Ketamine: new uses for an old drug?

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In 1996, we published an editorial ‘Ketamine, mechanism(s) of action and unusual clinical uses’ in the British Journal of Anaesthesia.1 In that editorial, we described the pharmacology of ketamine including bronchodilator, anti-shock, and neuroprotective actions along with some unusual clinical applications. The editorial has been cited more than 130 times in total with around 10 citations every year, which implies that ketamine is still of interest to a wide audience. However, as ketamine anaesthesia is associated with cardiovascular hyperdynamics and disturbing emergence reactions, this agent is often avoided, despite the ease with which these adverse reactions can be prevented by pre-administration, co-administration of sedatives, or both such as benzodiazepines, propofol, dexmedetomidine, or droperidol.

In the past 15 yr, ketamine has been reported to possess several new clinically beneficial properties such as potentiation of opioid analgesia, prevention of opioid-induced acute tolerance and spinal ischaemia, anti-inflammatory actions, preventive effects on recall and awareness during general anaesthesia, and anti-tumour actions. In this ‘update’ editorial, we have focused on these potential clinical advantages of ketamine.

Antinociception

Ketamine per se produces antinociceptive actions via inhibition of N-methyl-d-aspartate (NMDA) receptors1 and activation of descending inhibitory monoaminergic pain pathways. NMDA receptor-mediated spinal reflexes are intimately involved as the pharmacological basis for wind-up, which contributes to neuropathic pain. Ketamine prevents pain associated with wind-up.2 However, ketamine is rarely used as a sole analgesic agent for postoperative pain control as it produces psychotomimetic adverse reactions. Low-dose ketamine is often used as an adjuvant to opioid-induced analgesia.

Potentiation of opioid analgesia

Ketamine even at non-analgesic doses has been reported to potentiate opioid analgesia in rodents. An investigation of sub-analgesic doses of ketamine (30 mg kg−1 i.p.) on analgesia induced by morphine (2.5, 5.0, and 7.5 mg kg−1, s.c.) using the tail-flick test in rats found that the combination of morphine and ketamine resulted in a dose-related increase in both intensity and duration of morphine antinociception.3 This potentiation has also been reported clinically. A systematic review of randomized, controlled clinical trials of ketamine addition showed that ketamine reduced 24 h patient-controlled analgesia (PCA) morphine consumption and post-operative nausea or vomiting.4 In addition, they described that adverse effects were mild or absent. A recent review of randomized, double-blinded clinical trials of ketamine added to opioid in i.v. PCA for postoperative pain found that the ketamine–opioid combination could significantly reduce pain scores, cumulative morphine consumption, and postoperative desaturation in patients undergoing thoracic surgery, although this is less clear in orthopaedic or abdominal surgery.5 Ketamine may be useful as an efficient adjuvant analgesic in chronic pain or palliative care patients. Patients with uncontrolled severe pain receiving i.v. or epidural PCA obtained analgesia with ketamine.6 In a group of patients with intractable cancer pain, ketamine reduced the total daily dose of morphine required by 50% in 12 patients; eight patients were able to go home with a portable pump delivering morphine and ketamine.7

The mechanism of opioid acute tolerance and preventive effects of ketamine

Although opioids are often used as sole analgesics during anaesthesia and for postoperative pain control, opioids have been reported to produce hyperalgesia and tolerance.8,9 These effects are particularly important in patients suffering from intractable severe pain caused by malignancy, trauma, or neuropathy. Tolerance and dependence result from long-term exposure, high-dose exposure, or both to opioids. Basic research suggests that receptor desensitization comprising loss of receptor function and internalization is involved.8,9 Changes in opioid receptor conformation caused by agonist-induced receptor phosphorylation increase opioid receptor affinity for cytosolic β-arrestins. Interaction of β-arrestins with opioid receptors results in redistribution of opioid receptors from the plasma membrane to intracellular vesicles. This process has been defined as
opioid receptor internalization. β-Arrestin also desensitizes cells to opioid by functional uncoupling μ-opioid receptors.

It is important, however, to remember that these general processes are opioid-dependent. Noxious stimuli such as surgery may also produce opioid receptor internalization via NMDA receptor-mediated opioid release. Pretreatment with NMDA receptor antagonists (MK801, AP5, MRZ2/576, and MRZ2/596) significantly inhibited μ-opioid receptor internalization in neurones caused by laparotomy in guinea pigs.10 In this context, ketamine is a non-competitive antagonist of the NMDA receptor.1 In addition, at clinically relevant concentrations, ketamine interacts with the phencyclidine (PCP)-binding site leading to a significant inhibition of NMDA receptor activity.1 This interaction with the PCP-binding site appears to be stereoselective with affinity (K_i) values of 3.2 and 1.1 μM for S(+)- and R(−)-ketamine, respectively, implying that subanaesthetic concentrations of ketamine inhibit the NMDA receptor via the PCP-binding site.1 It could therefore be predicted that ketamine could inhibit opioid receptor internalization. Indeed, ketamine prevents opioid-induced hyperalgesia and acute tolerance. In rats, fentanyl produced analgesia but also induced early (hours) and long-lasting hyperalgesia (days) and acute tolerance to the analgesic effects of morphine, but ketamine pretreatment completely prevented both hyperalgesia and tolerance.11 After systemic administration, ketamine is treatment completely prevented both hyperalgesia and tolerance.

Interaction of ketamine with opioid receptors

Subanaesthetic doses of ketamine potentiate opioid-analgesia via NMDA receptor block, but what about anaesthetic doses? Ketamine has been reported to interact with MOP(μ)-, DOP(δ)-, and KOP(κ)-opioid receptors.1 Clinical studies show that S(+)-ketamine produces two to three times more potent antinociception than R(−)-ketamine,1 and in agreement with these clinical observations, S(+)-ketamine produces a two- to three-fold stereoselectivity (for binding not function) at μ- and κ- but not δ-receptor.1 11 Morphine, but not ketamine, analgesia can be reversed by microinjection of naltrexone into the periaqueductal gray (PAG) region of the rat brain, which contains μ- but not κ-receptor.1 Moreover, microinjection of ketamine into the PAG did not produce analgesia but antagonized the effects of morphine. We previously found that anaesthetic concentrations of ketamine reversed both μ- and κ-opioid inhibition of the formation of cyclic adenosine monophosphate (as a marker of receptor activation) in Chinese hamster ovary cells expressing recombinant μ- and κ-opioid receptors, similar to naloxone.13 These data suggest that anaesthetic concentrations of ketamine could exert antagonistic actions at both μ- and κ-opioid receptors. Therefore, high-dose ketamine may not be an appropriate addition to opioids.

Anti-inflammatory effects

We have previously reported that i.v. ketamine14 inhibits albumin extravasation in a rat model of chemical peritonitis. Recently, the immunoinhibitory effects of ketamine were found to be partly due to inhibition of transcription factor activator protein-1 and nuclear factor-κB (NF-κB), which regulate the production of proinflammatory mediators.15 In vivo, a subanaesthetic dose of ketamine produced a dose-dependent decrease in mortality with a significant reduction in the production of tumour necrosis factor-α and interleukin (IL)-6 in septic rats.16 An anaesthetic dose of ketamine attenuated lipopolysaccharide-induced liver injury with a reduction in cyclooxygenase-2, inducible nitric oxide synthase protein, and NF-κB-binding activity.17 These data clearly indicate that ketamine may exert anti-inflammatory actions in vivo. These anti-inflammatory effects of ketamine have also been found in clinical settings. A low dose of ketamine (0.25 mg kg−1) significantly suppressed intraoperative and postoperative increases in serum IL-6 in patients undergoing coronary artery bypass graft surgery (CABG) with cardiopulmonary bypass (CPB)18 and significantly decreased superoxide production after on-pump CABG.19 Similarly, low-dose ketamine (0.5 mg kg−1) attenuated the increases in serum C-reactive protein, IL-6, and IL-10 after cardiac surgery with CPB.20 However, low-dose ketamine was not shown to have any anti-inflammatory effects in low-risk patients undergoing off-pump coronary artery bypass graft surgery.21 The link remains controversial.

Prevention of awareness, recall, or both during general anaesthesia

Errando and colleagues22 reported that the incidence of awareness with recall and dreaming during general anaesthesia were relatively high, 1.1% with propofol–total intravenous anaesthesia and 0.59% with balanced anaesthesia (i.v. agent induction with halogenated maintenance). Long-term potentiation (LTP) or increased amplitude of excitatory post-synaptic potentials after high-frequency stimulation) of synaptic transmission in the hippocampal CA1 region contributes to learning and memory processes.23 As memories are thought to be encoded by synaptic modification in the hippocampus, LTP is considered as one of the major cellular mechanisms of learning and memory.23 A study of recall during spinal anaesthesia under propofol sedation (mean 4.2 mg kg−1 h−1) sufficient to maintain bispectral index 70 found that 56% of patients had recall.24 In contrast, several reports suggest that subanaesthetic doses of ketamine may inhibit LTP via NMDA receptor block.25 Indeed, clinical investigations26 clearly show that subanaesthetic doses of ketamine impair memory and recall. A comparison of sedation quality during bronchoscopy between propofol-
alfentanil (Group PA, \( n=138 \)) and propofol–ketamine (Group PK, \( n=138 \))-treated groups showed that recall was significantly lower in the PK group.\(^{27} \) Although these reports support our hypothesis that the preventive effects of propofol on recall might be weak, further clinical studies are required.

### Anti-tumour effects

Although a variety of surgical procedures for malignancy are performed under general anaesthesia, it is unclear how anaesthetics affect the behaviour of malignant tumours. Uncontrolled cell proliferation, local invasion, and metastasis are responsible for the progression of malignant tumours. It has been reported that glutamate receptor subunits are expressed in a variety of tumour cells such as glioma, colo-rectal and gastric cancer, oral squamous cell carcinoma, prostate cancer, melanoma, and osteosarcoma.\(^{28} \) In addition, glutamate and its receptors may regulate tumour growth as glutamate receptor antagonists limit proliferation.\(^{29} \) NMDA receptor block has been reported to inhibit several tumour-related actions. The NMDA receptor antagonist MK801 inhibited extracellular signal-regulated kinase 1/2 pathway, an intracellular signalling cascade, and the proliferation of lung carcinoma cells.\(^{30} \) MK801 also improved the survival of mice with metastatic lung adenocarcinoma and slowed the growth of neuroblastoma and rhabdomyosarcoma in mice. The NMDA receptor antagonist AP5, or silencing the NMDA receptor NR2A subunit, suppresses cell proliferation due to cell cycle arrest at G1 phase in MKN45 gastric cancer cells.\(^{31} \) It has been reported that most breast cancer cells expressed functional NMDA1 and NMDA2 receptors which play important roles in human breast cancer xenografts (e.g. Mc-f in mice).\(^{32} \) Moreover, daily administration of MK801 completely arrested the growth of the Mc-f-human mouse-xenograft. Accordingly, NMDA receptor antagonism with ketamine (which binds to the same site as MK801) should exert anti-tumour actions. Indeed, ketamine suppressed the proliferation of rat glioma (but not normal brain) cells and induced apoptosis (Niwa and colleagues, unpublished data). Clinical investigations are required to evaluate the anti-tumour effects of ketamine on postoperative outcome such as survival rate in patients undergoing tumour resection.

### Neuroprotective effects of ketamine

#### Cerebral ischaemia

As activation of NMDA receptors induces cerebral ischaemic damage, ketamine clearly has a neuroprotective potential. Indeed, experimental reports suggest neuroprotective effects of ketamine. Ketamine improved neuronal outcome from incomplete cerebral ischaemia in rats by a mechanism related to a decrease in plasma catecholamine levels, improved neurological outcome with a reduction in volume of haemorrhagic necrosis in head trauma rats, and attenuated damage in the caudoputamen of hypocapnic rats with chronic cerebral hypoperfusion.\(^{1} \) In the clinical setting, ketamine may also produce neuroprotective actions as several reports show that ketamine attenuated postoperative delirium and cognitive dysfunction in patients undergoing cardiac surgery.\(^{33} \) However, it remains unclear whether ketamine could exert neuroprotective effects in other surgical groups who are not subjected to the stress of CPB.

#### Opioid-induced spinal ischaemia

Several articles\(^ {34} \text{–} 35 \) suggest that opioids worsen spinal ischaemia. Intrathecal administration of \( \mu \)- and \( \delta \)-, but not \( \kappa \)-opioid, receptor agonists increased spasticity in a dose-dependent manner after a short period of spinal cord ischaemia in rats.\(^ {36} \) Although opioids such as morphine, fentanyl, and remifentanil are often used as analgesics for thoracoabdominal aortic aneurysm repair surgery, opioids may be involved in neuronal injury in the spinal cord after aortic cross-clamping as naloxone could attenuate neurological consequences of spinal injury in rats. NMDA receptor activation could contribute to this opioid-induced neurotoxicity.\(^ {37} \) Ketamine might therefore attenuate opioid-induced degeneration of spinal motor neurones.

We have introduced what we believe to be clinically important beneficial effects of ketamine. However, as most published clinical trials were of limited size, the data from these trials used to determine optimal dose and timing of administration are questionable. In addition, long-term follow-up data are lacking. Therefore, large clinical trials are required to address these issues.

### Conflict of interest

K.H. organized the 17th Japanese Society of Intravenous Anesthesia Meeting in 2010 that was partly supported by several Pharmaceutical companies including Daichi Sankyo Co. Ltd who provides ketamine in Japan. The support was used for meeting running costs. In addition, K.H. has received a lecture fee from this company in the past 5 yr. D.G.L. is a Director on the Board of the British Journal of Anaesthesia.

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