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 externalised 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 ITD 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 bolus 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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References

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

2. Current evidence has led to several recommendations for both maximizing efficacy and minimizing potential toxicity of IT drugs.
• 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. 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 μl 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. 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 lipidsoluble 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 pre-synaptic 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
ziconotide than morphine. It can likewise be used in combination with local anaesthetics and clonidine.

‘Fentanyl’ is a potent synthetic highly lipophilic opioid μ-receptor agonist well known and used by anaesthetists, but not used in the UK for IT infusions. It is rapidly absorbed across the dura which may limit its clinical effectiveness, but means that so far it has not been associated with IT granuloma formation.

‘Sufentanil’ is similar to, but yet more potent, than fentanyl. It is not currently available in the UK.

‘Diamorphine’ has been used very successfully for ITDD in the past, but evidence that its breakdown products can cause pump stall has stopped its use in Medtronic programmable pumps. It still has the potential to be used in other systems.

‘Bupivacaine’ either ‘neat’ or levo- (the l-optical isomer) is the traditional choice of local anaesthetic in the UK, although others could be used. It is effective by its action on sodium-channel blockade and thus impeding neuronal impulse transmission. Theoretically the small nerves responsible for pain transmission with little or no myelin (C and Aδ) will be blocked before the thicker myelinated nerves (Aα and Aβ), which are responsible for numbness and motor function. Autonomic nerves are easily blocked with even low doses of local anaesthetic.

Toxic doses of local anaesthetic (>2 mg kg⁻¹) are unlikely to be reached by ITDD, but the potential side-effects of numbness, motor weakness, and incontinence are well within the dose ranges used and are not well tolerated. There is some experimental rodent evidence that high continuous exposure to local anaesthetic is neurotoxic—low doses seem to be safe, but high dosage is probably best reserved for terminal cancer-related pain.

Bupivacaine is excellent at managing both nociceptive and neuropathic pain conditions that are either only partially or not sensitive to opioids. Options are to add it in to an opioid or opioid/clonidine mixture as a continuous background infusion or to use a background infusion with boluses as required. Now that 4% (40 mg ml⁻¹) bupivacaine is available, it is possible to use a pure opioid infusion with a low background and as required boluses without getting the tachyphylaxis associated with continuous infusions. Boluses of only 1 or 2 mg of bupivacaine may be sufficient; although up to 20 mg can be used—as the maximum rate of infusion of the Medtronic pump is 1 ml h⁻¹, the fastest infusion of this is >30 min. It is quite possible to alter local anaesthetic doses and rates of infusion to suit the patient and make side-effects more tolerable. Sometimes, however, some types of cancer-related pain are only relieved by local anaesthetic and the patient needs to be prepared for this before implant.

‘Clonidine’ is an α₂ adrenoceptor agonist that binds to both pre- and post-synaptic α₂ receptors in the dorsal horn. It acts by reducing the release of C fibre neurotransmitters, such as substance P and calcitonin gene-related peptide (CGRP), and possibly by also reducing pre-ganglionic sympathetic outflow. It also causes hyperpolarization of the post-synaptic membrane via a G-coupled potassium channel.

It is effective for neuropathic pain in IT doses of 60–1000 µg day⁻¹. It has a synergistic anti-nociceptive interaction with other drugs, no tolerance and may be protective against granuloma formation. It is the most stable drug in combination with ziconotide. However, abrupt withdrawal can be fatal and any reduction in dosage needs to be gradual.

‘Ziconotide’ is a new class of IT drug—an n-type calcium-channel blocker and non-opioid analgesic, which was approved by the FDA in 2004 and the EMEA in 2005. The exact mechanism of action in humans is unknown, but animal works show it to be a selective inhibitor of pre-synaptic n-type channels that are concentrated in the superficial laminae (I and II) of the dorsal horn of the spinal cord. These calcium channels are blocked directly by ziconotide and indirectly by opioids. Tolerance does not develop with ziconotide unlike opioids. Granuloma formation has not been reported.

Ziconotide is a synthetic analogue of α-conotoxin that originates from the fish-eating marine snail Conus magnus. The snail uses a mixture of conotoxins to kill its prey within seconds. The molecule itself is large, comprising 25 amino acids and weighing 2659 Da. It is completely ionized at physiological pH and freely soluble in water. Most other IT drugs are small unionized molecules. Whereas most drugs are poorly distributed in the neuraxis, ziconotide is widely distributed—radiolabelled ziconotide in rats reaches the neocortex, basal ganglia, forebrain, hippocampus, olfactory glomerulus, dorsal grey matter and also the CSF and dorsal horn. Ziconotide is effective for both nociceptive and neuropathic pain and the direct implication of its distribution is that both generalized pain problems and those featuring pain above the diaphragm, can be safely and effectively treated. It also raises the suspicion that central neurological side-effects might be a problem and this does indeed turn out to be the case. Dizziness, headache, nystagmus, somnolence, memory impairment and abnormal gait are the commonest with >20% of patients affected. Clinical psychosis is a contraindication but any degree of depression has the potential to deteriorate significantly such that therapy has to be terminated. Other side-effects are gastrointestinal – nausea, vomiting and constipation, and more generalized effects including fever. Most adverse events are transient and all stop with cessation of therapy, although this may take weeks to months. It is safe to stop infusions.

Creatine kinase levels may increase during therapy with the potential of developing myopathy and ultimately rhabdomyolysis. Enzyme levels need to be checked and infusion stopped if necessary.

Practical points include catheter tip position that, because of drug distribution, is not crucial. For a generalized pain problem, a mid-thoracic end-point is recommended.

Ziconotide has to be started at a very low infusion rate and titrated very slowly. It may take some weeks to months to reach an effective dose, as side-effects need to be minimized for the drug to be tolerated. The initial infusion rate is 2.4 µg day⁻¹ and the maximum recommended is 19.2 µg day⁻¹.

Other drugs have been used, but none in current routine UK practice—some have demonstrated neurotoxicity and others appear to be safe, but without significant evidence of efficacy (Tables 1 and 2). ITDD is a developing therapy and a group of experts has met in the form of a Polyanalgesic Consensus Conference in the USA with the stated aims of critically evaluating available data, using clinical
expertise and publishing guidance. The 2012 published guidelines present algorithms for managing nociceptive (Table 3) and neuropathic pain (Table 4) with recommended bolus doses for trials and starting doses (Table 5), concentrations and maximum doses (Table 6). It would be difficult not to adhere to these recommendations in a patient with a normal life expectancy, whereas there would be some room for flexibility at the end of life.

**Patient selection**

Theoretically any patient with severe intractable chronic pain unresolved by any other management strategy is a candidate given the constraints already alluded to. Practically for non-cancer pain patients, a minimum of 3 monthly hospital trips for refilling is a major limitation and an on-going restriction. The assessment and information exchange process must be rigorous, including test dosing and psychological evaluation. There are clear recommendations by the British Pain Society.

For patients with cancer-related pain, the decision-making process is more straightforward, although every stage of the decision-making process must be clear. It is worth mentioning that the treatment of any pain condition is the treatment of its cause. A diagnosis is crucial and, if this is not clear, then further referral and investigation are obligatory. Definitive surgical or medical management or radiotherapy or chemotherapy may ensue.

Contraindications are as for a spinal anaesthetic—systemic infection and bleeding diathesis and failure to give informed consent. Relative contraindications include spinal anatomy, local infections, and pre-existing leg oedema, which will be worsened.

**Test dosing and trials**

The recommendation is that some form of test dose or trial is useful, but exactly how this might be performed is not prescribed. The options are to use a single shot or a trial infusion. Single-shot techniques cannot replicate an infusion, but do give an idea of responses to opioid and local anaesthetic.

**Complications**

Most are predictable but some peculiar to the implants and drugs used are the development of IT granulomas, issues with MRI scanning and leg oedema.

IT granulomas are inflammatory masses in the dura adjacent to the catheter tip. They have been attributed to the use of all agents, except fentanyl, sufentanil, and ziconotide. Presenting symptoms include loss of analgesic effect and new and progressive neurological. Diagnosis is with MRI or CT myelogram. Drug precipitates may mimic inflammatory masses. The majority are associated with morphine and hydromorphone, but experimental work has shown them to be consistent with cutaneous mast cell activation rather than being mediated by opioid receptors. Animal work with morphine has shown that the concentration of the drug used is important rather than the actual total dose. It would seem intuitive therefore to use the lowest concentration of drug at the highest flow rate possible. In the animal model, stopping the opioid leads to resolution of the inflammatory mass. In a patient, the potential risk of long-term neurological damage means that surgical excision must be considered.

MRI scanning will cause stall of the rotor arm of the Synchromed II IT pump. It will restart once out of the magnetic field (more information can be found at www.medtronic.com).

Problematic leg oedema has been described with IT opioid infusions and may necessitate cessation of therapy.

**Evidence for ITDD systems**

There is good evidence for both cancer and non-cancer-related pain, but not in the form of randomized, controlled, double-blind trials. What does exist is more convincing for cancer-related pain than for non-cancer pain.

**Perioperative implications of ITDD systems**

Two considerations here: the physical presence of the pump and catheter and perioperative drug management.

Antibiotics are not routinely required to cover surgical procedures just because of the presence of an ITDD system, but the
potential for infection is obvious. Infection in the intrathecal space and pump pocket will usually lead to loss of a system.

Spinal anaesthesia is best avoided via lumbar puncture, although it is possible to utilize the side access port of the Medtronic implanted pump and, of course, an external catheter, to administer a spinal anaesthetic. It would have to be borne in mind that the catheter contains a volume of drug and if not aspirated beforehand (and this may not be possible as some catheters will collapse with negative pressures) this will be widely distributed intrathecally given that an anaesthetic bolus is normally performed with some gusto. Catheter level is still important.

Table 6 Concentrations and doses of ITagents by the Polyanalgesic Consensus Panelists 2012

<table>
<thead>
<tr>
<th>Drug</th>
<th>Maximum concentration</th>
<th>Maximum dose per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>20 mg ml⁻¹</td>
<td>15 mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>15 mg ml⁻¹</td>
<td>10 mg</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>5 mg ml⁻¹</td>
<td>No known upper limit</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>30 mg ml⁻¹</td>
<td>10 mg</td>
</tr>
<tr>
<td>Clonidine</td>
<td>1000 μg ml⁻¹</td>
<td>40–600 μg day⁻¹</td>
</tr>
<tr>
<td>Ziconotide</td>
<td>100 μg ml⁻¹</td>
<td>19.2 μg day⁻¹</td>
</tr>
</tbody>
</table>

It is possible for an ITDD system to malfunction, but extremely rare. Negative patient events such as collapse, hypotension, or drowsiness should not be ascribed to the mere presence of an ITDD system—they need full investigation and appropriate management.

The patient, their relatives or both would usually have contact details for their pain management specialist and there should be local arrangements for 24 h cover for at least telephone advice for ITDD system queries.

**Declaration of interest**

L.L. has been paid for lecturing for Codman and has both lectured and been a member of an advisory board for Medtronic.

**References**


Please see multiple choice questions 21–24.