Cut-off proposal for the detection of ketamine in hair

Highlights

- Ketamine is commonly misused because of its psychotropic properties.
- Unlike other drugs of abuse, a cut-off level for ketamine in hair has never been fixed.
- We propose a tentative cut-off of 0.5 ng/mg as suggestive of repeated exposure.
- Additionally, the detection of the metabolite norketamine should be mandatory.

Abstract

Ketamine is a powerful anesthetic drug used in both human and veterinary surgery, but it is also commonly misused because of its psychotropic properties. Since the abuse of this drug has been reported in many countries worldwide, its determination in hair samples is offered as a specialist test by hundreds of laboratories. However, unlike other common drugs of abuse, a cut-off level for ketamine in hair has not been fixed yet. Therefore, aim of this study is to propose a concentration value for ketamine in hair analysis, in order to discriminate between chronic and occasional use, and between active use and external contamination. After considering the chemical properties of this molecule, and the experimental data collected in our laboratory or reported in several other published studies, we propose a cut-off level of 0.5 ng/mg, as indicative of repeated exposure to ketamine. Additionally, we suggest that the detection of the metabolite norketamine should be mandatory to prove active intake and exclude false positive result from external contamination. Thus, a reasonable cut-off value for norketamine could be fixed at 0.1 ng/mg, while the minimal concentration ratio norketamine/ketamine may be positively established at 0.05.

Keywords

Hair; Cut-off; Ketamine

1. Introduction

Ketamine is a powerful anesthetic drug used in both human and veterinary surgery since the early 1960s. In pharmaceutical preparations, ketamine is normally found as injectable solution, but it can also be obtained as a powder or tablet. It is administered orally or injected [1], but it can also be snorted, or smoked [2] and [3]. The psychotropic properties of ketamine have induced its parallel misuse as a recreational drug in a variety of social settings, as well as in drug-facilitated sexual assault, owing to its dissociative and sedative properties [4]. The majority of ketamine abusers are likely teens and young working adults [5]. Since the misuse of this drug has been reported in many countries worldwide, its determination in hair samples is offered as a specialist test by hundreds of laboratories, using different analytical techniques [2], [3], [4], [5], [6], [7], [8], [9], [10], [11], [12] and [13]. Hair analysis currently represents a reliable and well-established means of clinical and forensic investigation, insomuch as it is regularly requested to evaluate drug exposure, to portray drug abuse history and/or withdrawal control, to perform workplace drug testing, driving re-licensing and post-mortem investigations, to ascertain drug-facilitated crimes, and occasional or prenatal exposure to drugs [14] and [15]. Consequently, the international community (in particular, The Society of Hair Testing) periodically meets to exchange scientific experiences, and establish new protocols and consensus documents in order to provide thorough interpretation of the analytical results and consequent clinical or legal judgments. As a matter of fact, few guidelines about hair testing do exist [16] and [17], and are constantly revised. In several circumstances, such as in workplace drug testing, accurate correlation between the degree of positive detection in hair specimens and the correct category of ketamine exposure is of extreme importance and may have serious consequences for the investigated subjects. Nevertheless, a specific cut-off value for ketamine in hair has never been proposed, nor it has been suggested for its main metabolite, norketamine, ultimately implying that their mere detection in hair represents a prove of drug exposure. Indeed, norketamine, which is generated by *N*-demethylation of ketamine, reaches blood concentrations similar to ketamine itself [18]. However, the concentration of ketamine in hair is expected to be higher than that of its metabolite, because norketamine is more polar than the parent drug, and the extent of hair deposition is widely known to correlate with the lipophilicity of the drug.

In the present study, we evaluated a miscellaneous of case reports, analytical results, and published data, either obtained in our laboratory and from peer-reviewed literature, all describing the detection of ketamine and its metabolite norketamine in the keratin matrix. Our aim was to identify a tentative discriminating concentration to be used as a cut-off in hair analysis, in order to distinguish chronic and illicit abuse from occasional use (e.g. for medical reasons) of ketamine, or between active use and external contamination.

2. Materials and methods

2.1. Sample preparation

Only the proximal 0–6 cm segment was analyzed whenever longer head hair samples were collected. Shorter head hair samples, as well as body hair samples, were analyzed in their full length. About 50 mg of hair was twice-washed with dichloromethane (2 mL, vortex mixed for 3 min). The solvent washes were completely removed and discarded, then the hair was dried at room temperature by a gentle nitrogen flow and subsequently cut with scissors into 1–2 mm segments. Hair samples were fortified with 2 µL of internal standard solution yielding a final concentration of 0.4 ng/mg. After the addition of 2 mL of methanol, the samples were incubated at 55 °C for 15 h without stirring. Lastly, the organic phase was collected and an aliquot of 1 µL was directly injected into the UHPLC–MS/MS system.

2.2. Instrumentation

The method normally used in our laboratory to detect the most common drugs of abuse [19] was modified to include ketamine and norketamine. SRM transitions and potential settings for the analytes are presented in Table 1.

Table 1. SRM transitions and corresponding potentials for the target compounds.

Compound	RT (min)	SRM transitions (*m/z*) [a]	DP (V)	CE (V)	CXP (V)
Cocaine-d3 (ISTD)	1.5	**307.1 → 185.1**	71	27	11
		238.0 → 125.0		35	11
Ketamine	2.2	238.0 → 207.0	45	19	9
		238.0 → 179.0		23	15
Norketamine	2.6	**224.1 → 125.0**	40	35	11
		224.1 → 207.1		19	9

[a]Target transitions used for quantitation are marked in bold.

The method was fully revalidated according to national and international guidelines [20] and [21]. Linearity was verified in the interval 0.05–5.0 ng/mg. Whenever the real samples concentrations were found to exceed the highest calibration point, the final extracts were diluted with methanol and re-injected into the system. Limit of Detection (LOD) and Limit of Quantitation (LOQ) for ketamine and norketamine were, respectively, 0.004 and 0.003 ng/mg (LODs) and 0.013 and 0.010 ng/mg (LOQs). Interday precision and accuracy were tested at 0.05 ng/mg, showing that all

experimental values were below the acceptable CV and bias limits of ±15%. Matrix effects for ketamine and norketamine were, respectively, +24% and −13%. Laboratory performances are constantly monitored through regular participation to inter-laboratory proficiency tests.

2.3. Detection of ketamine in the published literature

It is well-acknowledged that the concurrent detection of drug metabolites in biological specimens provides evidence of active intake, preventing false positive and misleading interpretation of the analytical results. In the following summary of the inherent published literature, only the articles presenting the detection of ketamine and its metabolite norketamine in real hair samples were included. The analytical techniques most frequently used to detect ketamine and norketamine in hair were GC–MS [2], [3], [5], [13], [22] and [23] and LC–MS/MS (or LC–HRMS) [4] and [7]. In one case, a specific method using HPLC-Chip–MS/MS [11] was developed. A summary of the reviewed methods is presented in Table 2.

Table 2. Analytical procedures for ketamine and norketamine determination in hair samples.

Hair amount	Sample preparation			Instrumentation		Detection Limits				Ref.
	Pretreatment	Extraction	Derivatization	Tecnique	Column	LOD (ng/mg)		LOQ (ng/mg)		
						K	NK	K	NK	
50 mg	MeOH 15 h at 55 °C	–	–	LC–ESI-MS/MS	Acquity UPLC BEH C18	0.004	0.003	0.010	0.013	Present study
25 mg	HCl 0.5 M overnight at 45 °C	SPE at pH 7 C18–Bond Elut	–	GC-EI-MS	J&W Scientific HP-5	0.4	0.4	0.6	0.8	[5]
10 mg	HCl 0.1 M 4 h at 45 °C	LLE at pH > 10 CH_2Cl_2:*n*-hexane 9:1	–	LC–Chip-ESI-MS/MS	Zorbax 80 SB-C18	0.5	0.5	1	1	[11]
25 mg	MeOH overnight at 25 °C	SPE at pH 6 Bond Elut	HFBA	GC–EI-MS	J&W Scientific DB-5	0.05	0.05	0.08	0.08	[21]
25 mg	MeOH:TFA 8.5:1.5 overnight at 25 °C	SPE at pH 6 Bond Elut	HFBA	GC–EI-MS GC–NCI-MS	J&W Scientific HP-5MS	0.05 0.25[a]	0.05 0.025[a]	0.08 1[a]	0.08 0.08[a]	[2] and [3]
30 mg	Methanolic HCl 0.25 M ultrasonication 2 h at 45 °C	–	TFAA MBTFA	GC–EI-MS	J&W Scientific DB-5MS	0.03	0.01	0.11	0.05	[13]
20 mg	Formic acid 0.01% ultrasonication 4 h	–	–	LC–ESI-MS/MS	Synergi Polar HPLC	0.1	0.1	0.5	0.5	[7]
10 mg	Phosphate buffer	MISPE at pH	–	LC–ESI-	Synergi	0.10	0.14	0.18	0.23	[4]

Hair amount	Sample preparation			Instrumentation		Detection Limits				Ref.
	Pretreatment	Extraction	Derivatization	Tecnique	Column	LOD (ng/mg)		LOQ (ng/mg)		
						K	NK	K	NK	
	0.1 M (pH 5) 18 h at 45 °C	5		MS/MS	Hydro RP					
50 mg	HCl 0.1 M 4 h at 45 °C	LLE at pH > 10 Diethyl ether	–	GC–EI-MS	J&W Scientific HP-5	0.02	0.02	0.05	0.05	[20]

3. Results

All results are summarized in Table 3.

Table 3. Comparison of ketamine and nor-ketamine concentrations in hair obtained from different studies.

Case study	Subjects (*N*)	K (ng/mg)	K_{Mean} (ng/mg)	K_{Median} (ng/mg)	NK (ng/mg)	NK_{Mean} (ng/mg)	NK_{Median} (ng/mg)	NK/K	NK/K_{Mean}	Comments	Ref
1	1	1.87	–	–	Not tested	–	–	–	–	Self-reported K consumer (*Italy*)	Present study
2	6	0.11 – 11.4	2.09	0.26	0.02 – 0.71	0.15	0.04	0.06 – 0.29	0.14	Driving relicensing (*Italy*)	Present study
3	8	0.32 – 7.22	2.75	1.96	0.06 – 0.65	0.31	0.25	0.09 – 0.26	0.19	Driving relicensing (*Italy*)	Present study
4	51	0.6 – 489	49	n/a	0.8 – 196.3	12.1	n/a	0.05 – 0.84	n/a	Self-reported/suspected K abusers (*Singapore*)	[5]
5	10	11.07 – 1548	341	51.9	1.67 – 130.74	59.8	22.6	0.08 – 1.13	0.29	Drug abusers (*China*)	[11]
6	1	4.5	–	–	0.35	–	–	0.08	–	Suspected K abuser (*South Korea*)	[13]
7	4	0.2 – 5.7	3.12	3.3	0.1 – 1.2	0.52	0.18	0.04 – 0.5	0.26	Hair from drug misuse prevention center (*Malaysia*)	[4]
8	6	0.63 – 371.8	83.6	47.7	0.56 – 6.58	2.86	2.51	0.01 – 1.46	0.31	Multi-drug abusers (*Spain*)	[7]
9	3	0.67 – 2.40	1.61	1.76	0.10 – 0.66	0.34	0.26	0.11 – 0.38	0.21	Hair from regional prevention centers for drug abuse (*Taiwan*)	[3]
10	4	0.46 – 28.15	12.3	10.2	0.02 – 5.28	2.12	1.58	0.04 – 0.27	0.16	Hair from regional prevention centers for drug abuse (*Taiwan*)	[2]
11	14	0.8 – 92.3	2.94	1.6	0.8 – 7.7	2.94	1.6	0.03 – 0.88	0.32	K abusers (*China*)	[22]

Case study	Subjects (*N*)	K (ng/mg)	K_{Mean} (ng/mg)	K_{Median} (ng/mg)	NK (ng/mg)	NK_{Mean} (ng/mg)	NK_{Median} (ng/mg)	NK/K	NK/K_{Mean}	Comments	Ref
12	1	0.141	–	–	0.063	–	–	0.45	–	Infant exposed to K during gestation (*Taiwan*)	[23]
13	5	<LOD-0.18	0.12	0.12	<LOD-0.06	0.05	0.05	0.32–0.80	0.56	Medical cases	Present study

3.1. Case study 1

A 20-years old male, black haired, declared intake of ketamine for recreational purpose. He estimated to have consumed ketamine about 10 times in the 6–8 months before the sampling. His hair length was 4.5 cm. Samples were taken and analyzed in our laboratory, according to the procedure previously described. Calculated concentration of ketamine (K) was 1.87 ng/mg, norketamine (NK) was 0.11 ng/mg, and the NK/K ratio was 0.06.

3.2. Case study 2

In 2013, we found 6 subjects (5 males, 1 female) positive for ketamine (range 0.11–11.4 ng/mg, mean 2.09 ng/mg, median 0.26 ng/mg). Norketamine was detected in all samples (range 0.02–0.71 ng/mg, mean 0.15 ng/mg, median 0.04 ng/mg). The NK/K ratios were in the range 0.06–0.29. Age range was 20–29 years (mean 24.2).

3.3. Case study 3

In 2014, we found 8 subjects (7 males, 1 female) positive for ketamine (range 0.32–7.22 ng/mg, mean 2.75 ng/mg, median 1.96 ng/mg). Norketamine was detected in all samples (range 0.06–0.65 ng/mg, mean 0.31 ng/mg, median 0.25 ng/mg). The NK/K ratios were in the range 0.03–0.53. Age range was 17–32 years (mean 24.1).

3.4. Case study 4

In this study [5], hair samples were obtained from either self-confessed or suspected ketamine abusers. The authors fixed an arbitrary cut-off level at 1 ng/mg. Fifty-one hair samples resulted positive for ketamine, with concentrations varying in the range 0.6–489.0 ng/mg (mean 49.0 ng/mg), whereas the concentration range of norketamine was 0.8–196.3 ng/mg (mean 12.1 ng/mg). The NK/K ratio varied from 0.05 to 0.84 (mean 0.33). According to voluntary

confessions from the abusers who snorted the drug about once a week, the resulting hair concentration of ketamine was in the range 1.1–42.7 ng/mg (mean 9.9 ng/mg).

3.5. Case study 5

Ten hair specimens from drug abusers were analyzed [11]. The resulting concentrations were relatively high, if compared to other studies. Ketamine ranged from 11.07 to 1548.12 ng/mg, while norketamine ranged from 1.67 to 130.74 ng/mg. The NK/K ratios were in the range 0.08–1.13.

3.6. Case study 6

This method was applied to the analysis of a hair sample from a suspected K abuser [13]. The concentrations measured in this sample were 4.50 ng/mg for K and 0.35 ng/mg for NK, their ratio being 0.08.

3.7. Case study 7

Four hair samples were supplied by a drug misuse prevention center in Malaysia [4]. Ketamine ranged from 0.2 to 5.7 ng/mg, while norketamine ranged from 0.1 to 1.2 ng/mg. The NK/K ratios were in the range 0.04–0.5.

3.8. Case study 8

Real hair samples from 25 multidrug abusers were analyzed [7]. Ketamine was found in 13 samples, only 6 of which also contained the metabolite norketamine. In the latter subjects, ketamine ranged from 0.63 to 371.8 ng/mg, while norketamine ranged from 0.56 to 6.58 ng/mg. The NK/K ratios were in the range 0.01–1.46.

3.9. Case study 9

Authentic hair samples were collected from regional prevention centers for drug abuse [3] and analyzed with GC–MS using two ionization methods. The average from the two results is presented hereafter. Ketamine was found in 4 subjects, but norketamine reached measurable levels only in 3 specimens. The parent drug ranged from 0.67 to 2.40 ng/mg, while the metabolite was in the range 0.10–0.66 ng/mg. The NK/K ratios for these subjects were 0.11, 0.15 and 0.38. The authors also presented a real case in which passive exposure to ketamine could be claimed.

In the corresponding hair sample, ketamine concentration was 0.18 ng/mg, norketamine was 0.007 ng/mg and, notably, their NK/K ratio was 0.04.

3.10. Case study 10

Authentic hair samples were collected from regional prevention centers for drug abuse [2]. Ketamine and norketamine were found in 4 samples, in the respective range of 0.46–28.15 ng/mg and 0.02–5.28 ng/mg. Their NK/K ratio was consequently in the interval 0.04–0.27.

3.11. Case study 11

Hair samples were collected from 15 ketamine abusers in various entertainment places [22]. In one case, norketamine was not detected. In the remaining 14 specimens, ketamine levels were in the range 0.8–92.3 ng/mg (mean 21.7 ng/mg, median 8.1 ng/mg). Norketamine levels were in the range 0.8–7.7 ng/mg (mean 2.94 ng/mg, median 1.6 ng/mg). The NK/K ratios varied in the range 0.03–0.88 (mean: 0.32).

3.12. Case study 12

The case of a female infant, whose mother had allegedly consumed ketamine during gestation, is described [23]. The concentrations of ketamine and its metabolite norketamine were 0.141 ng/mg and 0.063 ng/mg of hair, respectively, their NK/K ratio being 0.45.

3.13. Case study 13

We collected hair samples from five patients admitted within a hospital unit taking care of burned people and treated with ketamine at different dosages. The investigated subjects, who received ketamine for medical reasons, volunteered to provide hair samples and signed an informed consent. All the patients received from 40 up to 430 mg ketamine intravenously in 1 or 2 dosages within 3 months before hair sampling. Ketamine and norketamine were detectable in only 2 cases out of 5. In both positive cases, ketamine was below 0.2 ng/mg and norketamine was lower than 0.1 ng/mg. The results are presented in Table 4.

Table 4. Ketamine and nor-ketamine concentrations in hair obtained from clinical cases.

Subject	Quantity of ketamine (mg)	Dosages	Lenght of hair (cm)	K (ng/mg)	NK (ng/mg)	NK/K
1	430	2	2.5	<LOD	<LOD	–
2	120	1	2.5	<LOD	<LOD	–
3	40	1	4.0	<LOD	<LOD	–
4	125	2	6.0	0.05	0.04	0.80
5	180	2	6.0	0.18	0.06	0.32

4. Discussion

Ketamine is a weakly basic (PK_a = 7.5) substance, which is generally sold as hydrochloride salt and is mainly present in blood as a cation. In its neutral form, ketamine strongly interacts with melanin, facilitating its incorporation into hair. Therefore, its concentration in hair from chronic abusers is expected to be relatively high, compared to other common drugs of abuse. In the present study, we evaluated a miscellaneous of case reports, analytical results, and published data, either obtained in our laboratory and from peer-reviewed literature, all describing the detection of ketamine and norketamine in hair specimens. In our laboratory, we collectively found 15 positive samples for ketamine and norketamine (case studies 1–3). The minimum levels were 0.11 ng/mg and 0.02 ng/mg, respectively. The metabolite was detected in all samples, suggesting that the hair samples were presumably collected from active consumers. In 9 cases out of 15, ketamine levels were above 0.5 ng/mg, while norketamine levels were above 0.05 ng/mg. Their concentration ratio NK/K was higher than 0.05 in 14 cases out of 15.

In the published literature (case studies 4–11), we examined the results obtained in 8 independent studies, totalizing 93 positive samples for ketamine and norketamine. The minimum detected level for ketamine was 0.2 ng/mg. In 91 cases out of 93, the ketamine hair concentration was higher than 0.5 ng/mg. The lowest detected amount for norketamine was 0.02 ng/mg, but, besides this case for which the ratio NK/K was still 0.04, the lowest amount of norketamine detected in the remaining 92 samples was 0.1 ng/mg. Overall, the ratio NK/K was higher than 0.05 in 86 specimens out of 93.

In the case of pre-natal exposure (described in case study 12), the concentrations of ketamine and its metabolite norketamine were relatively low (0.141 ng/mg and 0.063 ng/mg, respectively), possibly as the result of sporadic exposure. However, this has to be considered as active consume, corresponding to a ratio NK/K of 0.45.

In the case of hospitalized patients (case study 13), ketamine and norketamine could not be detected in three cases out of five, while in the two positive cases, the concentrations were found to be below 0.2 ng/mg and 0.1 ng/mg, respectively.

After considering the chemical properties of ketamine, and the experimental data collected in our laboratory and those reported in several other published studies, we propose a tentative cut-off level of 0.5 ng/mg, as suggestive of repeated exposure to ketamine. Additionally, we suggest that the detection of the metabolite norketamine should be mandatory to prove active intake and exclude false positive result from external contamination. Thus, a reasonable cut-off value for norketamine could be possibly fixed at 0.1 ng/mg, while the minimal concentration ratio norketamine/ketamine may be positively established at 0.05.

5. Conclusions

Ketamine recently became a commonly abused drug, insomuch as hair analysis is regularly performed in laboratories worldwide for clinical and forensic purposes. Unlike other common drugs of abuse, a cut-off value for ketamine in hair has not been fixed up to now. In order to avoid false positive classification for illicit ketamine intake, we propose tentative cut-off values for ketamine and norketamine which may be of help in the interpretation of results. We believe that the hereby proposed criteria to discriminate between repeated and occasional exposure can be productively utilized. Surely, more in-depth studies are needed in the next future in order to reinforce or contradict our proposal.

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