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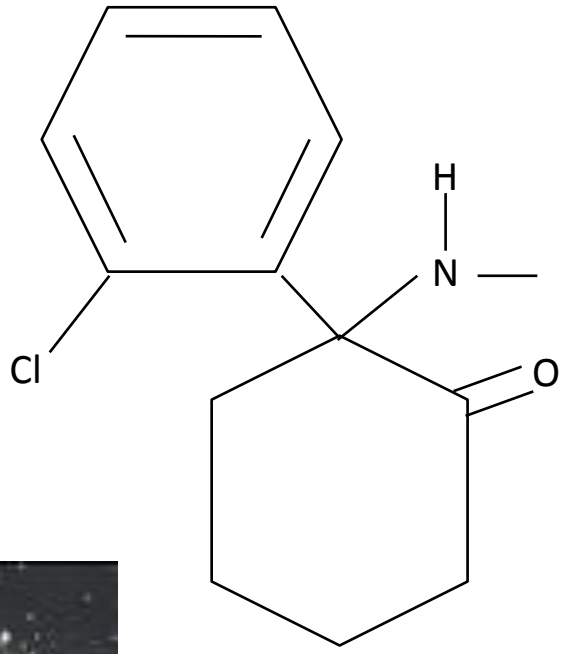
Ketamine



Introduction :

A) From Chemistry

Chemical formula	:	$C_{13}H_{16}ClNO$
IUPAC Name	:	2-(2-chlorophenyl)-2-(methylamino)cyclohexan-1-one
Drug form	:	The salt of ketamine, ketamine hydrochloride
State in standard condition	:	white, crystalline powder, having a slight characteristic odour
Melting point	:	262 to 263^{o}C
Molecular weight	:	274.21
Solubility	:	freely soluble in water, methanol and alcohol sparingly soluble in chloroform
pH ranges	:	3.5 to 5.5 (clear and colourless solution when dissolved in water)
Hazard :	:	It emits toxic fumes of hydrogen chloride and nitrogen oxide when heated to decomposition

B) From Pharmacy

Ketamine is a drug used in human and veterinary medicine. It is classified as an NMDA receptor antagonist. It induces a state referred to as ‘dissociative anesthesia’. It is also used as recreational drug.

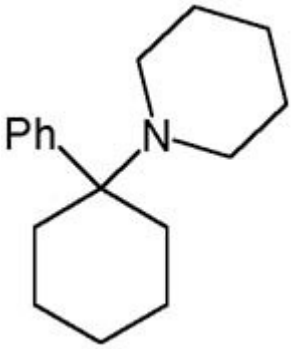
Lead compound discovery :

American pharmacist Calvin Stevens first synthesizes ketamine in the Parke Davis Lab and names it 'CI581' in 1962. Its discovery came out of the search for phencyclidine (PCP) replacements and it is used as a safer anesthetic to substitute PCP which was also an anesthetic but was likely to cause hallucinations, neurotoxicity and seizures. Compared to PCP, Ketamine leads to less serious side effects.

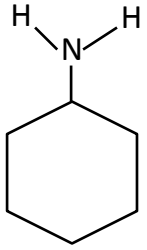
Molecular Modification :

A) Drug modification :

Year	Event
1958	Phencyclidine (phenyl cyclohexyl piperidine, PCP) was first introduced into clinical anesthesia. However, phencyclidine produced an unacceptably high incidence of hallucinations, confusion and delirium, so its development for use in human anesthesia was discontinued.
1959	Cyclohexamine was tried. It was found to be worse than PCP. It has similar adverse psychotomimetic effects with less analgesia.
1962	ketamine (Ketalar) synthesized by Calvin Stevens working for Parke Davis.



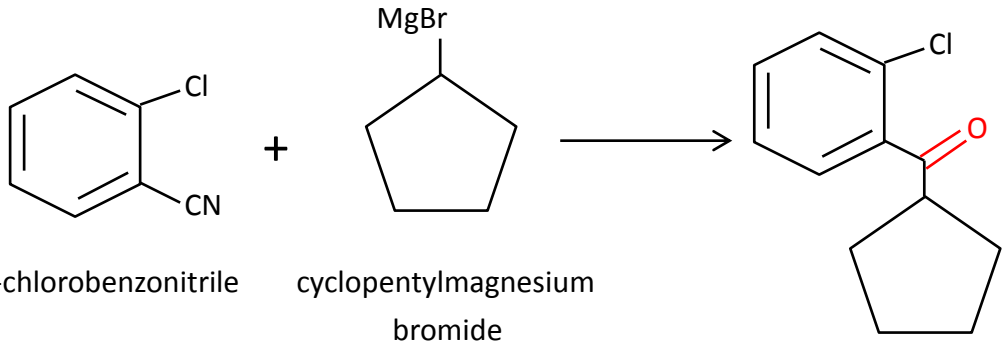
Phencyclidine



Cyclohexamine

B) Drug synthesis :

Step 1) Grignard reaction between 2-chlorobenzonitrile and cyclopentylmagnesium bromide to give 1-(2-chlorobenzoyl)cyclopentane

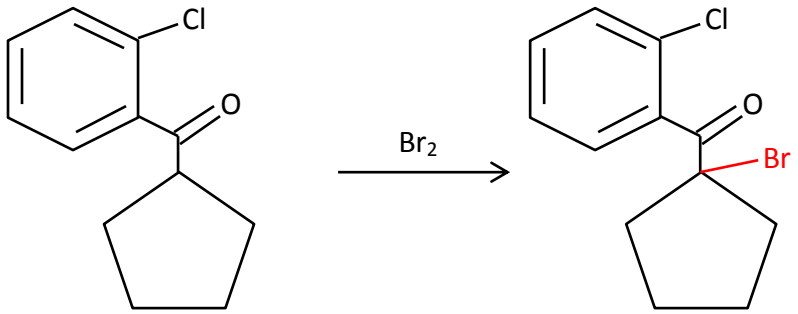


2-chlorobenzonitrile

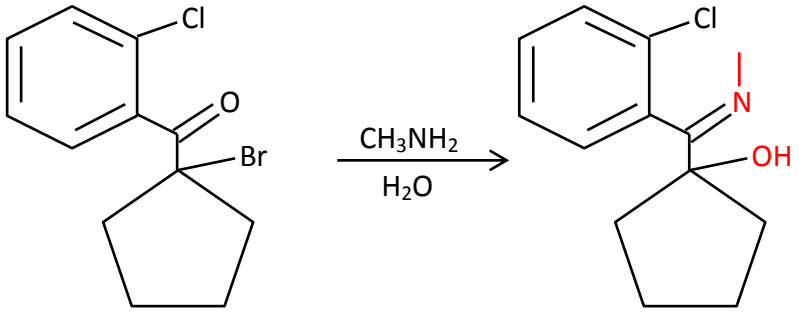
cyclopentylmagnesium bromide

1-(2-chlorobenzoyl)cyclopentane

Step 2) Bromination of 1-(2-chlorobenzoyl)cyclopentane

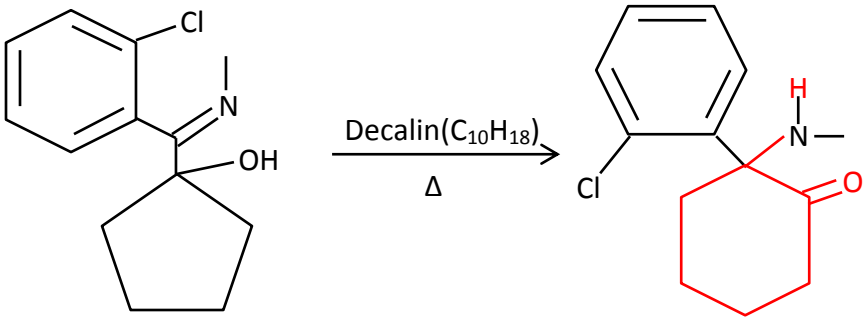


Step 3) Reaction with an aqueous solution methylamine to form the methylimino derivative and hydrolysis of the tertiary bromine atom



methylimino derivative

Step 4) Ring expansion rearrangement upon heating in decalin



Formulation Development :

A) Common mixture of Ketamine(Injection)

The most common mixture is 10% ketoprofen, 5% Lidocaine, and 10% ketamine. It may also include amitriptyline, cyclobenzaprine, clonidine, tramadol, and mepivicaine and other longer-acting local anaesthetics(麻醉藥).

B) Liquid Aerosol Formulation

The formulation of the present invention may include, as optional ingredients, pharmaceutically acceptable carriers, diluents, solubilizing or emulsifying agents, surfactants and excipients. Pharmaceutically acceptable diluents include sterile water, saline, buffered saline, dextrose solution. In a specific embodiment, the diluent may be phosphate buffered saline, or a buffered saline solution generally between the pH 7.0-8.0 range, or water. Carriers are soya lecithin, oleic acid and sorbitan trioleate, with sorbitan trioleate preferred. Other agents included are useful for pH maintenance, solution stabilization and the regulation of osmotic pressure. For example, sodium chloride, potassium chloride, and carbohydrates, like glucose, galactose or mannose may be included. Other therapeutically effective drug may also be included, such as a benzodiazepine(苯二氮平類藥物，作爲鎮靜催眠藥使用) or a narcotic analgesic(麻醉止痛劑)

C) Aerosol Dry Powder Formulation

This comprises of a finely divided dry powder containing ketamine, a dispersing agent and also a bulking agent. Examples of Bulking agents are lactose, sorbitol, sucrose, or mannitol. They facilitate the dispersal of the powder from the device. Other therapeutically effective drug may also be included, such as a benzodiazepine or a narcotic analgesic.

Safety tests and human trials :

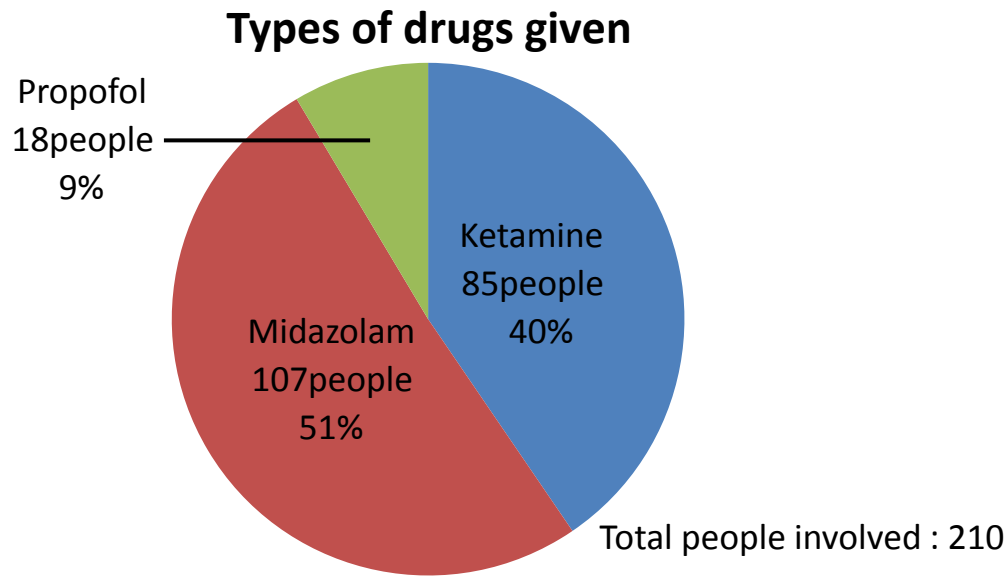
A) Human Trials

The drug was first given to American soldiers during the Vietnam War. A 2-year prospective audit of sedation practice was undertaken by the Department of Emergency Medicine. This specifically examined the rationale behind a doctor's choice of sedative agent, the depth of sedation(鎮靜狀態) achieved, adverse events and the time taken to regain full orientation. One of the trials is shown below.

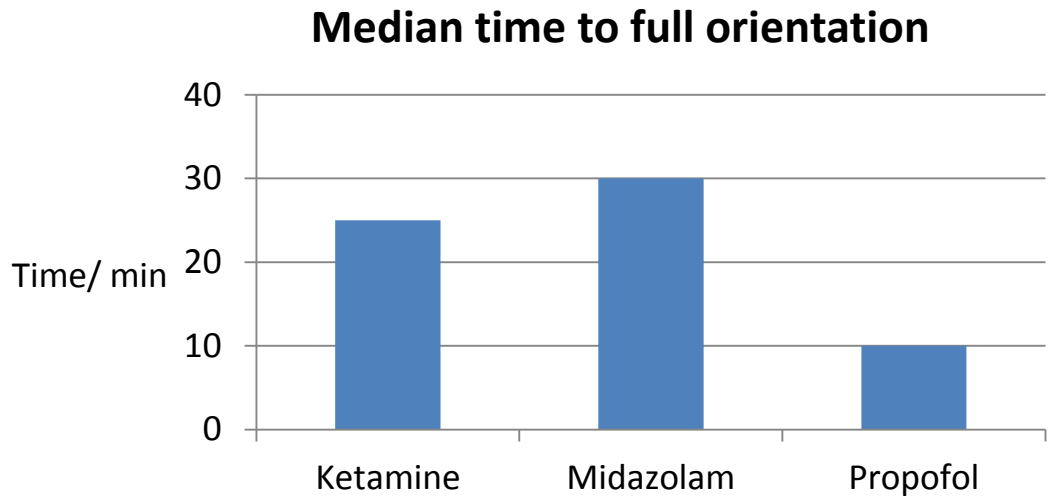
B) Safety tests

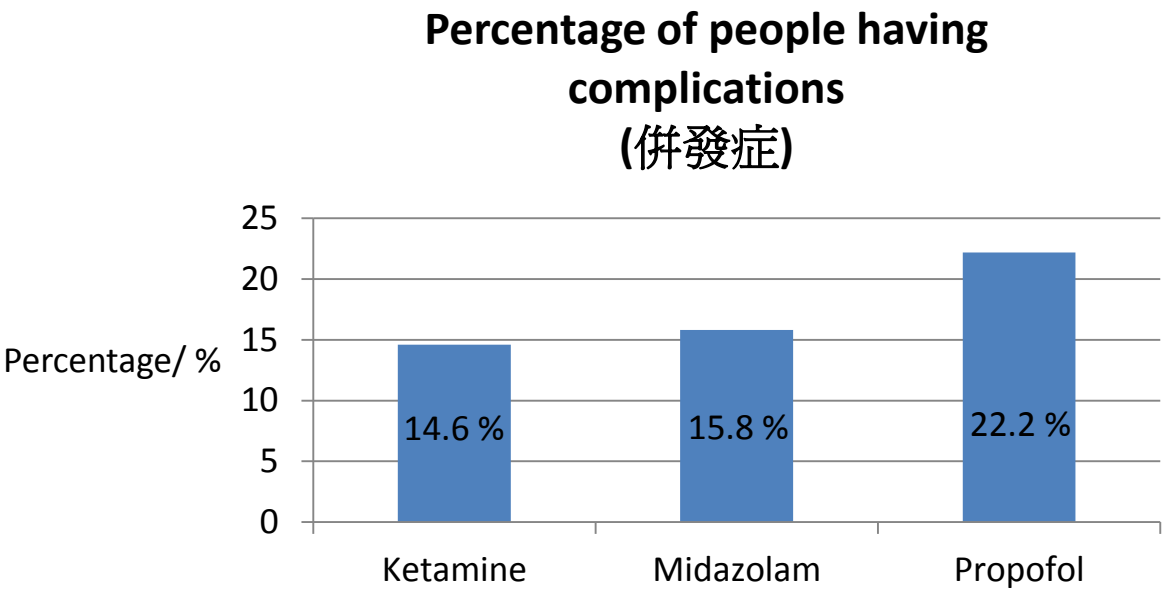
According to several research and studies, evidence shows that with repeated use, ketamine users can develop a tolerance and/or dependence to the drug. Tolerance in many instances can be very high and develop rapidly to the point where after a period of time users will no longer experience the dissociative effects for which they first began using. Ketamine has a great deal in common with other drugs linked with dependence including stimulants, opiates, alcohol, and cannabis. A common feature of ketamine dependence is that of repeated binges where the user indulges in the drug in excessive amounts over a short period of time. To date, identifying physical withdrawal symptoms has been limited to only personal accounts, but research is ongoing.

C)(I) Test



C)(II) Results





Also, Apnoea(窒息) and hypoxia(缺氧) most often occurred with midazolam and propofol, while hypertension(過度緊張) and hypertonicity(張力過高)were encountered more frequently with ketamine. In addition, 19.5% of patients given ketamine suffered from the reemergence phenomenon. The association between deep sedation with no response to pain and adverse events encountered with midazolam does not occur with ketamine.

C)(III) Conclusion

Ketamine is both safe and effective and compares favourably with midazolam as an agent for procedural sedation in the emergency department. Although the re-emergence phenomenon occurred, no psychological sequelae(後遺症) were encountered after return to full orientation. Ketamine may be particularly useful in groups of patients at high risk of adverse effects with midazolam.

Approval for marketing :

In 1970, the FDA approved ketamine for human use and it became popular as a battlefield anesthetic. It was (and still is) legally sold as Ketalar (Parke-Davis, for humans), Ketaset (For Dodge, for animals), and other brands.

Drug Name	Active ingredients	Strength	Dosage Form/Route	Marketing Status	RLD	TE code
Ketalar	Ketamine Hydrochloride	EQ 10MG BASE/ML	Injectable; Injection	Prescription	Yes	AP
Ketalar	Ketamine Hydrochloride	EQ 50MG BASE/ML	Injectable; Injection	Prescription	Yes	AP
Ketalar	Ketamine Hydrochloride	EQ 100MG BASE/ML	Injectable; Injection	Prescription	Yes	AP

Drug Name and FDA application Number	Dosage Form/Route	Strength	Marketing Status	Company
Ketamine Hydrochloride (ANDA # 074524)	Injectable; Injection	Multiple Strengths	Prescription	Bedford
Ketamine Hydrochloride (ANDA # 074549)	Injectable; Injection	Multiple Strengths	Prescription	Hospira
Ketamine Hydrochloride (ANDA # 076092)	Injectable; Injection	Multiple Strengths	Prescription	Bioniche Pharma