Novel additives to neuraxial blockade

Various drugs have been added to the local anaesthetic agents given intrathecally in an attempt to improve on the analgesic effect of the local anaesthetic agent, as well as the duration of analgesia. They range from the accepted to the bizarre. It is difficult to cover all drugs ever injected intrathecally in a short paper such as this one, particularly if one includes drugs injected intrathecally in animal models and that have as yet not been used in humans.

Intrathecal opioids

Intrathecal opioid administration is an attractive analgesic option, since the opioid is injected directly into the cerebrospinal fluid, close to the structures of the central nervous system where the drug acts.

Morphine

The first clinical study testing intrathecal morphine was published in 1979. Since then, this analgesic method has been the subject of a large number of trials and reviews. Morphine, being relatively less hydrophobic than other opioids, remains for a longer time in the cerebrospinal fluid and therefore reaches rostral sites over a longer period than other opioids. Therefore, there is the potential of achieving adequate and long-lasting analgesia with intrathecal morphine. However, this is at the cost of potentially increased risk of adverse effects, especially postoperative respiratory depression, which remains a particular concern.

A review of the use of intrathecal morphine in the British Journal of Anaesthesia came to the following conclusion: “Intrathecal morphine decreases pain intensity at rest and on movement up to 24 hours after major surgery. Morphine sparing is more pronounced after abdominal, than after cardiotoracic surgery. Respiratory depression remains a major safety concern”. However, the doses used in the studies reviewed in this meta-analysis ranged between 250-700 μg, which are fairly large. Despite this, only six cases of respiratory depression (respiratory frequency < 8 breaths/min, or oxygen saturation < 85 %, or the need for naloxone to maintain adequate tidal volume) were documented in three of the 21 trials that monitored respiratory depression. In the first trial, the dose was 300 μg, with postoperative morphine given via PCA. In the second, the dose was 560 μg with intravenous tramadol, or morphine given postoperatively. The third uses doses of 4 000 μg.

The most recent literature suggests that doses as low as 100 μg are just as effective in providing analgesia, but with reduced side-effects. In this paper, it was found that morphine gives excellent postoperative analgesia which is dose related. 200 μg of morphine was found to provide excellent analgesia up to 36 hours post-surgery. The incidence of nausea, vomiting and urinary retention were also dose related, but with no resultant respiratory depression.

Pethidine

Pethidine, a popular opioid for obstetric analgesia, is not commonly used as an adjunct to local anaesthetic for post-Caesarean analgesia. In a study comparing morphine and pethidine intrathecally, it was found that the duration of analgesia for pethidine was 4.93 ± 2.03 hours compared to 23 ± 7.19 hours for morphine. It was found that the incidence of nausea, vomiting, and hypotension was higher with pethidine. However, the morphine group experienced more itching.
None of the patients experienced respiratory depression.

**Sufentanil**

Preoperative intrathecal sufentanil can be used as a booster to achieve rapid and effective analgesia for the immediate postoperative period. The findings in most studies suggest that the opioid requirements are reduced intraoperatively with intrathecal sufentanil, but that the morphine requirements during the first 24 hours post-surgery do not differ significantly in the patients receiving intrathecal sufentanil.7

Side-effects, such as nausea, vomiting and respiratory depression, are less frequent with intrathecal sufentanil when compared with morphine. However, doses greater than 7.5 μg have been shown to be associated with an increased incidence of side-effects.8

**Fentanyl**

As with sufentanil, there is prolongation of the analgesic effect of intrathecal local anaesthetic. However, the onset of analgesic effect with fentanyl is significantly slower than with sufentanil.9 This is attributed to the lower lipophilicity of fentanyl compared to sufentanil. The incidence of side-effects with intrathecal fentanyl are comparable to sufentanil. However, doses higher than 6.25 μg of fentanyl caused increasing incidence of side-effects.10

**Tramadol**

Tramadol, an opioid agonist-antagonist, is known to provide adequate analgesia with less respiratory depression. Animal studies have confirmed the analgesic effect of intrathecally administered tramadol. However, there are not many human studies.

A dose of 10 mg tramadol intrathecally has definite analgesic benefits. This is postulated to be on the basis of interaction with mu receptors in the spinal cord, as well as an additional neurochemical mechanism of inhibiting the uptake of norepinephrine and serotonin, which produces a non-opioid basis of analgesia. The duration of analgesia is not prolonged as in morphine, and is probably in the order of five hours. With doses of 10 mg, there appear to be no significant side-effects.11

**Midazolam**

Since the early 1980s, intrathecal midazolam has been reported to have antinociceptive action.12 Numerous animal studies have demonstrated an effective analgesic action with intrathecal midazolam. Several human studies have demonstrated similar analgesic potential in humans.13

The addition of midazolam to intrathecal bupivacaine potentiated the analgesia of the bupivacaine. The addition of 1 or 2 mg prolongs the postoperative analgesic effect of bupivacaine by approximately 2 hours and 4.5 hours respectively. It is found that the amount of analgesic used postoperatively is reduced in the first 24 hours post-surgery. It appears that the effects are dose dependent.14

In vitro autoradiography has shown that there is a high density of benzodiazepine (GABA-A) receptors in lamina II of the dorsal horn in the human spinal cord, suggesting a possible role in pain modulation.15 An additional mechanism of action may be through delta opiate receptors. The delta-selective opioid antagonist, naltrindole, suppresses the antinociceptive effect of intrathecal midazolam,16 suggesting that intrathecal midazolam is involved in the release of endogenous opioid acting at spinal delta receptors.

Sedation is not observed at doses of 1 and 2 mg.17 However, sedation has been reported at higher doses of epidural midazolam (79-100 μg).18

A serious risk of intrathecal drugs administration is neurotoxicity. Most animal studies have revealed no neurotoxic effects,18,19 although two have observed signs of neurotoxicity.20,21 To date, no clinical signs of neurotoxicity in humans has been reported, but caution needs to be exercised.

**Ketamine**

Ketamine, a phencyclidine derivative, is an N-methyl-D-aspartate (NMDA) receptor antagonist. The activation by excitatory amino acids (glutamate) of spinal dorsal horn NMDA-receptors is believed to play an important role in the development of neuropathic pain, or central sensitisation. Ketamine is a non-competitive antagonist of the NMDA calcium pore and blocks the open calcium channel of the NMDA-receptor complex, thereby inhibiting excitatory transmission by decreasing depolarisation. Through this mechanism, ketamine prevents the development of alleviates, established neuropathic pain arising from the dorsal horn wind-up phenomenon.

The advantage of intrathecal ketamine is the lack of cardiovascular depression.22 The main drawbacks of intrathecal ketamine anaesthesia are the
frequency of psychomimetic reactions, inadequate motor blockade and short duration of action. When combined with intrathecal midazolam, the incidence of psychomimetic reactions is reduced.

Once again, concern has been expressed about neurotoxicity after neuraxial ketamine, because spinal myelopathy has been reported with intrathecal injection of large doses. However, in animals and humans, there is no evidence of neurological injury after repeated intrathecal injection of preservative-free ketamine in lower doses. Importantly, co-administration of a GABA-receptor agonist prevented these effects.

**Neostigmine**

Intrathecal neostigmine produces analgesia in animals and humans, but its side-effects, including nausea and vomiting, limit its use in clinical practice. Nevertheless, studies have shown that small doses of neostigmine (50 μg) can enhance sensory anaesthesia with few side-effects when combined with small-dose bupivacaine spinal anaesthesia.

Intrathecal neostigmine prolongs the effect of spinal anaesthesia in terms of both the duration of complete analgesia and the time until post-operative analgesia is requested. But it does so less effectively than morphine. Motor block may also contribute to the residual analgesia found with neostigmine.

Doses of 10 μg intrathecally have produced analgesia in patients undergoing Caesarean section, vaginoplasty and below knee orthopaedic surgery, but, in contrast, 100 μg of intrathecal neostigmine was unable to provide adequate analgesia for more painful surgery such as abdominal hysterectomy. It seems that the dose dependency of intrathecal neostigmine-induced postoperative analgesia depends on the nature of the noxious stimulus, the type of anaesthesia used, the methods of analgesic administration and the assessment of analgesic effect.

**Clonidine**

Intrathecal clonidine provides analgesia by acting on specific alpha2-adrenergic receptors located on the dorsal horn of the spinal cord. Intrathecal clonidine has been found to prolong the analgesic effect of intrathecal local anaesthetic agents by about six to 12 hours. In addition, many reports have shown an interaction between opioids and alpha2-adrenergic receptor agonists that is either synergistic or additive.

Additionally, intrathecal clonidine appears to have antihyperalgesic properties. As hyperalgesia is the physiological expression of central nervous system sensitisation, it may be useful in preventing the increased risk of patients with severe post-operative pain and central sensitisation from developing persistent, long-term or chronic pain after surgery.

The commonly used doses are in the range of 150-300 μg. However, clonidine intrathecally causes marked sedation in doses greater than 150 μg. It is found that there is a dose-dependent prolongation, of both the sensory blockade of spinal anaesthesia and the pain-free interval until the first request for supplemental analgesia, in the range of 75-150 μg. Patients receiving 150 μg in addition show a prolonged motor block. In this dose range, haemodynamic stability is generally maintained, but caution needs to be exercised in the pregnant patient.

**Cyclooxygenase inhibitors**

The role of spinal cyclooxygenase and prostaglandins in nociceptive processing has been examined, and reported on in many publications. Relevant findings include that constitutive expression of cyclooxygenase-1 and -2 in the spinal cord and up-regulation of cyclooxygenase-2 (primarily) and cyclooxygenase-1 occurs after peripheral injury, with release and production of spinal prostaglandins. Intrathecal injection of prostaglandins are found to cause hyperalgesia and allodynia. Targeted inhibition of spinal cyclooxygenase may be a viable strategy for treating pain in humans.

The pharmacokinetics of ketorolac in cerebrospinal fluid and spinal tissue are largely unknown, but data obtained in dogs suggest fast elimination and delayed tissue uptake. Continuous infusion of intrathecal ketorolac may be a more effective strategy than bolus administration.

Future studies will need to determine whether intrathecal NSAIDs have any role in pain management. It appears that pain conditions associated with significant inflammation may respond better. In chronic pain, this may include cancer-related pain or certain forms of neuropathic pain.

**Propofol**

Propofol's effects are thought to be mediated by GABA receptors, voltage-dependent sodium channels, or cannabinoid receptors in the central nervous system. These receptors also exist in...
the spinal cord and they play a crucial role in nociception.

Further studies need to be performed to show the benefit of intrathecal propofol in humans.

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