SOFT-DFC Snapshot – Ketamine

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SOFT-DFC Snapshots are short reports of critical information about the more common drugs associated with drug-facilitated crimes (DFCs). They are not complete literature reviews about the drug or drug class. One key aspect is their focus on the ability to detect a drug after a single-dose administration, as is often the situation in DFC investigations. As such, these summaries also point out instances in which available data is limited in the hopes that this will encourage further research studies. Finally, SOFT-DFC Snapshots point to the use of these drugs in actual DFC cases, as cited in the medical and open literature.

Ketamine is a 'dissociative anesthetic' that is commonly known for its ability to create a feeling of disconnect between mind and body. It is widely used clinically in both animals and humans for the induction and maintenance of anesthesia. Initially synthesized in the 1960's and clinically approved for use in the 1970's, it is chemically and pharmacologically related to phencyclidine (PCP, angel dust). Both drugs were studied concurrently, however, ketamine was found to exhibit a superior safety profile as compared to PCP. Ketamine is distinct from other anesthetics as it provides short-term analgesia and amnesia without suppression of breathing [1,2]. In recent years, sub-anesthetic intravenous and intranasal doses of ketamine have been used to combat symptoms of treatment-resistant depression[3].

Ketamine ("K", "Special K", "Vitamin K") is also used recreationally for its psychedelic and dissociative effects, and is popular in the electronic music/rave/dance scenes for its ability to produce dream-like hallucinations and depersonalization[1,2]. Novel analogues of ketamine are also available on the illicit market (e.g., 2-fluorodeschloroketamine, methoxetamine). Limited pharmacokinetic information for these analogs is available but the effects are generally similar to ketamine.

Ketamine has been implicated in cases of Drug Facilitated Crime (DFC) worldwide. Whether consumed voluntarily or surreptitiously administered, the dissociative, amnesic, and hallucinatory effects produced by the drug can be exploited to render an individual unconscious or incapacitated. Its relative safety, quick onset of action, and rapid elimination also makes ketamine an attractive drug of choice by perpetrators of DFC.

Drug Class

Dissociative Anaesthetic (non-barbiturate), CNS Depressant[1,4.]

Generic Name

Ketamine (racemic) or ketamine hydrochloride, Esketamine (S-ketamine), Arketamine (R-ketamine and not FDA approved)

Dosage Forms

Injectable liquid (Ketalar®)[5], Intranasal spray (Spravato®)[6], powder (illicit use)

Used clinically, dosing is based on body weight and anesthesia is generally achieved between 1 – 2 mg/kg intravenously, and 4 – 11 mg/kg intramuscularly[7].

Esketamine, used for treatment of depression, is administered intranasally, with doses ranging from 28 to 84 mg administered once or twice weekly[8].

When used recreationally, ketamine can be consumed orally, intra-nasally, intravenously, rectally, or by smoking. Single recreational doses can range from 10 to 500 mg, but may be used multiple times in a single session due to its short duration of effects[9].

FDA Approval

Ketamine is used therapeutically as an intravenous anesthetic in adults and children for short surgical and diagnostic procedures.

Intranasal esketamine has been approved as an adjunctive treatment for treatment-resistant depression in 2019 [3,10].

Ketamine is also widely used as an animal tranquilizer in veterinary medicine.

Non-FDA applications can include its use for the treatment alcoholism, post-traumatic stress syndrome, anxiety, depression, suicidal ideation, refractory status epilepticus, and chronic pain[4].

Pharmacological Effects:

Ketamine's effects are primarily due to its function as an N-methyl-D-aspartate (NMDA) non-competitive receptor antagonist, interrupting the effects of glutamate and aspartate, and producing amnesic, analgesic and psychedelic effects. To a lesser extent, ketamine also acts on opioid, serotonin, and muscarinic receptors[2]. As a partial opiate mu receptor agonist, ketamine can impart analgesic effects.

The effects produced by ketamine are dose dependent. At low (sub-anesthetic) doses, effects can include euphoria, depersonalization, and a trance-like state. At higher does, impaired motor function, vomiting, slurred speech, agitation, elevated heart rate and delirium can occur. When used recreationally, users may seek to achieve a state known as the "K-hole", characterized by a loss of sense of time and space, difficulty moving, distorted body image, and what can be described as an 'out-of-body' or near-death experience[1]. While overdose is rare, death can be caused by respiratory depression[2,9].

The most intense effects of ketamine are short-lived, owing to its short half-life (estimated at 1 – 4 hours, intravenously[11]). Effects begin rapidly (within seconds) when smoked or injected, within 5 – 10 minutes when snorted, and within approximately 30 minutes when used orally. Effects will typically last less than one hour when smoked, injected, or snorted, but can extend for 1 – 2 hours when used orally (which may be due, at least in part, to higher concentrations of the active metabolite norketamine produced by this route)[12].

Metabolism/Elimination

Ketamine is extensively metabolized in the liver, primarily by CYP 3A4, to the active metabolite norketamine[12]. Secondary metabolism occurs via CYP 2B6 and CYP 2C9 enzymes. The metabolic process includes N-dealkylation, hydroxylation, conjugation, and dehydration. Ketamine is subject to extensive first-pass metabolism when consumed orally[2], and metabolism may also be subject to CYP enzyme polymorphism and can be subject to drug-drug interactions[13].

R-Ketamine and S-Ketamine are similarly metabolized to norketamine and esnorketamine. Norketamine and esnorketamine are subsequently metabolized to the inactive dehydronorketamine by dehydrogenation[7, 12].

Single Dose Studies

Urine:

After a single dose, ketamine can typically be detected in urine for between 48 and 72 hours[14]. However, this time frame may be extended up to 120 hours when using sensitive methods with detection limits at the sub-nanogram level[15]. In cases of repeated administration, ketamine can be detected in urine for much longer. In a frequent high dose user, ketamine has been detected up to 61 days[16].

Norketamine and dehydronorketamine are detectable in urine for longer than the parent drug up to 14 days and 10 days, respectively, after a single dose[14, 17].

The SOFT DFC committee guidelines currently recommend a minimum method performance limit of 10 ng/mL for ketamine and norketamine in urine. The AAFS Standards Board similarly recommends a detection limit of 10 ng/mL or lower for norketamine[18].

Blood/Plasma/Serum:

Forensic interpretation of blood ketamine and norketamine concentrations can be complicated due to its short half-life and large inter-individual variability.

Psychedelic effects have been reported at plasma concentrations as low as 50 ng/mL, with intensity increasing with increasing plasma concentration[19]. Pain threshold elevation has been observed at plasma concentrations greater than 160 ng/mL[20].

When used intravenously in a clinical setting, plasma concentrations necessary to induce dissociative anesthesia range from 1.2 – 2.4 mg/L with awakening from anesthesia associated with concentrations of less than 1.1 mg/L[7, 21, 22].

Intranasal esketamine administration produces substantially lower blood concentrations, owing in part to the lower doses needed to achieve efficacy with this enantiomer. Following 3 escalating doses of 25mg, 50 mg, and 100 mg administered approximately 1 hour apart, plasma concentrations of less than 200 ng/mL, 300 ng/mL and 500 ng/mL were achieved, respectively, in healthy volunteers[23].

Hair Testing

Hair can also provide evidence of past drug exposure to ketamine[24]. It can provide a longer detection window as compared to blood or urine and might be more practical in DFC cases in which biological samples weren't collected or available close to the time of the incident.

At a hair growth rate of approximately 1 cm per month, a 3 cm hair shaft sample can potentially indicate ketamine exposure over a 3-month period[25]. Like other basic drugs, the concentration detected may vary due to hair color which is caused by variable binding to melanin[26].

In a study administering a single oral dose of 10 mg ketamine, ketamine and norketamine were detected in the 0 to 0.5 cm hair segment starting at one week following administration and ending at approximately 8 weeks[27, 28]. Occupational exposure may also cause a positive result for ketamine in hair. In a study of 13 veterinarians, who worked with ketamine, it was detected in hair samples from all participants[29].

DFC Cases

Ketamine has been implicated in DFC cases worldwide. Its dissociative, sedative, anesthetic, amnesiac, and hallucinatory effects make it an attractive drug to use for this purpose. Furthermore, it can be ingested voluntarily, or surreptitiously diluted into a beverage.

While its true prevalence in cases of DFC is not known, a Canadian study reported the prevalence of ketamine as an unexpected finding in cases of drug facilitated sexual assault to be 2.3%[30].

A case report in the literature describes the sexual assault of a young woman by her gynecologist who used intravenous ketamine and diazepam to sedate her. Effects described included loss of consciousness and vomiting upon waking. At approximately 30 hours after the assault, ketamine and norketamine concentrations detected in blood were 2 and 6 ng/mL respectively[31].

References

1. Mozayani, A. (2002). Ketamine - Effects on Human Performance and Behavior. Forensic science review, 14 (1-2), 123-31
2. Wolff, K., & Winstock, A. R. (2006). Ketamine. CNS Drugs, 20(3), 199–218. https://doi.org/10.2165/00023210-200620030-00003
3. Yavi, M., Lee, H., Henter, I. D., Park, L. T., & Zarate, C. A. (2022). Ketamine treatment for depression: a review. Discover Mental Health, 2(1). https://doi.org/10.1007/s44192-022-00012-3
4. Rosenbaum, S.B., Gupta, V., Patel, P., et al. Ketamine. [Updated 2024 Jan 30]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470357/
5. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/016812s046lbl.pdf, Ketamine FDA Label. Retrieved January 6, 2025.
6. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211243lbl.pdf, Esketamine FDA Label. Retrieved January 6, 2025
7. Zanos, P., Moaddel, R., Morris, P. J., Riggs, L. M., Highland, J. N., Georgiou, P., Pereira, E. F. R., Albuquerque, E. X., Thomas, C. J., Zarate, C. A., & Gould, T. D. (2018). Ketamine and

Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms. Pharmacological Reviews, 70(3), 621–660. https://doi.org/10.1124/pr.117.015198
8. Seshadri, A., Prokop, L. J., & Singh, B. (2024). Efficacy of intravenous ketamine and intranasal esketamine with dose escalation for Major depression: A systematic review and meta-analysis. Journal of Affective Disorders, 356, 379–384. https://doi.org/10.1016/j.jad.2024.03.137
9. Corkery, J. M., Hung, W.-C., Claridge, H., Goodair, C., Copeland, C. S., & Schifano, F. (2021). Recreational ketamine-related deaths notified to the National Programme on Substance Abuse Deaths, England, 1997–2019. Journal of Psychopharmacology, 35(11), 026988112110215. https://doi.org/10.1177/02698811211021588
10. Langmia, I. M., Just, K. S., Yamoune, S., Müller, J. P., & Stingl, J. C. (2022). Pharmacogenetic and drug interaction aspects on ketamine safety in its use as antidepressant - implications for precision dosing in a global perspective. British Journal of Clinical Pharmacology, 88(12), 5149–5165. https://doi.org/10.1111/bcp.15467
11. Domino, E. F., Domino, S. E., Smith, R. E., Domino, L. E., Goulet, J. R., Domino, K. E., & Zsigmond, E. K. (1984). Ketamine kinetics in unmedicated and diazepam-premedicated subjects. Clinical Pharmacology and Therapeutics, 36(5), 645–653. https://doi.org/10.1038/clpt.1984.235
12. Dinis-Oliveira, R. J. (2017). Metabolism and metabolomics of ketamine: a toxicological approach. Forensic Sciences Research, 2(1), 2–10. https://doi.org/10.1080/20961790.2017.1285219
13. Dutton, M., Can, A., Lagopoulos, J., & Hermens, D. F. (2023). Oral ketamine may offer a solution to the ketamine conundrum. Psychopharmacology. https://doi.org/10.1007/s00213-023-06480-x
14. Adamowicz, P., & Kala, M. (2005). Urinary Excretion Rates of Ketamine and Norketamine Following Therapeutic Ketamine Administration: Method and Detection Window Considerations. Journal of Analytical Toxicology, 29(5), 376–382. https://doi.org/10.1093/jat/29.5.376
15. Parkin, M. C., Turfus, S. C., Smith, N. W., Halket, J. M., Braithwaite, R. A., Elliott, S. P., Osselton, M. D., Cowan, D. A., & Kicman, A. T. (2008). Detection of ketamine and its metabolites in urine by ultra high pressure liquid chromatography–tandem mass spectrometry. Journal of Chromatography B, 876(1), 137–142. https://doi.org/10.1016/j.jchromb.2008.09.036
16. de Jong, L. A. A., Qurishi, R., Stams, M. P. J., Böttcher, M., & de Jong, C. A. J. (2020). Prolonged Ketamine and Norketamine Excretion Profiles in Urine After Chronic Use. Journal of Clinical Psychopharmacology, 40(3), 300–304. https://doi.org/10.1097/jcp.0000000000001191
17. Wieber, J., R. Gugler, J.H. Hengstmann and H.J. Denglet. (1975). Pharmacokinetics of ketamine in man. Anaesthesist. 24: 260-263
18. ANSI/ASB Standard 121 – Standard for Analytical Scope and Sensitivity of Forensic Toxicological Testing of Urine in Drug-Facilitated Crimes". Academy Standards Board. First Edition, 2021. Retrieved Aug 16, 2024.
19. Bowdle, Andrew T., Radant, Allen D., Cowley, Deborah S., Kharasch, Evan D., Strassman, Rick J., & Roy-Byrne, Peter P. (1998). Psychedelic Effects of Ketamine in Healthy Volunteers . Anesthesiology, 88(1), 82–88. https://doi.org/10.1097/00000542-199801000-00015

20. Clements, J.A. W.S. Nimmo and I.S. Grant. (1982). Bioavailability, pharmacokinetics and analgesic activity of ketamine in humans. J. Pharm. Sci. 71(5): 539-542
21. Idvall, J., Ahlgren, I., Aronsen, K. F., & Stenberg, P. (1979). Ketamine Infusions: Pharmacokinetics and Clinical Effects. British Journal of Anaesthesia, 51(12), 1167–1173. https://doi.org/10.1093/bja/51.12.1167
22. Grant, I. S., Nimno, W. S., & Clemenets, J. A. (1981). Pharmacokinetics and Analgesic Effects of I.M. and Oral Ketamine. *British Journal of Anaesthesia*, *53*(8), 805–810. https://doi.org/10.1093/bja/53.8.805
23. Jonkman, K., Duma, A., Olofsen, E., Henthorn, T., van Velzen, M., Mooren, R., Siebers, L., van den Beukel, J., Aarts, L., Niesters, M., Dahan, A. (2017). Pharmacokinetics and Bioavailability of Inhaled Esketamine in Healthy Volunteers. *Anesthesiology*. 127(4):675-683. https://doi.org/10.1097/ALN.0000000000001798.
24. Favretto, D., Vogliardi, S., Tucci, M., Simoncello, I., El Mazloum, R., & Snenghi, R. (2016). Occupational exposure to ketamine detected by hair analysis: a retrospective and prospective toxicological study. *Forensic Science International*, *265*, 193–199. https://doi.org/10.1016/j.forsciint.2016.03.010
25. Rhee, J., Lee, J., Kim, J., Jang, M., Shin, I., & Lee, S. (2020). Determination of Ketamine and Norketamine in Hair and Evaluation of Polydrug Use in Ketamine Abusers Using Hair Analysis in Korea. Journal of Analytical Toxicology, 45(9), 993–1005. https://doi.org/10.1093/jat/bkaa166
26. Xiang, P., Shen, M., & Zhuo, X. (2006). Hair analysis for ketamine and its metabolites. Forensic Science International, 162(1-3), 131–134. https://doi.org/10.1016/j.forsciint.2006.05.046
27. Xiang, P., Shen, M., & Drummer, O. H. (2015). Review: Drug concentrations in hair and their relevance in drug facilitated crimes. Journal of Forensic and Legal Medicine, 36, 126–135. https://doi.org/10.1016/j.jflm.2015.09.009
28. Favretto, D., Vogliardi, S., Stocchero, G., Nalesso, A., Tucci, M., Terranova, C., & Ferrara, S. D. (2013). Determination of ketamine and norketamine in hair by micropulverized extraction and liquid chromatography–high resolution mass spectrometry. Forensic Science International, 226(1-3), 88–93. https://doi.org/10.1016/j.forsciint.2012.12.013
29. Favretto, D., Vogliardi, S., Tucci, M., Simoncello, I., El Mazloum, R., & Snenghi, R. (2016). Occupational exposure to ketamine detected by hair analysis: a retrospective and prospective toxicological study. Forensic Science International, 265, 193–199. https://doi.org/10.1016/j.forsciint.2016.03.010
30. Du Mont, J., Macdonald, S., Rotbard, N., Bainbridge, D., Asllani, E., Smith, N., & Cohen, M. M. (2010). Drug-facilitated sexual assault in Ontario, Canada: Toxicological and DNA findings. Journal of Forensic and Legal Medicine, 17(6), 333–338. https://doi.org/10.1016/j.jflm.2010.05.004
31. Wille, S. M. R., Di Fazio, V., & Samyn, N. (2013). Drug-facilitated sexual crime by use of ketamine and diazepam by a gynaecologist. Drug Testing and Analysis, 5(9-10), 730–735. https://doi.org/10.1002/dta.1554