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ORIGINAL ARTICLE

Disposition of ketamine and norketamine in hair after a single dose

Ping Xiang · Qiran Sun · Baohua Shen · Min Shen

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Abstract As a rapid-acting dissociative anesthetic, ketamine has been used in drug-facilitated crimes. The aim of this study is to investigate the disposition of ketamine and its main metabolite norketamine in hair after a single dose of ketamine. Four healthy volunteers were recruited into the study. Hair was collected 1, 2, 3, 4, 8, 12 and 16 weeks after a single oral dose of ketamine solution (10 mg) and analyzed by liquid chromatography/electrospray ionization tandem mass spectrometry. The wet cotton swab wiped the scalp of the subjects at 1 h, 24 h, 48 h and 1 week after administration. Maximum hair concentrations (C_{max}) for ketamine and norketamine were 19.0±6.5 and 18.7± 13.3 pg/mg, respectively. Except for the first week, the ratio of ketamine to norketamine in most of segments (87.5%) was greater than 1. All the cotton swab samples collected at 24 and 48 h were positive. The results from cotton swabs and the concentrations of ketamine and norketamine in hair segments collected at different times showed that some of ketamine and norketamine incorporated into hair originated from sweat and sebum on the scalp of the subjects.

Keywords Disposition · Ketamine · A single dose · Segmental hair analysis · Diffusion

P. Xiang (✉) · Q. Sun · B. Shen · M. Shen
Department of Forensic Toxicology,
Institute of Forensic Sciences, Ministry of Justice,
Shanghai Key Laboratory of Forensic Medicine,
Guangfu Xi Road 1347,
Shanghai 200063, China
e-mail: xiangping2630@163.com

P. Xiang
School of Forensic and Investigative Science,
University of Central Lancashire,
Preston, Lancashire, UK

Introduction

The increase in drug-facilitated crimes (DFC) makes hair analysis an area of increasing interest [1–8]. Blood and urine are the conventional specimens for documenting drug exposures [9–11]. In most cases, because of the amnesia caused by the drugs, there will be a 24- to 72-h or longer delay between exposure to the drug and a victim's report. In addition, the drugs commonly used can be difficult to detect because low doses are often administered or because the active metabolite is chemically unstable. Some drugs are quickly cleared from body fluids [1]. Therefore, in such circumstances, blood samples and even urine samples, are often of limited usefulness in detecting the presence of these drugs. Segmental hair analysis has been proven to prolong the window of detection for DFC.

A series of papers about segmental hair analysis in DFC have been published [1–8]. However, there are still many sources of inter-individual variation in hair analysis, such as metabolic capacity, dosage, hair growth rate, drug incorporation rates, pigmentation, physical state of the hair, age, gender and body weight [12–15]. In addition, understanding the time course of drug deposition in hair shafts after a single-dose administration is essential when collecting hair specimens and interpreting results. Further research must be completed and more substantial guidelines developed to use segmental hair analysis in the investigation of DFCs.

Ketamine (K), also called K powder in China, is a rapid-acting dissociative anesthetic used on both animals and humans. Ketamine has increasingly been abused as a 'club-drug' at dance and rave parties since the late 1990s. As can be expected from its pharmacological effects, ketamine has been used in DFCs [8]. Many methods and techniques have been developed, including gas chromatography–mass spectrometry (GC-MS) [16–18], high-performance liquid

chromatography-mass spectrometry (LC-MS) [19, 20] and liquid chromatography-tandem mass spectrometry(LC-MS/MS) [21, 22], to the analysis of ketamine in hair. Identification of ketamine and its metabolites in hair following chronic drug use has been documented previously [16, 17, 20–22], but has rarely been documented after exposure to a single dose. Norketamine is the major metabolite of ketamine. The ratios of the concentration of ketamine to the concentration of norketamine in the hair of cavies given a high dosage of ketamine (i.e., 20 mg/day) were between 2.33 and 12.94 (mean=7.37) [16].

Building on previous work [15, 16], this study was designed to determine the levels of ketamine and its metabolite norketamine in hair segments of healthy volunteers after administration of a single dose of ketamine and to investigate the following: the relationship between the time of ketamine use and the position of ketamine or norketamine along the hair shaft; the time interval between ketamine use and the appearance of ketamine or norketamine in hair; and the appearance of ketamine or norketamine on the surface of the scalp of healthy volunteers.

Materials and methods

Chemicals and reagents

Ketamine, norketamine, ketamine-d4 and norketamine-d4 were purchased from Cerilliant (Round Rock, TX). Methanol and acetonitrile, both of HPLC grade, were bought from Sigma-Aldrich (St. Louis, MO). Ketamine hydrochloride used in volunteer experiment was supported by the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). Ammonium acetate and formic acid were obtained from Fluka Chemical Co. (Buchs, Switzerland). Other reagents were all of analytical reagent-grade and no further purification was undertaken. Deionized water was purified using a Milli-Q system (Millipore, Billerica, MA).

Sample collection

Four healthy volunteers (subjects #1–#4, female with straight black hair, ages 31–41 years) were recruited into the study. Subjects agreed to participate in the experiment part of the study through written consent. All protocols were approved by an institutional review committee. Some background data were collected from the subjects such as the frequency of washing hair and the type(s) of hair cosmetic products used, but no attempt was made to control these variables.

Hair was collected 1, 2, 3, 4, 8, 12 and 16 weeks after a single oral dose of ketamine solution (10 mg dissolved in water). Strands of about 100 hairs were cut from the posterior vertex as close as possible to the scalp, oriented and stored in clean paper bag at room temperature.

Besides, the scalp of the subjects was wiped 1 h, 24 h, 48 h and 1 week after administration with cotton swabs (Watsons Pharmacy, Shanghai, China), which were wet with deionized water before use. All the cotton swabs were analyzed right after sample collection.

Subjects #1, #2 and #4 washed their hair once per day. Their scalp and head hair were washed approximately 12 h after administration. Subject #3 washed her hair once every 2 days. Her scalp and head hair were washed approximately 36 h after administration for the first time.

Drug-free hair was donated by healthy volunteers in laboratory and preserved at room temperature.

Sample preparation

Hair samples collected in the first 4 weeks were carefully segmented into 0.5-cm lengths from the proximal end (root). From the eighth week, hair samples were segmented into 1-cm lengths. Hair segments were rinsed twice with 5 ml dichloromethane to avoid drug detection arising from environmental contamination. The last wash was stored for further analysis.

After being air-dried, hair segments were cut into small pieces of less than 3 mm, and pulverized in a freeze mill (Freezer/Mill, SPEX CertiPrep). Approximately 20 mg of powered hair was incubated in 2 ml sodium borate buffer, pH 9.2, for 1 h at room temperature under ultrasonication, in the presence of 20 μl of a 20 ng/ml internal standard solution (containing ketamine-d4 and norketamine-d4). Afterwards, 50 μl of 10% NaOH was added to the mixture and liquid–liquid extraction was performed with 3 ml diethyl ether at basic condition (pH>11). After vortex agitation (3 min) and centrifugation (868×*g* for 3 min), the organic phase was collected and evaporated to dryness at 60°C. The residue was reconstituted by adding 100 μl LC mobile phase (acetonitrile: 20 mM ammonium acetate=7:3, v/v). Five microliters of the prepared sample was injected into the LC-MS/MS system.

The wet cotton swabs were incubated in 1 ml deionized water for 20 min under ultrasonication, and then extracted with 2 ml diethyl ether at basic condition (pH>11). After solvent evaporation at 60°C, the residue was reconstituted with 100 μl LC mobile phase and 5 μl was injected into the LC-MS/MS system.

Instrumentation

The liquid chromatography-tandem mass spectrometry (LC-MS/MS) system consisted of an Aglient HPLC (Palo Alto, CA) including a quaternary pump, an on-line degasser

and an autosampler, equipped with an MDS Sciex API 4000 triple quadrupole mass spectrometer (Applied Biosystems, Foster City, CA). The Analyst 1.4.2 software package was used for instrument control and data acquisition.

The analytical column was a Resteck Allure PFP Propyl column (100 mm×2.1 mm i.d., 5 μm) fitted with an end-capped C18 guard column (12.5 mm × 2.1 mm i.d., 5 μm), at room temperature. Each chromatographic run was carried out with a mobile phase of acetonitrile–20 mM ammonium acetate (70:30, v/v), at a flow rate of 0.2 ml/min.

The mass instrument with electrospray ion source was operated in the positive ionization mode. Best results were obtained with an ion-spray voltage of 5.5 kV and source temperature of 450°C. CAD gas (nitrogen) was 4.83×10^4 Pa (7 psi), CUR gas was 1.72×10^5 Pa (25 psi), and GS1 and GS2 were both 2.41×10^5 Pa (35 psi). The entrance potential was 10 V and the collision cell exit potential was 15 V. Precursor ions, the corresponding product ions, retention times, decluster potential (DP) and collision energy (CE) were optimized for ketamine, norketamine and internal standards (IS). Multiple reaction monitoring mode (MRM) was performed. The transitions for the individual analytes were monitored: ketamine, *m/z* 238 → *m/z* 179, *m/z* 238 → *m/z* 125; norketamine, *m/z* 224 → *m/z* 207, *m/z* 224 → *m/z* 125; ketamine-d4 (IS), *m/z* 242 → *m/z* 183, *m/z* 242 → *m/z* 129; norketamine-d4 (IS), *m/z* 228 → *m/z* 211, *m/z* 228 → *m/z* 129. The first transitions for the individual analytes were used for quantification.

Method validation

Selectivity

Drug-free hair samples from ten healthy volunteers were analyzed to ensure no endogenous interfering peaks at retention times of the analytes.

Linearity and limit of detection and quantification

Mixed standard working solutions of ketamine and norketamine (diluted with methanol) were spiked to blank hair to get concentrations at 2, 5, 10, 20, 50, 100 and 200 pg/mg (n=2). The calibration curves were constructed by plotting the area ratio of analyte and IS against spiked concentration, with a weighting of 1/x.

Limit of detection (LOD) for both analytes were determined by decreasing their concentrations until a response equivalent to three times the background noise was observed. Limit of quantification (LOQ) was defined as the lowest concentration in the calibration curve, at which the signal of analyte was ten times the baseline. Samples at LOQ can still be quantified with acceptable precision and accuracy (≤20%).

Accuracy and precision

The analytical precision and accuracy were evaluated at three concentrations (low, middle and high), covering the linear dynamic range of each analyte. Quality control samples (n=6 at each concentration level) were extracted and analyzed on each of 4 days. The concentrations of the analytes were calculated via the daily calibration curves to account for possible daily variations in the curve. Accuracy, expressed as bias, was established as the percent deviation of the mean of all 24 measurements from the nominal value. Precision, expressed as repeatability (rep%, within-day) and time-different intermediate precision (int. prec%, combination of within- and between-day effects) were calculated using one-way ANOVA with Stata 7 software.

Extraction recovery and matrix effects

Extraction recovery and matrix effects were evaluated by the method proposed by Matuszewski et al. [24]. Extraction recovery was established, at low, medium and high concentrations, by comparing the analyte peak areas of extracted spiked samples (n=6) with those of blank samples spiked with the same amounts of the analyte after extraction (n=6).

The analyte signal in the spiked mobile phase (n=6) was compared with the analyte signal in the matrix fortified after extraction (n=6), and the matrix effects (ME) was defined as ME%=(extracted matrix area/mobile phase area) ×100.

Results

Method validation

Assay selectivity was confirmed by the absence of interfering peaks at the retention times for ketamine and norketamine in blank hair powders. The chromatograms of a blank hair sample and a sample spiked with 2 pg/mg are shown in Fig. 1.

Good linearity was observed in the range of 2–200 pg/mg for both ketamine and norketamine (r≥0.9997). The LODs for ketamine and norketamine in hair were 0.5 and 1 pg/mg, respectively. Compared with the sensitivity of the GC-MS method previously established by our laboratory [16], the sensitivity of the current method has been greatly improved.

Data for accuracy and precision were within the required limits [23], i.e., less than 15% (20% for LOQ) for precision

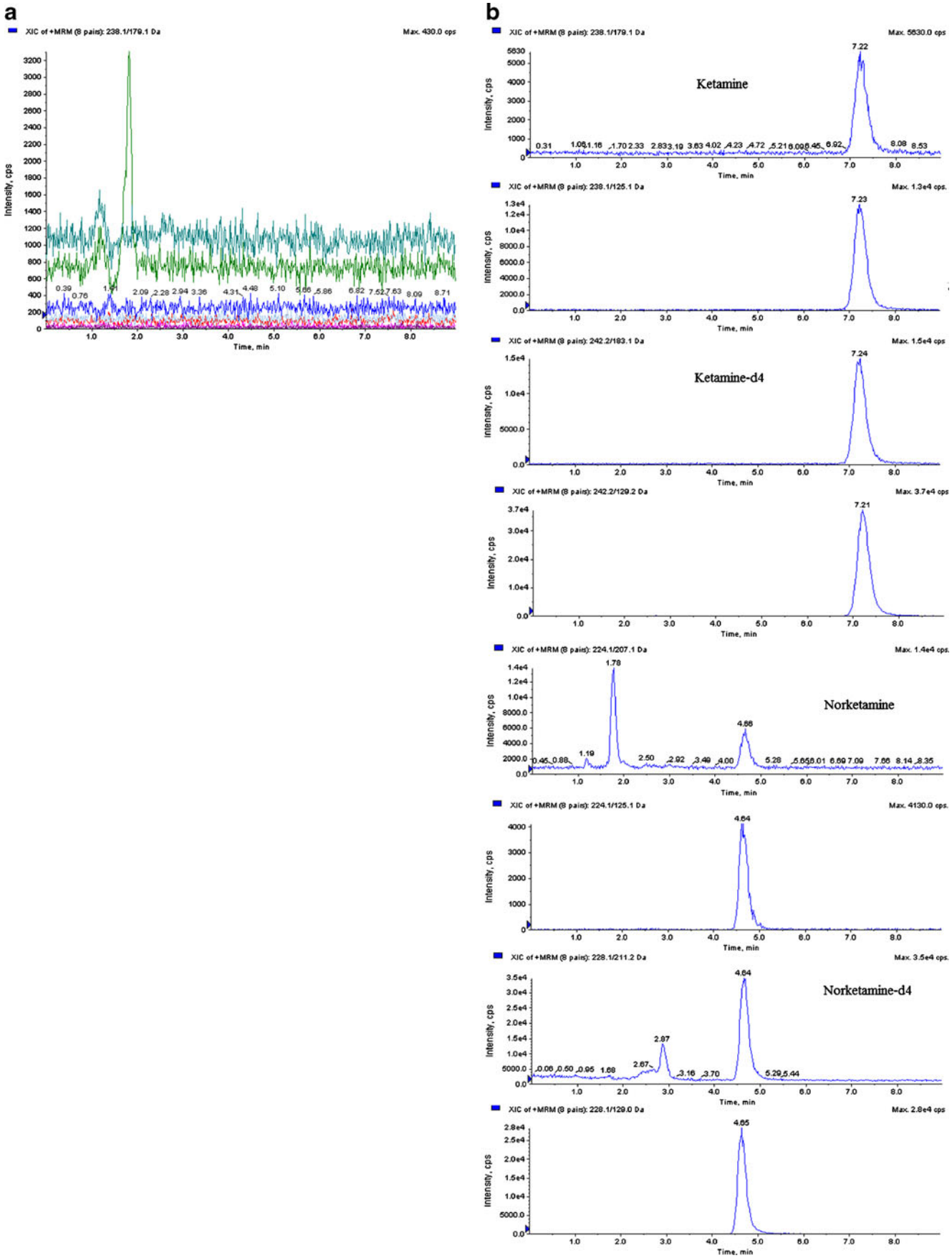
a
XIC of +MRM (8 pairs): 238.1/179.1 Da
Max. 430.0 cps
Intensity, cps
Time, min
b
XIC of +MRM (8 pairs): 238.1/179.1 Da
Max. 5630.0 cps
Ketamine
XIC of +MRM (8 pairs): 238.1/125.1 Da
Max. 1.3e4 cps.
XIC of +MRM (8 pairs): 242.2/183.1 Da
Max. 1.5e4 cps
Ketamine-d4
XIC of +MRM (8 pairs): 242.2/129.2 Da
Max. 3.7e4 cps
XIC of +MRM (8 pairs): 224.1/207.1 Da
Max. 1.4e4 cps.
Norketamine
XIC of +MRM (8 pairs): 224.1/125.1 Da
Max. 4130.0 cps.
XIC of +MRM (8 pairs): 228.1/211.2 Da
Max. 3.5e4 cps.
Norketamine-d4
XIC of +MRM (8 pairs): 228.1/129.0 Da
Max. 2.8e4 cps
Intensity, cps
Time, min

Table 1 Concentration of ketamine and norketamine in hair segments of subject #1

1# [a]	Ketamine(pg/mg)											
	0-0.5 cm	0.5-1 cm	1-1.5cm	1.5-2cm	2-2.5cm	2.5-3 cm	3-3.5 cm	3.5-4 cm	4-4.5 cm	4.5-5 cm	5-6 cm	Distal end
1st week	+ [b]	+										
2nd week	13.4	8.2	2.5									
3rd week	3.3	12.4	4.2	+								
4th week		7.1	10.4	2.8	+							
8th week	2.2		12.6		+							
16th week					+		+		2.8			
	Norketamine(pg/mg)											
	0-0.5cm	0.5-1 cm	1-1.5cm	1.5-2cm	2-2.5cm	2.5-3 cm	3-3.5 cm	3.5-4 cm	4-4.5 cm	4.5-5 cm	5-6 cm	Distal end
1st week	+											
2nd week	8.1	9.3	+									
3rd week	+	9.0	7.2									
4th week		2.9	8.8	2.7	+							
8th week			5.8		+							
16th week							+		2.3			

[a] Samples of 12th week for subject 1# were not collected

[b] Different colors illustrated different ranges of two analytes: +, detected, but not quantified; 2–5 pg/mg; 5–10 pg/mg; 10–15 pg/mg; 15–20 pg/mg; more than 20 pg/mg

and within the acceptance interval of 15% (20% for LOQ) of the nominal value for accuracy.

The matrix effect is known to be a shortcoming associated with LC-MS [25]. It is defined as the effect of co-eluting residual matrix components on the ionization of the target analyte. Suppression or enhancement of analyte responses will result in diminished precision and accuracy for subsequent measurements [26]. The results demonstrate that the hair matrix had some ion-suppression influence on ketamine and its metabolite at a low concentration (2 pg/mg). Nevertheless, because deuterated ketamine and norketamine, which have the same physicochemical properties as the analytes, were used as internal standards, these suppression effects can be partly overcome and would not interfere with the accuracy and precision of the quantification of these drugs.

◀ **Fig. 1** MRM chromatographs of **a** blank hair sample and **b** hair sample spiked at 2 pg/mg

Volunteer experiment

No surface contamination of the hair was detected in the last dichloromethane wash solution. The segmental analysis results are listed in Tables 1, 2, 3 and 4.

Ketamine and norketamine were found in the 0- to 0.5-cm segments 1 week after administration. The

Table 2 Concentration of ketamine and norketamine in hair segments of subject #2

	Ketamine(pg/mg)											
2#	0-0.5cm	0.5-1 cm	1-1.5cm	1.5-2cm	2-2.5cm	2.5-3cm	3-3.5cm	3.5-4cm	4-4.5cm	4.5-5cm	5-6 cm	Distal end
week	+[a]	+	+	+	+	+						
2nd week	14.1	10.5	4.5	+								
week	14.1	14.7	10.3	7.6	5.0	+						
week	+	8.6	13.3	4.9								
week	7.9		16.5		11.2		4.1					
12th week	2.4		4.3		15.5		10.0		7.2		+	
16th week					2.8		11.6		8.3			
	Norketamine(pg/mg)											
2#	0-0.5cm	0.5-1cm	1-1.5cm	1.5-2cm	2-2.5cm	2.5-3cm	3-3.5cm	3.5-4cm	4-4.5cm	4.5-5cm	5-6 cm	Distal end
1st week	+	+	+	+	+	+						
2nd week	8.1	9.3	+									
3rd week	4.6	11.1	10.8	6.5	+							
4th week	+	4.3	9.2	+								
8th week	+		7.4		3.2		2.1					
12th week			2.6		11.5		4.2					
16th week							3.6		+			

[a] Different colors illustrated different ranges of two analytes: +,detected, but not quantified; 2–5 pg/mg; 5–10 pg/mg; 10–15 pg/mg; 15–20 pg/mg; more than 20 pg/mg

incorporated band of ketamine and norketamine moved along the hair shaft at a rate of approximately 1 cm/month with some diffusion and concentration fluctuation. Until 8 weeks after administration, ketamine was detected in the 0- to 1-cm segments. Maximum hair concentrations (C_{max}) for ketamine and norketamine were 19.0±6.5 and 18.7±13.3 pg/mg, respectively, which demonstrated the high inter-subject variability in ketamine metabolism. Except for the first week, the ratio of ketamine to norketamine in most of the segments (87.5%) was greater than 1.

One hour after administration, ketamine and norketamine were detected in the wet cotton swabs of subject #2 and subject #4. All cotton swab samples collected at 24 and 48 h were positive for ketamine and norketamine. The concentration of norketamine was higher than that of ketamine in those

Table 3 Concentration of ketamine and norketamine in hair segments of subject #3

	Ketamine(pg/mg)											
3# [a]	0-0.5 cm	0.5-1cm	1-1.5 cm	1.5-2 cm	2-2.5cm	2.5-3 cm	3-3.5 cm	3.5-4cm	4-4.5cm	4.5-5cm	5-6 cm	Distal end
1st week	14.9	5.5	3.6	2.0	+ [b]							
2nd week	27.6	4.3	+									
3rd week	22.4	22.3	5.9									
4th week		27.7	15.4	+								
8th week	4.3		28.4		14.7		3.6					
16th week					+		10.1		14.6		+	
	Norketamine(pg/mg)											
3#	0-0.5cm	0.5-1cm	1-1.5cm	1.5-2cm	2-2.5cm	2.5-3cm	3-3.5cm	3.5-4cm	4-4.5cm	4.5-5cm	5-6cm	Distal end
1st week	38.2	14.1	5.9	3.6	2.7	2.2	+	+				
2nd week	22.7	5.7	+	+								
3rd week	10.8	20.9	4.1									
4th week	+	14.3	17.6	+								
8th week			12.9		14.6		2.1					
16th week							2.1		4.7		+	

[a] Samples of 12th week for subject #3 were not collected

[b] Different colors illustrated different ranges of two analytes: +, detected, but not quantified; 2–5 pg/mg; 5–10 pg/mg; 10–15 pg/mg; 15–20 pg/mg; more than 20 pg/mg

positive samples, as shown in Fig. 2. All cotton swab samples collected after 1 week tested negative.

Discussion

There were no obvious symptoms after a single 10-mg dose of ketamine for the subjects. With an LOD of 0.5 pg/mg and an LOQ of 2 pg/mg, our method has been demonstrated to be able to detect a single intake of 10 mg ketamine up to 4 months after administration. The data concerning the threshold dosage, which is related to the sensitivity of the method, can be useful in the interpretation of the results of the hair analyses.

There was a correlation between the amount of ketamine detected and the frequency of abuse. After a single 10-mg dose of ketamine, ketamine concentrations reached a mean peak of 19.0 pg/mg, whereas the mean peak for norketamine was 18.6 pg/mg. The amount of ketamine present was far below the levels in hair segments from ketamine abusers. Leong et al. [17] found that the concentration of ketamine detected in hair from suspected ketamine abusers ranged from 0.6 to 489.0 ng/mg (mean=49.0 ng/mg), whereas the concentration of norketamine ranged from 0.8

Table 4 Concentration of ketamine and norketamine in hair segments of subject #4

	Ketamine(pg/mg)											
4#	0-0.5cm	0.5-1cm	1-1.5cm	1.5-2cm	2-2.5cm	2.5-3cm	3-3.5cm	3.5-4cm	4-4.5cm	4.5-5cm	5-6cm	Distal end
1st week	7.9	4.7										
2nd week	8.7	5.6	2.4	+ [a]								
3rd week	5.8	13.9	7.0									
4th week		14.8	5.9									
8th week			15.9		11.3							
12th week			7.3		17.5		5.3					
16th week					7.4		15.6		5.9			
	Norketamine(pg/mg)											
4#	0-0.5cm	0.5-1cm	1-1.5cm	1.5-2cm	2-2.5cm	2.5-3cm	3-3.5cm	3.5-4cm	4-4.5cm	4.5-5cm	5-6cm	Distal end
1st week	15.9	4.3										
2nd week	7.0	6.3	+									
3rd week	2.1	7.2	+									
4th week	+	6.2	5.0	+								
8th week			8.7		3.6		+					
12th week					2.4		4.5		2.8			
16th week							2.7		5.8		2.5	

[a] Different colors illustrated different ranges of two analytes: +, detected, but not quantified; 2–5 pg/mg; 5–10 pg/mg; 10–15 pg/mg; 15–20 pg/mg; more than 20 pg/mg

to 196.3 ng/mg (mean=12.1 ng/mg). In our previous study [16], the concentration of ketamine detected in hair samples obtained from 15 ketamine abusers was in the range of 0.8 to 92.3 ng/mg (mean=20.5 ng/mg).

The mechanisms of drug incorporation into hair have not been established [12]. Three processes for incorporation have been proposed [13]. Drugs can enter the hair through (1) active or passive diffusion from the bloodstream feeding the dermal papilla, (2) diffusion from sweat and other secretions, or (3) external vapor or powder drugs diffusing into the mature hair fiber. Indeed, a combination of these routes is probably the most realistic model of ketamine incorporation. No ketamine was detected in the last dichloromethane wash. Given the oral administration of ketamine and the washing procedure used, the external contamination factor can be excluded in our study.

In our previous study [15], estazolam could be detected in the 2- to 4-cm segments in some subjects' hair when hair was collected 1 month after administration. In this study, the incorporated band of ketamine and norketamine

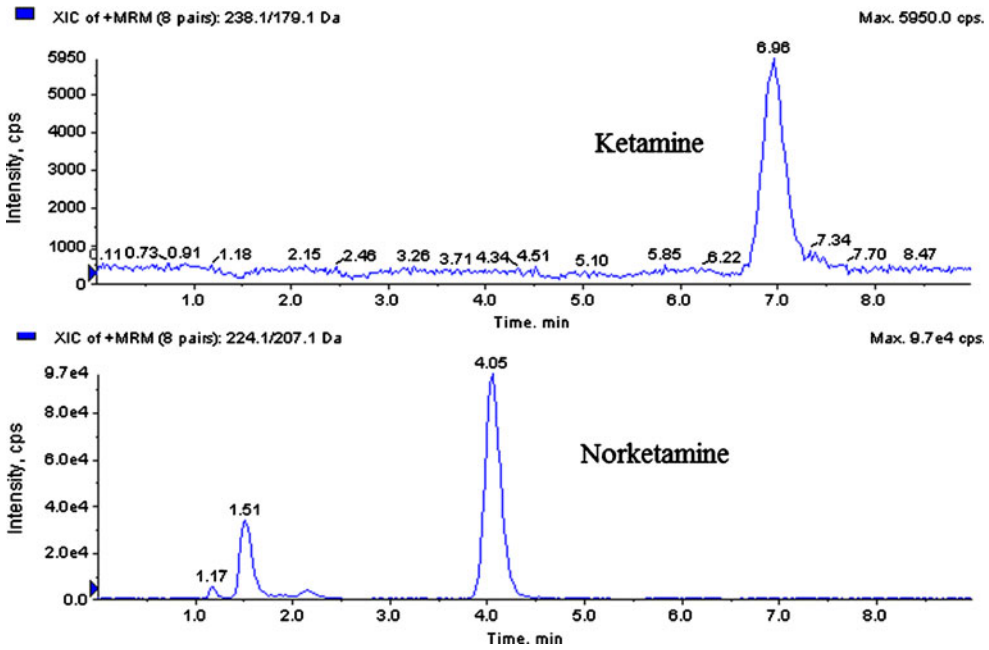

Fig. 2 Ketamine and norketamine detected in the cotton swab sample of subject #4 collected 1 h after administration

moved along the hair shaft at a rate of approximately 1 cm/month, with some diffusion and concentration fluctuation, and ketamine was detected in the 0- to 1-cm segments until 8 weeks after administration. The broadening of the ketamine-positive band of hair may be the result of the diffusion of the drugs and metabolites caused by sweat or other secretions during formation of the hair shaft.

In the present study, the diffusion caused by sweat and sebum was monitored by wiping the scalp of the subjects with wet cotton swabs. The experiment was conducted during summer when the temperature was about 25–35°C. Subjects produced more perspiration during this period than they did in other seasons, and they washed their hair once every 1 or 2 days. The results of the cotton swab tests showed that ketamine and norketamine appeared on the scalp of the subjects within a few hours after administration and persisted for at least 2 days. Thus, head hair was contaminated through diffusion from sweat and sebum over a period lasting at least 2 days. This result was confirmed by the identification of ketamine and norketamine in the hair segments 1 week after administration.

On the other hand, the ratio of ketamine to norketamine in human hair from ketamine abusers was found to be greater than 1 [16, 17]. In the present study, the concentration of norketamine was higher than that of ketamine in the proximal segments of hair from subject #1 (0–1.5 cm), subject #3 (0–3 cm) and subject #4 (0–0.5 cm). These results are consistent with the pattern of ketamine metabolism in body fluids. As time passed, the concentration of ketamine in the proximal segments increased slowly, and the concentration of norketamine decreased 2 weeks after administration. This is the result of the incorporation of ketamine into the hair through passive diffusion from the bloodstream and the removal of external norketamine (from sweat) when the hair was washed. Until 4 weeks after ketamine administration, the ratio of ketamine to norketamine in hair segments was greater than 1, except in the 1- to 1.5-cm segment collected in the fourth week from subject #3. According to Kintz's recommendation [27], it is best to wait 4 to 5 weeks after the event to obtain hair specimens.

Although the volunteers were from the same ethnic background and gender, there was inter-subject variability with respect to the time course and the diffusion of ketamine and norketamine at the same dosage. In addition to inter-individual differences in metabolic capacity, dosage, hair growth rate, drug incorporation rates, pigmentation, and the physical state of the hair [12–15], our results suggest that amount of perspiration is also an important factor in segmental hair analysis in DFC.

The results from the different lengths of segments (0.5 or 1 cm) in Tables 1–4 show that cutting the hair into more segments was useful in identifying the drug spot along the length of the hair shaft and in documenting the drug deposition in hair more clearly after a single dose of ketamine.

Conclusion

Ketamine and norketamine were readily detected in hair after a single oral dose of 10 mg ketamine. Significant inter-subject variability was observed in the time profile for ketamine disposition into hair. The results from cotton swabs and the concentrations of ketamine and norketamine

in hair segments collected at different times showed that some of the ketamine and norketamine incorporated into hair originated from sweat and sebum on the scalp of the subjects.

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