



Update on adjuvants in regional anaesthesia

LENNART CHRISTIANSSON

Consultant, Department of Surgical Sciences
Anesthesiology & Intensive care
University Hospital, 751 85 Uppsala, Sweden
E-mail: lennart.christiansson@surgsci.uu.se

Abstract

This is a review article on adjuvants to neuroaxial anaesthesia and peripheral nerve blocks used in clinical practice: opioids, vasoconstrictors, clonidine, NMDA antagonists, midazolam, glucocorticoids, nonsteroidal anti-inflammatory drugs and neostigmine. Mechanism and site of action of each of them is described. It is followed by discussion of experimental and clinical data published in the last five years.

INTRODUCTION

The suggestion that regionally applied opioids might be effective as analgesics dates back to the mid nineteenth's century when morphine was injected perineurally. For many years to come, the site of action of opioids was thought to be in the brain only. The first report on opioids for intrathecal anaesthesia was published in 1901 and on epidural morphine in 1979 (1). The existence of specific opioid receptors in the spinal cord and a segmental distribution of opioid analgesia were reported in the 70'ies. In addition to the direct spinal action, morphine conveys descending pathway inhibition by its influence on the periaqueductal grey matter and rostral ventromedial medulla (2). Analgesia produced by neuraxial opioids alone, or as adjuvants to local anaesthetics, has been demonstrated for acute postoperative pain, obstetric, paediatric, and cancer pain (3).

Besides morphine a number of different opioides and other adjuvants have been introduced to improve the efficacy of neuraxial/regional analgesia, including NMDA antagonists (ketamine, magnesium), GABA agonists (midazolam) and adrenergic agonists (clonidine, adrenaline), COX-inhibitors (ketorolac), Ach-esterase inhibitor (neostigmine) etc. (4). This review is based on articles published during the last five years.

OPIOID ADJUVANTS

Mechanism of opioid action and receptor types

Afferent noxious stimuli converge in the dorsal horn of the spinal cord, where the primary nociceptive neuron synapses with the wide dynamic range interneurons and the second order nociceptive neuron in the spinothalamic tract. Agonism of these opioid receptors helps to suppress afferent nociceptive input from pain sites via modulation of the release of pain-pathway associated peptides (5).

Opioids produce analgesia by mimicking the actions at specific receptors of endogenous opioid peptides, including met-enkephalin, beta-endorphin, and dynorphin. The three main types of opiate receptors,

each with its own subtypes, are mu (μ), delta (δ), and kappa (κ) (6). The most important target for opioids is the μ -receptor (endorphin), and intrathecal opioids appear to selectively modulate C- and A-fibres with minimal impact on dorsal root axons. The enkephalins are the primary endogenous ligands of the δ receptor and are involved with spinal analgesia. Dynorphin is the prototypic ligand for the κ receptor. Activation of the κ receptor results in segmental spinal analgesia and sedation. Most of the mixed agonist- antagonist opioids (e.g., buprenorphine) bind to the κ receptor.

Any drug given intrathecally rapidly redistributes within the CSF; opioid is detectable in the cisterna magna after lumbar intrathecal administration within 30 min, even with lipophilic drugs like sufentanil.

The lipophilic opioids rapidly traverse the dura where they are sequestered in the epidural fat and enter the systemic circulation; they also rapidly penetrate the spinal cord where they bind to both non-specific sites within the white matter as well as dorsal horn receptors and eventually enter the systemic circulation as they are cleared from the spinal cord. This rapid transfer from the CSF to both spinal cord and the epidural fat explains the rapid onset and the prompt decline in CSF levels of lipophilic opioid, accounting for the minimal rostral spread, lack of delayed respiratory depression, and relatively small dermatomal band of analgesia seen during chronic administration (7).

Morphine, the prototypic hydrophilic opioid, undergoes a similar transfer to both the spinal cord and the epidural space; however, there is limited binding to fat within the epidural space and limited binding to non-specific receptors within the spinal cord white matter. Transfer to the systemic circulation is likewise slower than for the lipophilic drugs (8).

Cephalad spread

Despite decades of use, controversy remains regarding the extent and time course of the cephalad spread of opioids in cerebrospinal fluid (CSF) after intrathecal injection. Eight healthy volunteers received intrathecal injection of morphine plus fentanyl at a lower lumbar interspace (9). CSF was sampled through a needle in an upper lumbar interspace for 60–120 min. At the end of this time, a sample was taken from the lower lumbar needle, and both needles were withdrawn. Fentanyl was found to be more rapidly cleared from CSF than morphine, although their initial distribution in the first hour after injection did not differ greatly. The pharmacokinetic model demonstrates that mixing is the primary determinant of early concentrations and is highly variable among individuals. Morphine moved cephalad with similar rapidity to fentanyl in this study, and its slow onset for analgesia presumably reflects slow penetration into spinal cord tissue rather than major differences in movement in CSF (9).

Site of action

In a study by Bernardis the residence time of hydrophobic opioids in the epidural space was prolonged (10). This is consistent with the findings in multiple human studies having shown that epidurally administered alfentanil, sufentanil, and fentanyl produce little, if any, of their postoperative analgesic effects via a spinal mechanism. They have negligible access to the spinal cord because of sequestration and/or rapid vascular uptake from the epidural space. Epidural pharmacokinetics did not predict CSF pharmacokinetics. The reason(s) behind this apparent dissociation is unclear. It may be that the opioids accumulate to varying degrees in intervening barriers (e.g., dura mater, arachnoid mater, epidural fat) and that their CSF pharmacokinetics are dependent on their pharmacokinetics in these tissues as much as on their pharmacokinetics in the extracellular fluid of the epidural space. The study confirmed that after epidural administration, morphine has much greater bioavailability in the spinal cord than alfentanil, fentanyl, and sufentanil (10).

Site of action and bolus vs infusion

Most published studies suggesting that epidural fentanyl acts predominantly at spinal sites administered the drug as a bolus injection, whereas most studies suggesting that it acts predominantly at supraspinal sites administered the drug as an infusion. Ginossar tested the hypothesis that the mode of administration (bolus versus infusion) of epidural fentanyl determines its site of action (11).

Ten healthy volunteers were enrolled in this randomized, double-blinded, cross-over study. On separate study days, fentanyl was administered into the epidural space as a bolus and as an infusion. Using a thermal and electrical experimental pain model, the heat and electrical current causing maximum tolerable pain were assessed repetitively. Plasma fentanyl concentrations were determined throughout the study. Epidural bolus administration of fentanyl resulted in segmental analgesia, whereas the epidural infusion of fentanyl produced nonsegmental analgesia. There was a significant linear relationship between the analgesic effect and the plasma concentration of fentanyl for the epidural infusion but not for the epidural bolus administration of fentanyl. Bolus administration resulted in significant segmental analgesic effects, whereas the infusion produced significant systemic analgesic effects. These findings might explain the apparent conflict in the literature regarding the site of action of epidural fentanyl (11).

Even if this study indicates that epidural fentanyl acts predominantly at spinal sites if administered as a bolus and at supraspinal sites if administered as an infusion, there are pharmacokinetic concerns (8). In an editorial, the fact that plasma concentrations corresponded with the analgesic effect of infusion but not bolus administration was called into question. The central argument that the editors present is that, given larger bolus doses, more fentanyl is likely to be distributed into the fatty tissues and be subsequently absorbed systemically. However,

larger bolus doses were not tested in the study and the dose administered in this manner was three times less than that administered by infusion (8). The editors postulated that, had bolus doses reached those of the infusion, the same linear pattern between plasma concentration and analgesia would emerge.

Ginosar's paper does not exclude the 'dual sites' theory, which suggests that epidurally administered opioids act both spinally and supraspinally with a reinforcing action, as this phenomenon would only become apparent when higher doses are used (11). Ginosar *et al.* suggest that the concentration gradient between the epidural and the intrathecal space is much larger after bolus administration than during an infusion, and that with a larger gradient more fentanyl is likely to be driven into the intrathecal space and thus reach the dorsal horn in sufficient quantities to elicit spinal analgesia. Large gradients are not generated during continuous infusion and thus the drug is redistributed to the systemic circulation. Although no studies appear to have investigated the amount of opioid required to set up a sufficient gradient, a threshold concentration of 10 µg/ml has been suggested. If an epidural opioid is administered via an infusion, and the concentration fails to equal or exceed this 10 µg/ml, then it is most likely that the opioid is producing analgesia via a supraspinal mechanism. Given that the vast majority of postoperative epidural regimes employ low-concentration infusions, it appears that these regimens are not capable of producing spinally mediated analgesia (8).

Spinal opioids and local anaesthetics in synergy

Spinal opioids and local anaesthetics have been shown to act synergistically at the spinal level in animal studies (12). Joris therefore tested the hypothesis that sufentanil requirements will be less when given epidurally than IV in patients simultaneously given epidural bupivacaine after major abdominal surgery. In a randomized, double-blinded fashion, the sufentanil was given either epi-

durally or IV. Pain scores, extension of sensory block, and the incidence of side effects did not differ between the two groups, but consumption of sufentanil in the epidural group was half that of the IV group. It was concluded that spinal mechanisms contribute to the analgesia produced by epidural sufentanil in combination with a local anaesthetic (12).

The advantage of combining the two types of agents in this manner is thought to be explained by their different analgesic properties and their ability to block pain at two different sites. Opioids produce analgesia by specifically binding and activating the opiate receptors in the substantia gelatinosa, whereas local anaesthetics provide analgesia by blocking impulse transmission at the nerve roots and dorsal root ganglia. When lipophilic opioids are injected into the epidural space as a bolus their systemic absorption pattern is biphasic. The initial 'portion' of the dose is absorbed relatively rapidly into the blood stream and quickly reaches the supraspinal centres, whereas the remaining 'portion;' is initially distributed into the fatty tissues in the epidural space and is then absorbed into the blood stream more slowly, typically over the course of several hours. In the absence of a plausible physiological explanation for synergistic action, it seems far more likely that the local anaesthetic provides a degree of spinal, segmental analgesia while, simultaneously, the opioid is systemically absorbed and provides additional analgesia supraspinally (8).

Summary of neuraxial opioid pharmacokinetics

The two tables contain data extracted from the literature regarding pharmacokinetic properties and dose recommendations for acute non-malignant pain treatment:

Synergistic interactions between α_2 -adrenergic and opioid receptors

Both α_2 -adrenergic and opioid receptors (α_2 ARs and ORs) mediate diverse physiological functions, including

TABLE 1

Epidural opioid analgesia regimens – Compiled data from the literature.

Opioid	Lipid Solubility	Dose range	Onset (min)	Duration (hrs)	Continuous Infusion
Morphine	~1	1–5 mg	30–60	12–24	0.1–1 mg/hr
Fentanyl	~800	50–100 µg	5–10	2–4	10–50 µg/hr
Sufentanil	~1800	10–30 µg	5	2–3	2–10 µg/hr

TABLE 2

Intrathecal opioid analgesia regimens – Compiled data from the literature.

Opioid	IV/IT Ratio	Dose range	Onset (min)	Duration (hrs)	Continuous Infusion
Morphine	2–300:1	0.1–0.5 mg	30	18–24	?
Fentanyl	10–20:1	5–25 µg	5	1–4	5–20 µg/hr
Sufentanil	10–20:1	2–10 µg	5	2–6	1–5 µg/hr

analgesia. Several reports have described enhanced **opioid-mediated** spinal antinociception following co-administration of low doses of α_2 AR agonists (13). Furthermore, it has been shown extensively through both behavioural and electrophysiological methods that co-activation of α_2 ARs and ORs produces synergistic interactions in the spinal cord. The mechanisms underlying this phenomenon have yet to be characterized. These aspects of analgesia may be important in managing chronic, opioid-insensitive pain because synergy-enabled decreases in dose may mitigate the unwanted side effects observed clinically (14).

Experimental data

It has been shown that both morphine and fentanyl have direct spinal action (15). In a recent study, Goodchild investigated the spinal cord actions of morphine given intrathecally to rats in a model that allows definition of drug action at the spinal cord level. This model has been used previously to show that fentanyl, a selective μ -opioid agonist, can cause antinociception after intrathecal injection by actions at spinal cord μ -opioid receptors (15). The opioid receptors were investigated by giving intrathecal antagonists selective for receptor sub-types at doses that produced 100% suppression of spinally mediated antinociception caused by drug actions at those receptors. The authors concluded that the antinociceptive effects following intrathecal morphine involve spinal and supraspinal opioid receptors. They also pointed out that the tail flick effect, frequently described in experiments with morphine administration to rats with an intact neuraxis, involves actions at opioid receptors in the brain that override any action that may be caused by combination of morphine with μ -opioid receptors in the spinal cord. This observation can be useful when interpreting other studies as well.

An experimental study by Chen provides new functional evidence that systemic morphine inhibits dorsal horn projection neurons through direct activation of spinal μ opioid receptors (16). Their data suggest that inhibition of spinal dorsal horn neurons, by activation of the local spinal cholinergic circuitry after systemic morphine, is independent of supraspinal descending pathways. This new information can prove important for our understanding of the role of spinal μ opioid receptors and cholinergic system in the analgesic action of systemic opioids. A study by Yamada demonstrated that morphine could produce thermal antinociception via the kappa opioid receptor in the spinal cord in the absence of the mu opioid receptor (17). The finding that the kappa receptor is a molecular target of morphine at higher doses suggests that the kappa receptor may play a role in the analgesia of high-dose morphine regimens used in cancer pain treatment.

It is possible that systemic morphine-induced increase in serotonin level in spinal cord activate 5-HT₇ receptors localized on inhibitory enkephalinergic or GABAergic interneurons that then evoke the release of enkephaline or GABA. This may then in turn inhibit nociceptive

transmission at sites either presynaptic or postsynaptic to the terminals of primary afferent fibers. The results of a recent study by Dogrul support the notion that systemically administered morphine activate the descending serotonergic pathways, and that 5-HT₇ receptors in the spinal cord play an important role in the systemic morphine antinociception (18).

Neuroplasticity and opioid-induced hyperalgesia

Fear of uncontrolled postsurgical pain is a major concern of patients undergoing surgery. Another concern is the more recent documentation of hyperalgesia with very high opioid doses. In some patients, even short-term opioid use may lead to opioid-induced hyperalgesia. Distinguishing between this condition and pharmacological tolerance has significant implications for managing postoperative pain (19). Sakurada reviews the potential mechanisms of spinally mediated nociceptive behaviour evoked by intrathecal morphine at high concentrations. The mechanism of action is still unclear but an intrathecal administration of morphine in a high concentration results in an increased release of substance P and glutamate from the primary afferents in the dorsal horn of the spinal cord (20). The increased levels of neurotransmitters could activate NK1 and NMDA receptors in the post-synaptic neurons. Morphine-3-glucuronide has also shown to act as a functional antagonist of the antinociceptive activities of morphine and morphine-6-glucuronide. It is therefore plausible that allodynia and hyperalgesia evoked by spinal morphine at a high concentration may result from an increasing accumulation of morphine-3-glucuronide in the spinal cord.

Peripheral mechanisms of pain and analgesia

In the late 1980s evidence began to accumulate that the antinociceptive effects of opioids can be mediated by peripheral opioid receptors located on sensory neurons (13). Several studies indicate that a substantial proportion of the analgesic effects produced by systemically administered opioids can be mediated by peripheral opioid receptors (17, 21, 22, 23). In addition, human studies indicate that opioid agonists that do not readily cross the blood-brain barrier are beneficial in patients with visceral and neuropathic pain and can have the same analgesic efficacy as conventional opioids. Thus, the analgesic efficacy of peripherally active opioids may be utilized under conditions of acute and chronic pain with the benefit of reduced side effects.

Research in the last three decades has proven the existence of opioid and other receptors for excitatory and inhibitory peptides at afferent nerve terminals in peripheral tissues (3). The complex interaction of these receptors with endogenous and exogenous compounds, inflammatory and immune responses, and sympathetic nerve endings continues to be elucidated. Targeting nociception with peripheral regional anaesthetic techniques will have application for the treatment of acute

postoperative pain. All three classical subtypes of opioid receptors have been demonstrated in peripheral tissues in afferent nerve terminals. Several clinical studies exist that demonstrate peripheral opioid analgesia following intraarticular opiate injection for knee surgery. A reviewer of this work concluded that morphine had a definite but mild benefit lasting 24 hours, exceeding any expected systemic effect. Clinical studies also exist on the effect of opioids injected perineurally (4, 22). The two aspects studied have been whether there is a statistically significant benefit of perineural opioid on sensorimotor block (intraoperative anaesthesia) or analgesia (postoperative) and also its extent and duration. The evidence so far has been inconclusive because of study design. With few exceptions, the studies were not done in such a way as to exclude a systemic opioid effect or central spread of the injected opioid to receptors on the dorsal root ganglia or the neuraxis. Another design weakness was that the systemic morphine control patients received an IV bolus, though an IM injection might more closely mirror or exclude a systemic effect of a perineural morphine injection.

Tramadol

The central and peripheral analgesic effects of tramadol have not been fully explained but it is a selective agonist of μ -receptors, many times weaker than morphine. Tramadol also prevents reuptake of noradrenaline and enhances both serotonin and noradrenaline release. The monoaminergic activity of tramadol increases the inhibitory activity of the descending pain pathways, resulting in a suppression of nociceptive transmission at the spinal level.

Only few studies have investigated the effect of tramadol added to peripheral plexus blockade, but the conclusion was that the addition of 100 mg tramadol to brachial plexus anaesthesia prolongs the duration of the sensory and motor block significantly. In one study there was a control group receiving the same amount of tramadol IV to exclude a central effect as a result of systemic absorption. With the potential for doses of tramadol other than 100 mg to provide analgesia, Robaux designed a double-blind RCT to study the dose-effect relationship and determine the optimal dose of tramadol added to brachial plexus anaesthesia for carpal tunnel release surgery (25). All 100 patients received 1.5% mepivacaine 40 mL plus a study solution containing either isotonic sodium chloride or tramadol (40 mg, 100 mg, 200 mg). This study suggests that tramadol added to 1.5% mepivacaine for brachial plexus block enhances in a dose-dependent manner the duration of analgesia with acceptable side effects. However, the authors pointed out that the safety of tramadol has to be investigated before allowing its use in clinical practice.

The results of a prospective, randomized, double-blind study by Kesimci demonstrated that the addition of 100 mg of tramadol to ropivacaine for axillary brachial plexus block did not improve the speed of onset of block or increase the duration of sensory or motor block or

post-operative analgesia (26). The lack of analgesic effect could be related to the choice of a long-acting local anaesthetic (ropivacaine) at a dose (40 ml, 7.5 mg/ml) that provides a long duration of analgesia, which could have masked any potential peripheral analgesic effect of tramadol 100 mg on the nerve block. Kaabachi studied 102 patients scheduled for hand surgery under axillary block with lidocaine 1.5% (epinephrine 1/200,000) and the addition of either saline or tramadol (100 mg, 200 mg) (27). The authors report that 200 mg tramadol prolonged both intraoperative blocks and postoperative analgesia in this setting. However, a high dose of tramadol (200 mg) was also associated with a delayed onset of anaesthesia. In another dose-ranging study, 200 mg tramadol added to mepivacaine 1.5% in axillary block prolonged only duration of postoperative analgesia and did not increase the onset time of anaesthesia. The discrepancy between these findings and those of Robaux *et al.* may be related to several differences in the study design, such as nerve stimulation technique, definitions of the onset time, the quality of sensory block and the surgical procedures as such (25).

The currently available data concerning the use of opioids (including tramadol) as adjuvants for plexus or peripheral blocks are limited and further studies of high quality are required before definitive recommendations can be made.

NON-OPIOID ADJUVANTS

Vasoconstrictor

It has been assumed that epinephrine's primary mechanism of action is to reduce drug clearance from the epidural space via local vasoconstriction. Decreased clearance is not the only possible explanation for the lower local anaesthetic peak plasma concentrations. This could also result from an epinephrine-induced increase in clearance from plasma or an increase in volume of distribution. Because systemic absorption of epinephrine from the epidural space produces a significant increase in cardiac output it is not unreasonable to expect that plasma clearance may be increased because of more rapid drug delivery to the liver or kidneys. In a recent study by Bernards, however, an equivalent dose of intramuscular epinephrine had no effect on the plasma pharmacokinetics of any of the study drugs (28).

Because the effects of epinephrine on blood flow are concentration dependent, one would expect epinephrine to reduce blood flow in tissues in which it was present at high concentrations (vasoconstriction) and increase flow in tissues in which it was present at low concentrations (vasodilatation). It is also important not to draw direct comparisons between the behaviour of local anaesthetics and opioids in the epidural space, because local anaesthetics, unlike opioids, can themselves increase local blood flow and thereby increase their own elimination. This ability may explain why the effects of epinephrine on local anaesthetic pharmacokinetics are more dramatic than those on opioids. After local anaesthetic infiltration into

tissue, blood vessels dilate (procaine > prilocaïne), resulting in increased blood flow to the site, which can lead to a higher rate of absorption of local anaesthetic into the circulation. Some local anaesthetics, on the other hand, demonstrate vasoconstriction in clinical use (cocaine, mepivacaine, ropivacaine). The addition of a vasoconstrictor (e.g. epinephrine) may further decrease the plasma concentration of these local anaesthetics, permitting use of higher doses of local anaesthetic.

The effect on duration of local anaesthetic action is variable, based on the agent used. Local anaesthetics with shorter durations of effect (lidocaine and procaine) demonstrate a greater degree of prolongation with the addition of 1:200,000 epinephrine compared with longer-acting anaesthetics (eg, ropivacaine). Addition of epinephrine has also been shown to increase the speed of onset of a regional block, along with increasing the depth of block.

Förster studied whether epinephrine 4 µg/mL improves the efficacy of ropivacaine-fentanyl lumbar epidural analgesia (LEA) after total knee arthroplasty (29). As part of the multimodal pain treatment used, the epidural adjuvant epinephrine (12–32 µg/h) did not improve LEA after total knee arthroplasty. The present findings contrast studies in which epinephrine as an adjuvant to thoracic epidural analgesia has proven beneficial.

Another aspect is that hydrophilic drugs are cleared from the epidural space by a different route than are very lipid-soluble drugs and that epinephrine affects clearance from these sites differently. If epinephrine affects epidural fat blood flow differently from dura blood flow, then one would expect epinephrine to affect the clearance of drugs that partition preferentially into epidural fat differently from drugs that do not. Epinephrine may not attain high enough concentrations in epidural fat to produce vasoconstriction. Instead, because of its hydrophilicity, epinephrine might be present in such relatively low concentrations in the epidural fat that it causes vasodilatation through α_2 -adrenergic receptors.

Not to forget is the fact that epinephrine itself is analgesic in the spinal cord via its activation of α_2 -adrenergic receptors.

Clonidine

The central α_2 -adrenergic agonist clonidine also inhibits nociceptive impulses by activating postjunctional α_2 -adrenoceptors in the dorsal horn of the spinal cord. This kind of receptors are located on primary afferent terminals (both at peripheral and spinal endings), on neurons in the superficial laminae of the spinal cord and within several brainstem nuclei implicated in analgesia. Clonidine enhances and prolongs sensory and enhances motor blockade from local anaesthetic used for epidural or peripheral nerve block (25). A postulated mechanism for this is that clonidine blocks conduction of C and A-delta fibres and increases potassium conductance in isolated neurons in vitro, thus intensifying conduction block. Secondly, clonidine causes local vasoconstriction

in the clinical setting, thereby reducing vascular uptake of local anaesthetic from around the neural structures. The α_2 -adrenergic agonists also enhance analgesia from intraspinal opioids by interactions both pre- and post-synaptically within the spinal cord. Neuraxial administration of clonidine also has a local effect on sympathetic nerves in the spinal cord. The clinical use of intrathecal clonidine is hampered by the side effects of sedation, bradycardia, and hypotension; whereas up to 150 µg of clonidine added to plexus blocks would prolong analgesia without increasing side effects.

An experimental study by Wolff was designed to investigate the local anaesthetic-like action of clonidine in superficial dorsal horn neurones (32). The superficial laminae contain important structures for pain transmission, receiving most of their primary sensory input from Ad and C fibres. It was shown that clonidine suppresses the generation of action potentials in tonic-firing spinal dorsal horn neurones, and that clonidine therefore could contribute to analgesia during local anaesthesia.

Dobrydnjov performed a double-blinded RCT of analgesia in patients having clonidine added to local anaesthetic during combined spinal-epidural anaesthesia for hip arthroplasty. Low-dose intrathecal clonidine provided a better quality of anaesthesia and longer-lasting analgesia (33). Epidural clonidine-ropivacaine infusion resulted in improved postoperative analgesia but was associated with a moderate decrease in blood pressure. Also the addition of intrathecal clonidine 15 µg to bupivacaine during combined spinal-epidural anaesthesia provided a higher quality of anaesthesia and longer lasting analgesia than bupivacaine alone. More dose-finding studies are needed in order to find the most effective dose in relation to side effects.

In a study by Kaabachi clonidine 1 µg/kg was used as an adjuvant to plain bupivacaine for spinal anaesthesia in adolescents. The addition of clonidine prolonged the duration of sensory block achieved with bupivacaine by 30 min and postoperative analgesia by 120 min without severe adverse events (34).

Bhatnagar *et al.* evaluated the effect of clonidine as an adjuvant to bupivacaine for continuous paravertebral nerve block. The authors concluded that using clonidine as an adjunct improves pain relief after thoracotomy, but hypotension and sedation are adverse effects interfering with its clinical application. The study did not rule out that systemically absorbed clonidine may have contributed to this (35).

There is little knowledge of the pharmacokinetics of local anaesthetics and adjunctive analgesics after paravertebral blockade. Pharmacokinetic data may help distinguish between a local or systemic site of action. Burlacu evaluated the pharmacokinetics of low-dose levobupivacaine, fentanyl, and clonidine after paravertebral analgesia for breast surgery (24). In this study, patients received opioid-free general anaesthesia and postoperative clonidine patient-controlled analgesia. In conclusion, after paravertebral bolus and infusion administration fentanyl

and clonidine in paravertebral block results in Cp_{max} concentrations less than the effective levels for these drugs when systemically administered. This would suggest but not prove that their mechanism of action is at least partly attributable to a local effect.

Kaabachi studied 98 children, scheduled for elective outpatient herniorrhaphy or orchidopexy, that were randomly allocated to receive an ilioinguinal–iliohypogastric bupivacaine nerve block either with or without 1 µg/kg clonidine (30). The study failed to demonstrate any advantage of adding clonidine to bupivacaine for ilioinguinal–iliohypogastric nerve block.

In axillary plexus block, some studies have shown that clonidine prolongs the local anaesthetic block whereas other trials found contrasting results (36). Duma *et al.* therefore studied clonidine as an adjuvant to local anaesthetic in axillary brachial plexus block. The results showed no significant difference in onset of motor or sensory block when plain local anaesthetic was compared with anaesthetic plus clonidine in axillary brachial plexus. With regard to prolongation of block, it is interesting to note that clonidine is recommended by many to prolong duration of axillary plexus block.

In a qualitative systematic review of the literature by McCartney the question was asked whether we should add clonidine to local anaesthetic for peripheral nerve blockade (37). Of the 27 studies reviewed, only 5 studies included a systemic control group. The total number of patients reviewed was 1,385. The dose of clonidine varied from 30 to 300 µg. Overall 15 studies supported the use of clonidine as an adjunct to peripheral nerve blocks with 12 studies failing to show a benefit. Based on qualitative analysis, clonidine appeared to prolong analgesia when added to intermediate-acting local anaesthetics (such as mepivacaine and lidocaine) for some peripheral nerve blocks (single shot axillary and peribulbar nerve blocks). Side-effects appear to be limited at doses up to 150 µg. It was also concluded that evidence is lacking for the use of clonidine as an adjunct to local anaesthetics for continuous catheter techniques, and that further research is required to examine the peripheral analgesic mechanism of clonidine. Despite some evidence for clonidine as an adjunct in other upper and lower limb blocks too few studies are available to make definitive conclusions.

The inclusion of a systemic control group is important in determining if clonidine has a peripheral or a systemic effect. Five studies in the review included a systemic control to investigate if clonidine had a local as opposed to systemic effect. Three studies were supportive of a purely peripheral analgesic effect of clonidine and two were negative.

Huang studied dose–response of epidural clonidine for postoperative pain after total knee arthroplasty (TKA) (38). The main finding of this randomized study was that the optimal epidural clonidine concentration in a morphine and ropivacaine solution after TKA was 1.0 µg/mL. This combination resulted in excellent pain re-

lief during the 72 h period after surgery and was not accompanied by significant hypotension or sedation. Motor and sensory blockade effects of local anaesthetics were enhanced by clonidine, and effects on the prolongation of sensory nerve blockade were clearly dose-dependent. However, an earlier study has demonstrated that addition of clonidine to local anaesthetic for continuous femoral nerve blockade can delay the recovery of motor function as well.

In a systematic review of randomized trials, Elia studied clonidine as an adjuvant to intrathecal local anaesthetics for surgery. In conclusion, adding clonidine to intrathecal local anaesthetics for surgery increases the duration of the motor block, improves intraoperative analgesia, and delays the regression of the sensory block and the time to first analgesic request. For some of the reported effects, there is evidence of dose-responsiveness, for others, there is not. None of these outcomes are likely to last longer than 2 hours, why the clinical relevance will be depending on the context. The most prominent adverse effect is intraoperative hypotension (31).

NMDA antagonists

L-glutamate is perhaps the most important excitatory neurotransmitter in the central nervous system. Blocking the NMDA subtype of glutamate receptor offers an attractive method of reducing afferent stimulation of the spinal cord and therefore blocking pain transmission. The primary reason for the restricted use of NMDA antagonists as postoperative analgesics is that at efficacious doses they can produce cerebral side-effects such as hallucinations. Magnesium ion was first identified as an inhibitor of NMDA receptors in the spinal cord. Ketamine produces central antinociception through the same mechanism, but may also enhance analgesia through various other mechanisms, such as interaction with spinal opioid receptors, α₂-adrenoreceptors, cholinergic and serotonergic system. Large doses of ketamine given intrathecally may have neurotoxic potential in humans. Epidural preservative-free ketamine, added to opioid-based epidural analgesia, can improve pain relief without increasing side effects.

The admixture of magnesium to prilocaine for axillary brachial plexus block provided a pronounced prolongation of sensory and motor block without side effects as studied by Gunduz (39). Magnesium has shown antinociceptive effects in both animal and human pain models. These effects are primarily based on the regulation of calcium influx into the cell and antagonism of the N-methyl-D-aspartate receptor. A significant difference in duration of sensory block occurred between the 100-mg and 150-mg perineural magnesium groups.

In a study by Turan it was concluded that the addition of magnesium to lidocaine in IVRA demonstrated decreased intraoperative fentanyl consumption and pain associated with the tourniquet (40). It also shortened sensory and motor block onset times, prolonged sensory and motor block recovery times, and improved the qual-

ity of anaesthesia while prolonging the time to the first postoperative analgesic requirement. The side effect seen with magnesium is injection pain. The authors claimed that the addition of magnesium to a local anaesthetic in IVRA is effective, but they also stressed the importance of performing further studies before recommending its routine use.

The efficacy of magnesium sulphate as an adjuvant to lidocaine for intravenous regional anaesthesia for upper limb surgery was evaluated by Narang in a prospective, randomised and double-blinded study (41). It was shown that adding the adjuvant hastened the onset of sensory and motor block and decreased tourniquet pain as judged by improved VAS scores and increased duration to the need for additional analgesia. No serious side-effects were caused but transient pain on injection of magnesium sulphate was common.

Midazolam

Intrathecal midazolam causes spinally mediated (segmental) analgesia by binding to the benzodiazepine receptors that form part of a typical benzodiazepine GABA receptor complex in the dorsal horn of spinal cord. Adding intrathecal (preservative-free) midazolam may potentiate the antinociceptive effect of morphine-like agents by acting as a direct agonist at kappa and delta opioid receptor sites in the spinal cord. A significant synergistic effect was shown experimentally after intrathecal injection of a combination of midazolam and clonidine. In earlier studies the potentiating of the analgesic effect sought for, after intrathecal addition of midazolam to bupivacaine, may have been masked by clonidine. A study by Boussofara evaluated the postoperative analgesic effect of adding midazolam to an intrathecal bupivacaine-clonidine mixture. Potentiating of pain relief with no change in duration of the motor blockade has also been reported after adding intrathecal midazolam to bupivacaine (42).

The use of intrathecal midazolam to improve perioperative analgesia was reviewed by Ho in a meta-analysis of 13 RCT's (43). Based on the limited data available, intrathecal midazolam appears to improve perioperative analgesia and reduce nausea and vomiting during caesarean delivery. For other applications of using midazolam in neuraxial anaesthesia, a multicentre registry or large randomised controlled study would be useful to confirm the clinical safety of intrathecal administration.

Glucocorticoids

Acute inflammation from tissue injury has an important role in the formation of surgical pain, and glucocorticoids may be useful for its anti-inflammatory effect. Studies using dexamethasone for postoperative pain relief have produced positive results mainly in surgery involving large amounts of tissue trauma. When added to solutions for intravenous regional nerve blocks, dexamethasone has been demonstrated to reduce pain

for the first 24 h after hand surgery. Bigat investigated the anaesthetic and analgesic effectiveness of adding dexamethasone to lidocaine for intravenous regional anaesthesia (IVRA) in 75 patients undergoing ambulatory hand surgery, and found a dose of 8 mg dexamethasone effective when added to lidocaine (44). Although there was prolonged sensory and motor blockade, time to request for first analgesic was significantly shorter in the dexamethasone group but the total analgesic requirement for the first 24 hours was less in this group. In a study by Movafegh, the same dose of 8 mg dexamethasone was added to lidocaine in order to prolong axillary brachial plexus blockade. Sixty patients were included in the study and the addition of glucocorticoid resulted in a significant increase in duration of sensory and motor blocks but with the onset time of blockade left unaffected (45).

Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs inhibit the production of prostaglandins from arachidonic acid in phospholipid membranes. The result is decreased afferent nociceptive signals arising from the site of surgery. Clinical studies have demonstrated an enhanced analgesic effect from NSAIDs when concentrated at a peripheral site compared to the systemic administration of the same drug. This would suggest a predominantly peripheral site of action. Concentrating the dose of NSAID at the site of surgery, either as part of IVRA or wound infiltration, could result in longer lasting analgesia than for the same dose administered parenterally. This has not been sufficiently studied but reports are available on the epidural injection of indomethacin and intraarticular administration of ketorolac and tenoxicam. However, these studies suffer from the lack of placebo groups or systemic controls.

Neostigmine

Intrathecal administration of the cholinesterase inhibitor neostigmine has been shown to produce analgesia, but also to cause adverse effect of motor block, dizziness, bradycardia, nausea or vomiting. The improved analgesia results from an increase in concentration of acetylcholine and consequent action at muscarinic and presynaptic nicotinic receptors, stimulation of the production of nitric oxide, release of gamma-aminobutyric acid, in the cholinergic interneurons of the dorsal horn of the spinal cord in proximity of opioid and adrenergic sites. Hence combining cholinergic and alpha adrenergic agents can be expected to enhance analgesia with side effects related solely to the dose of the individual drug. Neostigmine involved in epidural anaesthesia, intravenous regional anaesthesia or intraarticular injections shortened block onset times, prolonged sensory and motor block, and prolonged time to first postoperative rescue analgesic. Currently, however, data are insufficient to allow recommendations on the addition of neostigmine in regional anaesthesia.

REFERENCES

- BRILL S, GURMAN G M, FISHER A 2003 A history of neuraxial administration of local analgesics and opioids. *Eur J Anaesthesiol* 20: 682–9
- BERNARDS C M 2002 Understanding the physiology and pharmacology of epidural and intrathecal opioids. *Best Pract Res Clin Anaesthesiol* 16: 489–505
- WELLER R S 2004 Opioids as Local Anesthetic Adjuvants for Peripheral Nerve Block. *Techniques in Regional Anesthesia and Pain Management* 8: 123–128
- BUVANENDRAN A, KROIN J S 2007 Useful adjuvants for postoperative pain management. *Best Pract Res Clin Anaesthesiol* 21: 31–49
- GUAN Y, BORZAN J, MEYER R A, RAJA S N 2006 Windup in dorsal horn neurons is modulated by endogenous spinal mu-opioid mechanisms. *J Neurosci* 26: 4298–307
- MARKER C L, LUJAN R, LOH H H, WICKMAN K 2005 Spinal G-Protein-Gated Potassium Channels contribute in a dose-dependent manner to the analgesic effect of μ - and δ - but not κ -Opioids. *J Neurosci* 25: 3551–59
- RATHMELL J P, LAIR T R, NAUMAN B 2005 The role of intrathecal drugs in the treatment of acute pain. *Anesth Analg* 101: S30–43
- GEORGE M J 2006 The site of action of epidurally administered opioids and its relevance to postoperative pain management. *Anaesthesia* 61: 659–64
- EISENACH J C, HOOD D D, CURRY R, SHAFER S L 2003 Cephalad movement of morphine and fentanyl in humans after intrathecal injection. *Anesthesiology* 99: 166–73
- BERNARDS C M, SHEN D D, STERLING E S, ADKINS J E, RISLER L, PHILLIPS B, UMMENHOFER W 2003 Epidural, cerebrospinal fluid, and plasma pharmacokinetics of epidural opioids (1): differences among opioids. *Anesthesiology* 99: 455–65
- GINOSAR Y, RILEY E T, ANGST M S 2003 The site of action of epidural fentanyl in humans: the difference between infusion and bolus administration. *Anesth Analg* 97: 1428–1438
- JORIS J L, JACOB E A, SESSLER D I, DELEUSE J F, KABA A, LAMY M L 2003 Spinal mechanisms contribute to analgesia produced by epidural sufentanil combined with bupivacaine for postoperative analgesia. *Anesth Analg* 97: 1446–51
- STEIN C, CLARK J D, OH U, VASKO M R, WILCOX G L, OVERLAND A C, VANDERAH T W, SPENCER R H 2009 *Brain Res Rev* (in press)
- TRANG T, QUIRION R, JHMANDAS K 2005 The spinal basis of opioid tolerance and physical dependence: Involvement of calcitonin gene-related peptide, substance P, and arachidonic acid-derived metabolites. *Peptides* 26: 1346–55
- GOODCHILD C S, NADESON R, COHEN E 2004 Supraspinal and spinal cord opioid receptors are responsible for antinociception following intrathecal morphine injections. *Eur J Anaesthesiol* 21: 179–85
- CHEN Y P, CHEN S R, PAN H L 2005 Systemic morphine inhibits dorsal horn projection neurons through spinal cholinergic system independent of descending pathways. *J Pharmacol Exp Ther* 314: 611–7
- YAMADA H, SHIMOYAMA N, SORA I, UHL G R, FUKUDA Y, MORIYA H, SHIMOYAMA M 2006 Morphine can produce analgesia via spinal kappa opioid receptors in the absence of mu opioid receptors. *Brain Res* 1083: 61–9
- DORGUL A, BILSKY E J, OSSIPOV M H, LAI J, PORRECA F 2005 Spinal L-type calcium channel blockade abolishes opioid-induced sensory hypersensitivity and antinociceptive tolerance. *Anesth Analg* 101: 1730–5
- VAN ELSTRAETE, SITBON P, TRABOLD F, MAZOIT J X, BENVAMOUS D 2005 A single dose of intrathecal morphine in rats induces long-lasting hyperalgesia: the protective effect of prior administration of ketamine. *Anesth Analg* 101: 1750–6
- SAKURADA T, KOMATSU T, SAKURADA S 2005 Mechanisms of nociception evoked by intrathecal high-dose morphine. *Neurotoxicology* 26: 801–9
- DORGUL A, SEYREK M 2006 Systemic morphine produce antinociception mediated by spinal 5-HT₇, but not 5-HT_{1A} and 5-HT₂ receptors in the spinal cord. *Br J Pharmacol* 149: 498–505
- LU Y, SWEITZER S M, LAURITO C E, YEOMANS D C 2004 Differential opioid inhibition of C- and A delta- fiber mediated thermoreception after stimulation of the nucleus raphe magnus. *Anesth Analg* 98: 414–9
- CHEN S R, PAN H L 2006 Blocking mu opioid receptors in the spinal cord prevents the analgesic action by subsequent systemic opioids. *Brain Res* 1081: 119–25
- BURLACU C L, FRIZELLE H P, MORINARTY D C, BUGGY D J 2007 Pharmacokinetics of Levobupivacaine, Fentanyl, and Clonidine After Administration in Thoracic Paravertebral Analgesia. *Reg Anesth Pain Med* 32: 136–145
- ROBAUX S, BLUNT C, VIEL E, CUVILLON P, NOUGUIER P, DAUTEL G, BOILEAU S, GIRARD F, BOUAZIZ H 2004 Tramadol added to 1.5% mepivacaine for axillary brachial plexus block improves postoperative analgesia dose-dependently. *Anesth Analg* 98: 1172–7
- KESIMCI E, IZDES S, GOZDEMIR M, KANBAK O 2007 Tramadol does not prolong the effect of ropivacaine 7.5 mg/ml for axillary brachial plexus block. *Acta Anaesthesiol Scand* 51: 736–41
- KAABACHI O, OUEZINI R, KOUBAA W, GHRAB B, ZARGOUNI A, BEN ABDELAZIZ A 2009 Tramadol as an adjuvant to lidocaine for axillary brachial plexus block. *Anesth Analg* 108: 367–70
- BERNARDS C M, SHEN D D, STERLING E S, ADKINS J E, RISLER L, PHILLIPS B, UMMENHOFER W 2003 Epidural, cerebrospinal fluid, and plasma pharmacokinetics of epidural opioids (2): effect of epinephrine. *Anesthesiology* 99: 466–75
- FORSTER J G, LUMME H M, PALKAMA V J, ROSEMBERG P H, PITKANEN M T 2008 Epinephrine 4 microg/mL added to a low-dose mixture of ropivacaine and fentanyl for lumbar epidural analgesia after total knee arthroplasty. *Anesth Analg* 106: 301–4
- KAABACHI O, ZERELLI Z, METHAMEM M, BEN ABDEL-AZIZ A, MONCER K, TOUMI M 2005 Clonidine administered as adjuvant for bupivacaine in ilioinguinal–iliohypogastric nerve block does not prolong postoperative analgesia. *Pediatric Anesthesia* 15: 586–590
- ELIA N, CULEBRAS X, MAZZA C, SCHIFFER E, TRAMER M R 2008 Clonidine as an adjuvant to intrathecal local anesthetics for surgery: systematic review of randomized trials. *Reg Anesth Pain Med* 33: 159–67
- WOLFF M, HEUGEL P, HEMPELMANN G, SCHOLZA, MUHLING J, OLSCHIEWSKI A 2007 Clonidine reduces the excitability of spinal dorsal horn neurones. *Br J Anaesth* 98: 353–61
- DOBYRDNJOVI, AXELSSON K, GUPTA A, LUNDIN A, HOLMSTROM B, GRANATH B 2005 Improved analgesia with clonidine when added to local anesthetic during combined spinal-epidural anesthesia for hip arthroplasty: a double-blind, randomized and placebo-controlled study. *Acta Anaesthesiol Scand* 49: 538–45
- KAABACHI O, ZARGHOURNI A, OUZEINI R, ABDEL-AZIZ A B, CHATTAOUI O, KOKKI H 2007 Clonidine 1 microg/kg is a safe and effective adjuvant to plain bupivacaine in spinal anesthesia in adolescents. *Anesth Analg* 105: 516–9
- BHATNAGAR S, MISHRA S, MADHURIMA S, GURJAR M, MONDAL A S 2006 Clonidine as an analgesic adjuvant to continuous paravertebral bupivacaine for post-thoracotomy pain. *Anesth Intensive Care* 34: 586–91
- DUMA A, URBANEK B, SITZWOHL C, KREIGER A, ZIMPFER M, KAPRAL S 2005 Clonidine as an adjuvant to local anesthetic axillary brachial plexus block: a randomized, controlled study. *Br J Anaesth* 94: 112–6
- MCCARTNEY C J, DUGGAN E, APATU E 2007 Should we add clonidine to local anesthetic for peripheral nerve blockade? A qualitative systematic review of the literature. *Reg Anesth Pain Med* 32: 330–8
- HUANG Y S, LIN L C, HUH B K, SHEEN M J, YEH C C, WONG C S, WU C T 2007 Epidural clonidine for postoperative pain after total knee arthroplasty: a dose-response study. *Anesth Analg* 104: 1230–5
- GUNDUZ A 2006 Magnesium Added to Prilocaine Prolongs the Duration of Axillary Plexus Block. *Reg Anesth Pain Med* 31: 233–236
- TURAN A, MEMIS D, KARAMANLIOGLU B, GULER T, PAMUKCU Z 2005 Intravenous regional anesthesia using lidocaine and magnesium. *Anesth Analg* 100: 1189–92
- NARANG S, DALI J S, AGARWAL M, GARG R 2008 Evaluation of the efficacy of magnesium sulphate as an adjuvant to lignocaine for intravenous regional anaesthesia for upper limb surgery. *Anesth Intensive Care* 36: 840–4

42. BOUSSOFARA M, CARLES M, RAUCOULES-AIME M, SEL-LAM M R, HOM J L 2006 Effects of intrathecal midazolam on post-operative analgesia when added to a bupivacaine-clonidine mixture *Reg Anesth Pain Med* 31: 501–5
43. HO K M, ISMAIL H 2008 Use of intrathecal midazolam to improve perioperative analgesia: a meta-analysis *Anaesth Intensive Care* 36: 365–73
44. BIGAT Z, BOZTUC N, HADIMIOGLU N, CETE N, COS-KUNFIRAT N, ERTOK E. 2006 Does dexamethasone improve the quality of intravenous regional anesthesia and analgesia? A randomized, controlled clinical study. *Anesth Analg* 102: 605–9
45. MOVAFEGH A, RAZAZIAN M, HAJIMAOHAMADI F, MEY-SAMIE A 2006 Dexamethasone added to lidocaine prolongs axillary brachial plexus blockade. *Anesth Analg* 102: 263–7