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INVITED COMMENTARY

Ketamine stakes in 2018

Right doses, good choices

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This Invited Commentary accompanies the following original articles:
Boenigk K, Echevarria GC, Nisimov E, *et al*. Low-dose ketamine infusion reduces postoperative hydromorphone requirements in opioid-tolerant patients following spinal fusion: A randomised controlled trial. *Eur J Anaesthesiol* 2019; **36**:8–15.
Wang J, Echevarria GC, Doan L, *et al*. Effects of a single subanaesthetic dose of ketamine on pain and mood after laparoscopic bariatric surgery. A randomised, double-blind, placebo controlled study. *Eur J Anaesthesiol* 2019; **36**:16–24.

The studies from Wang *et al*.[1] and Boenigk *et al*.[2] published in this issue of the Journal raise fundamental questions about the current position of ketamine within modern multimodal analgesia.[3]

Synthesised in 1962 by Calvin Stevens, ketamine was first used in human experiments by Edward Domino and Guenter Corssen of the University of Michigan, who published the first clinical studies more than 50 years ago (1965). They described so-called dissociative anaesthesia, namely an electrophysiological and functional dissociation between thalamocortical and limbic systems.[4] From the outset, it was recognised that ketamine provided potent analgesia, but despite the fact that Sadove *et al*.[5] showed in 1971 that 'subdissociative' doses ($0.44\,mg\,kg^{-1}$) exhibited analgesic properties with only moderate adverse effects, psychomimetic effects and hallucinations were considered a problematic issue in the early 1970s, and were responsible for the subsequent fall of ketamine into relative oblivion (apart from unusual clinical settings such as shock, burns, cardiac tamponade or asthma).

The expansion of the use of remifentanil in the early 1990s changed the story.[6] Its short contextual half-life prompted a regular overdosage routine which was subsequently recognised as responsible for so-called opioid-induced hyperalgesia (OIH). The N-methyl-D-aspartate (NMDA) receptor involvement led to a triumphal comeback of ketamine as a NMDA blocking agent,[6] an action which was soon coined 'antihyperalgesic'.[7]

Nowadays, OIH and the so-called US opioid epidemic[8] which put the spotlight on the respiratory dangers of opioids have triggered a paradigm shift in the management of peri-operative pain. Some anaesthesiologists have dropped the obsolete concept of 'high-dose fentanyl anaesthesia'[9] for the promising one of 'opioid-free anaesthesia' (OFA).[10,11]

In spite of a lack of reduction in the visual analogue pain scores, the study by Wang *et al*.[1] tells us a new thing: as well as being the 'actor' of dissociative anaesthesia, ketamine is also responsible for 'dissociative analgesia', that is, preclusion of emotional translation of nociceptive perception. This finding may be put in perspective with the blossoming of ketamine use as a fast antidepressant in patients with a high suicide risk[12] (a property known for more than 40 years[13] and rediscovered about 15 years ago),[14,15] and the recent development of innovative psychedelic therapeutics, including ketamine, in palliative medicine.[16]

However, previous works had demonstrated the failure of single ketamine bolus doses to reduce postoperative pain.[17,18] Moreover, boluses of $1\,mg\,kg^{-1}$ administered at induction of anaesthesia were clearly inefficient in the recent Prevention of Delirium and Complications Associated with Surgical Treatments trial, where neither pain intensity nor opioid use was diminished.[19] It must be kept in mind that following a bolus dose of $0.5\,mg\,kg^{-1}$, ketamine concentration falls beneath $150\,ng\,ml^{-1}$ after only 10 min, and less than 25 min after a bolus dose of $1\,mg\,kg^{-1}$ (Fig. 1).

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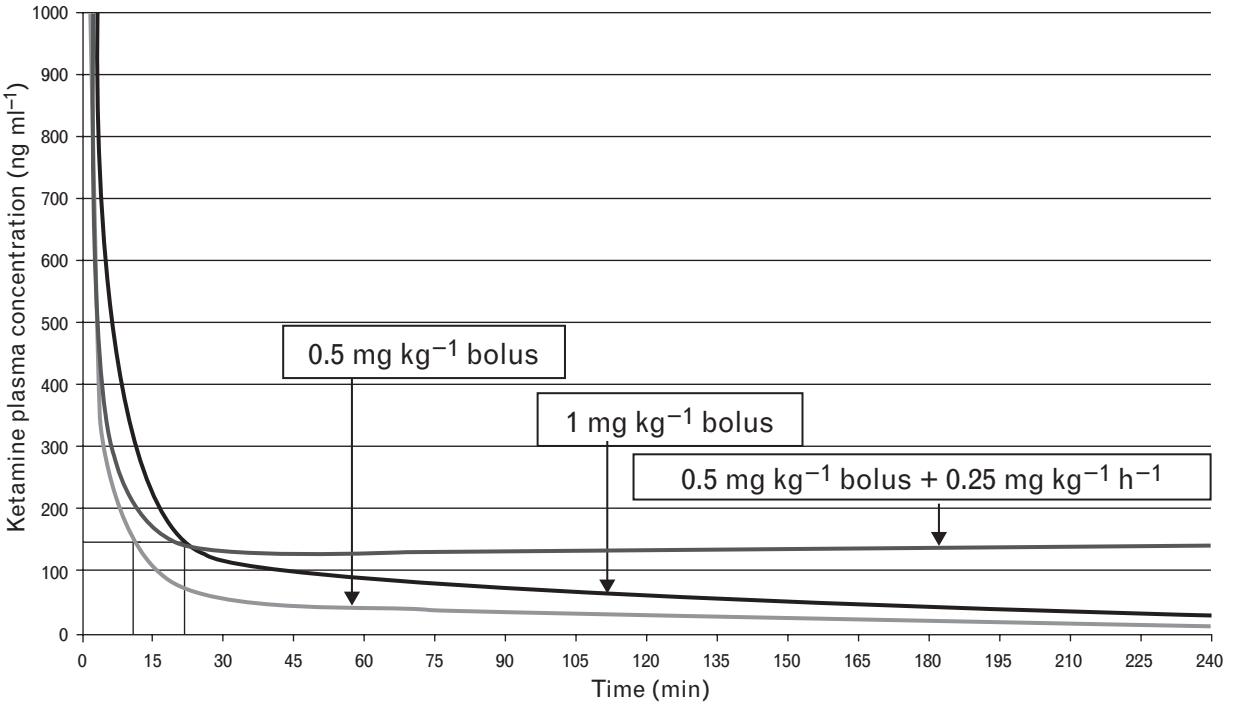
Fig. 1



The figure shows the plasma concentration obtained according to the Domino model (Rugloop II software; Demed, Temse, Belgium). Two single boluses are illustrated. After a 0.5-mg kg^{-1} ketamine bolus, plasma concentration falls below 150 ng ml^{-1} at 10 min. After a 1-mg kg^{-1} bolus, this concentration is obtained before the 25th minute. A 0.25 mg kg^{-1} h^{-1} infusion rate administered after a 0.5-mg bolus gives an analgesic concentration (around 150 ng ml^{-1}) aimed to attain preventive analgesia.

Ketamine is a 'use-dependent' drug: it blocks NMDA channels only if they have already been opened by intense or repeated noxious stimuli. This 'foot in the door' blockade[20] explains why administration prior to the start of surgery is of no peculiar interest. Moreover, the Boenigk *et al.*[2] study enlightens an interesting part of this fundamental concept: the fact that ketamine is much more efficient when the 'door has been opened' by prior use of opioids. We guess that the same happens when NMDA receptors are opened by intense nociceptive stimuli. Indeed, ketamine was shown 17 years ago to prevent chronic postoperative pain after major abdominal surgery, but to achieve this goal, it seems mandatory to use a continuous infusion of at least 0.25 mg kg^{-1} h^{-1}.[21] Finally, Zakine *et al.*[22] showed that it could be even better to administer ketamine during the early postoperative days.

To conclude, we were told as early as 2005 that continuous administration of ketamine was mandatory for preventive analgesia.[23] Nearly 15 years of use have confirmed that small concentrations of ketamine are safe and have no propensity to trigger the adverse effects (cardiac, cerebral) attributed to hypnotic doses.[2] In the era of OFA, it may be time to consider the use of a continuous infusion of ketamine for noxious surgery or to diminish opioid exposure in endangered patients such as those with respiratory disease, obesity or obstructive sleep apnoea.

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