Abstract

Objective: Ketamine is an anaesthetic agent with a unique dissociative profile and pharmacological effects ranging from the induction and maintenance of anaesthesia to analgesia and sedation, depending on the dose. This article provides information for the clinical use of ketamine in anaesthesia, in both conventional and special circumstances.

Methods: This is a non-systematic review of the literature, through a PubMed search up to February 2021.

Results: With a favourable pharmacokinetic profile, ketamine is used in hospital and prehospital settings for emergency situations. It is suitable for patients with many heart conditions and, unlike other anaesthetics, its potential for cardiorespiratory depression is low. Furthermore, it may be used when venous access is difficult as it may be administered through various routes. Ketamine is the anaesthetic of choice for patients with bronchospasm thanks to its bronchodilatory and anti-inflammatory properties.

Conclusion: With a favourable pharmacokinetic profile, ketamine is used in hospital and prehospital settings for emergency situations and is suitable for patients with many cardiac and respiratory conditions.

Keywords: anaesthesia, dissociative profile, ketamine.

Citation
Natoli S. The multiple faces of ketamine in anaesthesia and analgesia. Drugs in Context 2021; 10: 2020-12-8. DOI: 10.7573/dic.2020-12-8
channel, it can be reached and bound to only when the receptor is activated. Furthermore, the ability of ketamine to bind to and dissociate from the PCP binding site in vivo is dictated by the degree of activation of the receptor, which depends on glutamate release in the synapses, cell membrane depolarization and the levels of other modulatory factors (Figure 2). The affinity of ketamine to the NMDAR is similar to that of other non-competitive NMDA antagonists. In rodents, higher-affinity NMDA antagonists determine neurotoxicity, neuronal vacuolization and neurodegeneration, although this has not been demonstrated in primates. High-affinity compounds, which are administered in the therapeutic dose range, determine learning and memory impairment, sedation, ataxia, and psychotomimetic effects, such as hallucinations in humans, whereas low-affinity blockers, such as memantine, seem to have a better therapeutic index and an activity similar to that of magnesium, which is an endogenous NMDA channel blocker.

The effects of ketamine on the central nervous system (CNS) seem to go beyond NMDAR blocking; several molecular targets and neurophysiological properties are known, although many mechanisms of action remain to be understood. Ketamine interacts with opioid receptors and blocks monoaminergic reuptake and muscarinic receptors as well as voltage-sensitive ion channels (Table 1).

It is well known that the affinity of ketamine to opioid receptors may be relevant at high doses and related to its anaesthetic activity, whilst low doses (≤0.3 mg/kg intravenous (i.v.)) have an analgesic effect. Topically administered ketamine displays local anaesthetic properties due to the ability to block the conductance of ion channels.

Due to the lipid solubility of ketamine and its relatively low protein binding (about 20–50%), a considerably large volume of distribution (3–5 L/kg) is attained after either an i.v. or an intramuscular (i.m.) bolus dose. In addition, ketamine quickly crosses the blood–brain barrier, and concentrations in the cerebrospinal fluid may be four- to five-fold higher than in plasma. Due to these pharmacokinetic features, the analgesic effect of ketamine has a rapid onset.

Ketamine is mainly metabolized in the liver and several metabolites have been identified. Although there are some dissonant results regarding the contribution of enzymes to clinical ketamine metabolism, CYP2B6, CYP3A4 and CYP2C9 contribute to the production of norketamine via ring hydroxylation and N-demethylation pathways. This primary metabolite is pharmacologically active, with 30% of the anaesthetic and analgesic potency compared with the parent compound, and is further metabolized to 4-, 5- and 6-hydroxynorketamine by CYP2B6 and CYP2A6. Children are known to require relatively higher doses of ketamine compared with adults although the pharmacokinetics were found to be similar. It is possible that pharmacokinetic modelling may not apply to the paediatric population as analyses were scaled to a standardized 70 kg patient. Thus, dosing by titration to effect is advisable in children whilst dosing by body weight may not be reliable. Elderly patients behave as poor metabolizers, hence a lower dosing is recommended. In addition, the effect of metabolic enzyme variants or sex on pharmacokinetics is still unknown.

Ketamine can be administered through various routes. The more conventional route is i.v. but i.m. injection can be used
Figure 2. The activated primary nociceptive afferent from the periphery releases glutamate at the second-order sensory neuron in the dorsal horn of the spinal cord, which binds to N-methyl-D-aspartate (NMDA) receptors. Ketamine blocks the NMDA receptor, which attenuates the development of central sensitization as well as opioid tolerance and hyperalgesia.

Table 1. Pharmacological actions of ketamine.

| Molecular target                  | Mechanism          | Potency (μM) | References |
|-----------------------------------|--------------------|--------------|------------|
| NMDA receptor (PCP site)          | Antagonism         | Kᵢ 0.4–46   | 6,7,9,138  |
|                                   |                    | ICₛₒ 1.6–6.2 |            |
| μ-Opioid receptors                | Agonism            | Kᵢ 27       | 13,14,139  |
| δ-Opioid receptor                 | Agonism            | Kᵢ 101      | 13,139     |
| k-Opioid receptor                 | Agonism            | Kᵢ 85       | 13         |
| Sigma receptor                    | Agonism            | Kᵢ 66       | 13         |
| Noradrenaline transporter         | Inhibition of reuptake | Kᵢ 67    | 14,140     |
| Dopamine transporter              | Inhibition of reuptake | Kᵢ 162    | 140        |
| Serotonin transporter binding     | Inhibition of reuptake | Kᵢ 67    | 140        |
| Muscarinic, nicotinic receptor    | Antagonism         | IC₅₀ >50 or 100 | 16,17     |
| Voltage-dependent Na⁺, Ca⁺⁺ channels | Block              | Kᵢ 67  | 19,21      |
| Dopamine D₂                       | Partial agonism    | Kᵢ 0.5     | 141,142    |
| Serotonin SHT₃                    | Antagonism         | Kᵢ 15      | 141        |

IC₅₀, half-maximum inhibitory concentration; Kᵢ, inhibitory constant; NMDA, N-methyl-D-aspartate.
when venous access is not available, retaining a satisfactory bioavailability (93%).

Ketamine is used in children and adults as an anaesthetic agent for diagnostic and surgical procedures as either i.v. infusion, i.v. injection or i.m. injection. It is often used for short procedures, but it can be used for longer procedures with additional doses or by i.v. infusion. If skeletal muscle relaxation is desired, a muscle relaxant can be used together with ketamine. Ketamine is recommended for the induction of anaesthesia prior to the administration of other general anaesthetic agents and to supplement other anaesthetic agents. To induce anaesthesia, an infusion of 0.5–2 mg/kg is typically administered with a duration of action of 5–10 min. Anaesthesia may be maintained using a microdrip infusion of 10–45 µg/kg/min.

**The role of NMDAR in the CNS**

Some considerations on the role of NMDA in the CNS may be useful to understand the anaesthetic activity of ketamine. NMDARs are widely expressed in the CNS and play critical roles in excitatory synaptic transmission, excitotoxicity and plasticity by participating in neuronal regeneration and circuit formation, coordinating functional circuits and controlling dendritic growth. Hence, NMDARs are essential to memory, to learning and during development. Excitotoxic events involving NMDARs have also been linked to degenerative diseases such as Alzheimer disease and Huntington disease.

The blockade of NMDARs is neuroprotective in animal models of both stroke and seizure but the therapeutic use of NMDA antagonists has failed in humans due to the development of severe side-effects because NMDARs are essential to physiological neuronal function.

An important element is that the NMDAR hypofunction produced by any mechanism can be psychotogenic, possibly resulting in dopaminergic hyperactivity and behavioural changes characteristic of schizophrenia. However, the mechanism linking NMDAR blockade by ketamine and psychosis remains to be established.

**The role of NMDAR in pain**

Peripheral nociceptor activation by high-energy stimuli can evoke pain. On peripheral nociceptor activation, glutamate is released in the dorsal horns of the spinal cord and binds to postsynaptic glutamate ionotropic AMPA and kainate subtype receptors that generate excitatory postsynaptic currents. The summation of multiple sub-threshold excitatory postsynaptic currents in the postsynaptic neuron induces firing of the action potential and transmission of the pain message to second-order nociceptive projecting neurons. However, pain responses are enhanced following repetitive stimulation of nociceptive afferents, leading to the well-known ‘wind-up’ phenomenon, a progressive increase of nociceptive response to each successive stimulus. Wind-up is a form of short-lasting synaptic plasticity that leads to nociceptive pathway potentiation. In humans, pain wind-up results from a temporal summation of either subjective pain intensity or nociceptive flexor reflexes evoked by repetitive noxious stimuli and can be prevented by low-dose ketamine-blocking NMDARs. Wind-up can only be evoked if small-calibre afferents are involved, eliciting the release of substance P and calcitonin gene-related peptide along with glutamate in the dorsal horn. The presence of both glutamate and neuropeptides in the synaptic cleft induces a relatively more prolonged postsynaptic depolarization compared to glutamate alone. Under these conditions, the normally inactive NMDA glutamate receptor unblocks and lets calcium in. Indeed, at normal resting membrane potentials, NMDAR is blocked by magnesium ions in a voltage-dependent manner. Sustained membrane depolarization can reduce the blockage because a lower electrical gradient may force magnesium into the channel. Thus, a prolonged and lasting synaptic activity can amplify current flow through open NMDA channels. When nociceptive inputs are intense and prolonged (i.e. induce high-frequency nociceptor firing), NMDAR is involved, inducing wind-up in second-order nociceptive neurons and leading to short-term central sensitization. In the context of inflammation or tissue injury, this short-living synaptic plasticity induces secondary hyperalgesia, which may be an excessive response to nociceptive stimuli out of the primary injury site or stimulation site that can endure until healing occurs and inflammation fades. However, repetitive primary afferent stimulation at frequencies much higher than those that evoke wind-up may induce long-term potentiation (LTP) of the nociceptive pathway. LTP is a well-described event in several neural networks and is the neural basis of processes such as learning and memory. LTP mechanisms include the NMDA-mediated elevation of cytosolic Ca2+ in the postsynaptic neuron and subsequent downstream activation of signalling pathways and second messenger systems such as kinases (such as MAPK, PKA, PKC, PI3K and Src) as well as the release of nitric oxide by Ca2+-activated neuronal nitric oxide synthase and the release of prostaglandins by cyclooxygenase enzymes, which may further increase the excitability of these neurons in the long term.

Together, these downstream effects of NMDA activation result in the amplification of pain messages.

Under normal conditions, high-frequency firing able to induce LTP does not usually occur in nociceptive C-fibres. However, bursts of ectopic activity recorded from nociceptive primary afferents in pain patients with nerve injury can be sufficient to trigger sustained NMDA activation and LTP, which is the neural basis of chronic pain within the spinal cord.

Central sensitization is a major pathophysiological event common to inflammatory and neuropathic pain. It is important to understand that central sensitization is a physiological and reversible adaptive mechanism during inflammatory pain, whereas it is a pathological, hardly reversible and maladaptive event when neuropathic pain occurs. However, the diverse events that converge onto the mechanism of NMDAR-mediated pronociceptive plasticity and central sensitization can
potentially lead to chronic pain regardless of the trigger. When peripheral tissue damage occurs, the subsequent inflammatory process induces changes in peripheral nociceptive endings, resulting in peripheral activation and sensitization and a further increased firing rate that leads to rapid-onset homosynaptic and heterosynaptic facilitation in the dorsal horn of the spinal cord in a short-term wind-up-like manner. However, for some reason, the physiological short-term synaptic potentiation may turn into a longer-term LTP-like increase in synaptic strength and maintenance of central sensitization and hence into chronic pain, which most frequently occurs as a result of maladaptive repair of the injured nervous system in neuropathic pain.48

Clinically, manifestations of central sensitization are hyperalgesia (an increased pain response to mild noxious stimuli) and allodynia (abnormal pain caused by normally innocuous stimuli) and reduction in opioid responsiveness or opioid-induced hyperalgesia, in both neuropathic and inflammatory pain. This state can be prevented or reduced by i.v. infusion of low-dose ketamine either in the setting of acute inflammatory pain69–54 or in chronic pain conditions, including osteoarthritic and rheumatoid pain, neuropathic pain, fibromyalgia, irritable bowel syndrome and migraine.55–66

Based on this rationale, ketamine – the most potent of all NMDA antagonists currently available for use in humans – has been used in various pain states, including acute, chronic and neuropathic pain (Figure 2).

Ketamine advantages in anaesthesia

Ketamine has many attributes yet many drawbacks. It affects the CNS by producing a unique dissociative state wherein a patient’s eyes are open but disconnected from the surroundings, in a cataleptic condition with strong analgesia and sedation.67

Ketamine has undoubted advantages for anaesthetists (Table 2). Its unique pharmacokinetics properties that provide a high bioavailability (between 100% when administered by the i.v. route and 93% for i.m. administration) have led to its prevalent use in hospital and prehospital environments for emergencies. Ketamine can also be applied via rapid-sequence induction, producing dissociative anaesthesia ~1–2 min after administration.

Unlike other general anaesthetic agents, ketamine shows no direct interaction with GABA receptors at clinically relevant concentrations. Indeed, subanaesthetic doses of ketamine do not bind to GABA-A receptors in the human brain,68 and anaesthetic concentrations of ketamine do not alter GABA-A receptor function in vitro.69 Thus, at least at subanaesthetic doses, the effect of ketamine on GABA-A receptor activity might only be indirect. As a consequence, relevant cardiorespiratory depression after induction is unlikely, especially if ketamine is given slowly or as monotherapy.70

More recent literature highlights that ketamine may produce a dose-dependent GABA release in specific brain cortical areas, thus altering the overall glutamate–GABA balance. Another work suggests that ketamine may decrease GABA release by blocking NMDAR located on GABAergic interneurons, thus increasing cortical excitability.71 These latter mechanisms may underlie the antidepressant effects of ketamine in treatment-resistant depression.71

The possibility to administer ketamine by different routes has prompted its use when venous access is difficult such as in trauma patients with hypovolemic shock. Indeed, the low cardiorespiratory depressant effects and sympathomimetic effects of ketamine render this drug a valid alternative to other anaesthetic agents in trauma patients as well as in septic shock patients, as several clinical reports have indicated that ketamine produced either no change or a slight increase in arterial pressure and heart rate.1,72 Indeed, it has been observed that ketamine can improve the blood gas and pulmonary function index of patients with acute lung injury caused by mechanical ventilation.73 With a wide variation in individual response, ketamine leads to increased blood pressure, stroke volume and

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Table 2. Advantages of ketamine in anaesthesia.

| Characteristic                  | Advantage                                                                 | References |
|--------------------------------|--------------------------------------------------------------------------|------------|
| Dissociative sedation          | Strong sedation and analgesia, useful for emergency in uncooperative subjects | 67         |
| High bioavailability           | Rapid action, for emergency in prehospital or hospital setting           | 108        |
| No direct interaction with GABA receptors | Cardiorespiratory depression is unlikely                           | 69,68      |
| Multiple administration routes | Useful when venous access is difficult                                   | 108        |
| Bronchodilatory activity       | Anaesthesia in patients with bronchospasm                               | 29         |
| Preserves haemodynamic stability | Anaesthesia in patients with congenital heart disease, shocked and hypotensive subjects | 76,115,119 |
| Analgesic activity             | Use for postoperative pain control                                        | 129–132    |
heart rate, and maintains systemic vascular resistance. These effects are commonly observed at a maximum of ~2 min after the injection and resolve over 15–20 min. However, severe hypotension after a ketamine bolus dose has been described as the loss of sympathoadrenal activity that accompanies the loss of consciousness.\textsuperscript{74}

The haemodynamic changes induced by ketamine make it suitable for patients with congenital heart defects and other cardiac conditions.\textsuperscript{75,76} However, it must be mentioned that ketamine is contraindicated in patients with serious myocardial disease or serious heart failure and when blood hypertension or increased myocardial oxygen consumption may be dangerous.\textsuperscript{31}

Due to its bronchodilatory properties, ketamine is the anaesthetic of choice for patients with bronchospasm\textsuperscript{29,77,78} and has also been successfully used as a medication in the treatment of status asthmaticus.\textsuperscript{79} Joint to anticholinergic and spasmyotic actions, ketamine may have some anti-inflammatory effects, which may contribute to its efficacy in asthma patients.\textsuperscript{80–82} Other mechanisms are the inhibition of catecholamine uptake and L-type Ca\textsuperscript{2+} channel blocking,\textsuperscript{83–86} although the precise mechanism by which ketamine induces airway muscle relaxation is still to be elucidated.

**Drawbacks of ketamine in anaesthesia**

NMDAR occupancy is related to the potential of ketamine to produce adverse symptoms.\textsuperscript{87} Emergence phenomena, delusions, hallucinations, delirium and confusion, sometimes described as ‘out of body’ and ‘near-death experiences’, are amongst the adverse effects related to the use of ketamine.\textsuperscript{88} These events are more common in patients older than 16 years, in women, during shorter operative procedures and when large doses of ketamine are administered quickly.\textsuperscript{89,90} Benzodiazepines effectively prevent these disturbing psychotic phenomena. Midazolam reduced the incidence of unpleasant dreams when compared with diazepam (number needed to treat of 6).\textsuperscript{91,92} Propofol, lorazepam and diazepam are also effective.\textsuperscript{93} In clinical practice, and in the opinion of some authors, the regular coadministration of benzodiazepines needs to be increased.\textsuperscript{94} Finally, a recent trial (n=100) reported that a positive persuasion may reduce unpleasant sensations.\textsuperscript{95}

Intracranial pressure is increased during ketamine use. Cerebral blood flow is increased secondary to a decrease in cerebral vascular resistance. Hence, ketamine should be avoided in patients with intracranial disease or abnormal cerebral blood flow.\textsuperscript{96}

Psychotic symptoms similar to schizophrenia have been described in association with ketamine activity; these need to be managed to reduce any undesired effects.\textsuperscript{87,97} Moreover, semantic and episodic memory may be impaired by subanaesthetic doses of ketamine.\textsuperscript{98,99}

Other adverse effects have been described after ketamine administration. These include nausea and vomiting in 5–15% of patients\textsuperscript{100} and hypersalivation, which can be anticipated by atropine.\textsuperscript{101} Limb purposeless movements and clonus have been occasionally reported.\textsuperscript{100}

**Anaesthetic effects**

During the ketamine-induced dissociative state, patients may appear awake with preserved airway reflexes and respiratory drive, but they are unable to respond to sensory input.\textsuperscript{102,103}

**Clinical use of ketamine**

In 1966, the anaesthetic effects of ketamine were reported for the first time in 130 patients aged 6 weeks to 86 years undergoing a total of 133 surgical procedures.\textsuperscript{104} Ketamine produced profound and rapid analgesia with a unique state of altered consciousness; its duration of effect was limited but could be safely prolonged with repeated administration.\textsuperscript{105}

A well-established use of ketamine is anaesthesia induction in the emergency setting in shocked or hypotensive patients.\textsuperscript{104} Ketamine was used for anaesthetic induction and maintenance in patients with cardiac tamponade and restrictive pericarditis.\textsuperscript{106} A study showed that ketamine was as safe and effective as etomidate for endotracheal intubation in critically ill patients with sepsis.\textsuperscript{107}

Ketamine is considered the i.v. anaesthesia induction agent of choice in patients with active bronchospasm because of its bronchodilating properties and allowing the use of high oxygen concentrations.\textsuperscript{108}

Ketamine is the anaesthetic drug of choice for the induction of patients with congenital heart disease with a right to left shunt because it increases systemic vascular resistance, resulting in a reduced right to left shunt.\textsuperscript{109} In a study, i.v. or i.m. ketamine as induction agents did not significantly affect the proportion of SaO\textsubscript{2} in patients with Fallot’s tetralogy.\textsuperscript{109} Finally, ketamine preserves intraoperative and postoperative haemodynamic stability in patients with congenital heart disease and is an alternative to sevoflurane.\textsuperscript{76,110}

Ketamine has a major role in repeated anaesthesia for burn dressings and for sedation during excision and grafting, both in adults and in children.\textsuperscript{111–113} The major advantage of ketamine in patients with burns is that it usually preserves airway and spontaneous respiratory function whilst providing good sedation and analgesia.\textsuperscript{111,114} In addition, the venous access may be difficult in patients with extensive burns and ketamine i.m. administration may be useful.\textsuperscript{115} Ketamine can be used for burn dressings in adults and children in combination with midazolam/dexmedetomidine or with propofol to obtain effective sedoanalgesia without any significant side effects.\textsuperscript{111,116}

Low-dose ketamine alone (5–25 mg/kg/min infusion) can be used for sedation and analgesia during local or regional anaesthetic procedures.\textsuperscript{106,117} Low doses (i.v. 0.5 mg/kg) may be combined with i.v. diazepam or midazolam for local and regional anaesthesia techniques, including spinal anaesthesia in adults and children.\textsuperscript{106} Prophylactic i.v. ketamine 0.5 mg/kg
before neuraxial blockade decreases the incidence of shivering, improves the haemodynamic profile, provides good sedation and prevents recall. Ketamine 1 mg/kg i.v. given before spinal anaesthesia results in good haemodynamic stability in elderly patients undergoing transurethral resection of the prostate.

Several authors found that ketamine reduced postoperative pain. Perioperative low-dose ketamine was found to improve postoperative analgesia following caesarean delivery with general anaesthesia. In a randomized study on 52 women, a ketamine bolus of 0.5 mg/kg i.v. was administered at the time of induction of general anaesthesia. After induction, a ketamine infusion of 0.25 mg/kg/h was started and discontinued at the end of surgery. Low-dose regimens (0.25–0.5 mg/kg i.v. as an initial bolus followed by 50–500 μg/kg/h) have been proposed for postoperative analgesia and for the reduction of exogenous opioid-induced hyperalgesia. In a recent review on postoperative pain, it was found that ketamine administered in addition to opioids for i.v. patient-controlled analgesia significantly reduced pain scores, cumulative morphine consumption and postoperative desaturation in patients undergoing thoracic surgery.

Post-tonsillectomy pain was controlled by low-dose ketamine 0.5 mg/kg i.v./subcutaneous at the end of surgery. After tonsillectomy, ketamine 0.5 mg/kg added to fentanyl 1 mg/kg improved analgesia without delaying hospital discharge in a study on 60 children.

In a prospective randomized study on 30 patients undergoing coronary artery bypass grafting surgery, the combination of ketamine compared with propofol, with midazolam and fentanyl for the induction of anaesthesia provided better haemodynamic stability during induction and until the end of sternotomy.

A systematic review with a meta-analysis of 12 randomized clinical trials, which included patients undergoing major or minor surgery, assessed the effectiveness of ketamine in reducing morphine consumption and pain intensity scores after remifentanil-based general anaesthesia. Ketamine reduced the use of morphine in the first 24 postoperative hours whilst postoperative pain intensity was improved in the first 2 hours in the minor and major surgery groups. In addition, ketamine significantly reduced pain intensity in the first 24 hours in the minor surgery group. Patients administered with ketamine and undergoing major surgery had a longer time to the first rescue analgesia.

Use of ketamine in children

Traditionally, ketamine is considered the agent of choice in children. It is suitable for use in paediatrics for analgesia, procedural sedation and anaesthesia, overcoming some barriers to achieving adequate paediatric analgesia, such as a culture of underdosing and difficulty obtaining i.v. access, thanks to the possibility of using a number of routes of administration and the pharmacokinetic profile.

No major side effects were reported when ketamine was used in 164 awake non-trapped children with blunt trauma for procedural sedation and analgesia.

In general anaesthesia, ketamine was safely used in addition to fentanyl or other anaesthesia induction, improving analgesia and intubation conditions and preserving haemodynamics in children with congenital heart or oncological disease. Ketamine 0.25 mg/kg reduced sevoflurane-induced postoperative agitation (n=60), whilst propofol 1 mg/kg was not effective. Less agitation compared with saline was also reported by two other studies.

Ketamine in combination with propofol ensured stable haemodynamics, with reduced incidence of adverse events compared to single agents, during anaesthesia induction in 120 children subjected to short-term elective and urgent interventions.

Finally, it may be mentioned that the incidence of psychotic phenomena at awakening is lower in children than in adults.

Conclusion

Ketamine can be considered as the most versatile drug for anaesthesia. It can be used solely or in combination with other coadjuvant drugs, increasing their efficacy. Ketamine has been widely used in several clinical settings due to its specific properties, including its neuroprotective and anti-inflammatory effects. In addition, subanaesthetic regimens of ketamine represent a great clinical advantage. With a favourable pharmacokinetic profile, ketamine is used in hospital and prehospital settings for emergency situations. It is suitable for patients with many cardiac conditions.

It may be used when venous access is difficult as it may be administered through different routes. Finally, it is the anaesthetic of choice for patients with bronchospasm thanks to its bronchodilatory and anti-inflammatory properties.


Acknowledgements: Editorial assistance was provided by Laura Brogelli and Aashni Shah (Polistudium SRL, Milan, Italy). Unconditioned support to this assistance was provided by Minerva Medica and Molteni Farmaceutici.

Funding declaration: Minerva Medica and Molteni Farmaceutici (Firenze, Italy) funded editorial assistance to the article.

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Article URL: https://www.drugsincontext.com/the-multiple-faces-of-ketamine-in-anaesthesia-and-analgesia

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Provenance: Submitted; externally peer reviewed.

Submitted: 17 December 2020; Accepted: 8 March 2021; Publication date: 23 April 2021.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: Plaza Building, Lee High Road, London, England, SE13 5PT.

BioExcel Publishing Limited is registered in England Number 1003893. VAT GB 252 7720 07.

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