

INA (Intraspinal narcotic analgesia)

The "pump": this was originally developed for use in terminally ill cancer patients when it was not being considered for long term use. From the studies now performed of long term pump use emerge varying opinions as to its safety and efficacy.

One recent paper states:

"About one third of the patients get good long-term pain relief without complications or side effects, many require the addition of local anesthetics, and some never get effective relief. There are major questions to be answered before this form of therapy becomes widely disseminated."([\[1\]](#))

A recent study in the UK ([\[2\]](#)) showed that INA was effective as pain relief, for patients with failed back syndrome and chronic mechanical low back pain.

Diamorphine was used in all 37 patients, bupivacaine in 32, clonidine in 27 and baclofen in 3. The mean dose of diamorphine increased for the first 2 years but did not change 2-6 years post implant, averaging 4.5 mg/day. Revision surgery was necessary in 24% of cases.

The authors, Raphael et al. pointed out that whilst some authors had found tolerance requiring increasing doses, others had not. They found that the pain level reduced by 3 or more on an 11-point scale (0-10) which they regarded as clinically significant, with average implant duration of 4.38 years.

They remarked:

"Spinal opioids for low back pain is a therapy of last resort and is controversial."

Spinal opiates affect spinal nociceptive processing by reducing the release of excitatory neurotransmitters and decreasing the excitability of dorsal horn neurons. Extensive literature indicates that opiates delivered spinally induce strong analgesia.

The well researched pharmacology of this action has shown that μ , δ and κ , opiate agonists are effective.

Distribution of the opiate must extend beyond the spinal segment because sensory input into a given nerve root (from a specific dermatome) distributes several segments once the afferent has entered the dorsal root entry zone. (compare delivery of a local anaesthetic which is designed to affect a single root only). Small volumes and high concentrations may only be effective when there is adequate redistribution.

This may be impaired in the case of arachnoiditis where CSF flow is compromised.

Opiates are often supplemented with either local anaesthetics such as bupivacaine, or antispasmodics such as baclofen.

Principal problems with intraspinal drug therapy include system failure, infection and neurotoxicity. System malfunction varies according to manufacturer, but tends to run at about 20 % ([\[3\]](#)).

There are a number of papers documenting cases in which intrathecal granulomatous tissue has formed at the pump site. ([\[4\]](#) ; [\[5\]](#)) Bearing in mind that this is a form of scar tissue, this has special relevance to arachnoiditis patients who already have scarring problems.

The suspected causes include: infectious process, hypersensitivity to implant materials,

mechanical or chemical effect of the infusate, or local tissue (toxic/inflammatory) response to the drug.

A further paper ([\[6\]](#)) describes evidence of focal subdural fibrosis and discrete injuries to nerve roots in patients with intrathecal infusions of morphine and bupivacaine.

A report in a San Francisco newspaper in June 2002 ([\[7\]](#)) described cases of granuloma that are becoming ever more frequent and may be related to compounded opiate preparations being used to refill the pump. FDA- approved morphine for pump use (Infumorph) is not being used, instead mixtures of opiates with other agents are being prepared to cut costs and boost the income generated.

The newspaper article suggested that whilst a paper by Burchiel in the journal Neurosurgery stated 41 cases, in fact the number of cases to date was at least 74.

Interestingly, the Medtronic representative (who estimates that 30,000 patients in the United States are wearing portable infusion pumps) told the journalist that he did not attribute these granuloma cases to compounded drugs.

He stated that they have occurred in patients using FDA-approved morphine, so that he thought that the inflammation may be a chemical irritation

"related to the properties of morphine itself."

Scott Ward, president of Medtronic's neurological and diabetes division, stated,

"The fact of the matter is we do not know with medical certainty what causes these granulomas."

Coffey and Burchiel ([\[8\]](#)) reported on 41 cases of inflammatory mass lesions at the tip of intraspinal drug administration catheters.

They commented:

“Because of voluntary reporting and other methodological limitations, the actual number of cases must be higher than reported.”

The patients all had chronic pain and on average had had the pump for around 2 years. Most masses were in the thoracic region. 30 patients underwent surgical decompression.

They remarked:

“The most plausible hypothesis with regard to the cause of intrathecal catheter tip mass lesions implicates the administration of relatively high-concentration or high-dose opiate drugs or the use of drugs and admixtures that are not labeled for intrathecal use.”

Reported symptoms associated with the development of an inflammatory mass:

- Drug withdrawal symptoms
- Progressive change in character, quality or intensity of pain
- Considerable increase in the level and degree of pain despite dose escalation
- Sensory changes (i.e. numbness, tingling, burning, etc.)Hyperesthesia, hyperalgesia
- Sleep disturbances
- Bowel and/ or bladder dysfunction
- Myelopathy
- Conus syndrome
- Gait disturbances/ difficulty ambulating
- Paraparesis/ paralysis

Patients receiving long-term intraspinal therapy should be carefully monitored if any of these symptoms are observed.

These findings are of some concern considering a recent paper ([\[9\]](#)) on the use of INA in the UK for FBSS and chronic mechanical low back pain.

Other adverse effects of INA such as constipation, nausea, vomiting and itching tend to be short-term, whereas loss of libido and potency may persist for several months.

The most persistent side-effects are sweating and oedema (swelling), the latter of which may necessitate INA being discontinued. The most serious adverse effect is respiratory depression.

High concentrations of morphine may lead to allodynic effects which are not opiate receptor mediated but may be due to the metabolite. Chronic delivery of intrathecal morphine in high concentrations has been demonstrated as leading to the formation of aseptic inflammatory masses (granulomas).

Penn and Paice suggested the following prevalence of side effects: ([\[10\]](#))

Nausea and vomiting 25.2%

Pruritis 13.3%

Oedema 11.7%

Diaphoresis (sweating) 7.2%

Weakness 7.2%

Weight Gain 5.4%

Diminished Libido 4.9%

Aldrete, writing about leg oedema from intrathecal opiate infusions ([\[11\]](#)), noted that 5 patients who had had the pump for more than 24 months developed leg and feet oedema; they all had a previous history of foot oedema and venous stasis prior to pump insertion.

The complication caused lymphoedema, ulcerations and hyperpigmentation of the skin. The severity of the oedema reduced as the morphine dose decreased, and in 2 cases where the infusion was discontinued, the oedema resolved completely.

Aldrete suggested that pedal oedema and vascular stasis are relative contraindications for pump therapy.

A consensus conference on the continuous infusion of spinal drugs for chronic pain management, saw several points raised: morphine is the principle agent employed; doses up to 20 mg/day are "acceptable" and concentrations should be adjusted to allow as long an interval between refills as possible ([\[12\]](#)).

The pump and MRI scans: whilst an MRI will temporarily stop the pump motor and suspend drug infusion, the pump should resume normal operation after the MRI had finished. During the MRI scan, the patient may experience heating or peripheral nerve stimulation at or near the pump implant site.

(Tesla) MR scanners -- it is not recommended that patients have MRI scans using these scanners.

Note: Intrathecal Baclofen

Sampson et al. ([\[13\]](#)) recently conducted a review on the use of intrathecal baclofen in treating severe spasticity.

They concluded that this treatment

"produces functional benefits and is likely to be an appropriate use of resources in carefully selected patients."

They specified that patients must have severe, disabling spasticity that remains refractory to oral medication. Fortunately, most arachnoiditis patients do not seem to have this degree of spasticity.

Prescribing information about baclofen (Lioresal) intrathecal injection now includes a warning about possible problems following abrupt discontinuation of treatment, including high fever, altered mental state, exaggerated rebound spasticity, muscle rigidity and in rare cases rhabdomyolysis, multiple organ failure and death.

In order to avoid this, careful attention to possible signs of baclofen withdrawal as a result of pump system failure for example, must be maintained.

These signs include:

Spasticity, pruritus (itching), hypotension (low blood pressure) and paraesthesiae. Some of the clinical characteristics of withdrawal may resemble autonomic dysreflexia, infection, neuroleptic malignant syndrome, malignant hyperthermia or other syndromes associated with a hypermetabolic state.

Should it be impossible to reinstate the infusion, GABA agonists should be administered orally (baclofen or benzodiazepines).

[1] Stangl JA, Loeser JD *Current Review of Pain* 1997;1: 353-360 Intraspinal Opioid Infusion Therapy in the treatment of Chronic Nonmalignant Pain

[2] Raphael J, Southall J, Gnanadurai T, Treharne G, Kitas G. *BMC Musculoskelet Disord* 2002 Jun 20;3(1):17 Long-term experience with implanted intrathecal drug administration systems for failed back syndrome and chronic mechanical low back pain.

[3] Stangl JA, Loeser JD *Current Review of Pain* 1997; 1: 353-360 Intrapinal Opioid Infusion Therapy in the Treatment of Chronic Nonmalignant Pain.

[4] Bejjani GK, Karim NO, Tzortzidis F *Surg Neurol* 1997 Sep; 48(3): 288-91 Intrathecal granuloma after implantation of a morphine pump: case report and review of the literature.

[5] Cabbell KL, Taren JA, Sagher O *Neurosurgery* 1998 May; 42(5): 1176-80 Spinal cord compression by catheter granulomas in high-dose intrathecal morphine therapy: case report.

[6] Sjoberg M, Karlsson PA, Nordborg C, Wallgren A, Nitescu P, Appelgren L, Linder LE, Curelaru I *Anesthesiology* 1992 Feb; 173-86 Neuropathological findings after long-term intrathecal infusion of morphine and bupivacaine for treatment in cancer patients.

[7] San Francisco Chronicle June 9, 2002: Morphine pumps dangerous glitch, Sabin Russell; available at: <http://www.sfgate.com/cgi-bin/article.cgi?file=/chronicle/archive/2002/06/09/MN227684.DTL>

[8] Coffey RJ, Burchiel K *Neurosurgery* 2002 Jan;50(1):78-86; Inflammatory mass lesions associated with intrathecal drug infusion catheters: report and observations on 41 patients.

[9] Raphael J, Southall J, Gnanadurai T, Treharne G, Kitas G. *BMC Musculoskelet Disord* 2002 Jun 20;3(1):17 Long-term experience with implanted intrathecal drug administration systems for failed back syndrome and chronic mechanical low back pain.

[10] http://www.medtronic.com/neuro/paintherapies/pain_treatment_ladder/drug_infusion/risks/drug_risk.html

[11] Aldrete JA, Couto da Silva JM *Eur J Pain* 2000; 4 (4): 361-5 Leg edema from intrathecal opiate infusion.

[12] Bennett G, Serafini M, Burchiel K, Buchser E, Classen A, Deer T, Du Pen S, Ferrante FM, Hassenbusch SJ, Lou L, Maeyaert J, Penn R, Portenoy RK, Rauck R, Willis KD, Yaksh TL. *J Pain Symptom Manage* 2000; 20: S12-36, Evidence-based review of the literature on intrathecal delivery of pain medication.

[13] Sampson FC et al. *Journal of Neurosurgery* 2002; 96: 1052-1057 Functional benefits and cost/benefit analysis of continuous baclofen infusion for the management of severe spasticity.

