospital or hospice depending on the availability of trained staff in the community. Negatives also include the bulkiness of the pump itself and the on-going risks of accidental disconnection and infection. In the longer term, practically for any infusion intended to be running for longer than 3 months, a fully implanted system is a feasible economic option.

Current evidence has led to several recommendations for both maximizing efficacy and minimizing potential toxicity of IT drugs:[2]

- minimizing local concentrations of drugs against neural tissue by appropriate catheter placement,
- high flow rates,
- using the lowest drug concentration possible and more complex dosing,
- demand- or activity-based dosing,

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- variable flow rates,
- intermittent bolus delivery.

Spinal anatomy and CSF fluid dynamics

The aim of an ITDD system is to deliver the chosen drug to its receptor sites in the dorsal horn of the spinal cord in sufficient quantity to have a clinical effect. Some basic principles are involved; knowledge of these determines where the tip of the catheter needs to be positioned and explains why the effects of slow IT infusions and boluses do not mimic the effect of spinal drugs given in relatively large volumes over a fraction of a second during the course of an anaesthetic.

There is still some controversy regarding cerebrospinal fluid (CSF) fluid dynamics.[3] The old notion that CSF flows from its sites of production in the ventricles to the spinal canal where it flows caudally and then rostrally and a drug administered anywhere will be distributed equally throughout has been disproved. Instead, it is clear that at a spinal level, CSF circulates or oscillates in a pulsatile fashion related to heart rate in a series of doughnut-shaped entities with areas of local turbulence around the boundaries of the canal and points of exit of nerve roots. There is no overall flow, even for a drug injected into the ventricles.

Drug spread in the CSF depends on a variety of factors including buoyancy, streaming, injection rate, and enhanced diffusion. Diffusion itself is not particularly important as it takes 24 h for a drug to diffuse 1 cm. Slow continuous infusions from ITDD systems (e.g. 20 $\mu l\ h^{-1}$) do not distribute the drug much beyond the doughnut into which it is introduced. Experimental work using a pig model and methylene blue shows substantial dye at the level of infusion.[3] Levels decrease exponentially such that by four vertebral levels above and below the infusion, virtually no molecules are present. Staining is only visible at the site of exit of the drug from the catheter. Even a bolus does not break beyond these boundaries, although there is some improvement in distribution within it.

A high-volume (2–3 ml) anaesthetic bolus administered over a second or two, with maybe a bit of barbotage, is distributed far more widely and the drugs easily break through the local CSF fluid circulation.

Drug factors (physico-chemical properties and pharmacokinetics) are, of course, important and for a big highly ionized molecule like ziconotide mean that it is eventually widely distributed throughout the neuraxis, whereas the small opioids are not. Lipid solubility largely determines how a drug is partitioned in grey matter, white matter, blood, and fat. Lipid-soluble drugs are likely to be cleared rapidly from the CSF to the fat of the epidural space and to plasma. More water-soluble drugs are likely to be distributed more widely, but penetrate the layers of the spinal cord less well. Some lipid-soluble drugs are cleared so fast that they have no clinical effect at a spinal level at all.

It is clear that any spinal catheter needs to be sited at least at the dermatomal level of the pain for the infused drugs to have any chance of the drugs getting to the relevant receptor sites in the spinal cord. It should also lie posteriorly within the spinal canal. It is worth noting that most catheters are multi-ported, but that infusions leave the catheter through only one of those ports.

Drugs

There are only two drugs licensed for use in ITDD systems for use in patients with chronic pain—morphine and ziconotide—but other opioids, local anaesthetics, and clonidine are commonly used, both alone and in combination. It is mandatory that any drug used in the intrathecal space must be preservative free, not just because of the risk of neurotoxicity, but as there is the potential for some of the preservatives to react with CSF-proteins forming complexes that can cause catheter blockage.

Unlike anaesthetic practice, local anaesthetics are not so frequently used for a variety of reasons—tachyphylaxis and the tingling and numb sensations, sometimes with incontinence and motor weakness—not great in the long term even for patients with progressive cancer-related pain. Opioids too have side-effects, but the majority of patients will have been taking substantial doses of oral opioids and the intrathecal dose is in the realm of 1/50th of the oral dose. Clonidine works well for neuropathic pain. Ziconotide is a relatively new drug still finding its place in the armamentarium, but it is effective for both nociceptive and neuropathic pain and for more generalized pain conditions. Any other drug is not in mainstream use but may have an application in certain clinical circumstances.

Opioids work pre- and post-synaptically by depressing neurotransmitter release and hyperpolarizing neuronal membranes in the dorsal horn of the spinal cord. The μ-opioid receptor is linked to presynaptic calcium channels by a G-protein-coupled mechanism. Opioids inhibit this channel, but indirectly and partially as not all μ-receptors are linked to the calcium channels. With time there is a functional uncoupling of the link, reflected clinically by the development of tolerance. It is worth noting that ziconotide binds directly to the calcium channels with no development of tolerance with time.

Serous opioid-related side-effects include opioid-induced hyperalgesia, hypotension, respiratory depression, and hypogonadotropic hypogonadism that can result in sexual dysfunction and osteoporosis. However, continuous simple opioid infusions remain the mainstay of chronic IT practice.

'Morphine' is the only opioid approved for IT use by the FDA and is the most frequently used. It is a small hydrophilic molecule with a half-life in CSF of 80 min. It has a relatively longer onset and duration of action than other opioids, but significant problems with tolerance, hyperalgesia, IT granulomas, and endocrine effects. A 300 mg oral morphine equivalent is approximately converted to 1 mg IT. It can be used in combination with local anaesthetics and clonidine.

'Hydromorphone' is a synthetic opioid that is both more lipophilic and more potent (4–7×) than morphine. There are predictably fewer supra-spinal effects reported and more stable in combination with