

What's new in pain management?

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Introduction

The presentation will commence with a brief review of acute pain physiology. The purpose of the discussion will be to describe new agents that are soon to be available on the South African market, and exactly where they are applicable in acute and chronic pain management. Considerable data will need to be published on each of the agents, and it would be impossible to summarise it here. The data that are pertinent to the clinical practice of anaesthesiologists is highlighted below.

Tapentadol

This agent is representative of a new class of drugs known as the MOR-NRI (combines mu-opioid receptor stimulation with noradrenaline reuptake inhibition). Unlike other combination compounds that utilise multi-components to activate multiple receptors, this agent is a single agent, acting via more than one mechanism. Tapentadol combines mu-opioid receptor (MOR) agonism, and noradrenalin reuptake inhibition (NRI) in a single molecule. There is no indication of a serotonergic mechanism.

Given the mechanisms of action, tapentadol has been demonstrated to be effective in several different models of acute and chronic inflammatory pain. Literature is scanty in terms of its use in the postoperative scenario, but references abound for its use in chronic pain, including osteoarthritis and lower back pain. Safety studies have been concluded with regard to its use in hypertension. No significant changes in blood pressure, or heart rate, were observed following treatment with tapentadol, even when used in the sustained release form.

The majority of its metabolism is hepatic, and the excretion of the parent drug and its metabolites is almost exclusively renal. Data suggests that aging per se does not require a

dose adjustment when treating healthy elderly patients. Care should be taken in dose selection if there is any indication of severe hepatic disease or severe renal insufficiency. It has been demonstrated that prolonged use of tapentadol, in excess of one year, did not cause any clinically relevant changes in renal or hepatobiliary laboratory parameters. Tapentadol is already in clinical use, and should be available locally within 24 months.

Hydromorphone

Hydromorphone is an opioid analgesic, and is an analogue of morphine. Several forms of this agent are internationally available, and include an intravenous or intrathecal preparation, as well as a single short-acting oral formulation.

South African registration has only been concluded for the long-acting formulation. This formulation utilises the osmotically controlled release oral delivery system (OROS[®]) which delivered hydromorphone over a 24-hour period. Hydromorphone is released constantly during transit through the gastrointestinal tract, including the lower gastrointestinal tract. Drug release is not affected by the pH or motility of the gastrointestinal tract, and drug absorption seems to be unaffected by food or alcohol.

The agent is primarily metabolised in the liver, and a variety of water-soluble metabolites are excreted in the urine. None of the 6-gluconoride metabolites are active. No metabolism occurs via the cytochrome P450 (CYP450) pathway. Therefore, its activity is not influenced by genetic variability in analgesic response, and the absence of drug-drug interactions involving the CYP 450 system.

The efficacy of hydromorphone in chronic malignant and non-malignant pain management has been established. It provides similar pain relief to twice-daily sustained-release morphine, and is an effective analgesic with dose-related

clinical effect. It can be considered as a good alternative to morphine for the management of moderate-to-severe chronic pain, as well as for short-term use following major surgery.

The safety and tolerability of hydromorphone is well documented. Reported side-effects of the OROS® hydromorphone are similar to those associated with other opioids. Unsurprisingly, the most commonly reported adverse events are nausea, constipation, somnolence, vomiting, headaches and dizziness. The events are usually mild to moderate in severity, and easily managed by anaesthesiologists. Opioid side-effects such as nausea, sedation and pruritus, may occur less frequently with hydromorphone, compared to morphine.

Prolonged use studies (one year) confirm a favourable safety profile, and the drug is well tolerated. It is available in various strengths, including a low dose 4 mg that may prove particularly useful in patient populations such as the opioid-naïve, or elderly.

This agent has been used extensively in clinical practice, and should be available in South Africa at the time of the SASA Congress.

Oxycodone hydrochloride

Oxycodone is a μ -agonist, with some κ -agonist activity. It is metabolised by the CYP3A4/CYP2D6 system, with a very predictable pK profile. There is no active metabolite activity. Given these properties, like most opioids, it does not have a ceiling dose, and can be titrated to effect.

This agent will be available in a variety of strengths, and in two formulations. The immediate release capsules are 5, 10, and 20 mg strengths, while the prolonged release tablets will be available as 5, 10, 20, 40, and 80 mg.

The delivery system consists of two hydrophobic polymers forming a dual control matrix, resulting in biphasic release and absorption. This allows for a rapid release of oxycodone from the tablet surface, and an early onset of analgesia. The sustained second phase of dissolution and diffusion through the tablet matrix maintains effective blood concentrations. Experience in the international market demonstrates efficacy for cancer pain, some forms of neuropathic pain, as well as somatic and visceral pain.

The adverse event profile of oxycodone tablets is, as expected, similar to other strong opioids. The most frequently reported adverse events during clinical trials in cancer and chronic non-malignant pain include constipation, nausea, vomiting, sedation, dizziness and pruritus. Respiratory depression is a potentially serious side-effect, and appropriate monitoring and careful prescribing should

minimise the risk. The majority of adverse events diminish over time.

Oxycodone tablets must never be crushed, chewed, or broken, as this could lead to a potentially fatal overdose.

In terms of safety, there is no ceiling dose (proven efficacy with high dose). Given its metabolism, it has a predictable and reliable pharmacodynamic profile, with steady-state plasma levels reached within 24 hours. The lack of clinically significant metabolite activity contributes to a favourable adverse event profile. Hallucinations and itching are not a major problem.

This metabolic profile allows for conservative use in patients with mild renal or hepatic impairment. Similarly, no dose adjustment seems to be necessary, even among elderly patients. There is also a decreased risk of drug interaction in patients receiving concomitant drug therapy.

Buprenorphine

In South Africa, the transdermal patch is to be made available. Buprenorphine is a partial μ -opioid agonist with a long duration of action. It has a high analgesic potency (60-fold greater potency than morphine), and thus can provide effective analgesia with low plasma concentrations.

In order for an agent to be suitable for transdermal administration, it should be highly lipophilic and have a low molecular weight for ease of crossing the skin barrier, as well as highly potent, to allow adequate doses to be delivered through the skin. Buprenorphine is a suitable agent, as due to its low molecular weight and a partition coefficient of 1:217 octanol:water, facilitates good skin penetration. It also has a long duration of action, as it has a high affinity for, and slow dissociation from, opioid receptors.

The patches will be available in 5, 10, and 20 mg formulations.

Regarding the pharmacokinetics, the three strengths of the patch are dose proportional. This results in a consistent pharmacokinetic profile. Age, ethnicity and gender, do not significantly alter the pharmacokinetics. No dose adjustment is required for demographic groups, nor for the elderly population. Tolerability studies show no unexpected safety concerns. Buprenorphine is well tolerated by most patients for long-term use.

The most common adverse events (< 10% of patients) are gastrointestinal, which include constipation, nausea, vomiting, and a dry mouth. As with other opioids, central nervous system symptoms can be expected, such as dizziness, somnolence, and slight confusion. Typical skin and appendage opioid effects also occur, including pruritus. A rarer problem, reported in transdermal applications,

include pruritus at the application site, and erythema. Both are a local reaction. With the exception of constipation, opioid-related adverse events tend to diminish with time. Safety profiles need to be addressed.

Buprenorphine is a partial agonist, so compared with full agonists, has a lower liability for the induction of physical dependence. It has a lower risk of withdrawal symptoms, as there is a slow decrease in plasma concentrations. Concentrations decrease by 50% within 12 hours of patch removal. If withdrawal or abstinence syndrome occurs, it is generally mild, begins after two days, and may last up to two weeks. There is a comparatively low risk of tolerance development.

In comparison with many opioids, buprenorphine has a limited abuse potential, similar to that of mixed agonist-antagonist opioids. The patch has no liquid reservoir from which buprenorphine can be extracted.

There are potential drug interaction problems:

- Non-selective MAO inhibitors enhance the effect of buprenorphine. This can result in anxiety, confusion and respiratory depression. It should not be used concomitantly, or by patients who took MAO inhibitors in the last 14 days.
- Inhibitors of CYP450 3A4 result in higher plasma concentrations, e.g. macrolide antibiotics, protease inhibitors and calcium antagonists. There is also an efficacy reduction from increased hepatic clearance with concurrent use of CYP3A4 enzyme inducers, e.g. carbamazepine, phenytoin and phenobarbitone.

- Central nervous system (CNS) depressants and muscle relaxants. Be careful when using with drugs that depress respiration and the CNS, e.g. sedatives or hypnotics, general anesthetics, other opioid analgesics, phenothiazines, centrally-acting antiemetics, benzodiazepines and alcohol.
- What of the kinetics? No dose adjustment is needed in renal impairment, in mild-to-moderate hepatic impairment, or based on age, ethnicity, or gender. Alternative therapy should be used for patients with severe hepatic impairment.

Buprenorphine patches are not recommended for patients who are younger than 18 years of age. It is contraindicated in pregnancy, and should be avoided during lactation. Temperature may have an altering effect on absorption, so it is recommended that patients with fever are monitored.

The question arises as to whether or not these agents will be useful to anaesthesiologists in normal everyday practice, or whether the drugs are for pain management clinic use only. It is likely that some of them will be useful to anaesthesiologists in cases where moderate-to-severe postoperative pain is expected. Clinical experience should determine which agent, what strength, and which formulation, will be most appropriate for patients. Like all other newly-introduced formulations, these drugs will establish a specific niche in our armamentarium, and shall be used appropriately in everyday anaesthetic practice.

References are available on request.