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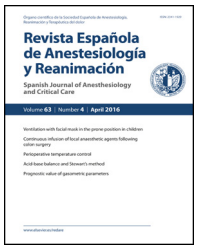

CONTINUING EDUCATION

Pharmacological advances in the multimodal management of perioperative analgesia☆

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KEYWORDS
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Abstract The concept of multimodal analgesia is currently widespread in our clinical practice.

The aim of multimodal analgesia is to reduce the side effects derived from the drugs or techniques used for the control of pain together with greater effectiveness (combination of multiple mechanisms of action) with the maximum efficiency, that is, to combine different pharmacodynamics (synergistic or additive effects) and pharmacokinetics, in the context of a predictable acute pain model, thus allowing a prior strategy such as the model of acute postoperative pain.

Pain is a complex physiological phenomenon. Postoperative pain involves multiple pathways including nociceptive, inflammatory, and neuropathic sources. In the transmission of pain therefore, different molecules participate, which means that there are multiple pharmacological targets on which to act, and therefore a wide range of drugs to be used following the physiology of pain.

PALABRAS CLAVE
Analgesia perioperatoria;
Analgesia multimodal;
Avances analgésicos

Avances farmacológicos en el manejo multimodal de la analgesia perioperatoria

Resumen El concepto de analgesia multimodal está actualmente muy extendido en nuestra práctica clínica.

El objetivo de la analgesia multimodal es la disminución de efectos secundarios derivados de los fármacos o técnicas utilizados para el control del dolor junto a una mayor efectividad (combinación de múltiples mecanismos de acción) con la máxima eficiencia, es decir, combinar diferentes farmacodinamias (efectos sinérgicos o aditivos) y farmacocinéticas en el contexto de un modelo de dolor agudo previsible y por lo tanto que nos permite una estrategia previa como es el modelo del dolor agudo postoperatorio.

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El dolor es un fenómeno fisiológico complejo. En el dolor postoperatorio intervienen múltiples vías incluyendo fuentes nociceptivas, inflamatorias y neuropáticas. En la transmisión del dolor por lo tanto, participan distintas moléculas; este hecho supone que existen múltiples dianas farmacológicas sobre las que actuar y por lo tanto una amplio abanico de fármacos a utilizar siguiendo la fisiología del dolor.

Introduction

There is ample evidence to support the use of different drug combinations in multimodal analgesia.[1,2] However, each drug has its advantages and disadvantages and specific safety profile, and it is imperative to select the right analgesic for each patient. Multimodal analgesia, therefore, must be planned according to the patient and the type of intervention performed at a given time, and this calls for the creation of a personalised multimodal analgesia strategy that takes advantage of the growing array of analgesics available.

New approaches are currently available that will probably allow us to maximise the benefits of perioperative analgesia and provide us with new analgesics that can be adapted to each type of intervention and patient.[3] These include traditional analgesics with novel routes of administration (intravenous ibuprofen, sulfentanil and intrathecal butorphanol), adjuvants (ketamine, magnesium, lidocaine, neostigmine, gabapentinides, dexmedetomidine, ondansetron) and combinations of opioids with different onsets of action.

The following is a review of the different pharmacological options used in perioperative multimodal analgesia.

Ketamine

Ketamine is pharmacologically classified as an N-methyl-D-aspartate (NMDA) receptor antagonist, although its action on different receptors is dose-dependent. Most ketamine preparations are racemic. The most active enantiomer, S-ketamine, has been available in Europe since 1994.[4]

The affinity of ketamine for opiate receptors has also been linked to its ability to produce analgesia at the level of the CNS and the spinal cord.

Subanaesthetic doses of ketamine ($\leq$0.3 mg/kg) are analgesic due to the drug's capacity to inhibit NMDA receptors. It also has an anti-inflammatory action by reducing IL-6 levels, and may prevent hyperalgesia in patients receiving remifentanil.

Because of this broad spectrum of action, ketamine has been used in multiple studies on multimodal analgesia for perioperative pain management.

Many anaesthesiologists are wary of using this drug due to its potent psychotogenic side effects. Most of these, however, appear after higher doses than those used in multimodal analgesia strategies.

Ketamine has been suggested as a concomitant drug in patients undergoing both general and regional anaesthesia.[5]

There is little consensus on the ideal route of administration of the drug in perioperative analgesia, but intravenous administration is generally thought to be better than epidural due to the risk of toxicity associated with the latter, and because other drugs (such as fentanyl or sulfentanil) can be administered via the epidural route. The correct dose, timing and duration of administration of intravenous ketamine is also unclear. Although many studies have explored this issue, we will focus on the conclusions published in the review by Gorlin et al.[6] in 2016:

- The ideal dose of sub-anaesthetic ketamine is <0.3 mg/kg (ideal weight).
- In interventions lasting <60 min, an induction dose of 0.1–0.3 mg/kg should be given.
- In longer surgeries, a dose of 0.1–0.3 mg/kg can be used for induction, repeating the bolus every 30–60 min.
- If ketamine will be administered in the immediate postoperative period, similar dosage as that given during induction should be used, followed by continuous infusion of 0.1–0.2 mg/kg, which can be maintained for 72 h. After the first 24 h, consider reducing infusion to a maximum of 10 mg/h.

Following the review published by Gorlin et al., Ramachandran and Rewari[7] called for more clinical guidelines to standardise administration of ketamine. All the evidence to date, however, shows that it is an effective analgesic and a useful additive in multimodal analgesia.

Magnesium

Magnesium is needed to maintain normal bodily functions.

At the pharmacological level, it acts as a non-competitive NMDA receptor antagonist and inhibits voltage-dependent calcium channels. Addition of magnesium reduces C-fibre activation by inhibiting the slow excitatory post-synaptic currents produced by NMDA receptor activation. NMDA receptor antagonists interfere with the influx of calcium and sodium into the cells that causes central sensitisation.[8] It also has a vasodilatory effect mediated by endothelium-nitric oxide.