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Ketamine—Can Chronic Use Impair Memory?

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Abstract

Ketamine, a congener of phencyclidine (PCP), can produce a range of psychological effects which have led to its nonmedical use. Recent discoveries concerning the effects of ketamine and similar substances in the brain suggest that they may interfere with memory processes when given acutely and may affect synaptic plasticity when given chronically in high doses in certain animal models. It is thus of interest to examine the consequences, if any, of chronic use in humans. A case is here presented of long-term, high-dose ketamine use, in which the user described impaired recall and attention, and a subtle visual anomaly persisting after cessation of the habit. This history is considered in the context of other relevant studies.

Ketamine is a substance with an accepted place in medicine as a dissociative anesthetic (White et al., 1982). It has a rapid action; does not usually affect pharyngeal–laryngeal reflexes; has a wide margin of safety; and in some persons can cause dream-like states, vivid visual hallucinations, and dissociative phenomena (Siegel and Jarvik, 1975; Ghoniem et al., 1985). These psychological changes, which are usually short-lived and not detrimental to health (Lofty et al., 1978), have made the drug attractive to some recreational drug users, par-

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ticularly hospital workers with access to the substances (Grinspoon and Bakalar, 1981; Weil and Rosen, 1983).

There has been a major research effort in the neurosciences recently to elucidate the effects of ketamine, phencyclidine, and related substances at the *N*-methyl-D-aspartate (NMDA)–PCP receptor complex (Kemp et al., 1987). For convenience, in this paper the whole complex is referred to as the NMDA receptor. Interest in the effects of substances which block NMDA receptors (i.e., antagonists) has arisen out of increasing evidence that the NMDA receptor may play an important role in memory, synaptic plasticity, epilepsy, and "excitotoxic" neuronal damage (Cotman and Monaghan, 1988; Barnes, 1988). Antagonists which block the receptor, such as ketamine (Anis et al., 1983; Martin and Lodge, 1986; Fagg, 1987), appear to protect neurons from certain conditions which are neurotoxic such as ischemia and hypoglycemia (Rothman et al., 1987). Ketamine given acutely may thus be neuro-protective in certain situations (Meldrum, 1985). However, such a receptor block also prevents "long-term potentiation," a neuronal event which may be important in memory (Morris et al., 1986; Cotman and Monaghan, 1988). This may be of no particular consequence in anesthesia and situations of occasional use. However, the NMDA receptor is also implicated in structural synaptic changes which could form the basis of long-term memory and developmental changes in the brain, that is, "synaptic plasticity" (Lynch and Baudry, 1984; Cotman and Monaghan, 1988). The consequences of chronic NMDA receptor blockade include the impairment of synaptic plasticity in certain animal models. For example, chronic ketamine administration will prevent the formation of ocular dominance in the kitten visual cortex, such formation being dependent upon the construction of new synapses and alteration of existing connections (Rauschecker and Sabine, 1987). While adult neurons do not divide, their synapses undergo considerable changes, including major structural alterations, thoughout life and it is thus possible that chronic NMDA receptor antagonism with substances such as PCP and ketamine will impair synaptic plasticity in the adult brain.

Studies of the effects of chronic use of these drugs in humans are thus of considerable interest. However, chronic high-dose ketamine users who do not take large quantities of other drugs and were unimpaired before starting the habit present very rarely, and it is thus difficult to compile a series of significant size. Studies of multiple ketamine administrations in an anesthetic context are of interest but do not involve multiple daily administrations for many months.

CASE REPORT

A 35-year-old, male anesthesiologist in Sydney gave the following account. Two years previously (1985) he had read of ketamine's use as a hallucinogen and decided to try the drug upon himself. The first dose of the Parke Davis

product Ketalar produced a disconcerting but nevertheless intriguing experience, and he thus took a second dose 2 weeks later which involved the sensation of flying and being outside his body. He began to take the drug with increasing frequency: 3-4 times during the working week and for quite long periods in the weekends, i.v. and i.m. in multiple doses of between 60 and 100 mg each. The next day there would be a deterioration in recall for both newly learnt and old data (with unimpaired recognition memory), impaired word-finding ability, and attentional problems. A year later he was taking 70-150 mg almost every evening. The previously described deficits were chronically present, and comments concerning his absentmindedness were made by colleagues. Of greatest concern to him was the effect of the substance upon his vision. At first, this was similar to "the picture slipping upwards" on a defective television set, an effect which occurred for about 10 minutes after he ceased to feel dissociated. After a year of use, however, he noticed a subtle visual effect persisting into occasional abstinent periods of up to 2 weeks. This was like "looking through very clear water" combined with a very slight "graininess," an effect aggravated by fatigue and stress. The visual change was the cause of some alarm, but he was unable to resist a strong compulsion to take the drug, which now no longer produced unusual states but only a "lack of awareness" similar to that of more conventional anesthetics. His frequency of use declined in the following year (1986), and the history was related in early 1987 when he had been abstinent for some months. At this time, he felt that his recall, attention, and linguistic skills were still mildly impaired, and, of much greater concern to him, the slight visual anomaly had shown little sign of abating.

Previous drug experience consisted of very mild alcohol use, rarely marijuana (which he disliked), and a single LSD trip 10 years before. He had never smoked cigarettes, avoided stimulants and depressants, and showed no other evidence of dependency traits or compulsive behavior. The reason behind his decision to use the drug was interest generated by some books which he had read, in combination with a marked dissatisfaction concerning his career choice.

The family history included an authoritarian father with dysthymic personality traits and periods of dependence upon sleeping pills, but was otherwise unremarkable. At both school and university he had felt alienated from his peers and had few friends, although his academic performance was excellent. His reasons for going to medical school were vague and he disliked the experience. He was in a de facto relationship, an apparently positive interaction, during the period of ketamine use.

In general, he appeared to have some dysthymic personality traits, to feel alienated from others, and to have had a strong desire "to escape" from a career which he disliked. There was no previous history of psychiatric illness or relevant physical illness. His mental status when seen included appropriate behavior and a pleasant manner. There was no evidence of any psychotic phenomena. Atten-

tion was markedly impaired for a man of his academic standing, with a very poor performance of a "serials sevens" task (i.e., 100 minus 7, 93 minus 7, etc.). His performance was also below average on such tasks as remembering names and addresses, and remembering telephone numbers. Unfortunately, it was not possible to perform a detailed neuropsychological assessment of the sort which has been developed for PCP users (e.g., Lewis and Hordan, 1986). An ophthalmologist could detect no abnormalities in his vision beyond a preexisting shortsightedness.

DISCUSSION

This case report describes an instance of chronic ketamine use associated with complaints of impaired memory and attention, and an alteration in vision. While these effects may have been due to ketamine use, it is also relevant to consider the possibility of a masked depression. In addition, it is possible that there was a functional component to his use as he disliked his job and the ketamine problem finally precipitated his departure from medicine to an occupation which he found more enjoyable. The persistence of the memory, attention, and visual complaints into apparently happier times does not completely rule out the possibility of a masked depression, but it does suggest that an impairment with an organic basis may actually have occurred.

During acute ketamine intoxication, attention, learning, and memory are impaired and visual hallucinations can occur (Harris et al., 1975; Siegel, 1978). There have been very few reports of long-term ketamine use. Siegel (1978) studied a population of 23 users, who had been recruited from previous studies of cocaine users and hallucinogenic drug users. Ten were intranasal users and 13 took ketamine by injection. The selection criterion was that ketamine had been used more than once in the last year. There were approximately equal numbers of men and women, 21-45 years of age. All subjects of this study had histories of multiple drug use, and many were currently using cocaine and LSD. Of this group, only one injecting user described herself as a compulsive user with high frequency and high intensity levels of long duration (no figures are given). Nevertheless, she had no difficulty in withdrawing from the substance. The case reported here never experienced any form of withdrawal syndrome. Siegel notes several desirable long-term effects in this study, including a chronic elevation of mood (43%), deeper insights into self and others (35%), and positive changes in attitudes and personality (17%). The undesired long-term effects included flashbacks (57%), attentional dysfunction (22%), and decreased sociability (9%). Siegel noted that there appeared to be an equal division between positive and negative effects. Standard psychometric tests did not reveal adverse effects on brain function which could be attributed specifically to ketamine, although the level of use of most subjects in this study was well below that described in

this case report. The use levels in reports from an anesthetic context (e.g., Wilson, 1969; Albin et al., 1970; Corssen et al., 1971, Schorn and Whitman, 1980; Byer, 1981) have also been well below this level, and these studies have generally concluded that ketamine is a relatively safe drug (Schorn and Whitman, 1980), although there have been occasional instances of prolonged hallucinations (Fine and Finestone, 1973; Perel and Davidson, 1976). Perhaps the most relevant account is that of Lilly (1978), a psychiatrist and neuroscientist who described his own very heavy use of ketamine over several years, involving multiple daily injections for prolonged periods. Although Lilly required several psychiatric admissions with what may have been a paranoid psychosis, he does not specifically describe any lasting cognitive impairment or visual abnormality persisting beyond the presence of the drug in the body. The case presented here showed no impairment of reality testing at any point. The possibility of a masked depression has been previously mentioned and may be relevant to poor attention and memory. It could also partially explain the visual change. The functional models proposed for certain forms of LSD flashbacks (Alarcon et al., 1982; Strassman, 1984) may also be applicable. However, ketamine has been shown to cause retinal abnormalities in some animal models (Antal, 1971; Magdolina, 1978; Schaller et al., 1981; Follman and Antal, 1981; Anal and Musci, 1984), and may cause raised intraocular pressure (Peuler et al., 1975; Antal et al., 1978) and transient blindness (Fine et al., 1974). Examination of the retina revealed no obvious pathology. It is possible that an organic change may have occurred in the visual and/or association cortex.

In conclusion, this case report suggests the possibility that chronic ketamine use may impair synaptic plasticity, although functional causes for the prescribed symptoms cannot be wholly excluded, and it was not possible to perform a detailed neuropsychological assessment. If the symptoms described in this case report are in fact due to ketamine, then it is also possible that they are an unusual, idiosyncratic side effect with little clinical significance for the general population.

Detailed studies of those heavy, chronic ketamine users who do present are clearly indicated so that these issues can be addressed. Although the problem is a rare one, such studies are valuable for the information which they may provide about normal brain function and about the response of the human brain to repetitive NMDA receptor antagonism, and also from the perspective of drug use and misuse.

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