Abstract: Potent opioids are excellent painkillers but their use is hampered by side-effects such as nausea, vomiting, bowel dysfunction, urinary retention, pruritus, sedation and respiratory depression. Co-analgesics are often combined with opioids to reduce the prevalence of these unwanted effects while maintaining or even improve the quality of analgesia. A search of the recent literature demonstrated that peripheral opioid antagonists are able to reduce opioid-induced bowel dysfunction without interfering with analgesia. Dexmedetomidine, gabapentin, and ketamine significantly reduce opioid consumption but have no effect on the incidence of opioid side-effects. In contrast, intravenous lidocaine and corticosteroids not only produce an opioid-sparing but also a significant reduction in the occurrence of postoperative ileus and nausea and vomiting. It remains unclear whether the perioperative use gabapentin, ketamine and corticosteroids has an effect on the development of postsurgical chronic pain states.

INTRODUCTION

The mainstay of systemic postoperative analgesia still consists of the intravenous (IV) administration of a potent opioid such as morphine or one of its newer (semi)synthetic derivatives. Unfortunately, potent opioids may also cause nausea, vomiting, bowel dysfunction, urinary retention, pruritus, sedation and respiratory depression. This had led to the concept of balanced or multimodal analgesia which implies the combination of various analgesics with different mechanisms of action and unwanted effects (40). A typical multimodal mixture involves the combination of paracetamol and/or non-steroidal anti-inflammatory agents (NSAIDs) as co-analgesic drugs with a potent opioid. Although smaller amounts of the individual painkillers are used, adequate analgesia is consistently produced with smaller doses of opioid, but this does not seem to lead to a reduction of side-effects (16, 61). The last five years have seen the publication of studies involving the use of other drugs as co-analgesics to potent opioids in the treatment of postoperative pain. The rationale for adding these drugs to opioids has not changed from the original concept of multimodal analgesia. In fact, an additional argument to use co-analgesics in combination with opioids has become apparent in the last decade. Potent opioids, when used alone or in high doses, can produce opioid-induced hyperalgesia (50). A number of drugs may actually prevent or reduce this hyperalgesia (58, 59, 70). Some of them can be used as co-analgesics (41).

The aim of this text was to review the efficacy of different co-analgesic drugs in improving opioid-produced analgesia and/or reducing opioid-induced side-effects. The co-analgesics discussed include peripheral opioid antagonists, dexmedetomidine, gabapentin, ketamine, lidocaine and steroids.

DRUGS

Peripheral opioid antagonists

Postoperative bowel dysfunction or ileus affects all segments of the gastrointestinal tract, may well last 48-72 h in the colon and has a profound impact on the postoperative course of the surgical patient. The pathophysiology of ileus involves sympathetic hyperactivity, the activation of intestinal inflammatory cells, the suppression of migrating motor complexes, and the use of opioids (46). Opioids have an important and dose-dependent inhibitory effect on gastrointestinal motility. The inhibitory effect of morphine is seen both after systemic and epidural administration, especially when compared to epidural local anesthetics. Although opioids have an unquestionable analgesic effect, the development of bowel dysfunction may reduce the value of pain relief by more than 30% (68). Moreover, postoperative opioid-induced ileus can increase morbidity and prolong postoperative stay as it may lead to nausea, vomiting, pseudo-obstruction, abdominal distention, wound dehiscence,
impaired breathing, atelectasis, pulmonary aspiration, and pneumonia. Opioid antagonists such as naloxone can neutralize these inhibitory effects, but will also antagonize analgesia and precipitate opioid withdrawal in opioid-dependent patients. Interestingly, the opioid-induced inhibition of gastrointestinal motility is predominantly a peripheral effect. Hence, it makes sense to develop peripheral opioid antagonists.

Methylnaltrexone is a quaternary derivative of naltrexone that is poorly lipid soluble and does not cross the blood-brain barrier. It does not antagonize central nervous opioid effects or precipitate opioid withdrawal (64). A study in human volunteers exposed to a single dose of morphine demonstrated the reversal of opioid-induced bowel dysfunction (ODB) using IV or oral methylnaltrexone (88, 89). Similar results were obtained in patients chronically treated with opioids (87). Even after repetitive IV administration methylnaltrexone was found to be well tolerated in humans, with no significant adverse events or changes in opioid subjective ratings and no clinically noteworthy alterations in pharmacokinetics (86).

Alvimopan or ADL 8-2698 is a trans-3,4-dimethyl-4-(3-hydroxyphenyl) piperidine that is a peripheral opioid antagonist (90). The first results of clinical studies with alvimopan are promising. In opioid-naïve volunteers and surgical patients, the oral administration of 4 mg alvimopan prevented the IV morphine-induced delays in gastrointestinal transit while leaving analgesia intact (47). When used in patients on chronic opioid therapy for chronic non-malignant pain or opioid-dependence with ODB, oral alvimopan in doses of 0.5 and 1 mg significantly reduced ODB and did not interfere with opioid analgesia or induce symptoms of opioid withdrawal (56). Two recent clinical trials showed that the perioperative oral use of alvimopan 6 mg, in patients undergoing partial colectomy or radical hysterectomy and treated with systemic opioids, significantly accelerated gastrointestinal recovery and hospital discharge while being well tolerated (10, 82).

Although these first results are encouraging, additional studies are underway to clearly establish the place of these drugs in surgical patients.

Dexmedetomidine

The clinical use of alpha-2 agonists in anesthesia is not new. The antinoceptive, sympatholytic, sedative and opioid-sparing effects of clonidine are well known since the seventies (73). Ever since then clonidine has been extensively used both in anesthesia and analgesia as an adjuvant to both general and regional anesthetic and analgesic techniques (4, 5, 15). However, clonidine being primarily an antihypertensive drug, a more widespread was prohibited by the cardiovascular effects of the compound. This explains the search for newer and more selective alpha-2 agonists that have a smaller or no impact on the cardiovascular function. As a result dexmedetomidine was recently introduced into clinical practice. Dexmedetomidine is a highly selective alpha-2 agonist with potent sedative, sympatholytic, and anesthetic- and analgesic-sparing properties that is predominantly used as a sedative in an intensive care setting (14, 26, 69). The fact that dexmedetomidine enhances the effects of potent opioids analgesics without increasing respiratory depression makes it a very attractive adjuvant to be used in postoperative analgesia.

To this date only a few studies have looked at the use of dexmedetomidine in combination with a potent opioid during the postoperative period. Arain et al. found that the intraoperative administration of a single dose of dexmedetomidine reduced the early postoperative need for morphine after major surgical procedures by 66% and was associated with a slower heart rate in the post-anaesthesia care unit (1). In a recent paper Unlugenc et al. administered 1 µg/kg of dexmedetomidine IV before induction of general anesthesia for abdominal surgery. The authors found a significant reduction in PCA-morphine use at 6, 12 and 24 h after surgery (81). However, as both studies failed to demonstrate a reduction of the typical opioid-mediated side-effects or a reduction in duration of postoperative stay, there is very little incentive left to promote the routine use of dexmedetomidine as a co-analgesic. Its cost will almost certainly outweigh any financial savings made by the reduction in morphine consumption.

Gabapentin

Gabapentin is a structural analog of gamma-aminobutyric acid (GABA) that does not bind to the GABA$_{a}$ receptors and is primarily marketed as an anti-epileptic. In addition gabapentin was rapidly found to be effective in the treatment of neuropathic pain. This can be explained by the high binding affinity of the compound for the $\alpha_2\delta$-subunit of presynaptic, voltage-gated calcium channels which are upregulated in the spinal cord after peripheral tissue injury (49). Interaction with these channels inhibits calcium influx and the subsequent
release of excitatory neurotransmitters and amino acids which results in an inhibition of the development of central sensitization and hyperalgesia. Animal experimental studies also found gabapentin to be effective in acute pain (19), and able to inhibit the development of opioid-induced hyperalgesia (23). These findings have led to a number of clinical studies investigating the use of gabapentin in surgical patients.

Oral gabapentin was used in the treatment of pain after abdominal surgery. It was found that a single preoperative dose of gabapentin 300 or 1200 mg vs. placebo significantly reduced pain scores and opioid consumption during the first 24 hours after laparoscopic cholecystectomy or abdominal hysterectomy, respectively (54, 79). Similar results were obtained after spinal surgery (54, 78), knee surgery (51), open kidney donor surgery (55), and mastectomy (12, 17).

When compared to or combined with 50 mg of rofecoxib, 1200 mg of gabapentin was equally effective in reducing pain scores and opioid consumption (80). In a study by Gilron et al., rofecoxib 50 mg was more efficient then gabapentin 1800 mg in reducing pain with movement, but equally effective in reducing opioid consumption (24). The combination of gabapentin with rofecoxib was always superior to either single agent (24, 80).

Only a few studies found that preoperative gabapentin reduced some of the typical opioid side-effects. For example, Turan et al. described a faster recovery of bowel function (79), and reduced incidence of vomiting and urinary retention (78).

One study prospectively studied the influence of perioperative gabapentin on the development of chronic pain after surgery. It is well known that mastectomy can cause a chronic post-surgical pain syndrome. In a retrospective cohort study of mastectomies over a 6 year period, the cumulative prevalence of persisting post-mastectomy pain was 43% overall, but was as high as 65% in a subgroup of younger women aged 30-45 yr (71). Turan et al. prospectively investigated the use of gabapentin 1200 mg/d vs. mexiletine 600 mg/d vs. placebo for 10 days, including the evening prior to surgery, the day of the operation and the following days (17). Three months after surgery, the prevalence of chronic pain was comparable in the three groups ranging from 45% (mexiletine), 54% (gabapentin), to 58% (placebo). However, there was a significantly increased incidence of burning pain in the placebo group.

Recently gabapentin has received a successor under the name of pregabalin. Pregabalin seems to have similar effects in the field of chronic pain therapy. In acute pain treatment, pregabalin has been compared to ibuprofen or placebo after dental surgery and found to improve pain relief vs. placebo (28).

Preoperative single dose gabapentin seems to consistently produce an opioid-sparing effect, which does not reliably lead to a significant decrease in opioid-related side effects. The main interest in the use of gabapentin (and its successor pregabalin) may therefore lie in the prevention of the development of chronic post-surgical states. Whether this is true remains to be confirmed by additional research (9).

Ketamine

The N-methyl-D-aspartate (NMDA) receptor complex plays an important role in nociception. It is involved in the initiation and maintenance of central sensitization and pathologic pain (83, 84). Ketamine is an anesthetic that interferes with various receptor systems, including the NMDA receptor, as a non-competitive antagonist (67). Since the beginning of the nineties, a large number of studies have investigated the analgesic and anti-hyperalgesic effects of IV ketamine in combination with opioids. Recently, two quantitative and qualitative reviews were published on the subject of racemic ketamine or S(+)-ketamine as co-analgesic to opioids (16, 74).

Subramaniam et al. analyzed all double-blind clinical trials of small dose IV ketamine added to opioid analgesia for postoperative pain relief published between 1966 and 2003 (74). They reviewed 37 trials including 2385 adults and children. The resulting meta-analysis found that adding ketamine to an IV patient-controlled analgesia (PCA) with potent opioids was not beneficial in improving the quality of postoperative analgesia. In contrast, the continuous IV infusion (0.07-0.6 mg.kg⁻¹.h⁻¹) or single dose (0.15-1 mg.kg⁻¹) administration of ketamine did improve perioperative opioid analgesia. No significant correlation was found between the timing of ketamine administration and its analgesic efficacy. However, the use of small dose ketamine also resulted in a reduction of wound hyperalgesia and the development of chronic post-surgical pain syndromes. Despite a reduction in postoperative opioid consumption the incidence of opioid side effects was comparable. The use of small dose ketamine was not associated with increased psychomimetic effects such as hallucinations or excessive sedation.
In another meta-analysis Elia et al. reviewed 53 randomized trials that tested ketamine in 2721 adults and children published between 1986 and 2003 (16). Not surprisingly, their results are consistent with those of Subramaniam (74). A consistent and significant decrease in visual analogue pain scores (VAS) up to 48 h postoperatively and a decrease in morphine consumption (weighted mean difference of -16 mg) were found. There was no difference in the occurrence of opioid-related side-effects.

The data on ketamine use in children are a lot more inconsistent. While Subramaniam et al. found a large variability in the results on the pediatric use of IV ketamine, Elia et al. stated that all authors reported decreased postoperative pain. Two more recent studies contribute to this confusion. Dix et al. did not find any differences in postoperative pain scores nor in IV PCA morphine consumption while the incidence of ketamine-related psychomimetic side-effects was increased (13). In contrast, Becke et al. reported a significant reduction in postoperative pain scores but no differences in morphine consumption nor in opioid- and ketamine-related side-effects (3).

Taken together both meta-analyses have positively answered a number of questions but also raised a few others. Small dose IV ketamine is indeed able to reduce postoperative pain intensity and morphine consumption. However, the decreased morphine use is not accompanied by a reduction in morphine-related side effects. Future investigations should more specifically look at the effects of peroperative small dose IV ketamine on: (1) the development of chronic pain states, (2) the treatment of surgical patients with opioid-resistant pain, and (3) postoperative analgesia in children.

**Lidocaine**

The beneficial effects of administering epidural local anesthetics to surgical patients for postoperative pain treatment are well known. Epidural local anesthetics have been shown to reduce the incidence of pulmonary complications (2, 39, 60), the incidence and duration of paralytic ileus (34, 46, 48), and the occurrence of thromboembolic events (60). These effects were thought to be caused mainly by the epidural nerve root blocking and sympatheticolytic effects of the local anesthetics involved. Unfortunately, a number of surgical patients cannot be treated with an epidural for different reasons: patient refusal of the technique, presence of relative or absolute contraindications, technical difficulties during placement, or incompatibility with the surgery performed.

Interestingly, a number of the previously described beneficial effects have recently also been described when local anesthetics were administered systemically. The IV administration of lidocaine was found to be analgesic (8, 25, 44), anti-hyperalgesic (11, 38, 42, 43, 45), and able to accelerate the return of bowel function after surgery (8, 25, 36, 44). Lidocaine use does not seem to influence the endocrine and metabolic responses to surgery (8). Intravenous lidocaine also has anti-thrombotic properties (30), which seem to be primarily caused by a systemic anti-inflammatory effect. This was demonstrated by the fact that epidural anesthesia (i.e. associated with significant systemic local anesthetic levels) prevents surgery-induced hypercoagulation while spinal anesthesia (i.e. associated with insignificant systemic local anesthetic levels) does not interfere with coagulation (35). The dosing regimes of lidocaine used to obtain these results included an initial loading dose of 1.5 mg.kg<sup>-1</sup> (25, 36, 44) followed by intraoperative maintenance infusions ranging of from 1.5 (44) to 2.0 mg.kg<sup>-1</sup>.h<sup>-1</sup> (8, 36). Grodine et al. used somewhat higher maintenance doses. They infused lidocaine 2 mg.min<sup>-1</sup> or 3 mg.min<sup>-1</sup> in patients with a bodyweight < 70 kg or 70 kg, respectively. Even with these doses, lidocaine plasma levels (1.3-3.7 µg.ml<sup>-1</sup>) remained well below toxic levels (5 µg.ml<sup>-1</sup>), which makes the need to monitor lidocaine levels questionable (25).

Possible mechanisms involved in the analgesic and anti-hyperalgesic effects of IV lidocaine are a reduction of activity in the A<sub>d</sub>- and C-fibers (52, 57), an anti-NMDA effect (45, 75), the suppression of dorsal horn neurons (72), and inhibition of G-protein coupled receptors (29, 32, 33). In chronic pain patients, the administration of IV lidocaine was able to relieve severe opioid-resistant neuropathic pain (77), and spinal cord injury pain (20). These effects are thought to be mediated through the interference of local anesthetics with upregulated voltage-dependent sodium channels (7).

As mentioned previously postoperative ileus results from a sterile inflammation of the peritoneum after abdominal surgery (44), visceral nociceptive processing, hyperactivity of the orthosympathetic nervous system, and perioperative opioid use (46). Systemic lidocaine has an anti-inflammatory effect (30), inhibits visceral nociceptive reflexes (53), and reduces postoperative opioid use and duration of postoperative ileus (8, 25, 36, 44).

All these results suggest that systemic lidocaine is able to improve postoperative outcome.
Hence, the perioperative use of this local anesthetic may well be considered “the poor man’s epidural” (31), but additional studies are needed to investigate whether a broader use of IV lidocaine can be safely employed in surgical patients.

Corticosteroids

Corticosteroids have a long tradition of being employed in the treatment of rheumatic and systemic diseases, but are also frequently used in cancer patients because of their anti-inflammatory, analgesic, antiemetic and antianorexic actions. Corticosteroids inhibit phospholipase A₂ and by doing so eventually block the production of both prostaglandins and leucotrienes both in peripheral tissue and in the central nervous system. More importantly, the inhibition of cyclooxygenase (COX) is primarily aimed at the COX-2 isoform, thus making glucocorticoids virtually selective COX-2 inhibitors (66). As central nervous system COX-2 is involved in the development of hyperalgesia (76), it can be expected that the inhibition of COX-2 will result in anti-hyperalgesic effects (21, 85). Corticosteroids will also inhibit the production of pro-inflammatory cytokines as interleukin 1β (IL-1β), interleukin 6 (IL-6), and tumor necrosis factor-alpha (TNFα) (18). A neuronal membrane stabilizing effect has also been described. Finally, glucocorticoids also have the ability to reduce postoperative nausea and vomiting (27). Taken together, all these effects make corticosteroids quite suited for the treatment of postoperative pain although until today they have only sporadically been used for this indication.

Recently, a number of papers have revived the interest in corticosteroids as co-analgesics to potent opioids in the treatment of pain after surgery. In 2003 KARST et al. investigated the opioid sparing effect of celecoxib after lumbar disc surgery (37). Their study protocol provided the possibility of administering 20-80 mg of dexamethasone when intraoperatively signs of nerve root compression were visible. Much to their surprise the use of a single dose of dexamethasone resulted in a much more profound opioid-sparing effect after 24 hours than found with repetitive doses of celecoxib 200 mg. In addition, pain scores on movement were significantly lower in dexamethasone treated patients. BISGAARD et al. administered dexamethasone (8 mg) preoperatively to patients undergoing laparoscopic cholecystectomy and found a significant reduction of pain scores, opioid consumption, postoperative fatigue, and postoperative nausea and vomiting (PONV) when compared to placebo (6). More recently, ROMUNSTAD et al. investigated the effects of a single dose of methylprednisolone 125 mg vs. ketorolac 30 mg vs. placebo in patients after orthopedic surgery (62). Pain scores were significantly lower in the methylprednisolone group at 24 h, while an opioid-sparing effect was seen until 72 h postoperatively. The same authors just published another study evaluating a single dose of methylprednisolone 125 mg vs. parecoxib 40 mg vs. placebo after breast augmentation surgery (63). Both methylprednisolone and parecoxib produced adequate analgesia and significantly reduced the use of rescue pain medication. More interestingly, postoperative nausea and vomiting and fatigue were also significantly reduced in the methylprednisolone treated patients.

In summary, the perioperative use of single dose corticosteroids not only results in a significant reduction of opioid use, but also in a reduction of PONV. Moreover, a systematic review including data of more than 1900 patients concluded that the perioperative use of a single high dose (15-30 mg/kg) of methylprednisolone was not associated with any adverse effects (65). So it seems that single dose corticosteroids can be safely used perioperatively. Whether the repeated corticosteroid administration has the same safety profile remains to be demonstrated. Finally, it is still unclear if perioperative corticosteroids can influence the development of post-surgical pain states (22).

CONCLUSION

The use of non-opioids as co-analgesics to potent opioids to reduce the typical side-effects of opioid therapy without interfering with or even improving opioid-induced analgesia is an interesting concept. Previous studies with “classic” co-analgesics such an paracetamol or NSAIDs have never been able to consistently demonstrate such an effect. However, recent studies with a drugs of completely different categories produced promising or at the least intriguing results. Clinical studies found that the selective alpha-2 agonist dexmedetomidine, the anti-epileptic gabapentin (and its successor pregabalin), the non-competitive NMDA-receptor antagonist ketamine, the local anesthetic lidocaine, and corticosteroids consistently produced an opioid-sparing effect while maintaining or improving analgesia. Unfortunately, the reduction in opioid consumption did not translate into a reduction of opioid side-effects in the case of dexmedetomidine,
gabapentin and ketamine. The most promising results were found in studies investigating the use of systemic lidocaine, and the peripheral opioid antagonists naltrexone and alvimopan. All these drugs significantly accelerated the recovery of postoperative bowel function. It was also found that the perioperative use of a single dose of corticosteroids clearly reduced PONV. Questions that remain to be answered concern the safety of a broad use of systemic lidocaine and corticosteroids, and a cost-benefit analysis of the peripheral opioid antagonists. Also, because of their respective mechanism(s) of action gabapentin, ketamine, and corticosteroids might interfere with the development of post-surgical chronic pain states. Although a number of studies do point in that direction further research will be needed.

References


