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Review Article

Illegal use patterns, side effects, and analytical methods of ketamine

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ABSTRACT

In Asian countries, such as China, Taiwan, and Hong Kong, ketamine (KT) is one of the most prevalent illicit use drugs. KT is regulated by various drug-related laws in many countries, such as Korea, Taiwan, China, U.S.A, Netherlands, UK, Australia, Mexico, and Canada. This review research explored pharmacology and side effects of KT, the illicit use patterns of KT, the analytical methods of KT in biological samples, and the concentrations of KT from abusers and non-abusers. Many side effects of KT have been reported mental and physical problems. Although many studies conducted various analytical methods for KT, this research focused on the urine and hair analysis and compared some parameters of samples, instruments, columns, extraction methods, internal standards, LOD/LOQ levels, metabolites, NK/K ratio, cut off values, and m/z values. Our research also compared the concentrations of KT in biological samples from abusers and non-abusers. Many rapid and precise analytical methods for illegal KT use are needed to be developed and applied to real samples. To minimize and prevent harm from KT, the authorities and appropriate agencies require a careful assessment, evaluation, early identification, and surveillance of KT users in both clinical and social settings. In addition, there is a need to construct a stricter legislative management and provide preventive education to younger individuals because illegal KT use is relatively common among the young populations.

Contents

1. Introduction

Ketamine (KT) is a general anesthetic agent for human and animals in clinical practice and is pharmaceutically manufactured as a 1:1 racemic mixture of enantiomers (*S*-(+)-KT and *R*-(−)-KT).

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The metabolite of KT, norketamine (NK) shows pharmacological action, including an anesthetic potency about one-third of KT [1]. The most commonly used illicit drugs in Asian countries are opioids, amphetamine-type stimulants (ATS), cannabis, and KT [2]. KT has become one of the most commonly illegally used drugs around the world [1,3–6] and it is the third most used illicit drug in Taiwan and China in particular [2].

KT has mental side effects including psychedelic, psychotic features, and depressive symptoms, physical side effects including blurred vision, out-of-body experiences, and numbness [1,7–11], and effects on organs including brain, kidney, and lung [7,8,12–14]. Also, KT has been reported to have genotoxicity [15,16].

KT is a popular drug in clubs and pubs, and major users of KT are young people [3,9,17–22]. Although it varies by country, common routes of administration are snorting followed by injection and oral ingestion [3,5,16,17,20,21,23–25]. To prevent people from abusing drugs and causing social problems, there are laws regulating the drug abuse including KT in many countries. For example, Korea regulates persons who use, possess, smuggle, and manufacture KT illegally [26–28] and U.S.A also regulates persons who have KT without permission [8].

In urine and hair analysis of KT, there are some pros and cons when GC/MS and LC/MS are used. Sample washing, instruments, columns, extraction methods, internal standards, the limits of detection (LOD) and quantification (LOQ) levels, metabolites, NK/K ratio, cut off values, and m/z values were compared through an in-depth literature reviews. Moreover, the concentrations of KT in the biological samples from both regular and non-regular abusers were described.

This review describes pharmacology and side effects of KT, the illegal use patterns of KT and regulated laws in some countries, the analytical methods from biological samples, and the concentrations of KT from regular and non-regular abusers.

2. Methods

Comprehensive literature search was conducted to determine the characteristics of KT including pharmacology of KT, differences in administration methods, use in combination with other drugs, side effects from KT abuse, toxicity, use pattern, common place of abuse, common ages of abuse, major administration method of KT abuse, related laws in many countries, analytical methods, range of LOD/LOQ for KT and NK, cut-off values for KT, and concentrations in biological samples from regular and non-regular abusers of KT. The search was completed with PubMed and Science Direct—including web search for the confirmation of relevant documents between 1996 and 2016. To identify the side effects and use patterns of KT, we searched for the following keywords: “ketamine”, “abuse”, “adverse”, “side effect” “adverse effect”, “HIV”, “administration”, “route”, “use pattern”, “abuse place”, “age”, and “common place”. We went through more than 16,000 related studies published within the aforementioned period. Also, the selected references were considered for additional relevant studies on KT. For analytical data, we searched for ketamine with the following keywords: “urine”; “hair”; “analysis”; “analytical method”; “LC/MS”; “GC/MS”; “metabolite”; “LOD”; “LOQ”; “cut off value”; “concentration”; “regular abuser”; “non-regular abuser”; “patient”; “precision”; and “accuracy”. In particular; a search for “ketamine analysis” populated a total of 3487 papers; including 914 papers published in the last 5 years. The search had no limitation with respect to language of the documents. Furthermore; we investigated web sites related to laws about KT; these sites were also included in our references.

3. Results

3.1. Why has KT become a recreational drug?

KT has an original purpose as an anesthetic but illegal KT users use KT because of its dissociative and hallucinogenic effects [6]. Although there are many drugs abused in Asia, KT abuse and related problems has been increased recently. Therefore, we focused on KT and tried to figure out the characteristics of KT in this review.

Recently, KT superseded originally used drugs in Asia countries such as China, Taiwan, and Vietnam. This seems to be related to the penalty. In particular, KT is regulated as the Class III drug by the Drug Prevention and Control Act in Taiwan. Because there is no penalty for using the Class III drugs, it is required to reclassify KT from a Class III to a Class II because the users of Class II drugs are served penalty sentence up to 3 years. This reclassification is expected to reduce the illegal abuse of KT among youth in Taiwan [18].

3.2. Pharmacology

KT treatment intravenously is used for the management of chronic pain [29]. KT is generally administered in doses of 1–2 mg/kg intravenously over 1–2 min or 4–5 mg/kg intramuscularly [1,8,11,22]. KT may be effective in patients who have bipolar depression, post-traumatic stress disorder, and acute suicidal ideation [30]. The use of KT (10 mg/kg ip, once every 7 days) with citalopram (20 mg/kg po, once daily) for 21 days showed more rapid and longer antidepressant-like effects than a single use of citalopram [31].

KT acts with opioid receptors and type A gamma-amino-butyric acid receptors in high concentrations of plasma and inhibits *N*-methyl-daspartate (NMDA) glutaminergic receptors non-competitively [1,8]. KT as an NMDA receptor antagonist interrupts the effects of excitatory amino acids, such as glutamate and aspartate [8]. With an acute dose, KT stops calcium ions from rushing, prevents the sensory input, and injures limbic functions [1]. Because of electrophysiological dissociation between the limbic and thalamoneocortical systems, KT shows dissociative anaesthesia and produces a trance-like cataleptic state [22].

There are some differences in the methods of administration of KT. The subcutaneous (SC), intravenous (IV), and intramuscular (IM) routes of KT to treat depression showed antidepressant effects, and the SC route presented fewest side effects [32]. For pain management, oral route is suitable for treatment-resistant depression with high tolerability and few adverse effects [21,33]. The bioavailability of KT was reported as follows: intranasal/snorting were about 25–50% and oral intake was 17–20% [21].

3.3. Reported side effects and toxicology of KT

Table 1 lists the reported side effects of KT. KT has mental and physical side effects. The mental effects are psychedelic, hallucination, sedation, vertigo, schizophrenic-like symptoms, withdrawal syndrome, psychotic features, morbidity, manic-like symptoms, depressive symptoms, delirium, amnesia commonly lasting for about one hour [34], and physical effects, including an inability to speak, blurred vision, lack of co-ordination (occurring when reducing the dose or stopping use), melting into the surrounding, visual hallucinations, out-of-body experiences, uncontrolled laughter, difficulty with walking and balance resulting in falls, numbness, dizziness, nausea, headaches, spasms, twitches, emesis, a high incidence of flashbacks, attentional dysfunction, laryngospasm, emesis, decreased semantic memory, and impaired learning ability [2,7–11]. The side effects of KT use also include

Table 1
Reported side effects of the KT in various organs.

Target organs	Reported side effects	References
Brain	Intracranial hypertension, cognitive impairments, a reduction in frontal gray matter volume in brain, chronic damage to episodic memory, dissociative actions, alterations in regional homogeneity of resting-state brain activity, neurogenesis from neural stem progenitor cells in the developing brain toxic changes in the rat brain, changes in the dorsolateral prefrontal cortex, brain immaturity, neuroapoptotic cell death, neurodegeneration in the developing brain, alter the development of embryonic brains	[7,8,11,12,36,37,42]
Heart	Tachycardia, hypertension, increased cardiac output	[7]
Kidney	Bladder dysfunction, KT cystitis (KT-induced uropathy), ureteral inflammation with hydronephrosis and renal function impairment	[12–14]
Liver	Abnormal liver function	[38]
Biliary tract	Biliary tract abnormality	[38]
Respiratory tract	Respiratory depression and increased respiratory secretions	[8]

effects on various organs, such as the brain, heart, kidney, liver, biliary tract, and lung. KT has many reported side effects on the brain, such as cognitive impairment, a reduction in frontal gray matter volume in the brain, and chronic damage to the episodic memory, etc. [7,11,12,35–37]. In the case of the heart, there are many side effects such as tachycardia, hypertension, and increased cardiac output [7], and the side effects in the kidney include bladder dysfunction, KT cystitis (KT-induced uropathy), ureteral inflammation with hydronephrosis, and renal function impairment [12–14]. Other reported side effects on the liver and biliary tracts are abnormal liver function and abnormality of the biliary tract [38], and the side effects in the lung were respiratory depression and increased respiratory secretions [8]. In particular, administration from oral route as powder or tablet forms can create nitroso derivative of KT, *N*-nitrosoketamine (NKT) [17]. NKT has been reported to have stronger genotoxicity than KT [16]. Also, both KT and NKT have been shown to possess genotoxicity in Chinese hamster ovary cells. Therefore, genotoxicity of KT and NKT should also be considered [15]. In East Asia, the rate of HIV increased in the 1990s, along with prevalence of HIV related to drug injection. It has been determined that drug injection was the major reason for HIV infection and transmission in Asia including China, India, Malaysia, Taiwan, and Vietnam [15,17,18,39]. However, recent studies concluded that the main cause for HIV was has been overtaken by sexual transmission [40,41]. Although the prevalence of HIV related to drug injection has declined, drug injection and needle sharing still remain to be a problem for HIV transmission. Therefore, there is a need to regulate drug injection and needle sharing to prevent further HIV transmission.

3.4. Drug use patterns and related laws

Table 2 lists the trends and regulated laws from some countries. KT has become popular in many countries as a “club drug”, and is often used by teens and young adults [9,19]. Because KT is inexpensive and widely available in Karaoke TV bars and pubs, young people abuse KT easily in Taiwan [17,18]. It was reported that KT users take KT at techno clubs and rave parties in France, USA, and Italy [9,20,21]. The recreational use of KT is increasing in the UK [22]. KT use was much more prevalent among 15–24 year olds than among those 25-year-olds and older in France [20], and is often used by teens and young adults in the USA and Italy [9,21]. The mean age of first intentional use of KT was 25.8 years (S.D. 4.8; range 16–41 years) in Australia [3]. The common routes of administration are snorting followed by injection and oral ingestion [3,5,16,17,20,21,23–25]. KT has been injected as an anesthetic and analgesic, while the tablet form of KT has been become a recreational drug in Japan [16]. The main method of intake is snorting and some people use KT in a tablet form unconsciously in the UK [5].

In particular in Asia, such as China, Taiwan, and Hong Kong, KT is one of the most illegally used drugs. In Korea, KT has been included in the Act on the Control of Narcotics that regulates illicit use, possession, smuggling, and manufacturing since November 2005 and a person who violates the law is sentenced to a term of imprisonment [26–28]. In Taiwan, KT is a serious problem, especially to young people, and some legislators claimed to tighten the legislation management, such as a more severe criminal offence [18]. Illegal KT use has been a growing problem in Taiwan since 2008 [39]. Illegal KT use by youths has become a severe public health issue [19] and KT is the third most illegally used drug and emerging drug in Taiwan [2]. For example, KT-positive urine samples increased drastically from 47 in 2002 to 13,468 in 2012 [38]. Taiwan regulates possession, smuggling, and manufacturing of the KT by the Statute for the Prevention and Control of Illicit Drugs. According to the law, people who possess over 20 g KT may be sentenced to up to one year imprisonment and people who smuggle and manufacture KT will be liable to more than seven years imprisonment [18]. However, possession of a small amount of KT ($<$20 g) does not carry criminal penalties in Taiwan [13]. Therefore, there is a movement to upgrade criminal classification of KT from a Class III to a Class II drug in the Drug Prevention and Control Act because of the rise in prevalence in Taiwan [18]. In China, KT has emerged since 1997 and has become the most illegally used psychotropic substance from 2004 to 2013, with a peak of >5000 users in 2009 [39]. In Hong Kong, urine or hair specimens (n = 2000) were collected between 1 November, 2011 and 31 July, 2013 and KT had significantly higher detection rates in acute subjects [43]. The U.S.A regulates the possession of KT without a license or prescription by federal offences and Netherlands considers KT as a medication and does not regulate it [8]. Thirty frequent users interviewed in the UK used KT without stopping until the supplies were out and the average increase in dosage was six fold from initiation [44]. The legal status of KT in the UK has been changed from Class C to a Class B illicit drug [44]. Australia has the Drug Misuse and Trafficking Act 1985 that regulates KT when used illicitly, Mexico considers KT as a category 3 drug, and Canada regulates the sale of KT by pharmaceutical laws [8].

3.5. Urine and hair analysis of KT

In many studies, the analysis of KT has been conducted using urine, hair and plasma. This study focuses on urine and hair

Table 2
Regulated laws and features of illegal KT use in some countries.

Country	Regulated law (category)	Regulated target and punishment	Features (trends or reported side effects)	References
Korea	Act on the Control of Narcotics (Psychoactive agents II)	Illicit use: imprisonment for not more than ten years Possession: imprisonment for life sentence, or not less than five to ten years Smuggling and manufacturing: imprisonment for life sentence or not less than five years	The use of KT by drug-rape criminals	[26–28]
Taiwan	Statute for the Prevention and Control of Illicit Drugs The Drug Prevention and Control Act (Class III)	Possession: over 20 g (net)—imprisonment for not more than one years Smuggling and manufacturing: imprisonment for more than seven years	Upward trends The amounts of yearly KT seizures by judicial systems: from 9.5 kg in 2002 to 1371.9 kg in 2011 and highest rank since 2006 (KT data of 2013 article could be added) average age: 20–29 the most widely used illicit drug among youth under 19 long-term adverse health effects: tolerance, dependence, and bladder syndrome	[17,18,45]
China	(class II psychiatric drug) In July 2004, the state of Sichuan placed KT in class I	Trade is limited to licensed wholesalers and retail sales are prohibited	Upward trends 222 thousand KT users (National Narcotics Control Commission 2015)	[2,8,17]
Hong Kong	Pharmacy and Poisons Ordinance added in 2000	Substances Required by Regulation 9 to be Sold by Retail only upon a Prescription Given by a Registered Medical Practitioner, Registered Dentist or Registered Veterinary Surgeon	Upward trends Prevalent especially amongst young people In 2014, 96% of illegal young drug users took psychotropic substances. A matter of personal choice, low motivation to seek help, difficulty in identification	[17,46,47]
U.S.A	Controlled Substances Act (CSA) (Schedule 3 (III) Drugs)	Federal Trafficking Penalties—first offense: ~10 years, second offense: ~20 years		[8,48,49]
Netherlands	Geneesmiddelenwet (treated as a medication)			[8]
U.K	The Medicines Act The Misuse of Drugs Act 1971 Reclassifies (2014): from Class C to Class B drug under Schedule 2	Possession: up to five years in prison and/or an unlimited fine. Dealing: up to 14 years in prison and/or an unlimited fine		[8,50]
Australia	The Drug Misuse and Trafficking Act 1985	Illegal manufacture, supply, possession: Fines or imprison (2 years)		[8]
Mexico	Mexico's General Health Law Medicines Administration Regulations (category 3 drug: have a therapeutic value but constitute a problem for the public health)	Only veterinarians can manage and follow up the products		[8]
Canada	Pharmaceutical laws Controlled and illegal drugs (Schedule I)	Possession: imprison (~7 years) first offence: fine or imprison (~6 months) or both a subsequent offence: fine or imprison (~1 year) or both. Obtaining: imprison (~7 years) first offence: fine or imprison (~6 months) or both subsequent offence: fine or imprison (~1 year) or both		[8,50]

Table 3
Analytical methods of KT in urine and hair samples.

Sample	Instrument	Column	IS	Sample preparation	Precision(%) Accuracy(%)	LOD/LOQ[a]	Refs.
Urine (n = 11)	HPLC	Atlantis T3	KT-d_4	SPE: methanol/TFA, ultrasonication Urine: LLE (ammonium carbonate 1 M, and ethyl acetate)			[6]
Sprague-Dawley rats' urine (n = 3 groups)	PCI-GC–MS (positive ion chemical ionization-gas chromatography–mass spectrometry)	HP-5MS capillary	Cocaine-D_3	SPE (solid phase extraction) Precondition: methanol, distilled water, 5N-HCl Wash: 0.1 N-NaOH, distilled water, hexane Elute: methylene chloride/isopropanol	Precision 1.44–14.38 for KT 0.49–11.15 for NK Accuracy −21.54 to 15.90 for KT −2.33 to 2.54 for NK	LOD: 25 LOQ: 50	[26]
Urine (n = 2000)	LC–MS/MS			Urine: initial glucuronidase digestion, SPE			[43]
Urine (n = 52)	LC–MS/MS with SPEESI + (electrospray in positive ionization)	SPP (120 EC-C_{18})	KT-d_4, NKT-d_4, DHNK-d_4	SPE 20 mM phosphate buffer, conc. (29 wt.%) ammonium hydroxide	Precision 1.3–6.8 for KT 1.0–8.6 for NK 3.4–10.9 for DHNK Accuracy −17.1 to 9.9 for KT, NK, DHNK	LOD: 2.0 for KT, 0.2 for NK, DHNK LOQ: 4.0 for KT, 0.3 for NK, 0.4 for DHNK	[58]
Urine (n = 964)	LC–MS/MS	Eclipse Plus C8 (positive) Extend C18 column (negative)	KT-d_4	100 mM phosphate buffer Acidic fraction elution: methanol in ethyl acetate basic fraction elution: ethylacetate/isopropanol/ 20% ammonium hydroxide	Precision 0.42 for KT 0.37 for NK 0.68 for methoxetamine	LOD: 5 for KT, methoxetamine, 10 for NK	[59]
Urine (n = 2)	GC-MSD (mass selective detector) SIM (selected ion monitoring) mode	HP-5MS capillary	KT-d_4, NK-d_4	Alkalization: NaOH 2 mol/L solution 10% NaCl	Precision 2.9–10.1 for KT 3.6–9.2 for NK 9.3–16.9 for DHNK Accuracy 88.3–108.0 for KT 92.0–105.4 for NK 106.3–118.9 for DHNK	LOD: 0.25 for KT, 0.1 for NK, LOQ: 0.5 for KT, NK	[60]
Urine (n = 28)	CE system: Beckman P/ACE		1,1-Dimethylbiguanide HCl	CZE: fused-silica capillary CSEI-Sweep-MEKC (Cation-selective exhaustive injection and sweeping micellar electrokinetic chromatography) Capillary: (1) phosphate buffer with 30% methanol (2) HCB (3) phosphate buffer with 20% methanol and 100 mM SDS	Precision 1.4–5.0 for KT Accuracy 1.4–5.0 for KT	LOD: 5	[61]
Urine (n = 5)	GC with FID (flame ionization detector)	HP-5 capillary		12.5 by 1 mol/L NaOH solution	Precision 1.1–12.1 for KT	LOD: 8000 for KT, LOQ: 3000 for KT	[62]
Hair (n = 8)	LC-HRMS positive ESI	Atlantis T3	KT-d_4	Acetonitrile, TFA 1 M, water	Precision 0.4–4.0 for KT 0.3–3.8 for NK Accuracy 8–20.1 for KT 8–16.3 for NK	LOD: 0.02 LLOQ: 0.05	[3]

Table 3 (*Continued*)

Sample	Instrument	Column	IS	Sample preparation	Precision(%) Accuracy(%)	LOD/LOQ[a]	Refs.
Hair (n = 20)	UHPLC–MS/MS system LC–ESI-MS/MS	Acquity UPLC BEH C_{18} C_{18}		Methanol		LOD: 0.004 for KT, 0.003 for NK LOQ: 0.01 for KT, 0.01 for NK	[4]
Hair (n = 1371)	LC–MS/MS	C_{18} column	KT-d_4, NK- d_4	Extraction solution: methanol: acetonitrile: 20 mM ammonium formate	Precision 2.1–12.1 for KT 2.6–14.0 for NK Accuracy −7.6 to 0.6 for KT −15.9 to −0.6 for NK	LOD: 0.02 for KT, 0.1 for NK LOQ: 0.02 for KT, 0.1 for NK	[5]
Hair (n = 11)	Hair: HPLC-HRMS positive ESI conditions	Atlantis T3	KT-d_4	SPE: methanol/TFA, ultrasonication Hair: water/acetonitrile/TFA 1 M		LOD: 0.003 LLOQ:0.01	[6]
Hair	GC/MS with EI SIM mode	DB-5MS	KT-d_4, NK- d_4	0.25 M methanolic HCl under ultrasonication Derivatization: BTFA(*N*- methyl bis (trifluoroacetamide))	Precision 0.5–7.4 for KT 0.9–11.5 for NK Accuracy −13.4 to 1.4 for KT −5.8 to 0.9 for NK	LOD: 0.03 for KT, 0.01 for NK LOQ: 0.11 for KT, 0.05 for NK	[27]
Hair (n = 2000)	LC–MS/MS			Hair: micro-pulverisation			[43]
Hair (n = 15)	GC–MS	HP-5 capillary	KT-d_4	HCl (0.1 M) extraction, 0.4% NaOH diethyl ether	Precision 4.6–8.1 for KT 1.5–6.0 for NK Accuracy −20 to −2 for KT −16.5 to 17.5 for NK	LOD: 0.02 LOQ: 0.05	[51]
Hair (n = 10)	QQQ-MS/MS with an HPLC-Chip Cube interface coupled with a nano-LC	ZORBAX 80 SB-C_{18}	KT-d_4, NK-d_4	HCl (0.1 M) 2.5 M NaOH Neutralization: phosphate buffer Extraction: dichloromethane: *n*-hexane	Precision 2.0–9.7 for KT 1.8–3.7 for NK Accuracy 88.21–99.96 for KT 89.73–114.42 for NK	LOD: 0.0005 LOQ: 0.001	[52]
Hair (n = 10)	LC–MS/MS Positive EI mode	Alltima C 18 guard column	KT-d_4, NK-d_4	Extraction: ethyl acetate Acidification: 1% formic acid in ethyl acetate		LOD: 0.03 for KT, 0.03 for NK	[53]
Hair (n = 8)	LC–MS–MS positive ESI mode	Kinetex column packed with C_{18} particles	KT-d_4, NK-d_4	Methanol–TFA Methanol–HCl Incubation: phosphate buffer, methanol TFA Extraction conditions: the microwave-assisted extraction(MAE) process Methanol–HCl	Precision 1.5–4.9 for KT 2.2–6.6 for NK 2.7–7.3 for DHNK Accuracy 1.9–4.2 for KT 2.5–3.6 for NK 1.9–3.5 for DHNK	LOD: 0.0005 for KT, NK LOQ: 0.002 for KT, NK	[54]

Hair (n = 4)	CSEI-Sweep-MEKC	RP_{18} column	1,1-DimethylbiguanideHCl	Sonication: 0.1 M HCl. Incubation mixture: (1) equimolar NaOH Extract: ethyl acetate CSEI-Sweep-MEKC fused-silica capillaries The capillary : (1) phosphate buffer containing 30% methanol (2) HCB (1) phosphate buffer containing 20% methanol and 100mM SDS	Precision 0.0–11.1 for KT Accuracy −5.0 to 8.0 for KT	LOD: 0.05	[55]
Hair (n = 6)	GC/EI-MS GC/NCI-MS SIM mode	HP-5MS	KT-d_4, NK-d_4	Methanol–TFA (1) 0.1 M phosphate buffer (2) conditioning with 1 mL of methanol and a 0.1 M phosphate buffer Derivatization: ethyl acetate & HFBA	Precision 5.9–10.3 for KT 1.2–4.8 for NK Accuracy 3.7–10.3 for KT 1.3–7.1 for NK	LOD: 0.00025 for KT, 0.000025 for NK LOQ: 0.0001 for KT, 0.00008 for NK	[56]
Hair (n = 8)	GC/MS—EI mode	HP-5MS	KT-d_4, NK-d_4	Overnight with methanol/TFA Derivatization: ethyl acetate & HFBA (heptafluorobutyric acid anhydride	Precision 1.9–15.8 for KT 0.6–4.8 for NK Accuracy 6.3–13.7 for KT 2.5–9.5 for NK	LOD: 0.05 for KT, NK LOQ: 0.08 for KT, NK	[57]

[a] ng/mg in hair, ng/mL in urine and plasma.

analysis and compares several analytical methods according to the samples, instruments, columns, extraction methods, internal standards, and the limits of detection (LOD) and quantification (LOQ) levels (Table 3). To minimize the effect of external contamination, washing was needed for the hair samples [5]. Therefore, washing was conducted with water, CH_2Cl_2, acetone, sodium dodecyl sulfate (SDS), methanol, ethanol, phosphate buffer, and dichloromethane (DCM) to remove the environmental contamination [3–6,27,51–59].

Some urine analysis was conducted by gas chromatography (GC), gas chromatography–mass spectrometry (GC–MS), liquid chromatography (LC), and capillary electrophoresis (CE) [6,26,43,58–62] and hair analysis was conducted by liquid chromatography–mass spectrometry (LC–MS), GC–MS and LC–MS/MS [3–6,27,43,51–57]. GC/MS has high standardization and robustness [52] and conducts more sensitive analysis for low concentrations of substance in hair when NCI mode is used [56], while it provides not only quantitative information and but also qualitative information about urine samples when PCI mode is used [26]. However, GC/MS is needed in the derivatization or in the comprehensive sample cleaning process [54,56]. Analysists do not have to conduct the derivatization and the clean-up process for sample by using LC/MS [52,54,56]. LC–MS/MS can detect many conventional and new psychoactive compounds and metabolites in urine samples simultaneously and identify the drug abuse through application of authentic samples [6,58,59]. LC/MS, however, is more expensive than GC/MS [56] and requires a longer time for the re-equilibration when using gradient elution in LC–MS/MS with SPE [58]. The commonly used internal standard is KT-d_4 [3,5,6,27,51,53,54,56–60] and cocaine-D_3 [26] and 1,1-dimethylbiguanide HCl [55,61] are also used.

The LOD for KT ranged from 0.25 to 8,000 ng/mL and LOQ ranged from 0.5 to 3,000 ng/mL in urine samples using GC/MS [26,60,62]. The LOD was 2 ng/mL [58] and 5 ng/mL [59] and LOQ was 4 ng/mL [58] in urine samples using LC/MS.

The LOD for KT ranged from 0.00025 to 0.05 ng/mg and LOQ ranged from 0.001 to 0.08 ng/mg in hair samples [27,51,56,57]. The LOD for KT ranged from 0.0005 to 0.05 ng/mg and LOQ for KT ranged from 0.02 to 0.05 ng/mg in hair samples using LC/MS [3–6,52–54].

The determination of metabolites is important in drug use to make a difference with the passive exposure or external contamination. The major metabolite is NK in many studies [3–6,27,51–54,58,60,63–67] and dehydronorketamine (DHNK) was also determined as a metabolite of KT [51,54,58,60]. The NK/K ratio ranged from 0.28 to 2.04 in the urine samples from abusers [26] and ranged from 0.03 to 0.88 in hair samples from abusers using GC/MS [51]. Moreover, the NK/K ratio ranged from 0.06 to 0.80 [4] and ranged from 0.08 to 1.13 [52] in the hair samples from abusers using LC/MS.

The cut off values of KT and its metabolites were determined in some studies [4–6,56] and established officially by the United Nations Office on Drugs and Crime (UNODC) [60]. For precise determination of drugs and metabolites in the hair samples, it was also suggested to establish the cut off values in accordance with the minimum detection level (LOD) [56]. Although the guidelines established by the Substance Abuse and Mental Health Services Administration (SAMHSA) has been used to check the cut off value of drugs in the USA, the cut off value for KT has not been determined thus far [56]. In the hair samples, for examples, the cut off value for KT was fixed at 0.5 ng/mg to identify illegal abuse except for medical purposes [4], at 0.4 ng/mg from 977 KT users, which showed a concentration of KT in the hair, when more than 90% of samples were detected including NK [5], and at 0.050 ng/mg for KT [6]. The cut off value for NK in the hair sample was fixed at

0.1 ng/mg [4], and the cut off value for DHNK in the urine sample was 0.1 ng/mL, established from UNODC [60].

In many studies, there are mass ion values of KT. In the case of derivatization, the m/z values of hair samples with TFAA and MBTFA were 236 and 270 for KT; 256 and 284 for NK; 274 for KT-d_4; and 288 for NK-d_4 in GC–MS [27]. The m/z values of urine samples with TFAA and ethyl acetate were 262, 270, and 305 for KT; 216, 256, and 284 for NK; 266 and 274 for KT-d_4, and 260 and 288 for NK-d_4 in the GC–MS SIM analyses [60]. The m/z values of hair samples with water/acetonitrile/TFA were 238.09931 for KT, 224.08367 for NK, and 242.12443 for KT-d_4 in HPLC-HRMS [6]. When there was no derivatization, however, the m/z values of the urine samples were 238 ($M \pm 1$) for KT, 224 ($M \pm 1$), 207 for NK in PCI-GC–MS [24], and the values of hair samples were 238 for KT in MS [55].

3.6. The concentrations KT in the biological samples from both regular and non-regular abusers

The analytical study of the biological samples from non-regular abusers has rarely been reported [6,66,67], while that of the biological samples from regular abusers have frequently been reported [3–5,26,27,43,51–57,59–61,63,64,68,69]. Table 4 shows the concentrations KT in the biological samples from both regular and non-regular abusers.

The concentrations of KT and NK were 0.35 μg/mL and 0.81 μg/mL, respectively, in the urine samples from laboratory staffs using GC/MS [67].

The concentrations of KT and NK ranged from 0.01 to 0.84 ng/mg and from 0.01 to 0.06 ng/mg, respectively, in the head hair of veterinary physicians using LC/MS, while those of KT and NK ranged from 0.04 to 2.04 ng/mg and from 0.01 to 0.10 ng/mg, respectively in pubic hear of veterinary physicians using LC/MS. The concentrations of KT in head hair ranged from 0.04 to 0.10 ng/mg in naïve males and from 0.01 to 0.02 ng/mg in naïve females using LC/MS [6].

The concentrations of KT ranged from 0.27 to 1.02 μg/mL (3 mg/kg nasally), from 0.56 to 3.13 μg/mL (9 mg/kg nasally), and from 0.32 to 1.38 μg/mL (9 mg/kg rectally or 3 mg/kg i.v) in plasma samples from children who underwent urological surgery [66].

The concentrations of KT, NK, and DHNK ranged from 0.007 to 56.16 μg/mL, from 0.005 to 29.31 μg/mL [26,60,61], and from 0.007 to 8.76 μg/mL, respectively [60] in the urine samples from KT abusers using GC/MS and those of KT ranged from 0.11 to 14.16 μg/mL in the urine samples from drug-impaired drivers using LC/MS [64].

The concentrations of KT and NK ranged from 0.15 to 111.1 ng/mg and from 0.8 to 6.4 ng/mg, respectively, in the hair samples from KT abusers using GC/MS [27,51,56,57,68]. The concentrations of KT, NK, and DHNK ranged from 0.002 to 1548.12 ng/mg, from 0.002 to 130.74 ng/mg [3–5,52–55,69], and from 0.24 to 1.06 ng/mg, respectively [54] in the hair samples from KT abusers using LC/MS.

In other samples of KT abusers, the concentrations of KT ranged from 0.102 to 12.00 ng/mg in the saliva samples using LC/MS [64] and those of KT and NK ranged from 0.170 to 0.85 ng/mg and from 0.190 to 1.40 ng/mg, respectively, in the blood samples using GC/MS [63].

4. Conclusions

KT has become one of the most commonly used drugs around the world, particularly in China and Taiwan, where KT is the third most illegally used drug. The adverse effects of KT include mental and physical effects, as well as negative effects on some organs. KT is a popular drug in clubs and pubs, and the major users of KT are

Table 4
The concentrations of KT in biological samples from both regular and non-regular abusers.

Subjects	Sample	KT conc.[a]	NK conc.[a]	DHNK conc.[a]	Instrument	Refs.
Non regular abusers	Urine	0.35	0.81		GC/MS	[67]
	Hair (veterinary)	0.01–0.84 (Head)	0.01–0.06 (Head)		LC/MS	[6]
		0.04–2.04 (Pubic)	0.01–0.10 (Pubic)			
	Hair (naïve)	0.04–0.10 (M)	<0.01 (M)			
		0.01–0.02 (F)				
	Plasma	0.27–1.02 (3 mg/kg nasally)			GC	[66]
		0.56–3.13 (9 mg/kg nasally)				
		0.32–1.38 (9 mg/kg rectally or 3 mg/kg i.v)				
Regular abusers	Urine	0.03–56.16	0.42–29.31		GC/MS	[26]
		0.007–0.09	0.005–5.81	0.007–8.76	GC/MS	[60]
		0.23–1.00			GC/MS	[61]
		0.11–14.16			LC/MS	[64]
	Hair	0.15–25.0	0.10–40.0		GC/MS	[27]
		1.1–42.7 (once in a week)			GC/MS	[68]
		13.5–111.1 (twice or three times)				
		>45. 1 (everyday)				
		0.8–92.3	0.8–6.4		GC/MS	[51]
		0.21–2.42			GC/MS	[56]
		0.46–28.15			GC/MS	[57]
		0.002–0.03	0.002–0.04		LC/MS	[69]
		1.6–7.7	0.2–0.3		LC/MS	[3]
		0.10–99.30	0.10–91.80		LC/MS	[5]
		11.07–1548.12	1.67–130.74		LC/MS	[52]
		1.31–5.39	0.18–0.59		LC/MS	[53]
		0.02–23.60	0.68–2.90	0.24–1.06	LC/MS	[54]
		1.18			LC/MS	[55]
		0.11–11.4	0.02–0.71		LC/MS	[4]
	Saliva	0.10–12.00			LC/MS	[64]
	Blood	0.17–0.85	0.19–1.40		GC/MS	[63]

[a] ng/mg in hair, μg/mL in urine and plasma.

young people. Although there is a difference by country, the major administration method of KT is snorting. In many countries, there are laws that regulate its abuse.

In urine and hair analyses, the ranges of LOD and LOQ for KT, NK, and DHNK were various by the sample types and analytical methods used. Because UNODC has not set an official cut off value of KT, the values of KT were established by experiments in accordance with the sample type. Moreover, the concentrations of KT, NK, and DHNK were diverse based on the subjects, sample types, and analytical methods.

In terms of the analysis of biological samples, it is required to develop specific and quick analysis techniques. In addition, KT abusers should be monitored by both clinical measurement and social environment to minimize the risk of health and other relevant problems, such as relapse. Comprehensive reforms are needed in laws and policies associated with KT abuse, particularly, in Asian countries further reinforcing laws and systems as well as developing stricter prevention measures. Furthermore, there is a need for international cooperation, such as collaborative research projects between several countries to share views and overcome of dealing with the problems from KT abuse.

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