Ketamine

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Abstract There are two optical isomers of the 2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone ketamine: S(+) ketamine and R(−) ketamine. Effects of this drug are mediated by *N*-methyl-d-aspartate (NMDA), opioid, muscarinic and different voltage-gated receptors. Clinically, the anaesthetic potency of the S(+)-isomer is approximately three to four times that of the R(−)-isomer, which is attributable to the higher affinity of the S(+)-isomer to the phencyclidine binding sites on the NMDA receptors. Ketamine is water- and lipid-soluble, allowing it to be administered conveniently via various routes and providing extensive distribution in the body. Ketamine metabolism is mediated by hepatic microsomal enzymes. It causes

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J. Schüttler and H. Schwilden (eds.) *Modern Anesthetics.*
Handbook of Experimental Pharmacology 182.

bronchodilation and stimulation of the sympathetic nervous system and cardiovascular system. In clinics, ketamine and particularly S(+)-ketamine are used for premedication, sedation, and induction and maintenance of general anaesthesia, which is than termed “dissociative anaesthesia”. Ketamine and its S(+)-isomer are ideal anaesthetic agents for trauma victims, patients with hypovolemic and septic shock and patients with pulmonary diseases. Even subanaesthetic doses of this drug have analgesic effects, so ketamine is also recommended for post-operative analgesia and sedation. The combination of ketamine with midazolam or propofol can be extremely useful and safe for sedation and pain relief in intensive care patients, especially during sepsis and cardiovascular instability. In the treatment of chronic pain ketamine is effective as a potent analgesic or substitute together with other potent analgesics, whereby it can be added by different methods. There are some important patient side-effects, however, that limit its use, whereby psycho-mimetic side-effects are most common.

1 History

In 1959 the search for a safe but potent sedative agent led pharmacologists to the phencyclidines (PCPs) (CI-395 and CI-400). Although CI-395 and CI-400 produced reliable sedation, the hallucinogenic effects that patients experienced upon reawakening were too severe to warrant widespread use, and therefore the search for related, but less hallucinogenic, compounds began (Johnson 1959). This finally led to the discovery of ketamine (CI-581), which was first synthesized in 1962 by Calvin Stevens at Parke-Davis and Co. Ketamine showed fewer severe adverse effects of the PCPs and was introduced into clinical practice by 1970, in time for use during the Vietnam War. But in the 1970s patients began also to report unwanted visions during ketamine’s influence.

2 Pharmacology of Ketamine

Ketamine is frequently described as a “unique drug” because it shows hypnotic (sleep producing), analgesic (pain relieving) and amnesic (short-term memory loss) effects; no other drug used in clinical practice combines these three important features at the same time. Ketamine is chemically (+/−) 2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone (Ketalar, Pfizer, Karlsruhe; Ketaject, Phoenix Pharmaceutical, St. Joseph, MO; Ketaset, Wyeth, Madison, NJ; Vetalar, Fort Dodge Animal Health, Fort Dodge, IA) and most commonly comes as a white crystalline powder, but can also be seen in liquid and tablet form.

Ketamine is characterized by a molecular weight of 274.4 M with the chemical formula: $C_{13}H_{16}ClNO$ (Fig. 1). The melting point of ketamine is found between 258°C and 261°C. Ketamine is water- and lipid-soluble, allowing it to be administered

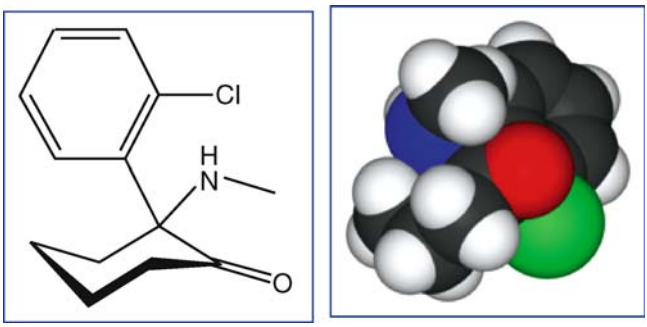

Fig. 1 Chemical structure of ketamine

conveniently via various routes while still rapidly crossing the blood–brain barrier. This agent has been administered by intramuscular injection, intravenous drip and bolus injection, intranasal solution, rectal solution and as an oral elixir.

Ketamine is characterized by a chiral structure consisting of two pure optically isomers. This is the result of an optic active centre in the C2 position of the molecule, which allows the existence of two molecules with the same empirical formula but different spatial structures resulting in an image and its mirror image. Both isomers possess identical chemical and physical properties except that one isomer turns polarized light left (−) and the other turns it right (+). As racemate—containing 50% of each isomer—the polarized light is not turned, since it turns to the left from half of the isomers and then back again from the other half. In order to denominate the assembly of the substitutes at the optic active centre, isomers are named S- and R-ketamine (Fig. 2).

Both enantiomers exhibit different clinical potencies and different affinities to the various receptors, which are also optically active. Different bindings of the enantiomers to receptors are called stereoselective bindings. Clinically, the anaesthetic potency of the S(+)-isomer is approximately three or four times that of the R(−)-isomer (White et al. 1980).

2.1 Pharmacokinetic Properties

Ketamine produces an anaesthetic state, which has been termed “dissociative anaesthesia”, characterized by analgesia and changes in vigilance and perception, but it is not a sedative or hypnotic. It appears that ketamine selectively interrupts the thalamocortical system. The patient rapidly goes into a trance-like state, with widely open eyes and nystagmus. He is unconscious, amnesic and deeply analgesic. His airway is remarkably open, with only slightly depressed pharyngeal-laryngeal reflexes preserved while the patient’s head in almost any position, far more so than with any other anaesthetic. Dissociative anaesthesia is a result of reduced activation in the thalamocortical structures and increased activity in the limbic system and hippocampus (Domino et al. 1965).

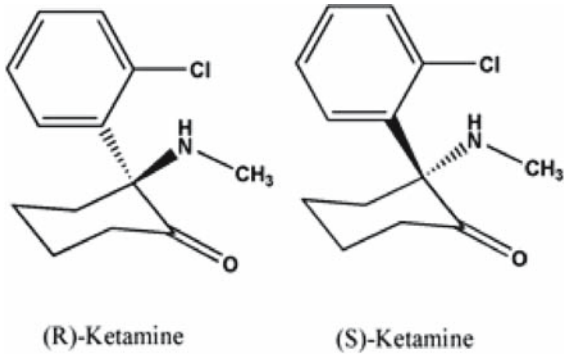

Fig. 2 Optical isomers of ketamine

Bioavailability following an intramuscular dose is 93%, an intranasal dose 25%–50%, an oral dose only 17%. Ketamine is rapidly distributed into the brain and other highly perfused tissues; 12% are protein-bound in the plasma. Therefore oral administration produces lower peak concentrations of ketamine, but increased amounts of the metabolites norketamine and dehydro-norketamine (Larenza et al. 2007). When intravenously administered, the onset of the first effects is seen within seconds, 1–5 min if injected intramuscularly, 5–10 min if snorted and 15–20 min if orally administered. If injected effects generally last 30–45 min, if snorted 45–60 min, and 1–2 h following oral ingestion. There is no direct correlation between ketamine concentrations and behaviour. Drowsiness and perceptual distortions may be dose related in a concentration range of 50–200 ng/ml, and analgesia begins at plasma concentrations of about 100 ng/ml. During anaesthesia, blood ketamine concentrations of 2,000–3,000 ng/ml are used, and patients may begin to awaken from a surgical procedure when concentrations have been gradually reduced to 500–1,000 ng/ml.

Both ketamine isomers are characterized by a short α half-life (2–4 min). The β half-life as determined mainly by redistribution is 8–16 min in adults. Ketamine has a low protein binding of 20%–30%. In vivo, S(+)-ketamine is not inverted to R(−)-ketamine; however, after racemate administration a statistically significant smaller clearance and volume of distribution for R(−)-ketamine compared with S(+)-ketamine was seen (Geisslinger et al. 1993). By hepatic biotransformation cytochrome P450 (CYP) 3A4 is the primary enzyme responsible for *N*-demethylation (metabolite I) of ketamine to norketamine, with minor contributions from CYP2B6 and CYP2C9 isoforms. The unconjugated *N*-demethylated metabolite was found to be less than one-sixth as potent as ketamine. Potential inhibitors of these isoenzymes could decrease the rate of ketamine elimination if administered concurrently; in contrast, potential inducers could increase the rate of elimination.

Additional breakdown via hydroxylation of the cyclohexanone ring results in hydroxyl-ketamine with a 0.1% anaesthetic potency. Ketamine and its metabolites undergo hydroxylation and conjugation with the water-soluble conjugates which

are excreted in the urine. Metabolism half-life is 2.5–3 h. The plasma clearance is 15–20 ml/kg per minute in adults and higher for S(+)-ketamine than for the enantiomer (Geisslinger et al. 1993). There are no other significant differences between the pharmacokinetic properties of the S-(+) and R-(−)-isomers. Even repeated doses of ketamine administered to animals did not produce any detectable increase in microsomal enzyme activity.

The urinary excretion of unmetabolized drug is approx. 4%. In forensic medicine, ketamine use can be detected in the urine for about 3 days. Concentration ranges for ketamine in urine have been reported as low as 10 ng/ml and up to 25 μg/ml.

2.2 Dosage

The therapeutic range of ketamine or S(+)-ketamine makes them one of the safest sedative agents for most emergency clinical and preclinical situations. Distinct and useful effects are obtained when the drugs are administered at different doses. Low-dose ketamine infusion provides potent analgesia, which is useful in conjunction with sedation or as a narcotic in areas with scarce resources.

2.2.1 Racemic Ketamine

Intravenously administered, the induction dose for general anaesthesia is 1–2 mg/kg; after induction, a continuous dose of 1–6 mg/kg per hour is necessary. In lower concentrations of 0.25–0.5 mg/kg an adequate analgesia can be seen. The same concentration is necessary for sedation, whereby a permanent dose of 0.4–1 mg/kg per hour is required for continuous sedation. To get the same effects by intramuscular injections 2–4 times higher doses have to be injected. Higher doses are also necessary for rectal (8–10 mg/kg) and nasal admission (5 mg/kg).

2.2.2 S(+)-Ketamine

The purely optical S(+)-isomer of ketamine is characterized by a higher affinity or potency to specific receptors, so that lower doses are required. For general anaesthesia 0.5–1 mg/kg followed by a continuous infusion of 0.5–3 mg/kg are necessary. For analgesia, doses of 0.125–0.25 mg/kg are helpful, whereby using these doses an additional sedation can be observed. In parallel to racemic mixtures for rectal as well as nasal administered, a dose reduction of 50% is recommended. These results are in a wide spread of plasma concentrations and absorption times. Rapid and high-level drug absorption after nasal drug administration is possible.

2.3 Ketamine Binding Sites

2.3.1 Glutamate Receptors

The major excitatory synaptic transmission in the mammalian CNS is mainly mediated by L-glutamate. This amino acid acts via ligand-gated ion channels: ionotropic glutamate receptors (iGluRs) and G protein-coupled (metabotropic) receptors (Hirota and Lambert 1996b). The iGluRs are ubiquitously expressed in the brain and spinal cord. Mammalian iGluRs are encoded by 18 genes which constitute three families of ionotropic glutamate receptors: *N*-Methyl-d-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and kainate.

Seven genes encode for the NMDA receptors (*NR1*, *NR2A–D*, *NR3A–NR3B*), four genes encode for the AMPA receptor (*GluR 1–4*) and five for the kainate (*GluR 5–7*, *KA1* and *KA2*) receptor. They can either exist as homomeric or heteromeric assemblies. Co-assembly of iGluRs within but not between families generates a large number of receptor subtypes. KA subunits are capable of forming channels when co-assembled with members of the GluR5–7 family (McBain and Mayer 1994; Mori and Mishina 1995; Mayer and Armstrong 2004).

iGluRs consist of multimeric assemblies of four or five subunits. Each subunit consists of three membrane-spanning segments with a pore loop forming the ion channel, a cytoplasm domain of variable length, the binding core, which consists of two domains, and the amino-terminal domain located on the cell surface. There is a great variety among the glutamate receptors. Multiple receptor isoforms with distinct brain distributions and functional properties emerge by selective RNA splicing of the NR1 transcripts and differential expression of the NR2 subunits.

2.3.2 NMDA Receptor

The NMDA receptor (Fig. 3) consists of a heterodimer formation between NR1 and one form of NR2 (NR2A-D). The glutamate-binding domain is located at the junction of the NR1 and NR2 subunits. The receptor contains binding places for glutamate, NMDA and, in the spinal cord and the lower brain regions, glycine. They allosterically influence the activity of the receptor. The NMDA receptor is a trans-membrane protein and forms an ion channel for Na^+, K^+ and Ca^{2+}. Thereby it spans the electric field generated by the membrane potential. Depending on agonist binding, the channel has different conducting states. The magnesium blockade of the open NMDA receptor channel is voltage-dependent. The magnesium binding site within the receptor is physically located within this electric field. The magnesium ion carries a double positive charge. When the cell is hyperpolarized, magnesium is stabilized inside the negative charged channels. At resting membrane potentials the NMDA receptor is inactive because of a voltage-dependent block of the channel pore by magnesium ions. As the cell is depolarized, the negative field effect weakens and the magnesium ions are released out of the channel and are rapidly substituted by another magnesium ion during repolarization. During the

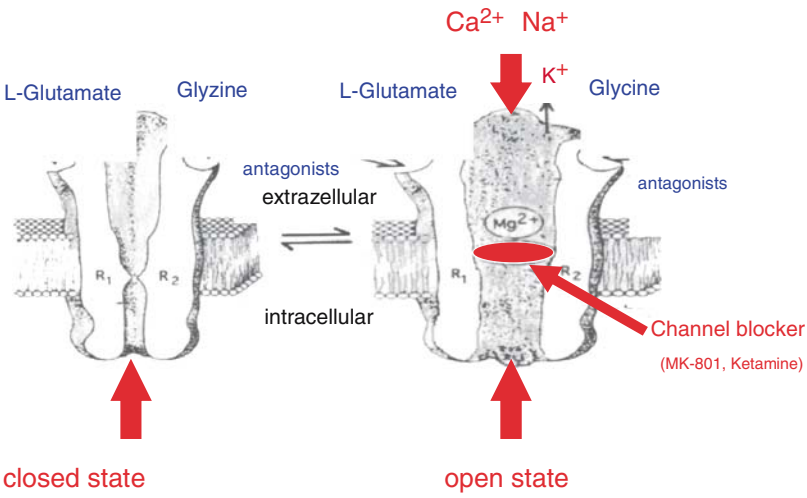

Fig. 3 *N*-Methyl-d-aspartate receptor

brief phase in which magnesium is absent from the open channel, Ca^{2+}-, Na^{+}- and K^{+}-ions flow through the channel. The Ca^{2+} influx is crucial for the induction of the NMDA receptor-dependent long-term potentiation (LTP), which is thought to underlie neuronal plasticity, learning and memory. NMDA receptors are included in the wind-up phenomenon, which is the result of central sensitization causing hyperalgesia and hyperexcitability and seems to be responsible for the development of chronic pain syndromes.

The activation of the NMDA receptor leads to a Ca^{2+}/calmodulin-mediated activation of NO synthetase, which plays a crucial role in nociception and neurotoxicity. NMDA receptors are involved in global and focal ischaemia and in various neurological diseases such as schizophrenia (Lindsley et al. 2006). While the NMDAR channel itself displays no voltage-dependency, the magnesium block confers voltage dependency to the channel. Effectively, the NMDA receptor is both a ligand-gated and voltage-gated ion channel.

Ketamine acts as an antagonist on the glutamate receptors (Irifune et al. 1992). Primarily like PCP, ketamine blocks the NMDA receptor non-competitively resulting in a use-dependent block. The binding site is located within the receptor at the PCP binding site. The PCP binding site is localized within the receptor and partially overlaps with the Mg^{2+} binding site. Ketamine blocks the open channel and reduces channel mean open time. Ketamine also decreases the frequency of channel opening by allosteric mechanisms. Both ketamine stereoisomers act via the same binding sites but with different affinities and potencies. The S(+)-isomer has a 3–4 times higher affinity than the R-enantiomer (Zeilhofer et al. 1992). As the NMDA receptor consists of various subunits, ketamine isomers possess different affinities to the various subunit compositions, resulting in different clinical effects. In addition, in

the spinal cord ketamine exerts its effects also via the NMDA receptor in clinically relevant concentrations.

2.3.3 Opioid Receptors

Currently there are four different opioid receptors (μ, κ, σ, δ) that belong to the group of G protein-coupled receptors inhibiting the adenylate cyclase (Fig. 4). The receptors mediate supraspinal (μ) and spinal (κ) pain. In animal experiments ketamine acts on all opioid receptors (Sarton et al. 2001) with different affinities (μ>κ>δ) (Smith et al. 1987; Sarton et al. 2001). S(+)-ketamine is about 2–4 times more potent on μ- and κ-receptors than the R-isomer whereas there is no stereoselective difference on the δ-receptor (Hustveit et al. 1995). The analgesic effects of ketamine are only partly reversible with high doses of naloxone, indicating an effect on the κ- rather than on the μ-receptors. Recent studies indicate a more antagonistic action on the μ- and an agonistic action on the κ-receptor. In a human study the analgesic and the sedative effects of ketamine could not be reversed by naloxone (Mikkelsen et al. 1999). κ-Agonists are known to induce psycho-mimetic reactions, which resemble the phenomenon observed during ketamine anaesthesia.

The role of the σ-opioid receptor is not yet clear. There are two types of σ-binding places: the naloxone-sensible σ1 binding place and the non-naloxone-sensible σ2 binding place. The R(−)-enantiomer has a higher affinity for both receptors than the S(+)-ketamine. Both isomers seem to induce negative inotropic (σ-1) and excitatory (σ-2) effects via σ-receptors.

In conclusion, ketamine has an analgesic effect on the spinal cord level but this probably does not involve opioid receptors (Hao et al. 1998) since the effects of

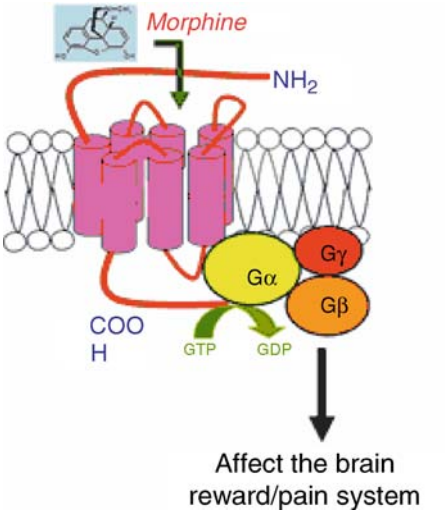

Fig. 4 Opioid receptor

ketamine on spinal or supraspinal opioid receptors play only a minor role in analgesia.

2.3.4 Nicotinic Acetylcholine Receptors

Human nicotinic acetylcholine receptors (nAch) consist of different α- and β-subunits of various compositions. Ketamine antagonizes nAch receptors non-competitively; receptors with mainly β-subunits are especially sensitive vs α-subunits (Yamakura et al. 2000). Ketamine lacks a stereoisomeric effect on the nicotinergic acetylcholine receptors at concentrations necessary for anaesthesia (Sasaki 2000) but interacts stereo-specifically with nAch receptors in human sympathetic ganglion cells (Friederich et al. 2000). This effect is antagonized by the central activating enhancement of the sympathetic nervous system.

2.3.5 Muscarinic Acetylcholine Receptors

Ketamine profoundly inhibits muscarinic signalling via m1 muscarinic receptors . This effect might explain some of the anti-cholinergic clinical effects of ketamine, both central (effects on memory and consciousness) as well as peripheral (prominent sympathetic tone, bronchodilation, mydriasis) (Durieux 1995; Fisher and Durieux 1996). Ketamine also affects m2 and m3 muscarinic receptors. This might contribute to amnesia and mydriasis bronchodilatation, and at least partly explains the increase of bronchial and mucus secretion.

2.3.6 $GABA_A$ Receptors

γ-Aminobutyric acid (GABA) is the major inhibitory transmitter system in the mammalian brain. The $GABA_A$ receptor (Fig. 5) is a pentameric structure consisting of five subunits which incorporates a Cl^- channel. The activation results in hyperpolarization of the neuronal membrane. Ketamine has only a very weak affinity to the $GABA_A$ receptor, leading to an increase in Cl^--permeability. In addition, GABA reuptake is attenuated by ketamine. In conclusion, the effects of ketamine on $GABA_A$ receptor do not significantly contribute to its clinical effect.

2.3.7 Local Anaesthetic Effects/Sodium Channels

Ketamine, similar to local anaesthetics, reduces sodium permeability in isolated neurons in clinically relevant concentrations (Dowdy et al. 1973; Arhem and Rydqvist 1986). After spinal or epidural application in rats, ketamine induces a decrease in blood pressure and an increase in heart rate comparable to the sympathicolysis and limb weakness that results from increasing the dosages of classical

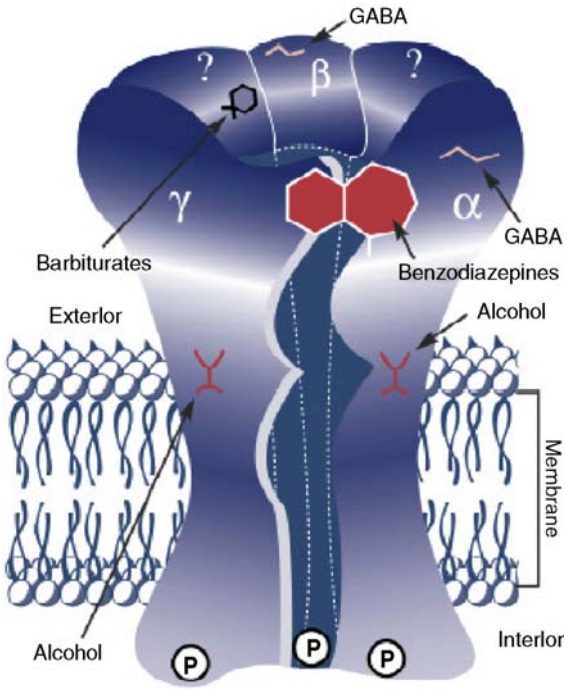

Fig. 5 Model of the γ-aminobutyric acid $(GABA)_A$ receptor

sodium channel blockers. Moreover, Durrani and colleagues reported that ketamine (>0.3%) produced adequate i.v. regional anaesthesia with complete sympathetic, sensory and motor block (Durrani et al. 1989). So far, systematic effects have not been observed.

2.3.8 Calcium Channels

In neurons, L-type Ca^{2+} channels are mainly involved in neurotransmitter release. Pharmacologically the L-type Ca^{2+} channel can be blocked by dihydropyridine or verapamil at different binding sites. Neither binding site is a target for ketamine as both binding sites could only be blocked in concentrations exceeding those required to produce general anaesthesia (Hirota and Lambert 1996a, b). The anaesthetic effects of ketamine are not supposed to be mediated via Ca^{2+} channels. In large concentrations ketamine blocks T-type Ca^{2+} channels in rat sensory neurons (Todorovic and Lingle 1998). In muscles and in the myocardium, ketamine affects the Ca^{2+} influx by blocking the L-type Ca^{2+} channels. This explains the vasodilatation, bronchodilatation and negative inotropic effects of ketamine (Baum and Tecson 1991; Yamakage et al. 1996).

3 Clinical Effects

3.1 Intracranial Pressure and Cerebral Blood Flow

Ketamine can be used safely in neurologically impaired patients under conditions of controlled ventilation, co-administration of a $GABA_A$ receptor agonist (such as benzodiazepines) and avoidance of nitrous oxide. Ketamine increases cerebral blood flow (CBF) and metabolism in spontaneously breathing patients. Under controlled ventilation, however, ketamine does not increase intracranial pressure (ICP) (Himmelseher and Durieux 2005). In combination with isoflurane/nitrous oxide, ketamine reduces ICP and middle cerebral artery blood flow but has no impact on mean arterial blood pressure (Mayberg et al. 1995). By maintaining a greater cerebral perfusion pressure, the application of ketamine is associated with a reduction in catecholamine treatment.

3.2 Neuroprotection

Numerous in vitro studies have reported neuroprotective effects of ketamine when applied prior, during or after the induction of neuronal damage. This might be related to a reduction in glutamate-induced neurotoxicity which results from the blockade of the NMDA receptor (Himmelseher et al. 1996). There is evidence that neuronal damage leads to an increase in NMDA receptor density resulting in an increased neuronal glutamate input. This input activates the up-regulation of further NMDA receptors and finally induces cell death. Ketamine seems to reduce the effects of this vicious cycle (Himmelseher and Durieux 2005). Additionally, a decrease in DNA fragmentation and apoptotic protein activation might be responsible (Chang et al. 2002; Engelhard et al. 2003).

Although a great variety of animal studies reveal neuroprotective effects of ketamine, the animal data cannot be extrapolated to human brains. Future clinical studies will have to show short- and long-term benefits from ketamine treatment associated with neuronal damage.

3.3 Neurotoxicity

The neurodegenerative properties of ketamine were first noted in adult rats 2 h after exposure to ketamine (Olney 1989). Extending these observations on the developing brain, a series of repeated ketamine injections resulted in extensive neuronal apoptosis (Ikonomidou et al. 1999). These observations are also detectable in mammals. After exposing pregnant or newborn rhesus monkeys to ketamine for 24 h, extensive neuronal cell death could be detected, depending on the development stage

(Slikker et al. 2007). In addition to its apoptotic effects, ketamine also affects dendritic arbour development (Vutskits et al. 2006). And in addition to the effects on the developing brain, in the ageing brain experimental data reveal ketamine-induced apoptosis (Jevtovic-Todorovic et al. 2003; Jevtovic-Todorovic and Carter 2005). There are also clinical and experimental data concerning the neurotoxicity of ketamine on the spinal cord (Vranken et al 2005). Single doses applied intrathecally were without neurotoxic properties. In contrast, the repeated application of ketamine in adult rabbits resulted in extensive neuronal necrosis. In a patient with chronic cancer pain the continuous application of ketamine in combination with bupivacaine, morphine, and clonidine revealed severe histological abnormalities (Vranken et al. 2006). It is not clear, however, whether the results from the animal experiments can be directly transferred to humans. Further research is therefore absolutely necessary.

3.4 Cardiovascular Effects

On the isolated heart, ketamine and both ketamine stereoisomers possess negative inotrope, chronotrope and dromotrope effects. These effects are highly stereoselective because the R(−)-isomer is significantly more cardio-depressive and shows negative chronotropy vs the S(+)-isomer, which in low concentrations even possesses positive inotrope qualities. These effects are diminished after complete depletion of the catecholamine storage, which leads to the conclusion that the stereoselective effects are dependent on the presence of catecholamines (Graf et al. 1995). Neuronal catecholamine reuptake is inhibited by both ketamine isomers, with S(+) being more potent than R(−)-ketamine. The S(+)-isomer also inhibits the extra neuronal uptake whereas R(−)-ketamine is without any effect (Lundy et al. 1986). Consistent with the results from mechanical experiments, electrophysiological experiments using whole cell voltage clamp techniques revealed that both isomers suppressed identically the trans-sarcolemmal Ca^{2+} current (ICa^{2+}), which plays a role in the generation of the force of contraction and the spontaneous firing of sinoatrial node cells (Sekino et al. 1996). In the isolated heart, ketamine increases coronary perfusion and coronary oxygen supply. Although the increase in heart rate and contractility increases oxygen demand, the coronary reserve is not restricted (Graf et al. 1995).

Racemic ketamine has been reported to block ischaemic preconditioning, and this effect was attributed more to the R(−)- than the S(−)-isomer (Molojavyi et al. 2001). However, in vitro experiments have demonstrated preconditioning properties for racemic and S(+)-ketamine (Hanouz et al. 2005). The activation of adenosine triphosphate-sensitive potassium channels and stimulation of α- and β-adrenergic receptors seem to be at least in part involved.

Ketamine also possesses significant and stereoselective vasodilator activity in the pulmonary vascular bed (Kaye et al. 2000). The vasodilator responses are mediated via the L-type calcium channel (Kaye et al. 1998). The effect of S(+)-ketamine is significantly weaker compared with that of the racemate and R(−)-ketamine. This

stereoselective difference is not due to nitric oxide release, activation of adenosine triphosphate-sensitive potassium channels, or differential inhibition of L-type calcium channels in rat isolated aortic rings (Kanellopoulos et al. 1998).

3.5 Bronchopulmonary Effects

Racemic ketamine relaxes tracheal smooth muscle. This effect, mediated probably via the L-type Ca^{2+} channel, is not stereoselective. In contrast, the Ach-induced bronchodilatation is more enhanced by the R(−)-isomer than the S(+)-isomer (Pabelick et al. 1997). In bronchial epithelium of asthmatic patients, endothelin 1 is detectable in the serum during severe asthmatic attacks. Ketamine attenuates the endothelin 1-induced bronchial smooth muscle constriction (Sato et al. 1997). Histamine-induced bronchoconstriction is not attenuated stereo-specifically, but the potentiation of the adrenalin-induced dilatation is, however, more enhanced by the S(+)-isomer (Graf et al. 1995). Clinically, ketamine reduces bronchoconstriction via antagonistic effects on the vagal nerve and attenuates opioid-induced hypoventilation (Brown and Wagner 1999). Limited evidence is available in the literature to support administration of ketamine in severely exacerbated asthma.

4 Clinical Application

4.1 Analgosedation

Ketamine and S(+)-ketamine are suitable drugs for analgosedation for diagnostic and surgical procedures due to its acceptable analgesic quality and mild deactivation of the consciousness. Both drugs preserve respiratory activity, in contrast to other anaesthetics, and increase blood pressure and heart rate by sympathetic activation. The dissociative properties of ketamine disallow its application as a sole analgosedative drug. Psychotomimetic reactions can be blunted by co-application of sedatives or hypnotics as benzodiazepines or propofol in subclinical concentrations (Adams et al. 2001).

The sympathomimetic effects on the cardiovascular and respiratory system characterize the position as an adjunctive in analgosedation of cardiovascular- or pulmonary-compromised adults and paediatric patients in intensive care and emergency medicine. By stimulating the sympathetic nervous system, ketamine reduces the exogenous catecholamine demand. In contrast to opioids, ketamine has no negative impact on gut motility. This is independent of the combination with either propofol or midazolam. During continuous haemodiafiltration only 0.5% of the administrated ketamine and a minimal fraction of norketamine is eliminated. Ketamine has been shown to reduce the need for inotropic support in septic patients, an effect that may be related to inhibition of catecholamine uptake. In addition, infusion of ketamine resulted in better sedation, increased arterial pressure and diminution of

bronchospasm in a patient with acute lymphatic leukaemia who developed bilateral fulminating pneumonia with marked agitation, hypotension and bronchospasm (Park et al. 1987; Yli-Hankala et al. 1992).

In long-term exposure, high tolerance, drug craving and flashbacks have been described. There is, however, little evidence of a physiological withdrawal syndrome, except with abrupt discontinuation in chronic users.

4.2 Anaesthesia

Because of the favourable cardiovascular profile related to central sympathetic stimulation and inhibition of neuronal catecholamine uptake, ketamine is preferred in haemodynamically unstable patients. The sympathetic activation counteracts its direct negative inotropic effect. In patients with a failing myocardium, however, the negative inotropic effects may be unmasked, resulting in deterioration in cardiac performance and cardiovascular instability (Bovill 2006). The bronchodilatory properties of ketamine make it a possible drug for the induction and maintenance of anaesthesia in patience with asthma and life-threatening acute bronchial exacerbation. Although a few cases suggest possible benefits from ketamine, controlled clinical trials to demonstrate that such benefits outweigh the risks are missing (Brown and Wagner 1999).

Ketamine also belongs to the small group of drugs approved for the induction of caesarean section. In concentrations exceeding 2 mg/kg or 1 mg/kg S(+)-ketamine, respiratory depression of the newborn must be anticipated.

4.2.1 Neuromonitoring

Ketamine/S(+)-ketamine produces high-amplitude θ-activity in the EEG, with an accompanying increase in β-activity that appears to represent activation of thalamic and limbic structures. It has been reported to provoke seizure activity in persons with epilepsy but not in normal subjects. Ketamine in doses of 0.25–0.5 mg/kg sufficient to produce anaesthesia has no impact on Bispectral Index value (BIS) (Aspect Medical Systems, Norwood, MA) monitoring. In combination with propofol, BIS changes are attributed to propofol (Sakai et al. 1999). Like etomidate, ketamine increases cortical somatosensory evoked potentials (SSEP) amplitude, with the maximum effect occurring within 2–10 min of bolus administration (Schubert et al. 1990; Stone et al. 1992). No effect on cortical latency or subcortical waveforms is evident so far. However, the addition of nitrous oxide or 1.0 MAC (minimal alveolar concentration) enflurane to a ketamine background anaesthetic depressed SSEP amplitude by approximately 50%. An increase in amplitude of muscle and spinal recorded responses after spinal stimulation was also observed (Kano and Shimoji 1974). Similarly, ketamine does not suppress the mid-latency auditory evoked potential (Schwender et al. 1993).

4.3 Pain Therapy

The analgesic effects of ketamine are mediated primarily via NMDA receptors and the opioid receptors.

4.3.1 Acute Pain

To treat acute post-operative pain, opioids are traditionally an integral part of therapy. Unfortunately, opioids produce hyperalgesia, resulting in increased analgesic requirements. The neurophysiological mechanisms are alterations in inhibitory and excitatory pathways mediated by wind-up phenomena, neurokinins and the NMDA receptor (Ali 1986; De Conno et al. 1991; Mao et al. 1995). Blockade of these mechanisms by subanaesthetic and repeated doses of ketamine has been shown to prevent the development of increased pain sensitivity and opioid tolerance (Laulin et al. 2002). For post-operative pain, subanaesthetic doses of ketamine are effective at reducing morphine requirements in the first 24 h after surgery and reducing post-operative nausea and vomiting. To date, the optimal route of administration and dosing regimen is unclear.

4.3.2 Chronic Pain

Ketamine can be a suitable option for pain therapy in patients with chronic pain where standard analgesics such as opioids, anti-depressants and anti-convulsants are insufficient. This includes the reduction of allodynia and hyperpathia in cancer pain, fibromyalgia, ischaemic, phantom or orofacial pain and in complex regional pain syndromes (Hocking and Cousins 2003).

The possible route of application can be i.v., subcutaneous (0.125–0.3 mg/kg per hour), epidural (20–30 mg per day), oral (30 mg-1 g per day, mean 200 mg), or i.m. The rate of non-responders is variable and can be as high as 70%. Psychomotor side-effects result in a reduced acceptance of ketamine as an analgesic. The incidence can be influenced by co-application of midazolam, increasing of the dose slowly, creating a quiet and relaxed atmosphere or application at night rather than during the day.

Currently the most widely accepted indication for ketamine is the acute aggravation of chronic neuropathic pain. These patients are often afflicted by hyperalgesia resulting from large opioid dosages for pain control (Mao et al. 1995). Ketamine is supposed to reduce the hyperalgesia by blocking the NMDA receptor, which seems to be partly involved in the development of opioid tolerance (Hocking and Cousins 2003).

4.4 Neuroanaesthesia

Ketamine racemate can increase ICP especially when the ICP is already increased and when the dose exceeds 1 mg/kg i.v. Two reasons seem to be responsible:

increased cerebral perfusion as a result of accelerated arterial pressure and increased $PaCO_2$ due to hypoventilation and concomitantly increased cerebral volume. Independent of pre-existing ICP, ketamine does not increase ICP when normocapnia is maintained by controlled ventilation (Bourgoin et al. 2003). A mild increase in ICP during controlled ventilation can be attenuated by hyperventilation or the co-administration of benzodiazepines or propofol (Albanese et al. 1997).

Ketamine increases CBF when administered in combination with nitrous oxide or in cases of pre-existing increased cerebral vascular resistance (Takeshita et al. 1972). Mechanisms involved seem to be hypercapnia, regional metabolic demand and L-Type Ca^{2+} channel-mediated vasodilatation. In summary, cerebral autoregulation is not affected by S(+)-ketamine (Engelhard et al. 2001).

5 Side-Effects of Ketamine/S(+)-Ketamine

Ketamine has a wide therapeutic range, making overdose difficult or even impossible. Patients have recovered uneventfully after receiving 10 times the normal dose. The median lethal dose (LD_{50}) observed in animals is approximately 100 times the average human intravenous dose and 20 times the average human intramuscular dose.

Other potential adverse effects of ketamine administration include hypersalivation, hyperreflexia, muscle hypertonicity, transient clonus, increased intraocular pressure, emesis, transient rash and agitation. Hypertension, tachycardia, increase pulmonary pressures and even pulmonary oedema can also be seen as an effect of sympathomimetic stimulation by ketamine. In combination with halothane, catecholamine or thyroid hormones, hypertension and arrhythmias can be aggravated.

Although continuous of spontaneous breathing is a positive effect of ketamine, in higher concentrations respiratory depression is seen and artificial ventilation is necessary. Laryngospasm is frequently cited as an adverse effect of ketamine, but it is rarely observed. Especially in children (who are more susceptible), it is usually caused by stimulation of the vocal cords by instrumentation or secretions. Based on pooled data, the previous literature shows the risk of laryngospasm that required intubation during ketamine anaesthesia at 1 per 5,000 individuals (0.02%), which is nearly 100 times lower compared to other anaesthetic agents (Green and Krauss 2004).

Psychotomimetic reactions include anxiety, chest pain, palpitations, agitation, rhabdomyolysis, flashbacks, delirium, dystonia, psychosis, schizophrenic-like symptoms, dizziness, seizures, and paranoia.

6 Contraindications

Ketamine/S(+)-ketamine is appropriate for painful procedures; however, there are a few contraindications which should be considered using ketamine:

- Severe cardiovascular disease, such as angina, heart failure, or malignant hypertension (because of cardio stimulant effects of ketamine; however, this is controversial, particularly in combination with other anaesthetic agents) or during preclampsia
- CSF obstructive states (e.g. severe head injury, central congenital, or mass lesions; however, this is also controversial particularly in combination with artificial ventilation)
- Intraocular pressure pathology (e.g. glaucoma or acute globe injury; however, so far only seen in animal studies)
- Previous psychotic illness (because of potential activation of psychoses)
- Hyperthyroidism or thyroid medication use (because of potential for severe tachycardia or hypertension)
- Porphyries (because of possibility of triggering a porphyric reaction)
- First trimester, since ketamine is ranked category B for pregnancy. Animal reproduction studies have not demonstrated a risk to the foetus and there are no adequate and well-controlled studies in pregnant women or animal studies which have shown an adverse effect. Adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the foetus in any trimester.

7 Abuse

Ketamine psychedelic side-effects prompted its first recreational abuse in 1965; today ketamine is used as a party drug with the following synonyms:

- K, Ket, Special K, Lady K, Jet, Super Acid, Bump, Special LA Coke, KitKat, Cat Valium, Vitamin K, Keller, Barry Keddle, HOSS, The Hoos, Hossalar, kurdamin and tranq
- Users have likened the physical effects of ketamine to those of PCP, and the visual effects to LSD.

Decreased awareness of the general environment, sedation, a dream-like state, vivid dreams, feelings of invulnerability, increased distractibility, and disorientation are common, and subjects are generally uncommunicative. Intense hallucinations, impaired thought processes, out-of-body experiences, and changes in perception about body, surroundings, time and sounds have been reported. Similarly, delirium and hallucinations can be experienced after awakening from anaesthesia.

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