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Pharmacological properties of ketamine

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Abstract

Ketamine is a dissociative anaesthetic that is being used in non-medical contexts. The effects of ketamine are very similar to those of phencyclidine, another dissociative anaesthetic that has enjoyed considerable popularity as a recreational drug. The effects of ketamine include analgesia, cardiovascular and respiratory stimulation, dissociation, hallucinations and anaesthesia. The potential dangers of uncontrolled ketamine use include psychosis and violence, accidents and marked psychomotor and cognitive impairment. Although studies have shown potential for tolerance to and physical dependence on ketamine, further investigation of these phenomena is needed. Ketamine is thought to produce most of its effects through antagonist activity at the PCP site of the NMDA receptor complex. Ketamine has sympathomimetic properties resulting from enhancement of catecholamine, and particularly dopamine, activity. While opioid receptor activity has been identified, this is relatively weak and the contribution to the effects of ketamine is not clear. Although much is known of the clinical uses and effects of ketamine, as yet little is understood of ketamine as a recreational drug and potential drug of dependence. [White JM, Ryan CF. Pharmacological properties of ketamine. *Drug Alcohol Rev* 1996;15: 145–155]

Key words: ketamine; recreational drugs.

Introduction

In the last few years reports have appeared indicating that the anaesthetic drug ketamine is being used in social rather than medical settings. Jansen [1] described ketamine use in the United Kingdom, indicating that it was most commonly taken at "rave" parties and nightclubs. Jansen warned of the dangers associated with this uncontrolled use. In Australia there have also been reports of non-medical use of ketamine. It has appeared both as a drug in its own right and as an adulterant of other drugs [2]. This should be considered a re-emergence of non-medical use of ketamine: reports of ketamine diversion for its hallucinogenic properties began within a few years of its introduction as an anaesthetic [3]. This review will examine the pharmacology of ketamine including the behavioural changes induced by this drug and potential toxicity arising from its use.

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History of ketamine

In 1956 the Parke Davis Company synthesized phencyclidine (PCP). This compound was found to have a very high therapeutic index (margin of safety) when used as an anaesthetic. Many other anaesthetics in use at the time were lethal at concentrations that were not very far above the effective anaesthetic concentrations; this was not the case with PCP. After pre-clinical testing, it was first evaluated with humans in 1957. While an effective anaesthetic, a major problem was the presence of so-called emergence phenomena reported by approximately 30% of the patients [4]. During the period of time the anaesthetic effects were wearing off, patients experienced vivid dreams and hallucinations, often of an unpleasant nature. Given the great potential of PCP as an anaesthetic, Parke Davis began to search for an analogue of this compound that did not produce the undesirable emergence phenomena. The major outcome of this search was ketamine. Clinical trials in 1964 showed it to be an effective anaesthetic with properties similar to PCP, but somewhat shorter-acting. While it could produce an emergence delirium, the symptoms did not appear to be as severe as those produced by PCP [5].

The term "dissociative anaesthetic" was coined to describe PCP, ketamine and similar compounds. Domino [5] relates adopting this term because patients under the influence of these drugs reported being very disconnected from their environment. Since then PCP and ketamine have had somewhat different histories. The principal use of PCP has been in veterinary anaesthesia, although that has now ceased. While it also has veterinary applications, ketamine has been extensively used in human anaesthesia for a variety of functions described below. Both drugs have histories of street use, but PCP has been the more widely used in this context.

PCP first appeared on the streets in the United States in 1966, but was sold for a few years only before disappearing. It emerged from time to time principally as an adulterant or substitute. For example, a substance was sold on the streets in the United States for some years that was claimed to be THC, the major active compound in cannabis, but was actually PCP [6]. Poor quality cannabis was also laced with PCP to produce a greater drug effect. PCP re-emerged as a drug in its own right in the late 1970s in the United States and it is extensively used in a small number of geographic areas. In contrast, reports of non-medical use of ketamine have been relatively infrequent. In Australia non-medical use appears to have begun only recently. Whether this is a transient phenomenon or the beginning of a significant increase in ketamine use is not yet apparent.

Clinical uses of ketamine

The principal use of ketamine is as an anaesthetic. In this context it is frequently used with other drugs. In particular, in the 1970s it was found that if a benzodiazepine is co-administered with the ketamine, then the emergence phenomena are markedly reduced [7]. Another method used to minimize this problem has been supplementation with an additional anaesthetic agent such as nitrous oxide/oxygen, allowing reduction of the dose of intravenous ketamine required for anaesthesia [4].

Ketamine is a valuable anaesthetic in the aged and critically ill. In these patients the reduction in blood pressure and decrease in respiration rate associated with most anaesthetics can be life-threatening. Ketamine does not have the same pulmonary and cardiovascular depressant effects, and therefore has a much greater margin of safety in this particular group of patients [8].

It is also used where surgical procedures are relatively brief and rapid recovery is of benefit [4]. For example, in burn units ketamine may be used to carry out procedures such as changing dressings and skin grafting. Its rapid onset together with its amnestic and analgesic properties make it an ideal compound for this purpose. It is also employed in various outpatient procedures including dental anaesthesia.

Other uses for ketamine include pre-operative medication where it is used to reduce anxiety and facilitate the induction of general anaesthesia. Its analgesic properties are also exploited post-operatively and it may be given to patients likely to experience significant pain following recovery.

Effects of ketamine

Ketamine has been investigated in detail to determine its respiratory, cardiovascular and central nervous system effects.

Cardiovascular and respiratory effects

Unlike many other general anaesthetics, ketamine has cardiovascular stimulatory properties. It increases heart rate, blood pressure and cardiac output [9]. Evidence suggests that these sympathomimetic actions result from direct central nervous system (CNS) stimulation. When ketamine is administered centrally it produces pronounced cardiovascular changes immediately [10]. In addition, the direct cardiovascular effects of ketamine appear to be opposite to those when it acts centrally. Thus, ketamine has myocardial depressant and vasodilatory effects peripherally, but these are weaker than, and consequently masked by, the central sympathomimetic effects [11].

Ketamine also differs from most anaesthetics in not producing significant respiratory depression. An exception to this occurs when the increase in ketamine plasma concentration is very rapid. Zsigmond and colleagues [12] showed that a dose of 2 mg/kg of ketamine given intravenously as a rapid bolus injection produced significant reductions in Pa_{o2} which lasted approximately 10 minutes. This study has significant implications for non-medical use, suggesting that rapid intravenous administration of ketamine has potentially dangerous respiratory depressant effects.

Ketamine also has the property of relaxing bronchial smooth muscle, an effect it shares with other compounds possessing sympathomimetic properties. This has been exploited therapeutically in the treatment of asthma [13].

Analgesic effects

In addition to its properties as an anaesthetic, ketamine has analgesic effects that may involve a different mechanism of action. The analgesic effects occur at doses which do not produce anaesthesia and the duration of analgesia may be greater than that of anaesthesia. In one study, subjects reported their response to ischaemic pain induced by reducing blood supply to forearm muscles exercised to exhaustion [14]. Scores on visual analogue scales of pain severity revealed dose-related analgesic effects over the sub-anaesthetic range (0.05–0.2 mg/kg of R(−)ketamine and 0.2–0.8 mg/kg of S(+)ketamine) with approximately 75% analgesia at the highest dose tested. The mechanism of analgesia has not yet been determined but, as discussed below, some evidence suggests that ketamine binds to opioid receptors to achieve this effect.

Hallucinatory and subjective effects

The emergence phenomena described following early clinical experience with ketamine included patient reports of hallucinations, vivid dreams and a variety of other sensations. These symptoms were found to be reduced by concurrent use of benzodiazepines, putting the patient in a low stimulus environment and by providing information on the possible emergence reactions preoperatively.

While there have been a variety of case reports of these emergence reactions, several studies have directly examined the subjective effects of ketamine. In one unique study [15], seven male volunteers with a range of medical training consumed between five and 12 doses of ketamine intermittently over a period of 18 months. The doses were approximately 10–25% of the anaesthetic dose. It was thought that this may reflect the dose level that occurs during emergence from anaesthesia.

Three different routes of administration were used and the onset of action varied accordingly: 30 seconds after intravenous administration, 2–4 minutes after intramuscular injection and 10–20 minutes after oral administration. The subjective effects terminated after approximately 60 minutes and subjects were able to eat and act as observers to other users after 3 hours.

The authors describe a series of phenomena experienced by most of the participants:

(1) A sensation of light throughout the body.
(2) Novel experiences concerning "body consistency" (e.g. feeling as though they are made from wood or plastic).
(3) Grotesquely distorted shape or size of body parts.
(4) Sensation of being weightless and floating or hovering.
(5) Radiantly colourful visions (including geometrical patterns and figures).
(6) Absence of sense of time.
(7) Sudden insights into the nature of existence or the self.
(8) Strong feelings of association with others in the environment.
(9) Out-of-body experiences.

Some of these are clearly similar to those effects experienced with other hallucinogens such as LSD (e.g. colourful visions, sudden insights) but others are less commonly reported after these drugs (e.g. distorted body shape). The authors remark on the insight that the experience of ketamine provided them, and suggested that the drug may be useful in the training of psychotherapists.

Ghoneim and colleagues [16] studied the behavioural effects of ketamine in a sample of 34 healthy volunteers. The doses of ketamine used, 0.25 and 0.5 mg/kg, were similar to those that produce analgesia and sedation in clinical studies. They were believed to approximate the doses employed by recreational users. While the main aim of these authors was to study the cognitive and psychomotor impairment induced by ketamine, subjects reported a number of subjective effects. These included numbness of various body parts, dizziness, floating sensations, visual distortions and illusions, hallucinatory dreams and paranoid feelings. The illusions and hallucinations were visual rather than auditory. While all subjects had explained to them the possibility of occurrence of these side effects prior to administration of the drug, they were divided as to whether the dreams were pleasant or unpleasant. One of the subjects reported experiencing flashbacks for 3 months after the experience.

A similar, but more detailed study evaluated the effects of 0.1 and 0.5 mg/kg ketamine administered intravenously to healthy volunteers over 40 minutes [17]. Using the Brief Psychiatric Rating Scale [18], subjects reported increases in the occurrence of the four key positive symptoms of schizophrenia (conceptual disorganization, hallucinatory behaviour, suspiciousness and unusual thought content) and the three key negative symptoms (blunted affect, emotional withdrawal and motor retardation). The effects on anxiety were biphasic, with decreased anxiety following the 0.1 mg/kg dose and increased anxiety after 0.5 mg/kg. A significant "high" occurred only after the 0.5 mg/kg dose.

Subjects in this study reported varied forms of perceptual, cognitive and affective changes. They included altered body perception, altered time perception, illusions, loose associations, unusual thought content, paranoia, depersonalization, blunted affective responses and emotional detachment. In contrast to the report in [15], no subject experienced flashbacks.

A range of visual, auditory and somatosensory disturbances were recorded in a study comparing the R- and S-enantiomers of ketamine described above [14]. These included blurred vision, tunnel vision, increases in loudness of background noises, impaired recognition of body parts and sensations of floating in the air and detachment from the body. Both enantiomers produced these subjective changes, with the S-enantiomer having greater potency than the R-enantiomer.

Jansen [19] reviewed a number of studies which suggested that ketamine can reproduce every feature of the near-death experience. These features include out-of-body experiences, mystical states, rapid trips through dark tunnels into light and a conviction that the person is dead. Jansen argued further that ketamine can be used as a model of the near-death experience, thereby facilitating controlled experimental study of the phenomenon.

It is unclear how many people experience flashbacks—episodes of a few seconds' duration in which a user re-experiences some of the subjective effects of ketamine. Flashbacks have been reported by patients administered ketamine for anaesthesia [20,21]. The one experimental subject described above [15] who reported flashbacks was found to have personality problems that were not disclosed at the initial screening. Predisposing psychological factors may account for the relative infrequent occurrence of flashbacks.

Impairment of cognitive function

In several of the studies that reported on the subjective effects of ketamine measures were also made of cognitive function. One [16] examined the effects of two doses of ketamine (0.25 and 0.5 mg/kg) on memory function. In several different tests the authors found dose-related impairment of immediate and delayed recall, but little effect on recognition memory. They concluded that ketamine had little effect on acquisition of information, but impairs memory retrieval processes. They argued that this differentiates ketamine from many other drugs that affect memory (e.g. alcohol, marijuana, diazepam, scopolamine).

Later studies have challenged these conclusions. One [14] found no impairment when subjects had to recall of a set of pictures first shown to them before ketamine was administered. When the pictures were presented after ketamine administration there was a slight reduction in recall. This study examined the

effects of both the R- and S-enantiomers (0.2–0.8 mg/kg i.v. and 0.05–0.2 mg/kg i.v., respectively). Another study [17] reported a dose-related (0.1 versus 0.5 mg/kg, i.v.) impairment in delayed recall with little effect on immediate recall or recall after distraction. Others have also found effects of ketamine on learning and memory [22,23], but as yet the exact nature of the impairment has not been determined.

Ketamine has also been evaluated in three tests that were reflective of frontal lobe function [17]. This research was guided by the hypothesis that ketamine primarily disturbs integration of sensory information rather than perception. Results from the Wisconsin Card Sorting Test showed an increase in perseverative errors. Subjects failed to learn rules and develop strategies to minimise errors. Their performance indicated a failure to modify their responding according to feedback. There was also an increase in errors on a vigilance task, while the same doses of ketamine did not have any effect on reaction time. Finally, in a test of verbal fluency there was impairment of performance by ketamine. While clear impairment on these various tasks was demonstrated, it remains controversial whether the impaired performance can be attributed to decrements in frontal lobe function, rather than altered function across a range of areas of the central nervous system.

Animal behaviour

Administration of doses of ketamine to the rat which are below those that induce sleep increases activity levels. For example, a study of R- and S-ketamine on activity measured by photocell chambers showed increases in spontaneous locomotor activity up to four-fold following administration of 15 and 60 mg/kg i.p. of each enantiomer [24]. Interestingly, it has been found that locomotor activity is also elevated in the period in which animals emerge from ketamine induced anaesthesia[25]. A biphasic pattern, with stimulation at low doses and profound sedation accompanied by sleep at higher doses, is typical of drugs such as alcohol and barbiturates [26].

Amphetamine-like effects have been described in studies of schedule-controlled behaviour in the rat [24], mouse [27] and pigeon [28]. Ketamine was observed to produce both increases in low rates of responding and decreases in higher rates of responding. In common with amphetamine, the temporal pattern of responding under a fixed interval was disrupted by ketamine in a dose-related manner.

Ketamine self-administration has also been assessed in the monkey. Moreton and colleagues [29] gave rhesus monkeys access to intravenous ketamine. They found that ketamine maintained self-administration behaviour in a manner similar to a range of other drugs. Drug intake was directly related to the dose of ketamine over the range 0.8–1600 μg/kg/injection, so that greater total intake was associated with larger doses. With dose constant at 200 μg/kg/injection, increasing the requirement for each dose produced compensatory increases in the rate of responding until high ratios were achieved, at which point responding abruptly ceased. Similar results were obtained from two studies [30, 31] that examined self-administration of phencyclidine in monkeys. It was concluded that ketamine maintains self-administration behaviour in a manner similar to that of other drug classes [29].

Basic pharmacology

Ketamine comes as a hydrochloride salt which is soluble in water and stable in solution over a long period of time [4]. There are two enantiomers of ketamine, S(+) ketamine and R(−) ketamine. S(+) ketamine appears to be more potent than R(−) ketamine although the difference is not marked: across a range of effects in humans and animals, including sensory disturbances [14], locomotor activity [25] and schedule-controlled behaviour [24], S(+) ketamine is approximately two to five-fold more potent than the R(−) enantiomer. One study in surgical patients has suggested that the S(+) enantiomer produces more effective anaesthesia with fewer emergence reactions and less agitation than the R(−) enantiomer [32].

Disposition and pharmacokinetics

Ketamine can be given by a number of routes of administration. The peak plasma concentrations of the drug occur approximately 1 minute following intravenous administration, 5–15 minutes after intramuscular administration and 30 minutes after oral administration [33]. As a highly lipid soluble compound, ketamine readily crosses the blood–brain barrier.

Termination of the actions of ketamine involves two processes: redistribution and hepatic metabolism

[4,33]. Immediately after administration, ketamine is distributed to highly perfused tissues including brain. Redistribution of ketamine from these vessel-rich tissues to less well perfused tissues occurs 10–20 minutes after intravenous administration. Biotransformation of ketamine occurs predominantly in the liver. The major metabolic pathway involves n-demethylation of ketamine via the cytochrome P450 3A enzyme to form norketamine. This compound is active with an anaesthetic potency approximately one-third that of ketamine. Norketamine is subsequently hydroxylated.

Following oral administration, ketamine is subject to high first pass metabolism, and plasma concentrations of norketamine are higher than those of ketamine itself [34]. Whether this alters the duration or the nature of the effects of ketamine has not been studied.

The rate of metabolism of ketamine may be altered by prior administration of the drug. In rats, chronic pretreatment with ketamine caused a two-fold increase in the rate of its *in vitro* hepatic metabolism [35]. It also increased the *in vivo* rate of plasma decay of ketamine following intravenous administration. Thus, it would appear that ketamine is able to induce the enzymes responsible for its own metabolism. This may be an important mechanism in ketamine tolerance.

Site of action

Since the development of PCP and ketamine, and particularly following observation of the psychotomimetic effects of these drugs, considerable effort has gone into understanding their mechanisms of action. In part, this has been motivated by a desire to find dissociative anaesthetics without the adverse effects of these compounds. Ketamine- and PCP-induced changes have also been proposed as models of psychosis [17,36]. Finally, interest has been sparked because certain opioids have been noted to have subjective effects similar to ketamine and PCP [37]. Studies of the ketamine mechanism of action have shown that it produces its effects through activity at multiple sites, the most important of which are the NMDA receptor complex, opioid receptor(s) and catecholamine systems.

NMDA receptors. Three major types of excitatory amino acid receptors have been identified: N-methyl-D-aspartate (NMDA), kainate and quisqualate. The NMDA site is thought to play a role in learning and memory, ischaemia and neuronal development [38]. Within the NMDA receptor complex are a number of modulatory sites, including glycine, PCP and Zn^{2+} sites. Ketamine binds to the PCP site, producing a non-competitive blockade of the effects of glutamate, but with a considerably lower affinity than PCP itself [36,38].

Drug discrimination has been used as an animal model of the subjective effects of a range of different drug classes. In a number of animal studies ketamine has been shown to possess discriminative properties similar to both PCP and dizocilpine (MK-801), a highly selective antagonist at the PCP site [39,40]. These properties are not shared by NMDA antagonists acting at sites other than the PCP site. These findings demonstrate a central role of the PCP site in the discriminative effects of ketamine and, potentially, in the subjective effects.

The activity of dizocilpine has also been used to delineate the role of the NMDA receptor in mediating the behavioural effects of ketamine. Dizocilpine shares with ketamine and PCP the ability to induce sedation and ataxia [41], impair learning and memory [42,43], increase locomotor activity of animals at low doses [44] and induce bizarre behaviour at high doses [44].

It is important to distinguish the PCP site at the NMDA receptor from the σ receptor. In earlier research the two had often been confused, with the σ receptor being identified as the major site of action of PCP and ketamine. Although the properties and function of the σ receptor have not been well characterized, it is clearly a different entity from the PCP site [45]. Furthermore, both ketamine and PCP have much greater activity at the PCP site compared with the σ site [46]. In addition, the more active S-enantiomer has greater affinity for the PCP site than the R-enantiomer, but relatively less affinity for the σ-site [46]. Thus, the σ receptor may not be an important site of action for ketamine.

Opioid receptors. A number of studies have provided evidence indicating that opioid receptors are important substrates for the actions of ketamine. The analgesic effects of ketamine have been shown to be reversed by opioid antagonists such as naloxone [47,48]. The reversal is not always complete, suggesting that ketamine-induced analgesia has both opioid and non-opioid components.

The opioid properties of ketamine appear to be

important only at high concentrations and the affinity of ketamine for opioid receptors is relatively weak [49]. However, Smith and colleagues [50] showed that in a rat model the concentrations of ketamine in brain and spinal cord following administration of an analgesic dose were sufficient to activate opioid receptors.

Other opioid-mediated effects may also occur following administration of relatively high doses. For example, ketamine induces excitatory cardiovascular effects following low doses, but inhibitory effects at high doses. While the latter are blocked by naloxone, the former are not [51]. Similarly, Latasch & Freye [52] observed respiratory depression and EEG hypersychronization following administration of high doses of ketamine to dogs. Both effects were reversed, at least partially, by opioid receptor antagonists.

Some debate remains as to the particular opioid receptor sub-type that mediates the effects of ketamine. Of the studies described above, one [50] found evidence for a μ selective action of ketamine. In contrast, Latasch & Freye [52] concluded that both μ and δ receptors mediate the effects of ketamine. Species differences may account for this variation.

Catecholamines. Some effects of ketamine may be due to its actions on catecholamine, and particularly dopamine, systems. The predominant change seems to be an enhancement of dopamine activity, although the mechanism by which this occurs is not entirely clear. One proposed mechanism is enhancement of release of dopamine in the manner of amphetamine and methylphenidate. Ketamine, PCP and dizocilpine have all been shown to enhance dopamine turnover in the mesocortex, but not in the striatum [53]. Other compounds acting at NMDA receptors, but not at the PCP site, did not produce this increase. The authors argued that there is a PCP site independent of the NMDA receptor that modulates dopamine release.

Similarly, ketamine and dizocilpine were found to induce stereotypy in mice by a mechanism that involved enhanced dopamine release [54]. However, these authors did not rule out the possibility that the effect was mediated via NMDA receptors. Stimulation of dopamine neurones in the ventral tegmental area was also found to be produced by PCP receptor ligands such as ketamine [55].

PCP and ketamine may differ in one important respect. There is now considerable evidence that PCP enhances dopamine activity in part by blocking the re-uptake process, a mechanism similar to that of cocaine [56]. In contrast, ketamine shows only weak affinity for this site, at least in the central nervous system [56,57]. The situation may be different in peripheral tissues as ketamine has been shown to block catecholamine re-uptake in the heart [58].

Ketamine-induced changes in dopamine activity could be important in a number of respects. Ketamine may activate central reward systems through enhancement of dopamine activity in the mesolimbic system. Enhanced dopamine activity can also result in hallucinations, paranoia and stereotyped behaviour at high doses. Both euphoria and hallucinations are characteristics of ketamine intoxication and dopamine systems may play a role in each.

Tolerance and physical dependence

A number of studies have demonstrated tolerance to the effects of ketamine. For example, Meliska & Trevor [59] administered 15 mg/kg of ketamine to rats and observed a depression of food-reinforced responding for approximately 40 minutes. By the second administration of this dose the depression of responding lasted only 10 minutes and was followed by an elevation in response rates. The rapid development of ketamine tolerance has been noted in other studies. In one [60], plasma and brain concentrations of the drug were measured in mice and rats at the time of recovery from ketamine-induced sleep. Over four injections spaced 24 hours apart, the sleeping time of rats decreased from 24 to 16 minutes while the brain concentrations at the time of awakening increased slightly over the same series. This indicates that tolerance was due to changes at the site of action rather than any increase in rate of metabolism.

Animal studies have demonstrated that both ketamine and PCP have the capacity to induce physical dependence evidenced by withdrawal on cessation of use. Rats chronically exposed to ketamine exhibited subcortical withdrawal seizures for up to 5 days after self-administration was discontinued [61]. Disruption to operant behaviour has been observed after discontinuation of PCP administration to rats [62]. Overt signs of PCP withdrawal in

animals include seizures, irritability, pilo-erection and weight loss [63]. The adaptational changes underlying ketamine tolerance and physical dependence have not been identified.

Toxicity

Acute medical conditions

Cardiovascular and respiratory stimulation are the most common outcomes of ketamine administration. In general, neither is problematic. However, in a subset of cases effects opposite to these may be produced; such outcomes are considerably more dangerous. Cardiodepressant effects are noted in some critically ill patients [11]. This may be due to chronic catecholamine depletion, preventing any sympathomimetic effects of ketamine and unmasking depressant actions.

Similarly, as described above, rapid intravenous administration of ketamine can result in respiratory depression [12]. In certain circumstances this reaction may occur even with more gradual onset of ketamine action. Smith & Santer [64] report a case of routine ketamine use for paediatric sedation. The drug was administered by intramuscular injection to a 4-year-old boy who stopped breathing 3 minutes later. He was ventilated with oxygen and subsequently resumed spontaneous respiration. The case illustrates that the potential danger of ketamine-induced respiratory depression is not confined only to instances of rapid intravenous administration.

Hyperthermia may also be a potential problem with ketamine. This property is shared with other sympathomimetics such as amphetamine, and it is likely that catecholamines are involved in each instance. In practice, the relatively short duration of action of ketamine will limit the danger of hyperthermia.

Ketamine has been recognized as having both pro- and anti-convulsant activity. In patients with known seizure disorders ketamine ($\geqslant 2$ mg/kg i.v.) can activate cortical EEG activity and clinical seizure activity [65]. In animal models ketamine prevents electrical- and drug-induced seizures [66]. Consistent with these findings, case reports have emerged of seizure termination following ketamine administration to patients [65]. However, it should also be noted that reports of seizures have been associated with PCP intoxication [67].

Behavioural changes

The major behavioural and subjective changes induced by ketamine were clearly documented many years ago, and have been described above. Numerous case reports from people receiving ketamine anaesthesia have noted hallucinations, delirium and feelings of unreality [4]. Although there is no evidence to date, it is likely that recreational users would have similar reactions. While these may frequently be benign, evidence from use of PCP suggests potentially more severe adverse effects, including violence [68], psychosis and personality changes [69]. Unfortunately, this evidence is frequently of an anecdotal nature only. In addition, the reports are mainly concerned with PCP, leaving open the question of whether ketamine has effects of comparable severity.

Conclusion: future research directions

Our current knowledge of ketamine largely reflects the history of the drug. As an anaesthetic agent its basic pharmacology and clinical uses and effects have been relatively well studied. Ketamine is a drug with multiple mechanisms of action and at least some of these are beginning to be understood. However, the degree to which each contributes to the different effects of ketamine is not yet clear.

In contrast, as a recreational drug and potential drug of dependence, relatively little is known about ketamine. Areas where greater research is needed include animal and human studies examining tolerance, dependence and self-administration and human studies of the subjective and behavioural effects at different doses. In non-medical contexts ketamine may be used by a number of routes of administration, and there is evidence that the effects may vary according to route of administration as well as dose, but this has yet to be examined systematically. Consideration also needs to be given to the potential for interaction with drugs such as opioids, amphetamine and amphetamine analogues.

What is clear from the research to date is that ketamine is a potentially toxic drug. This danger will be exacerbated if it is used in a manner where purity and hence dose is relatively uncontrolled, as is the case with many street drugs. The most important of these adverse effects may be the behavioural changes induced by ketamine. Psychotic reactions have been frequently associated with use of high doses of PCP. Whether or not the same reactions can be expected

with ketamine has yet to be determined. In this, as in a number of other areas, we do not yet know the degree of similarity between the effects of PCP and ketamine. In practice, the research needed for a better understanding of ketamine is only likely to be carried out if non-medical use of the drug becomes a significant public concern. Unfortunately, that is likely to mean that major adverse consequences of ketamine use will need to be reported with sufficient frequency before we examine this drug more closely.

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