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REVIEW ARTICLE

History of anaesthesia: the ketamine story – past, present and future

Georges Mion

Ketamine's history begins in the 1950s in Detroit, Michigan, at Parke-Davis Laboratories. On 26 March 1956, Harold V. Maddox synthesised phencyclidine or PCP. Domino studied PCP effects in animals and in 1958, Greifenstein made the first trials of PCP in humans under the name of Sernyl. Sernyl did not cause depression of cardiovascular and respiratory functions, but elicited severe excitation with a very prolonged postoperative recovery. Because of its psychedelic effects, it became a street drug under the name of 'angel dust' and was placed on schedule II of Federal Controlled Substance Act (CSA) in 1978. Eticyclidine or PCE had no medical career. The chemist Calvin Stevens, consultant to Parke-Davis, synthesised ketamine in 1962. The drug was studied in humans in 1964, by Domino and Corssen. These authors described the so-called 'dissociative anaesthesia'. Ketamine was patented in 1966 under the name of Ketalar for human use and was administered to soldiers during the Vietnam war. Because of abuse, ketamine was placed among the class III substances of CSA in 1999. The psychedelic effects and the arrival of propofol prompted the shelving of ketamine. However, the discovery of the NMDA-receptor and its non-competitive inhibition by ketamine revolutionized the pathophysiology of hyperalgesia and mental functioning. In early 1990s, the arrival of remifentanil preceded the discovery of opioid-induced hyperalgesia, eliciting a paradigm shift in the management of pain, and a comeback of ketamine, as and antihyperalgesic drug. Ketamine is nowadays under the spotlight in the field of treatment-resistant depression and has been proposed as a potential fast antidepressant in patients with high suicidal risk. In a near future, we may observe new practices like increased *S*-(+)-ketamine availability, new ultra-short-acting ketamine analogues or the development antagonists.

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The history of ketamine begins in the 1950s at Parke-Davis and Company's laboratories in Detroit, Michigan, USA. At that time, Parke-Davis were searching among cyclohexylamines for an 'ideal' anaesthetic agent with analgesic properties.

Maddox, a chemist, discovered a process which led to the synthesis of phencyclidine or PCP [*N*-(1-phenyl-cyclohexyl)-piperidine] on 26 March 1956.[1,2] Parke-Davis pharmacologist, Dr Chen, received the compound CI-395 (Fig. 1) from Maddox on 11 September 1958. Chen and, in the same period, Dr Domino,[1] began to study the experimental effects of the drug on animals. Phencyclidine created potent analgesia in animals: laparotomies were performed in monkeys without pain, but the animals were in a cataleptic state with their eyes open, and muscle relaxation was of poor quality. Chen[3] defined catalepsy as a 'characteristic akinetic state with a loss of orthostatic reflexes but without impairment of consciousness, in which the extremities appear to be paralysed by motor and sensory failure'.

Parke-Davis then investigated the potential of phencyclidine as a human anaesthetic under the trade name of Sernyl (Parkes-Davis). In 1958, the first human trials of PCP (Sernyl) were published by Dr Greifenstein (1915 to 1997), professor of anaesthesiology at the Wayne State University, Detroit. PCP caused increases in blood pressure, respiratory rate and minute volume, with conservation of corneal and laryngeal reflexes. The presence of nystagmus and increased salivation were noted. These studies revealed genuine narcosis, with a cataleptic state, potent amnesia and analgesia produced by ketamine anaesthesia.[4] Greifenstein and John Stirling Meyer, head of neurology at Wayne State University, concluded that

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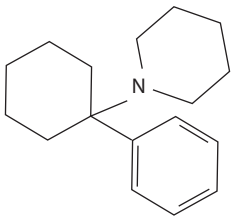
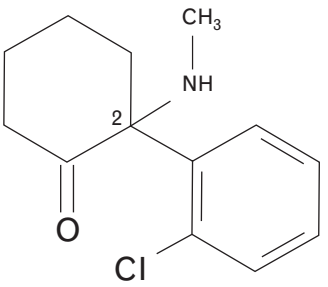
Fig. 1



CI-395, Phencyclidine or *N*-(1-phenyl-cyclohexyl)-piperidine.

Fig. 3



CI-581, Ketamine [2-(*O*-chloro-phenyl)-2-methyl-amino cyclohexanone].

phencyclidine produced a 'centrally mediated' sensory deprivation syndrome.[1]

Surgical incision, and in 30 patients of Greifenstein's series, the complete operation, could be performed under Sernyl alone. But Sernyl was unsatisfactory for surgery in 13 patients, five of whom suffered severe excitation. Ten of the 64 patients were unmanageable in the postoperative period, and some had a very prolonged postoperative recovery (3 to 18 h). It was immediately observed that in no instances did the electroencephalographic (EEG) trace resemble that obtained following the administration of a barbiturate, nor did it resemble the pattern of sleep.[4]

Johnstone and Evans published their clinical experience in the *British Journal of Anaesthesia* in 1959.[5] They stated that 'Sernyl was undoubtedly the most potent general analgesic agent which had been used in clinical medicine'. It had the unique advantage over other sedatives and analgesics that it did not cause depression of cardiovascular and respiratory function, nor depression of pharyngeal and laryngeal reflexes, and could be used safely in elderly patients. However, the usefulness of the drug was limited by the excitation which sometimes persisted for more than 12 h after a single dose. The authors spoke of psychotic reactions.[5]

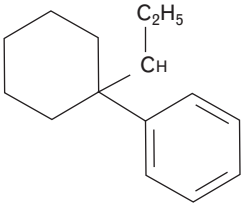
With growing clinical knowledge, it became clear that phencyclidine was not suitable for human anaesthesia. Eticyclidine, CI-400 or PCE (*N*-ethyl-1-phenyl-cyclohexylamine; Fig. 2), was developed by Parke-Davis in the late 1950s,[6] but, because of frequent hallucinations and the concomitant discovery of ketamine, it was not used extensively in clinical practice. The molecule induced a state of catatonia with generalised rigidity and had, like PCP, neither respiratory nor circulatory depressant effects. In 1960, Collins *et al.* analysed the provided state of consciousness as a kind of trance resulting in a 'dissociation' from the environment. On the EEG, delta waves appeared to be related to the analgesic effect. They supposed that the mechanism could possibly be a direct cortical dissociation, or a block of the thalamus or thalamocortical paths.[7] PCE was placed into the Schedule I list of illegal drugs in the 1970s.

Dr Cal Bratton, head of pharmaceutical research at Parke-Davis, promoted further synthesis of related compounds in the hope of reducing PCP side-effects.[1] Calvin Lee Stevens PhD (1923 to 2014) was a chemical consultant to Parke-Davis. He was a professor of organic chemistry at Wayne State University (Detroit, Michigan). Stevens now decided to synthesise a unique series of phencyclidine derivatives in his laboratory. Drs Chen and McCarthy and others,[8] screened these in animals, especially monkeys.

One of the agents, synthesised in 1962 by Calvin Stevens, produced excellent anaesthesia and was short-acting. It was selected for human trials as CI-581 [2-(*O*-chloro-phenyl)-2-methyl-amino cyclohexanone],[1] and because it was a ketone together with an amine, was named ketamine (Fig. 3). Surprisingly, McCarthy *et al.*[8] described it in 1965 as being a compound with cataleptic, analgesic and anaesthetic action but without hypnotic properties.

One day in early 1964, Domino was contacted by Parke-Davis to study CI-581 in humans. As he was not an anaesthesiologist, he called his colleague Dr Corssen, a professor in anaesthesiology at the University of Michigan, who was interested in intravenous anaesthetics. Dr Corssen (1916 to 1990), who had been a war hero in the Wehrmacht during World War II, emigrated to the United States after the war and practised anaesthesiology

Fig. 2



CI-400, Eticyclidine or *N*-ethyl-1-phenyl-cyclo-hexylamine.

and pain medicine. The first human administration was conducted by Corssen and Domino on 3 August 1964, to volunteer prisoners at the Jackson Prison in the state of Michigan.[9] The incidence of adverse effects was one in three. Corssen and Domino observed that patients described their feeling of floating in outer space and having no feelings in the limbs.[1] Domino *et al.*[10] published the first clinical studies in 1965. They had 'a good deal of discussion' about how they would publish the data. The term 'schizophrenomimetic' would probably have nipped in the bud the future of the new molecule, and the three researchers were about to coin the term 'dreaming' to describe the peculiar anaesthetic state, when fortunately, as Domino spoke to his wife Toni of the fact that patients seemed to be 'disconnected', she suggested the term 'dissociative anaesthetic'.[1] So was ketamine finally characterised.[11] Dissociative anaesthesia was later described as the electrophysiological and functional dissociation between thalamocortical and limbic systems.

Domino *et al.*, continued to research and publish on ketamine,[12–15] and the literature soon had contributions from German,[16–18] Italian,[19] Brazilian,[20] Japanese[21] and Danish[22] teams. Ketamine arrived in France in 1970 after the 1968 publication by Lassner in 'Les Cahiers d'Anesthésiologie'.[23] The teams of Vourc'h *et al.*[24] and Gauthier-Lafaye *et al.*[25] published the first French clinical trials. Ketamine provided potent analgesia but was less potent and of considerably shorter duration of action than PCP, particularly with regard to psychic problematic effects. The introduction of ketamine in Britain in late 1969 had been described as a 'disaster' from which the drug never recovered.[9] In 1970, hallucinations were considered so unpleasant that patient acceptance was much lower than with the barbiturates.[26]

Ketamine began as a veterinary anaesthetic when it was patented in Belgium in 1963. After being patented by Parke-Davis for human and animal use in 1966, ketamine became available by prescription in 1969 in the form of ketamine hydrochloride, under the name of Ketalar. It was officially approved for human consumption by the United States Food and Drug Administration in 1970 and, because of its sympathomimetic properties and its wide margin of safety, was administered as a field anaesthetic to soldiers during the Vietnam war.

The analgesic properties of the molecule were at that time a major argument for its development. Soon, chlorpromazine,[27] diazepam[28] or droperidol[29] were proposed to limit the emergence excitement, which remained a real problem for procedures in which ketamine was used as an induction agent.[30] Gorringe *et al.*[31] warned in 1970 about the necessity to inject the induction dose in no less than 60 s and to avoid useless stimulation during emergence. In 1971, Sadove *et al.*[32] demonstrated that 'subdissociative' doses ($0.44\,mg\,kg^{-1}$) of ketamine possessed analgesic properties with moderate side effects.

In subsequent years, many works clarified ketamine handling, such as intramuscular administration,[33] its pharmacokinetics[34–37] and that of its isomers,[38] and its indications of choice (shock,[39] asthma, emergency and crisis situations, burns, obstetrics, analgesia, etc.) as well as controversies regarding raised intracranial pressure[40,41] or epilepsy.[42] White *et al.*,[43] one of the first to study ketamine isomers in man, published a shining review in *Anesthesiology* in 1982.[44]

Concerns over the so-called psychedelic effects of ketamine and the arrival of new intravenous hypnotics such as propofol prompted a marked decrease in the use of ketamine in the affluent world. Moreover, ketamine abuse[45] appeared during the Vietnam war and on the East Coast of the United States and increased from 1978 onwards following the publication of two books; Marcia Moore's (1928 to 1979) 'Journeys into the Bright World' and John Lily's (1915 to 2001) 'The Scientist' put forward the authors' psychedelic experiences. Because of this abuse, ketamine was placed among the class III substances of the US Controlled Substances Act in 1999. An interesting collateral effect of the psychedelic properties of ketamine, especially the induction of near-death experiences,[46] was the development of a therapeutic use of ketamine in palliative medicine.[47] In his book 'Ketamine: Dreams and Realities', Dr Jansen PhD, an English psychiatrist, suggested that under medical supervision, the drug's potent healing powers could be used to treat certain mental distresses (the so-called KPT: Ketamine Psychedelic Therapy).

Over the past 20 years numerous studies have revolutionised the field of ketamine knowledge. In 1980 Collingridge[48] discovered that activation of the glutamate *N*-methyl-D-aspartate calcium channel (NMDA receptor) was responsible for induction of synaptic plasticity, and in 1986 Morris showed that NMDA receptor blockade induced inability to form a spatial memory in rodents. The discovery of the NMDA receptor and its noncompetitive inhibition by ketamine,[49] first observed by David Lodge's team at the beginning of the 1980s,[50] prompted large advances in the pathophysiology of hyperalgesia,[51] schizophrenia[52] and mental functioning.[53] It became evident that memory, thinking and consciousness were the result of synaptic plasticity and of the fine tuning of glutamatergic influences via NMDA receptor-mediated phenomena.

In the early 1990s, with the arrival of remifentanil,[54] the grail of high-dose opioid anaesthesia was close to being achieved. On the contrary, the high plasma concentrations of opioid allowed by the very short contextual half-life prompted an unexpected problem of opioid-induced hyperalgesia.[55] The cause of this was not immediately recognised, and it was thought that in the

immediate postoperative period, patients only suffered from a decrease of opioid analgesia. The active research in the field of NMDA receptor blockade led to decisive progress in the understanding of this phenomenon.[56] In fact, it was demonstrated that opioids, together with eliciting a potent analgesia through μ-receptors, were able to open NMDA receptors in a dose-dependent manner and to trigger opioid-induced hyperalgesia.[57] This led to a paradigm shift in the management of perioperative and other categories of pain, particularly chronic pain,[58] and to a comeback of ketamine, as an NMDA receptor blocking agent and a so-called anti-hyperalgesic drug.[59]

Ketamine is now being used to manage treatment-resistant depression.[60] Indeed, 25 years before the first randomised controlled trials of ketamine in depression by Berman *et al.*[61] and by Kudoh *et al.*[62] demonstrated that low-dose ketamine improves the postoperative state of depressed patients, Sofia had experimentally observed that ketamine possessed an antidepressant activity.[63] As, contrary to ordinary antidepressants, ketamine does not act within weeks, but within only a few hours, it has been proposed as a potential fast antidepressant in patients with high suicidal risk.[64]

Today, the interest in ketamine continues. Its value and safety in anaesthetic and analgesic management have been demonstrated in thousands of patients, and after more than 50 years, ketamine makes a true clinical comeback in the affluent world. In the less affluent world, and since the Vietnam war 40 years ago, it has remained a crucial sole anaesthetic agent enabling surgery to be performed where, without it, nothing would be possible.[65]

During the 2000s, ketamine acquired the original position of an antihyperalgesic drug with a rightful place in the modern multimodal analgesic armamentarium.[66] In the near future, its chemistry could change. In addition to the possible spreading of *S*-(+)-ketamine use, new ultra-short-acting ketamine analogues[67] or even antagonists[68] may become available. Could this be the definite end of half a century of emergence problems?

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