SCIENCE AND TECHNOLOGY

Alternative Uses and Effects of Ketamine

TIFFANY BRUNO
ANESTHESIA TECHNOLOGY PROGRAM,
OKLAHOMA CITY COMMUNITY COLLEGE

While ketamine is usually seen in operating rooms, it has also proven to be of more significant value than many researchers would think. It has evolved from both IV use to intranasal use. Ketamine has been used anywhere from postoperative analgesia to treating bipolar depression, treatment-resistant depression, and post-traumatic stress disorder in veterans. While there is not much research from a psychological standpoint, the research that has been done has proved the significance that ketamine has made on common issues that should be addressed on a more severe level. With increased suicides over the past ten years, ketamine could help those at a higher risk because of their depression.

HISTORY

Ketamine has had a long-standing history of use on the battlefield, helping wounded soldiers be able to live while having limited resources. Because ketamine was said to produce what is known as a dissociative form of analgesia, the patients could endure surgeries in the field with little to no anesthetic. It has also gone through both intravenous and intranasal stages to help veterans with treatment-resistant depression and post-traumatic stress disorder to figure out which has the better response.

The discovery of ketamine started with the search for an ideal anesthetic agent with analgesic properties among cyclohexylamines (Mion, 2017, p.571). This led to the first synthesis of phencyclidine or PCP in 1956 (Wei et al., 2020). During human trials to investigate the potential of PCP as an anesthetic, it was noted that it caused increases in blood pressure, respiratory rate, and minute volume, conserving the laryngeal and corneal reflexes (Mion, 2017, p.571). PCP also caused nystagmus (involuntary eye movement) and an increase in salivation. There was some success in the trials conducted with the drug because it did not cause depression in cardiovascular or respiratory functions (Mion, 2017, p.571). However, it did cause severe excitation in some patients, sometimes lasting over 12 hours on a single dose, making PCPs use extremely limited. Eticyclidine, or PCE, was then discovered in the late 1950s as an alternative; however, it was not extensively used in clinical practice with the hallucinations and discovery of ketamine shortly after (Li & Vlisides, 2016). There was further synthesis of the related compound in the hopes that it would reduce the side effects of PCP (Mion, 2017, p. 572). It was then that the laboratories decided to synthesize a unique series of phencyclidine derivatives, using animals to screen these drugs, especially monkeys. One of the agents was synthesized in 1962 that produced an excellent short-acting anesthetic and was selected for human trials as CI-581 (Mion 2017, p. 572). Because it was a ketone together with an amine, it was named ketamine (Mion, 2017, p.572). It was later described in 1965 as a compound with cataleptic, analgesic, and anesthetic actions without hypnotic properties (Wei et al., 2020).

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(Butterworth, 2021, p.171)

After being patented in Belgium in 1963, ketamine began as a veterinary anesthetic (Li & Vlisides, 2016). The first human administration was conducted in 1964 to volunteer prisoners at the Jackson Prison in the state of Michigan, with the incidence of adverse effects in one of three. Patients described their feeling as floating in outer space and having no feeling in their limbs, and the researchers published their first clinical studies in 1965 (Li & Vlisides, 2016). Thus, ketamine was officially coined as a 'dissociative anesthetic' due to the apparent disconnect in the patients (Butterworth, 2021, p.171). It was then formally patented for both animal and human use in 1966, becoming available by prescription in 1969 in the form of ketamine hydrochloride under the name Ketalar (Mion 573).

It was officially approved for human consumption by the FDA in 1970 (Pardo & Miller, 2017, p.115). Its sympathomimetic properties and wide safety margin started as a field anesthetic for soldiers in Vietnam (Mion, 2017, p.573). During a conflict between the Palestine Liberation Army and the Jordanian Army in 1970, many casualties started to overwhelm the hospitals, most of which were children (Mercer, 2009, p.146). A medical team was called from the UK to Cyprus to assist with the overwhelming number of patients, and the surgical team recorded their use of ketamine (Mercer, 2009, p.146). Due to their demographic, many patients were frightened and found the procedures painful (Mercer, 2009, p.146). A dose of 10 mg/kg treatment of ketamine allowed a procedural time of 30-50 minutes before signs of discomfort (Mercer, 2009, p.146). The nurses could give doses of ketamine to the children to keep them in a trance-like state for 20 minutes at a time to change the dressing on burns (Mercer, 2009, p.146). In this aspect, it has shown to excel in situations with little access to complete medical supplies and to assist patients that might otherwise be difficult to work on.

The value and safety of ketamine as an anesthetic and analgesic continue to demonstrate its effect on the patient population. While there are other drug options on today's market, ketamine has still been used in the operating room in situations that might otherwise impede the healing process. Its uses have also extended to manage treatment-resistant depression in lower dosages (Mion. 2017, p.573). Evolution can be seen from when it started to what it has become today.

PHARMACOKINETICS AND PHARMACODYNAMICS

Ketamine is highly lipid soluble, meaning that it can dissolve in fatty tissues, so it undergoes a rapid breakdown and redistribution to the peripheral tissues in the body (Butterworth et al., 2021, p.171). Ketamine then gets metabolized by the liver using N-demethylation (removing the methyl group from a molecule) and ring hydroxylation pathways (converting the lipid-soluble into water-soluble), making it easier to excrete it from the body (Kurdi et al., 2014). It is then excreted through urine and feces as norketamine and hydroxylated derivatives, norketamine being the primary metabolite for ketamine and being one-third to one-fifth as potent as an anesthetic (Kurdi et al., 2014).

Since ketamine stimulates the cardiovascular system, it does increase heart rate, blood pressure, and cardiac output mediated mainly through the sympathetic nervous system (Butterworth et al., 2021, p.172). It does, however, have minimal effects on the central respiratory drive, producing airway relaxation by acting on various receptors, inflammatory cascades, and bronchial smooth muscles (Pardo & Miller, 2014, p.116). Ketamine increases salivation and muscle tone and creates catalepsy, amnesia, analgesia, and some anesthetic actions (Kurdi et al., 2014). Catalepsy created by ketamine is a unique dissociative state where the patient appears awake with their eyes open but is detached from their surroundings (Kurdi et al., 2014).

"Even though ketamine went through the phase of what they called the 'nightclub' drug during the 1970s, it has gone from abuse to therapeutic in the effects that it causes."

~ Tiffany Bruno ~

USES ON PAIN

The first documentation of ketamine's usage was that of pediatric patients undergoing ophthalmologic procedures and adults and children undergoing wound dressing changes (Subramanian, 2022, p.6). It was chosen for such surgeries because it preserves airway and respiratory function while providing sedation and local anesthesia (Butterworth et al., 2021, p.174). The use of ketamine has been used as an adjunct with opioids to help minimize opioid side effects and reduce opioid analgesic requirements (Pardo & Miller, 2017, p. 116). It has been shown in pre-clinical studies to diminish immediate hyperalgesia while improving the analgesic effect of fentanyl (Subramanian, 2022, p.6). Ketamine has also helped reduce the need for morphine in patients with cancer-related pain, especially those with a neuropathic element (Subramanian, 2022, p.7). The onset and severity of chronic pain have been reduced up to a month after perioperative ketamine administration; however, for sustained chronic pain relief, the patient may require more frequent or extended periods of administration (Pardo & Miller, 2017, p.116). With how variable pain control is in clinical trials, there is no consensus on IV ketamine dosage or duration (Subramanian, 2022, p.7). As an alternative to IV ketamine, intranasal has shown success as a breakthrough pain relief, with an onset of around 10 minutes lasting up to an hour (Butterworth et al., 2021, p.172).

USES ON DEPRESSION

Though its original uses were to find an alternative anesthetic agent, ketamine has become much more than that over the years. It has become the thing that has helped mental illness in those suffering from depression, post-traumatic stress disorder (PTSD), and even those with suicidal thoughts. It has even been successful as an adjunct to drugs like lamotrigine in treating unipolar and bipolar treatment-resistant depression. Even though ketamine went through the phase of what they called the 'nightclub' drug during the 1970s, it has gone from abuse to therapeutic in the effects that it causes.

Future studies should be done on the effects that ketamine has in conjunction with other drugs. However, the studies that have been posted have only shown positive results. The study of ketamine and lamotrigine aimed to find any scientific ground for combining the two in treating mood disorders (Wilkowska 1). Lamotrigine is a first-line agent used for bipolar depression as a monotherapy and adjunctive treatment for resistant cases (Wilkowska 3). It is approved by the FDA for the long-term treatment of bipolar disorder to prevent relapse in adult patients who suffer predominantly from depressive states (Wilkowska 3). Though little is known about the interactions between ketamine and other drugs, the studies for treatment-resistant depression are piling up (Wilkowska 3). During these studies with the simultaneous use of ketamine and lamotrigine, no serious adverse events were observed, showing relative safety (Wilkowska, 2022, p.4). Though information from the studies is limited, we can conclude that preclinical suggests a possible synergistic antidepressant effect of lamotrigine and ketamine (Wilkowska, 2022, p.1). Because one of the possible side effects of ketamine is seizures, there is evidence that lamotrigine could reduce those effects (Wilkowska, 2022, p.1). Lamotrigine can be used alone or with other medications to prevent and control seizures (*National Center*, 2022).

"This could be the start of a future to help reduce the number of suicides that happen daily."

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In a study done with cancer patients experiencing severe depression and suicidal ideation, 26 hours into a ketamine infusion, the patient was observed to have a euthymic effect and no suicidal ideation (Subramanian 7). A couple of things were recorded in a clinical trial observing IV ketamine as a depression and pain agent (Subramanian 7). The researchers provided all the treatment-resistant depressed patients with six subanesthetic ketamine infusions over two weeks. They found that those with pain and depression had higher responses and remission than those that started with no pain symptoms (Subramanian 7). A headache also occurred in around 19% of ketamine infusions and resolved after the administration (Subramanian 7).

Mental disorders are a growing problem in the world, coinciding with the increase in disease and economic costs, while also maintaining studies that show suicide becoming an increasing problem (Coelho da Costa 15). It has become a major problem in the middle to low-income countries among people aged 15-29 and has become the second leading cause of death in that age group (Coelho da Costa 16). It should be addressed to make treatment accessible to those who usually have problems affording it.

USES IN THE OR

Like on the battlefield, ketamine is used in the operating room on higher-risk patients. It has been utilized in patients that are in shock or are hypotensive, as it can help to raise their blood pressure (Kurdi et al., 2014). It has been shown to work advantageously on hemodynamically compromised patients during a rapid sequence induction used in emergent cases when the patient has not undergone proper pre-operation checks (Kurdi et al., 2014). A study also showed ketamine as a safe alternative to etomidate (a short-acting anesthetic agent that creates a stable hemodynamic profile) for intubation in critically ill patients with sepsis (Kurdi et al., 2014). It is also effective in patients with brain injury, as it creates a neuroprotective effect against cerebral ischemia and anticonvulsant activity and has the potential to limit hypotension and hypotension-related secondary brain injury (Kurdi et al., 2014).

Ketamine's bronchodilation properties make it great for intubating patients with reactive airway diseases (Kurdi et al., 2014). It can also help to protect against the precipitation of asthma and bronchospasms (Kurdi et al., 2014). Ketamine has been the bronchodilator of choice in the ICU as rescue therapy for refractory bronchospasm (Kurdi et al., 2014).

Finally, ketamine is widely used in the burn unit to provide analgesia during dressing changes, excision, grafting, and sedation (Kurdi et al., 2014). The significant advantage over other agents is that it helps preserve the airway and spontaneous respiratory function while providing sedoanalgesia (Kurdi et al., 2014). It is especially desirable for intramuscular injection when finding a suitable vein proves difficult (Kurdi et al., 2014). Ketamine therapy studies have shown significant improvement in survival in rats with

severe burn injuries (Kurdi et al., 2014). This is estimated to be due to eliciting heat-shock response due to the evidence by the expression of the heat-shock protein 70 in myocardial cells and cerebral tissue (Kurdi et al., 2014).

ADVERSE EFFECTS

The scientific community was hesitant to use ketamine as a treatment option for mental disorders and pain for three reasons: first, it had the potential for abuse; second, it was thought that the NMDA antagonism would exacerbate underlying mental illnesses; third, ketamine has the potential to lead to psychotomimetic effects like catatonia, hallucinations, delusions, and maniacal excitation, especially at higher doses (Subramanian 5). Psychotomimetic side effects can show within 10 minutes of infusion and subside within 40 minutes (Subramanian 5). It can cause acute psychotic reactions at higher concentrations, with reports of subjects experiencing a feeling of 'well-being' (Subramanian 5). It has also shown that a co-administration of oral clonidine has helped to decrease these effects (Subramanian 5). Ketamine can cause impairment even with subanesthetic doses given over 40-120 minutes in healthy volunteers (Subramanian 5). Hemodynamic changes have also been reported as increases in heart rate and blood pressure that reverts to baseline after 10-30 minutes (Subramanian 5). Chronic recreational use has led to urinary urgency, dysuria, and hematuria, as well as an association with the thickening of the bladder wall and peri-vesical inflammation (Subramanian 5). There have been increases in exposure for recreational uses to ketamine which has had some linked seizure effects. However, it is still uncommon (Palamar 2046)

CONCLUSION

Though ketamine is seen as a dissociative drug used in the field of war or the operating room, it has shown that it has more capability than many researchers would come to realize. It has the possibility of helping mentally ill patients that feel like they have no other options. This could be the start of a future to help reduce the number of suicides that happen daily. More research should be done to showcase what ketamine can handle, and it should be made more available to those who genuinely need it.

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To test your knowledge on this issue's article, provide correct answers to the following questions on the form below. Follow the instructions carefully.

1. Ketamine is a lipid-soluble medication.
A. True
B. False

2. What is the time needed to breakthrough pain using intranasal ketamine?
A. 5-minutes
B. 10-minutes
C. 15-minutes
D. 20-minutes

3. What effect will the use of lamotrigine and ketamine together produce?
A. Hypotension
B. Sinus tachycardia
C. Ventricular tachycardia
D. Seizure reduction

4. Ketamine does not at act as a bronchodilator.
A. True
B. False

5. Chronic recreational use of ketamine results in _____.
A. Neoplasm
B. Sardonic lordosis
C. Hematuria
D. Ischemic Stroke

6. Ketamine is used on burn units during dressing changes.
A. True
B. False

7. Ketamine is used in incidences of shock for its ability to raise blood pressure.
A. True
B. False

8. Why is ketamine chosen for induction?
A. Lowers blood pressure
B. Preserves airway/respiratory function
C. Decreases HR
D. Increases SpO2

9. Why is ketamine being explored for its analgesic properties?
A. Reduction of vasopressor use
B. Increase use for intraoperative opioid use
C. Reduction of opioid use

10. Ketamine does not increase cardiac output.
A. True
B. False

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4: A B		**9:** A B C D
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