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Update on the role of non-opioids for postoperative pain treatment

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Non-opioids play an ever increasing role in the treatment of postoperative pain; either on their own for mild to moderate pain or in combination with other analgesic approaches, in particular opioids, as a component of multimodal analgesia. The analgesics paracetamol (acetaminophen) and dipyrone (metamizole) as well as compounds with an additional anti-inflammatory effect (non-selective non-steroidal anti-inflammatory drugs and selective cyclo-oxygenase-2 inhibitors) are used widely in the perioperative period.

Paracetamol is gaining renewed interest in this setting due to its minimal adverse effects and recent availability in a parenteral preparation, but its benefits are insufficiently studied.

Dipyrone continues to be used in many countries despite the ongoing debate on the incidence and relevance of its ability to cause agranulocytosis.

Among the anti-inflammatory drugs, selective cyclo-oxygenase-2 inhibitors have the most supportive data for their beneficial effects as a component of multimodal analgesia and offer benefits with regard to their adverse effect profile.

Key words: non-opioids; multimodal analgesia; balanced analgesia; paracetamol; dipyrone; NSAID; coxib.

INTRODUCTION

Non-opioid analgesics are the group of medications most commonly used worldwide, usually for the treatment of acute and chronic pain states. Over the last 20 years, they

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have gained increasing usage for the treatment of postoperative pain; for pain of mild or moderate intensity used on their own, but even more importantly as components of multimodal analgesia.[1] Therefore, a thorough understanding of their pharmacology, their efficacy and their adverse effects is essential for the successful use of this important group of medications in the treatment of postoperative pain.

In principle, non-opioid analgesics can be classified as acid and non-acid antipyretic drugs.[2] This classification is based on the pKa value, i.e. the pH at which 50% of the compound is dissociated and 50% is undissociated. Compounds with a pKa value less than 5 are regarded as acid antipyretic analgesics. These physicochemical properties influence the pharmacodynamics of antipyretic analgesics in so far as acidic antipyretic analgesia distributes preferentially to organs with a lower pH such as the kidneys, stomach and inflamed tissues, while non-acidic analgesics are found ubiquitously in the body.[2]

The group of non-acidic antipyretic drugs contains the aniline derivatives with its only representative paracetamol, and the phenazone derivatives with its major representative dipyrone. These compounds are analgesic and antipyretic, but devoid of anti-inflammatory effects.

Acidic antipyretic drugs are represented by acetylic salicylic acid (ASA) and the non-steroidal anti-inflammatory drugs (NSAIDs). The term NSAIDs has historical origins, when an attempt was made to distinguish NSAIDs from steroids, which also show anti-inflammatory effects. The mechanism of action of these compounds is interference with the formation of prostanoids, primarily by inhibition of the enzyme cyclo-oxygenase.[3] All NSAIDs discovered until recently were non-selective for the isoenzymes of cyclo-oxygenase (COX); however, selective inhibitors of the isoenzyme COX-2 have now become available in the form of the coxibs. New research on the role of prostaglandins in peripheral and central sensitization processes occurring after injury seems to open new opportunities for the use of nonopioid analgesics with an anti-inflammatory effect in the postoperative period. The results of these processes are the symptoms of hyperalgesia and allodynia, i.e. increased sensitivity to suprathreshold and subthreshold stimulation.[4] Understanding these mechanisms makes it obvious, that although opioids will be able to provide significant relief of postoperative pain and will remain the gold standard of severe pain treatment, compounds such as the non-selective NSAIDs and the selective coxibs, can provide analgesia by a more causal approach.[5]

PARACETAMOL (ACETAMINOPHEN)

Discovered in the late 19th century, paracetamol is a non-acidic antipyretic analgesic.[6] It is the active metabolite of two other aniline derivatives which were used as antipyretic and analgesic medications in the past, acetanilide and phenacetin, but devoid of their toxic effects. Today, paracetamol is not only the most popular and most widely used antipyretic and analgesic compound worldwide, but also ranks usually number one or two of all drugs worldwide by turnover (http://www.imshealth.com), mainly due to its minimal adverse effects and its proven analgesic efficacy.[7]

Mechanism of action

Despite its long history, uncertainty remains about the mechanism of action of paracetamol. Endogenous binding sites for paracetamol have not yet been identified, but it is clear that it lacks the inhibiting effect of NSAIDs on peripheral cyclo-oxygenase activity.[8]