

Intrathecal Drug Delivery Therapy with Implantable Pump System in Refractory Cancer and Non-Cancer Pain

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Introduction

Chronic pain is the major cause of discomfort for any patient. Unfortunately there is still a present low efficacy of analgesic drugs to relief neuropathic pain [1]. The intrathecal drug delivery systems (IDDS) have been used for more than 30 years to deliver analgesic drugs into the cerebrospinal fluid and close to their site of action. These systems are being used in patients with both malignant and non-malignant pain. Moreover much smaller doses of drugs are used when they are administered intrathecally and, sometimes, fewer products of the molecule degradation of the drug are obtained through that route thus decreasing their toxicity [2].

Morphine, Ziconotide and Baclofen are the only drugs presently approved for intrathecal use for pain although a number of other off-label drugs are worldwide being used to improve cancer and non-cancer chronic pain.

Rationale for intrathecal analgesic delivery

The discovery that opioid receptors are present to some degree in nearly all of Rexed's laminae of dorsal horn at the spinal cord level, with the highest concentration found in laminae I through III, together with the diffuse poor results obtained with the conventional drugs by oral route opened the door to the development of neuraxial analgesic therapy to treat chronic pain both in cancer and non-cancer patients brought to the opening of new therapeutic avenues with the use of intrathecal administration of drugs. It means that analgesic drugs can be directly delivered to the dorsal horns of the spinal cord where mu-opioid receptors, GABA receptors, acetylcholine and adrenergic receptors are present [3]. Analgesics can thus act both presynaptically and postsynaptically at those sites.

Drugs administered by bolus injection first mix with the surrounding cerebrospinal fluid (CSF) and then are carried by bulk flow both cranially and caudally throughout the neuraxis. This initially produces a high local concentration of the drug, which gradually decreases over time and distance from the injection site. By contrast, continuous slow administration of the drug creates a gradual increase in local concentration until a steady-state level is reached. The concentration profile along spinal canal of a water-soluble (hydrophilic) drug administered into the lumbar subarachnoid space remains constant, with a lumbar: cervical ratio of 4:1, regardless of the concentration of drug administered initially and its rate of delivery [4]. Lipid-soluble (lipophilic) drugs on the other hand, do not diffuse significantly in the CSF and are largely absorbed locally. The concentration of the drug is thus much higher at the site of delivery and drops off above and below this area. In addition, lipophilic drugs are cleared rapidly from the CSF into the systemic circulation,

decreasing their eventual steady-state CSF concentration and increasing their systemic effects.

Patient's selection

The most important inclusion criteria for a patient to be treated with the implant of intrathecal drug delivery system is a chronic pain that is refractory to any other drug administered through ordinary routes. Although there are still no strong and evidence-based indications for this kind of treatment we chose to consider a refractory pain as suggested by Deer et al. in 2014 [5]. Pain is considered to be refractory when properly used multiple evidence-based therapies fail to reach an adequate pain reduction or they produce undesired side effects. The second element to define refractory pain is the coexistence of psychiatric disorders that interfere with the outcome of any analgesic treatment. Moreover as far as patients with cancer are concerned an additional possible high toxicity of antiblastic drugs and intolerance to oral pain-killers have to be taken into account to indicate an alternative intrathecal drug pain treatment [6].

Definite contraindications to the use of intrathecal drug delivery systems is the allergy or intolerance to the drugs selected and to the materials these systems are made of. Additional exclusion criteria are septicemia, local infections close to the implant site and a psychiatric trait of unstable mental disorder [7,8]. Non treated coagulation disturbances are an absolute contraindication. There was a consensus opinion on the contraindication of intrathecal drug delivery treatment in patients showing active substance abuse [7]. Other minor exclusion criteria are related to cardiopathy, diabetes mellitus, immunosuppression, metabolic syndromes.

Method

Every patient should undergo a careful psychological assessment even before a trial for intrathecal drug delivery system implant to assess their expectations for results after a surgical procedure such as an implant of a pump or of a stimulator. The psychological assessment is not applied to patient with malignant pain due to cancer. In these last patients' life expectancy and disease status should be taken into account before any neuromodulation procedure. Although a trial with the administration of intrathecal bolus of both morphine or baclofen have been recommended by the Polyanalgesic Consensus Conference there is still debate over the outcomes of the trial and related clinical decision. Once a patient is submitted to a trial showing remarkable improvement of pain during the day of the trial without undesirable side effects, the indication to implant a drug delivery system can be given. After informed consent the patient is submitted to the surgical procedure that is normally performed under general anaesthesia or, sometimes, under local anaesthesia with a light sedation.

Choice of device

There are two types of intrathecal pumps on the market. The first types of pump do deliver a constant flow of drug solution through the thrust of a pressurized gas chamber pushing the drug reservoir to flow. Any variation in the daily dosage of the drug is operated via a change in the drug concentration of the solution the pump is refilled with. The advantages of this type of pumps are their low price and their low weight. The first advantage has to be considered when implanting a patient with cancer pain and poor life expectancy. The second type of pump consists of a programmable pump. There are two types of pumps on the market with these characteristics. There is a peristaltic MRI compatible pump (SynchroMed II, Medtronic, USA) and a gas-propelled programmable pump (Prometra, USA). Both are totally implantable and can be controlled by telemetry with an external programmer. These pumps are connected with a one or two-pieces catheter that enters the dural sac. One of these catheters is made of a peculiar plastic jacketing to prevent kinking and puncture (Ascenda, Medtronic, USA) while another one has a metal coiling jacket to prevent puncture and kinking (Surestream, Codman, USA).

Surgical procedure

The patient is positioned in park bench position on the slab. Sterile draping to let the lumbar region and the abdominal left quadrant free is performed. The left abdominal quadrant is commonly chosen as that is the region that is normally less involved in further surgeries during life. Should a patient have a peculiar posture or the presence of a PEG access in that region, the contralateral quadrant will be chosen for implant. The pump is refilled with drug solution and programmed according to what observed during the trial test. A catheter is introduced through a Tuohy needle into the intradural lumbar space and the outer end is then connected to a distal catheter previously tunneled from the lumbar incision to an abdominal pocket created at the left abdominal quadrant. CSF flow through the catheter is verified. The distal catheter is then connected to the pump that is inserted into the subcutaneous pocket. Skin sutures complete the procedure that normally takes 20 minutes to be performed.

Precautions with a patient having an intrathecal drug delivery system

If the patient has been implanted with an MRI compatible pump, an MRI examination can be performed at 1.5 T without any problem while if a patient is has to be submitted to an MRI examination with a non MRI compatible pump the system has to be emptied, refilled with saline, rechecked after MRI and refilled with a new drug solution. When the patient has a gas-propelled pump any hyperbaric procedure should be avoided. This should be generally be avoided even with a peristaltic pump to avoid any damage to the rotor. There are no elements against the use of radiotherapy with an implantable intrathecal pump although a shielding of the pump is suggested to avoid any possible damage. Patients with intrathecal drug devices have been submitted to external cardioversion without any damage to the pump.

Refill procedure

Every refill procedure of any pump must be performed under sterile conditions. Special care should be taken during the refilling of the pumps to avoid injection of medication into the catheter access port (leading to direct instillation of high doses of medications into the

intrathecal space) or injection into subcutaneous tissue and programming of parameters of infusion must be done carefully to avoid overdosing and underdosing [9,10]. Serious disability and death may result from intrathecal drug overdose.

Possible complications

The formation of a granuloma at the tip of the intradural catheter has been described during chronic morphine intrathecal delivery and it seems to be dependent on the drug solution concentration used. Catheter dislodgement, fracture or kinking were described mainly when the old conventional type of intradural catheter were used. A low percentage of skin erosion mostly appearing over the implanted pump is reported in the literature. The presence of an occasional seroma around the pump was rarely reported. Hardware failure is rare while undesired side effects and complications due to a human error during refill and programming of the pump have been reported. Hardware failure was reported to be 2.8 times more frequent when off-label drugs were used (Medtronic for Healthcare professionals. MRI information for SynchroMed II pump.) Like all the foreign bodies implanted there is a potential occurrence of infection that ranges from a surface infection of the wounds to meningitis. The infection rate doesn't vary between cancer patients and non-malignant pain patients. Thus an antibiotic prophylaxis is commonly administered before implant.

Choice of a drug

Three are the molecules so far approved for intrathecal infusion: baclofen, morphine and ziconotide. A higher rate of pump failures has been reported when those systems were used with unapproved substances. (US-FDA info on Medtronic pumps, May 2015)

Baclofen

Baclofen is a GABA_A-agonist drug acting at the dorsal horns of the spinal cord giving a marked reduction of spasticity but a poor effect on chronic pain. The experiences reported in the literature over the use of baclofen in patients affected by both spasticity or dystonia and chronic pain would demonstrate that a reduction in pain is secondary to the reduction of spasticity or a reset of a dystonic trait. Thus baclofen should not be considered a drug of first choice in the treatment of chronic pain although its additional contribution in patients undergoing to epidural chronic stimulation for chronic pain has been reported.

Opioids (morphine, hydromorphone, fentanyl, sufentanil)

They act at the dorsal horn level in the spinal cord thus their use through intrathecal drug delivery with a lumbar catheter is recommended and it avoids the spread of opioids at the brain level thus avoiding undesired side effects due to their concentration at the brain level (dizziness, confusion, drowsiness, respiratory depression). Opioids may have additional undesired side effects such as urinary retention, pruritus, myoclonic jerks, constipation, amenorrhea and impotence [8]. The intrathecal administration of opioids have been reported to occasionally give origin to a granuloma at the tip of the catheter that seems to be related to the drug concentration of the solution that is chronically infused [11,12]. These granulomas were reported to resolve after replacement of opioids infusion with saline infusion [13]. The huge amount of cases reported to be on long term therapy with intrathecal morphine showed the effectiveness of the treatment even on very long term although a progressive periodical

daily dosage increase was frequently reported [14,15]. A marked improvement in pain, quality of life and psychological trait has been commonly reported with intrathecal morphine both in non-malignant and malignant chronic pain patients [16,17]. Intrathecal morphine is thus devoted to the oral drug resistant cases of both nociceptive and neuropathic pain. Moreover, recent studies, have demonstrated that a combined therapy with intrathecal ziconotide and morphine gave a rapid control of opioid-refractory cancer pain [18], although there are still poor data related to the use of intrathecal ziconotide for the treatment of chronic neuropathic cancer pain. Morphine has even been used together with Robivacaine for pain management in intractable cancer thus observing a marked decrease of the patients NRS scores with lower dosage of morphine [19].

Hydromorphone seems to have a more powerful analgesic effect than morphine although the rate of side effects is similar. There is no literature reporting data on hydromorphone treatment on long term. As far as fentanyl and sufentanil molecules are concerned these two molecules have a worse spread in the CSF thus a proper positioning of the tip of the catheter for intrathecal administration seems to be crucial to obtain pain controlled where needed [20]. These two molecules have not yet been approved for long-term intrathecal chronic treatment. No literature differentiating the use of these two molecules in both cancer and non-cancer pain is available so far. The addition of local anesthetics such as Bupivacaine to intrathecal morphine did not show any significant improvement in the control of pain [21].

Clonidine

Clonidine is an Alpha-2-agonist molecule used as a sympatholytic agent acting both pre and postsynaptically on descending noradrenergic ways at the dorsal horns. It is supposed to improve the central inhibition of pain but although there are well reported data on its use and efficacy in acute postoperative pain no relevant data are reported on chronic malignant and non-malignant chronic pain with additional side effects such as hypotension, nausea, pruritus, insomnia, sedation, nightmares and depression. Notwithstanding the possible risk of a peak of blood hypertension as a rebound effect after withdrawal.

Ziconotide

Ziconotide is an calcium channel antagonist that was first found in the venom of a marine snail. By blocking the calcium channels at the level of the nervous system thus decreasing both nociceptive and neuropathic pain. This drug has been approved by the FDA for intrathecal use in chronic pain. Side effects are similar to those encountered with morphine although at a higher percentage. Relevant alterations of mood have been described during intrathecal ziconotide treatment. One limitation to the use of ziconotide is the lack of significance of a bolus test due to its latency in response. The latency in response brings to slow and small eventual variations of the daily dosage of ziconotide during chronic treatment. A relevant number of cases on ziconotide had to withdraw the treatment on long term due to a marked increase in adverse events.

Conclusion

Intrathecal infusion devices used for the treatment of refractory chronic cancer and non-cancer pain provide positive long-term outcomes and may have a role as an advanced-stage therapy. The refinement of chronic spinal delivery systems, the discovery of new

intrathecal drugs and the improvements in ability to tailor drug kinetics and control spinal distribution will render the spinal drugs delivery of greater importance and safety.

References

1. Pilat D, Piotrowska A, Rojewska E, Jurga A, Ślusarczyk J, et al. (2016) Blockade of IL-18 signaling diminished neuropathic pain and enhanced the efficacy of morphine and buprenorphine. Mol and Cell Neurosci 71: 114-124.
2. Yaksh TL, Rudy TA (1976) Analgesia mediated by a direct spinal action of narcotics. Science 192: 1357-1358.
3. Hodgson PS, Neal JM, Pollock JE, Liu SS (1999) The neurotoxicity of drugs given intrathecally (spinal). Anesth Analg 88: 797-809.
4. Penn RD (1996) Central nervous system drug infusion for pain. In: Tindall GT, Cooper PR, Barrow DL, The Practice of Neurosurgery. Baltimore: Williams and Wilkins.
5. Deer TR, Caraway DL, Wallace MS (2014) A definition of refractory pain to help determine suitability for device implantation. Neuromodulation 17: 711-715.
6. Stearns L, Boortz-Marx R, Du Pen S, Friehs G, Gordon M, et al. (2005) Intrathecal drug delivery for the management of cancer pain: a multidisciplinary consensus of best clinical practices. J Support Oncol 3: 399-408.
7. Pope JE, Deer TR, Bruel BM, Falowski S (2016) Clinical Uses of Intrathecal Therapy and Its Placement in the Pain Care Algorithm. Pain Pract.
8. Demartini L, Fanfulla F, Bonezzi C, Armiento L, Buonocore M, et al. (2015) Excessive daytime sleepiness in patients on intrathecal analgesia for chronic pain. G Ital Med Lav Ergon 37: 260-267.
9. Sauter K, Kaufman HH, Bloomfield SM, Cline S, Banks D (1994) Treatment of high-dose intrathecal morphine overdose. J Neurology 81: 143-146.
10. Wu CL, Patt RB (1992) Accidental overdose of systemic morphine during intended refill of intrathecal infusion device. Anesth Analg 75: 130-132.
11. Turner JA, Sears JM, Loeser JD (2007) Programmable intrathecal opioid delivery systems for chronic noncancer pain: a systematic review of effectiveness and complications. Clin J Pain 23: 180-195.
12. Brogan SE (2006) Intrathecal therapy for the management of cancer pain. Curr Pain Headache Rep 10: 254-259.
13. Falco FJ, Vikram B Patel, Salim M Hayek, Timothy R Deer, Stephanie Geffert, et al. (2013) Intrathecal infusion systems for long-term management of chronic non-cancer pain: an update of assessment of evidence. Pain Physician 16 (2 Suppl): SE185-216.
14. Duarte RV, Raphael JH, Sparkes E, Southall JL, LeMarchand K, et al. (2012) Long-term intrathecal drug administration for chronic nonmalignant pain. J Neurosurg Anesthesiol 24: 63-70.
15. Kumar K, Kelly M, Pirlot T (2001) Continuous intrathecal morphine treatment for chronic pain of nonmalignant etiology: long-term benefits and efficacy. Surg. Neurol 55: 79-86.
16. Lara NA, Teixeira MJ, Fonoff ET (2011) Long term intrathecal infusion of opiates for treatment of failed back surgery syndrome. Acta Neurochir 108: 41-47.
17. Duse G, Davià G, White PF (2009) Improvement in psychosocial outcomes in chronic pain patients receiving intrathecal morphine infusions. Anesth Analg 109: 1981-1986.
18. de la Calle Gil AB, Peña Vergara I, Cormane Bornacelly MA, Pajuelo Gallego A (2015) Intrathecal ziconotide and morphine for pain relief: a case series of eight patients with refractory cancer pain, including five cases of neuropathic pain. Neurology and therapy 2: 159-168.
19. Huang Y, Li X, Zhu T, Lin J, Tao G (2015) Efficacy and Safety of Ropivacaine Addition to Intrathecal Morphine for Pain Management in Intractable Cancer: Mediators Inflamm 2015: 439014.
20. Guy J, Hindman BJ, Baker KZ, Borel CO, Maktabi M, et al. (1997) Comparison of remifentanil and fentanyl in patients undergoing

- craniotomy for supratentorial space-occupying lesions. Anesthesiology 86: 514-524.
21. Mironer YE, Haasis JC, Chapple I, Brown C, Satterthwaite JR (2002) Efficacy and Safety of Intrathecal Opioid/Bupivacaine Mixture in Chronic Nonmalignant Pain: A Double Blind, Randomized, Crossover, Multicenter Study by the National Forum of Independent Pain Clinicians (NFIPC). Neuromodulation 5: 208-213.

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