Surveillance of emerging drugs of abuse in Hong Kong: validation of an analytical tool

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A B S T R A C T

Objective: To validate a locally developed chromatography-based method to monitor emerging drugs of abuse whilst performing regular drug testing in abusers.

Design: Cross-sectional study.

Setting: Eleven regional hospitals, seven social service units, and a tertiary level clinical toxicology laboratory in Hong Kong.

Participants: A total of 972 drug abusers and high-risk individuals were recruited from acute, rehabilitation, and high-risk settings between 1 November 2011 and 31 July 2013. A subset of the participants was of South Asian ethnicity. In total, 2000 urine or hair specimens were collected.

Main outcome measures: Proof of concept that surveillance of emerging drugs of abuse can be performed whilst conducting routine drug of abuse testing in patients.

Results: The method was successfully applied to 2000 samples with three emerging drugs of abuse detected in five samples: PMMA (paramethoxymethamphetamine), TFMPP [1-(3-trifluoromethylphenyl)piperazine], and methcathinone. The method also detected conventional drugs of abuse, with codeine, methadone, heroin, methamphetamine, and ketamine being the most frequently detected drugs. Other findings included the observation that South

Asians had significantly higher rates of using opiates such as heroin, methadone, and codeine; and that ketamine and cocaine had significantly higher detection rates in acute subjects compared with the rehabilitation population.

Conclusions: This locally developed analytical method is a valid tool for simultaneous surveillance of emerging drugs of abuse and routine drug monitoring of patients at minimal additional cost and effort. Continued, proactive surveillance and early identification of emerging drugs will facilitate prompt clinical, social, and legislative management.

New knowledge added by this study
- A locally developed method is a valid tool for monitoring the penetrance of emerging drugs of abuse into our society whilst performing regular drugs of abuse testing.

Implications for clinical practice or policy
- Implementation of the analytical method in the routine drug monitoring of drug abusers will enable simultaneous surveillance of novel drugs of abuse at minimal extra cost and effort.
- Continued and proactive surveillance of emerging drugs of abuse in the population will facilitate prompt measures in the clinical, social, and legislative management of these constantly changing and potentially dangerous drugs.

Introduction

Despite continuous efforts, drug abuse remains a major social and medical problem in today's society. In particular, there has been a rapid and continued growth of 'emerging' drugs of abuse (DOA) on a global scale.[1,2] Emerging DOA, also called designer drugs or

novel psychoactive substances, bear a chemical and/ or pharmacological resemblance to conventional DOA and pose a threat to public health, but are often (initially) not controlled by law. They are easily accessible from street dealers or through the internet, and are often presumed to be safer than conventional

DOA owing to their 'legal' or 'herbal' nature.[1,3] In Hong Kong, the drug scene has also been penetrated in recent years by such substances as the piperazine derivative TFMPP [1-(3-trifluoromethylphenyl) piperazine],[4] the synthetic cannabinoids,[5] the methamphetamine derivative PMMA (para-methoxymethamphetamine),[6] and the NBOMe (N-methoxybenzyl derivatives of phenethylamine).[7] Some of these novel drugs pose a significant health threat and numerous fatalities have been reported worldwide.[8-10] In particular, PMMA and the NBOMe drugs have been associated with severe clinical toxicity and fatalities in Hong Kong.[6,7]

Effective diagnosis and treatment of emerging DOA intoxication rely on the timely and accurate detection of these substances. Whilst immunoassay and drug screening methods are well-established for conventional DOA, laboratory analysis of novel drugs is not so readily available. This inevitably leads to the delayed discovery of emerging drugs and consequently early medical and social intervention is compromised. Recently, a liquid chromatography–tandem mass spectrometry (LC-MS/MS)–based method has been established locally that allows the simultaneous detection of 47 commonly abused drugs in addition to over 45 emerging DOA and their metabolites in urine[11] and hair (the latter manuscript in preparation). The aim of the current study was to validate this analytical method as a tool to monitor emerging DOA whilst performing regular DOA testing by applying the method to 2000 urine and hair specimens collected from drug abusers as well as high-risk individuals.

Methods

Sample collection

Between 1 November 2011 and 31 July 2013, 964 urine and 1036 hair specimens (n=2000 in total) were collected for analysis. Subjects who were included in the study were patients/clients of the units listed, and who were suspected to be actively using DOA and who agreed to participate in the study: (i) substance abuse clinics within the Hospital Authority (Castle Peak Hospital, Kowloon Hospital, Kwai Chung Hospital, Pamela Youde Nethersole Eastern Hospital, Prince of Wales Hospital, Queen Mary Hospital); (ii) accident and emergency (A&E) departments within the Hospital Authority (Pamela Youde Nethersole Eastern Hospital, Pok Oi Hospital, Princess Margaret Hospital, Queen Mary Hospital, Tuen Mun Hospital, United Christian Hospital, Yan Chai Hospital); (iii) the Hong Kong Poison Information Centre (HKPIC) toxicology clinic; (iv) counselling centres for psychotropic substance abusers (CCPSA; Evergreen Lutheran Centre, Rainbow Lutheran Centre, Cheer Lutheran Centre); (v) various rehabilitation centres including the Society of Rehabilitation and Crime

香港新興毒品的監察：一種分析方法的驗證

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目的：驗證本地研發的色譜測量方法作為一種於濫藥者進行定期毒品測試時，同時調查新興毒品的工具。

設計：橫斷面研究。

安排：香港十一所分區醫院、七個社會福利機構及一間專科臨床毒理學化驗室。

參與者：2011年11月1日至2013年7月31日期間共招募972位參與者，當中包括急症、復康及高危人士。部份參與者為南亞裔。此研究共收集二千個尿液或頭髮樣本。

主要結果測量：驗證於進行定期毒品測試時同時監察新興毒品的概念。

結果：測量方法成功應用於二千個樣本的分析，並於五個樣本中驗出三類新興毒品，包括PMMA、TFMPP及methcathinone。測量方法同時檢測出傳統毒品，當中以可待因、美沙酮、海洛英、甲基安非他命及氯胺酮最為普遍。研究亦發現南亞裔人士較多使用鴉片類藥物如海洛英、美沙酮及可待因。另外，於急診患者中檢測出氯胺酮及可卡因亦較復康人士普遍。

結論：這個本地研發的測量方法是一個用於同時進行定期毒品測試和檢測新興毒品的有效及低成本工具。持續並主動的監察有助早期識別新出現的毒品，並有利於迅速採取相應的臨床、社會和立法管理措施。

Prevention (SRACP), Operation Dawn and Caritas Wong Yiu Nam Centre; and (vi) Youth Outreach. Pregnant women and individuals aged under 18 years were excluded from the study. The majority of the participants were Chinese, although those recruited from SRACP were exclusively South Asians.

The study was approved by the institutional ethics review boards (Kowloon West Cluster: KW/FR-11-011 (41-05); Kowloon Central/Kowloon East Cluster: KC/KE-11-0170/ER-2; Hong Kong West Cluster: UW 11-398; Hong Kong East Cluster: HKEC-2011-068; New Territories West Cluster: NTWC/CREC/989/11; New Territories East Cluster: CRE-2011.427). Subjects donated samples on a voluntary basis and informed consent was obtained. Each subject donated either urine or hair, or both, at each donation episode. Some gave repeated sample(s): donations were at least 8 weeks apart. Urine was collected in a plain plastic bottle and frozen until analysis. For hair, a lock of hair was collected from the back of the head for analysis. The root end was identified to facilitate segmental analysis.

Sample analysis

The methodology for urine analysis has been detailed in a separate publication.[11] In brief, the urine sample was subjected to an initial glucuronidase digestion, followed by solid phase extraction and sample

TABLE 1. The conventional and emerging drugs of abuse being analysed for

Drug class	Drug (or metabolite)
Amphetamines	4-Fluoroamphetamine*
	4-Methylthioamphetamine*
	Amphetamine
	Bromo-DragonFly*
	Chloroamphetamine*
	DOB*
	DOET*
	DOM*
	HMMA
	MBDB*
	MDA
	MDEA*
	MDMA
	Methamphetamine
	N-ethylamphetamine*
	PMA*
	PMMA*
Opiates	Codeine
	Codeine M (nor)
	Heroin
	Heroin M (6-MAM)
	Morphine
	Morphine M (nor)
Cocaine and metabolites	Cocaine
	Cocaine M (benzoylecgonine)
	Cocaine M (cocaethylene)
	Cocaine M (nor)
Ketamine and metabolites/ analogues	Ketamine
	Ketamine M (nor)
	Methoxetamine*
	Tiletamine*
Benzodiazepines and metabolites	Chlordiazepoxide
	Diazepam
	Diazepam M (nor)
	Estazolam
	Flunitrazepam
	Flunitrazepam M (7-amino)
	Midazolam
	Midazolam M (1-OH)
	Midazolam M (4-OH)
	Nimetazepam
	Oxazepam
	Temazepam
	Triazolam
	Triazolam M (1-OH)

Abbreviation: M = metabolite
* Emerging drugs of abuse

TABLE 1. (cont'd)

Drug class	Drug (or metabolite)
Cannabinoids	Cannabis M (carboxy-THC)
	Cannabis M (THC-OH)
	JWH-018*
	JWH-018 M (4-OH-indole)*
	JWH-018 M (N-5-OH-pentyl)*
	JWH-073*
	CP-47,497*
	C8 homologue of CP-47,497*
Phenethylamines	2C-B*
	2C-H*
	2C-I*
	2C-T-2*
	2C-T-4*
	2C-T-7*
	Mescaline*
Piperazines	BZP*
	mCPP*
	MDBP*
	pFPP*
	pMeOPP*
	TFMPP*
Cathinones	Cathinone*
	Ethylone*
	Mephedrone*
	Methcathinone*
	Methedrone*
	Methylone*
Tryptamines	5-MeO-DIPT*
	Alpha-methyltryptamine*
	Bufotenine*
	Dimethyltryptamine*
	Psilocin*
Miscellaneous (emerging drugs of abuse)	MDPV*
	Mitragynine*
	Salvinorin A*
Miscellaneous (conventional drugs of abuse)	Dextromethorphan
	Dextromethorphan M (dextrorphan)
	LSD
	LSD M (nor)
	LSD M (OH)
	Methadone
	Methadone M (EDDP)
	Methaqualone
	Phentermine
	Zolpidem
	Zopiclone
	Amobarbital
	Butabarbital
	Secobarbital

concentration. The hair sample (first 3-cm segment) was first decontaminated and subsequently subjected to simultaneous micro-pulverisation and extraction in solvent. The final filtrates were analysed by LC-MS/MS performed on an Agilent 6430 triple-quadrupole mass spectrometer (Agilent Technologies, Singapore) coupled with Agilent 1290 Infinity liquid chromatography system. The 47 conventional and 47 emerging DOA identified for analysis are listed in Table 1. The analytical method had previously been validated according to international guidelines.[12]

Statistical analysis

Statistical analysis was performed using Fisher's exact test, with a P value of less than 0.05 considered statistically significant. Comparison of the drug detection rates was made between (i) different ethnic groups and (ii) samples collected in the rehabilitation and acute settings.

Results

Subject demographics

In total, 972 individuals took part in the study (720 males, 252 females). Their respective mean and median age was 35 and 33 years (range, 18-74 years). Of the 972 subjects, 815 were single-time donors and 157 donated repeated samples (between 2 and 6 donations each). There were 1224 donation episodes (815 from single-time donors; 409 from repeated donors) and 2000 specimens collected in total, of which 964 were urine and 1036 were hair (Fig 1). Of the 1224 donation episodes, the subjects were

recruited from: substance abuse clinics (n=822), drug rehabilitation and counselling centres (n=320), youth hangout centre (n=41), HKPIC toxicology clinic (n=28), and A&E departments (n=13).

Emerging drugs of abuse

In the 2000 specimens analysed, five specimens were found to contain three emerging DOAs: PMMA, TFMPP, and methcathinone. A methamphetamine derivative, PMMA, was detected in three hair specimens (cases 1-3, Table 2). All three hair samples
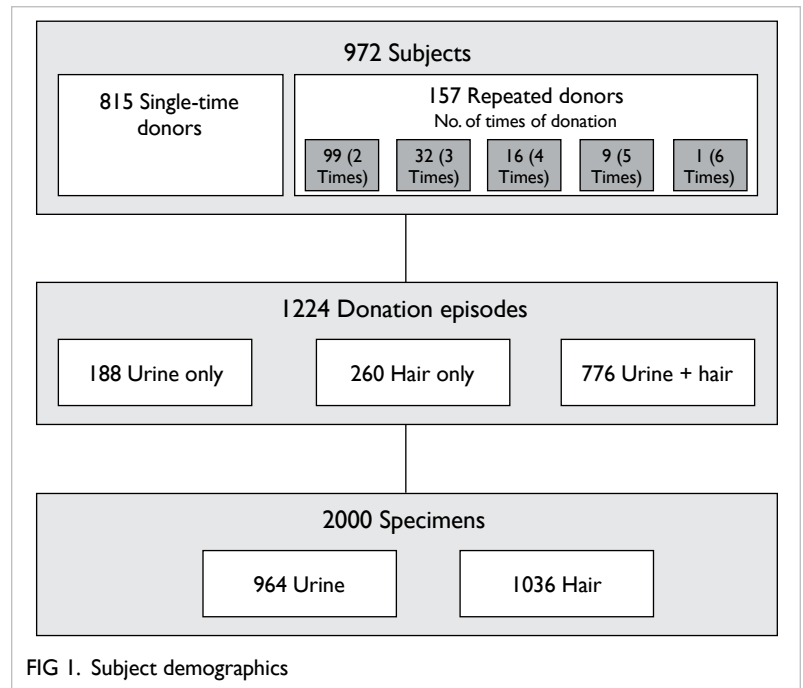

FIG 1. Subject demographics

TABLE 2. Emerging drugs of abuse detected in the study

Case No.	Sex/age (years)	Setting	Drugs detected in hair	Drugs detected in urine
1	M/28	A&E	PMMA Cocaine and metabolite Ketamine and metabolite	Cocaine metabolite Ketamine and metabolite
2	M/45	SAC	PMMA Amphetamine Methamphetamine Cocaine and metabolites Ketamine and metabolite Zolpidem	Methamphetamine Cocaine and metabolite Ketamine and metabolite Phentermine
3	M/28	Drug rehabilitation centre	PMMA Cocaine and metabolites Ketamine and metabolite	Ketamine and metabolite Cannabis metabolite
4	F/26	HKPIC toxicology clinic	Cocaine Ketamine	TFMPP Cocaine metabolite Ketamine and metabolite
5	F/27	SAC	(Hair not collected)	Methcathinone Amphetamine Methamphetamine HMMA (metabolite of amphetamine-like substances) Cocaine metabolite

Abbreviations: A&E = accident and emergency department; HKPIC = Hong Kong Poison Information Centre; PMMA = paramethoxymethamphetamine; SAC = substance abuse clinic; TFMPP = 1-(3-Trifluoromethylphenyl)piperazine

were also found to contain cocaine and ketamine. Nonetheless, PMMA was not detected in the subjects' concurrent urine sample.
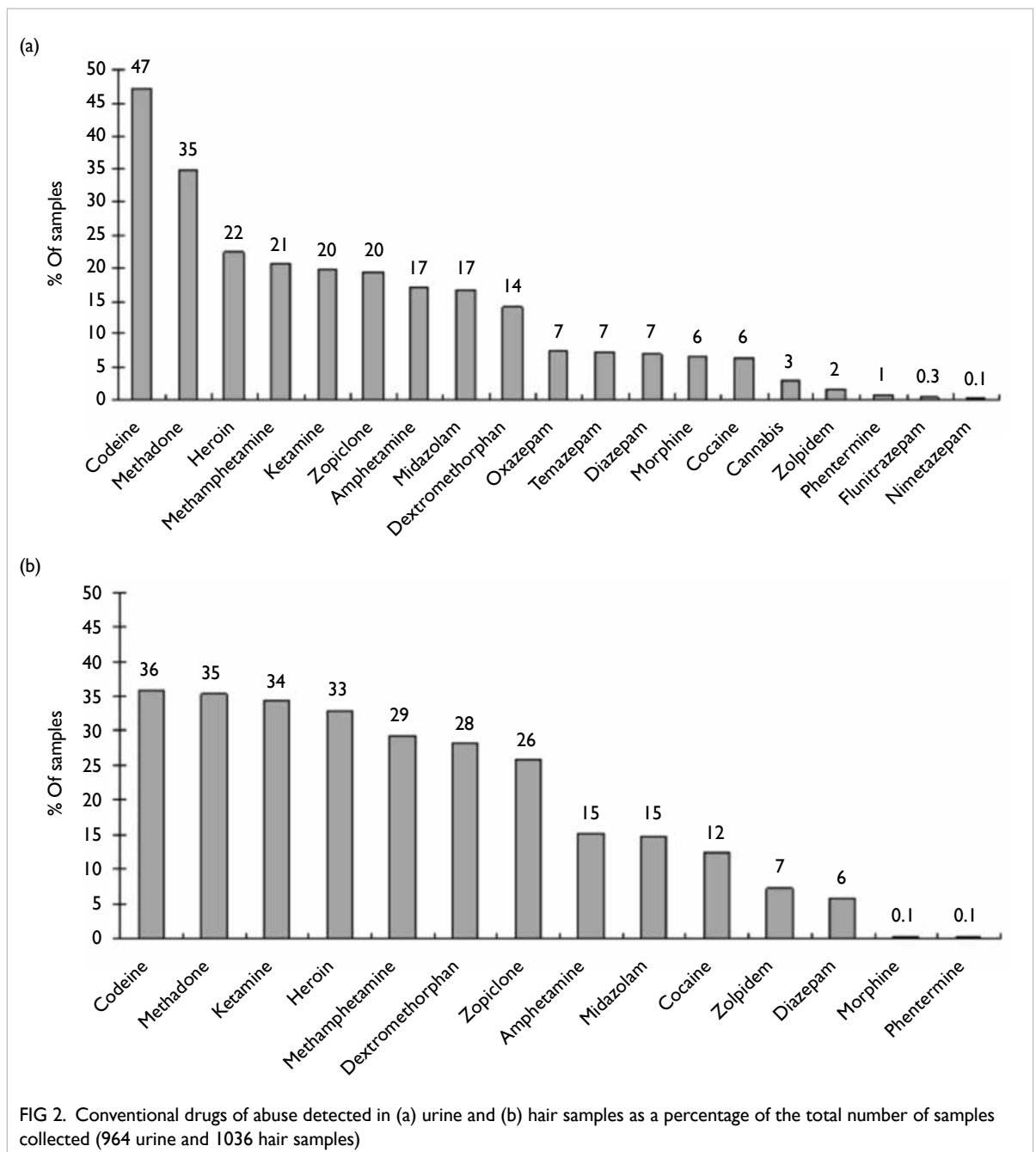
A piperazine derivative, TFMPP, was detected in one urine specimen (case 4, Table 2), together with cocaine and ketamine. Nonetheless TFMPP was not detected in the parallel hair sample.

Methcathinone, also known as ephedrone, is a cathinone (beta-keto amphetamine) analogue. It was detected in combination with amphetamine, methamphetamine, and cocaine metabolite in one urine specimen (case 5, Table 2). No parallel hair specimen was available from this subject.

Conventional drugs of abuse

Analysis of the 964 urine samples revealed the presence of 19 types of conventional DOA (Fig 2a). Codeine was the most common, being detected in 47% of the urine samples, followed by methadone (35%), heroin (22%), methamphetamine (21%), ketamine (20%), zopiclone (20%), amphetamine (17%), midazolam (17%), and dextromethorphan (14%). Cocaine and cannabis were detected in 6% and 3% of urine samples, respectively.

In hair specimens (1036 in total), 14 types of conventional DOA were detected (Fig 2b). Codeine (36%) and methadone (35%) were the most

FIG 2. Conventional drugs of abuse detected in (a) urine and (b) hair samples as a percentage of the total number of samples collected (964 urine and 1036 hair samples)

prevalent, followed by ketamine (34%), heroin (33%), methamphetamine (29%), dextromethorphan (28%), and zopiclone (26%). Cocaine and zolpidem were detected in 12% and 7% of the samples, respectively.
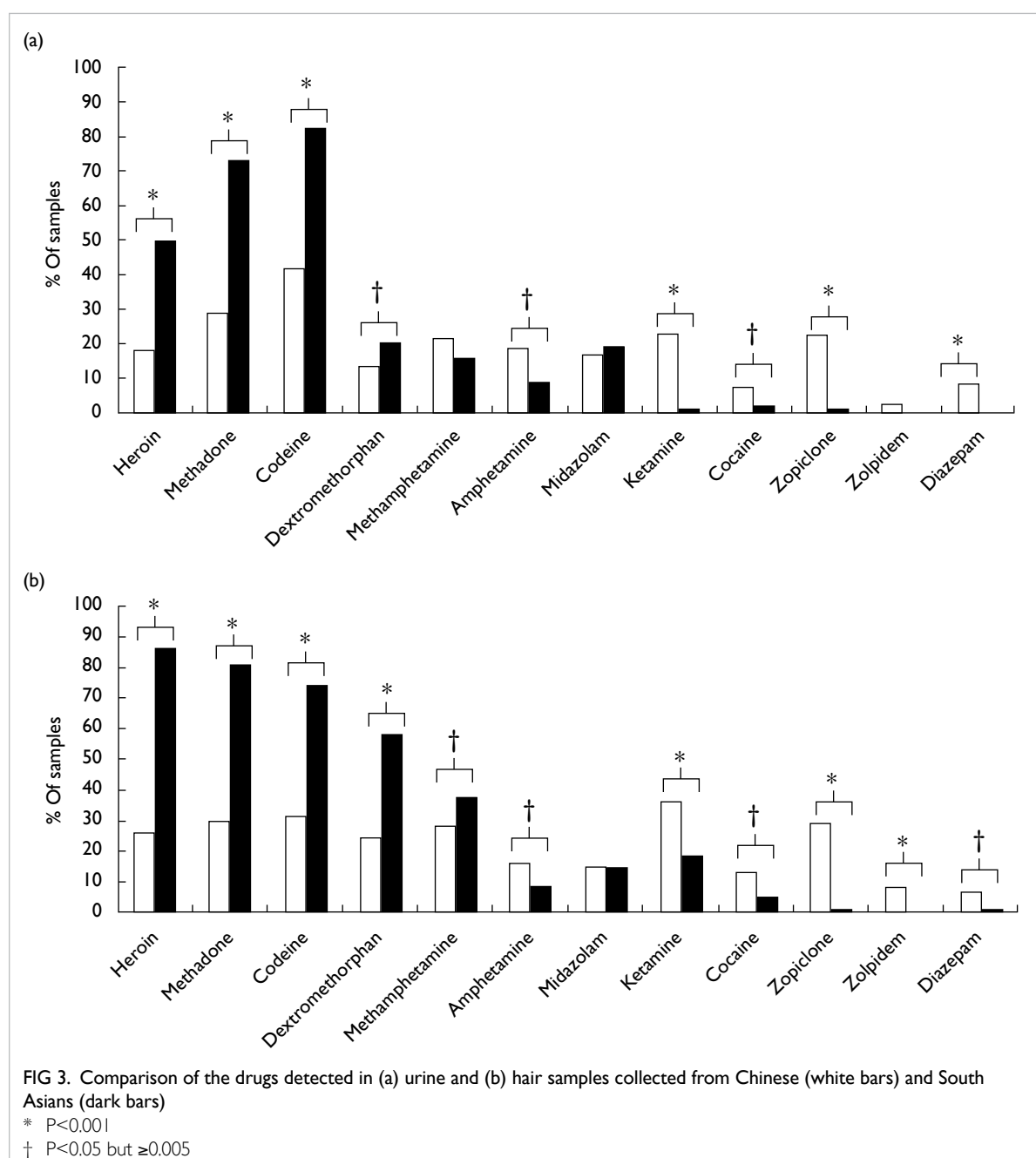
Ethnic minority

A subset of participants (n=130) were of South Asian ethnicity. These subjects donated 248 specimens in 130 episodes. Their drug use pattern was significantly different to that of Chinese. Comparison of urinalysis results revealed that South Asians had a significantly higher proportion of opiate use such as heroin, methadone, and codeine (P<0.001) as well as dextromethorphan (P<0.05; Fig 3a). On the contrary,

ketamine, zopiclone, and diazepam (P<0.001) as well as cocaine and amphetamine (P<0.05) were detected at significantly higher rates in Chinese compared with South Asians. Analysis of hair specimens showed a largely similar pattern of discrepancy between the two ethnicities (Fig 3b).

Collection site setting

The urine samples in the current study were collected from different settings: 38 samples from acute setting (A&E departments and HKPIC toxicology clinic); 885 samples from drug rehabilitation setting (substance abuse clinics, CCPSA and other rehabilitation centres); and 41 from a high-risk population (youth

FIG 3. Comparison of the drugs detected in (a) urine and (b) hair samples collected from Chinese (white bars) and South Asians (dark bars)
* P<0.001
† P<0.05 but ≥0.005

hangout). A comparison of drugs detected between the acute and rehabilitation settings revealed a significantly higher detection rate of ketamine and cocaine (P<0.001) in the former (Fig 4). Drugs such as codeine, methadone, heroin, zopiclone, and dextromethorphan were detected at higher rates in samples collected in a rehabilitation setting.
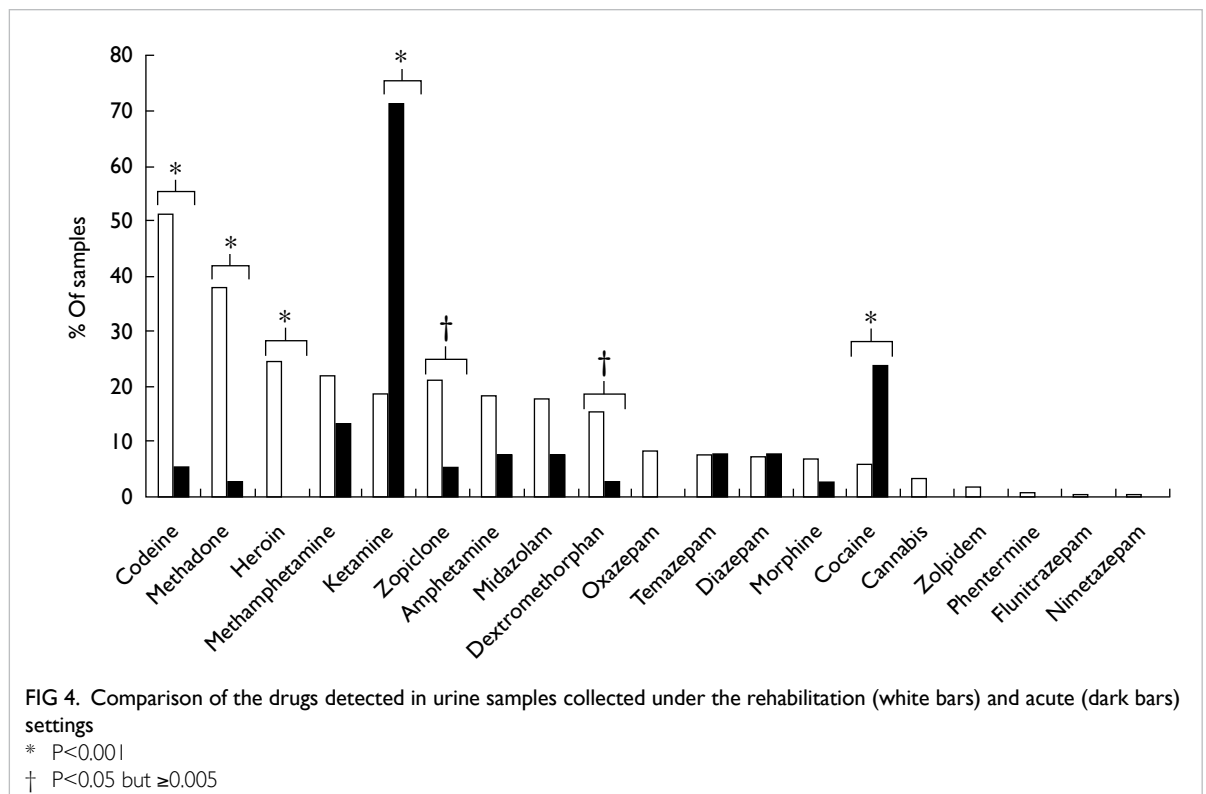
Discussion

Emerging DOA are constantly being monitored worldwide by agencies such as the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). In 2008, 13 emerging DOA were reported for the first time to EMCDDA; by 2012, 73 new drugs had been reported within a year.[1] Recent years have also seen the emergence of such designer drugs in Hong Kong, some of which have caused severe morbidity and fatalities.[4,5,7] The early identification of emerging drugs enables prompt counteractive measures in terms of their clinical and social management, and the surveillance of emerging drugs in the population is increasingly being adopted globally as a proactive approach to combat drug abuse.[13-15] In view of this, the present study was conducted to validate a locally developed LC-MS/MS method to screen for emerging DOA in the local population whilst simultaneously monitoring routine DOA. The study was conducted over a 21-month period. Multiple clinical and social service units from across the city collaborated in the study for a wider geographical coverage and

more representative results. In 2013, approximately 10 069 drug abusers were reported in Hong Kong.[16] This study population (972 subjects) was estimated to represent 9.7% of the total potential subjects. Regarding the response or participation rate, due to practical concerns and limited manpower, it was not possible for every collaborating unit to document fully the number of subjects approached or the number who refused consent.

The current results revealed the presence of three emerging drugs (PMMA, TFMPP, and methcathinone) in five specimens. This low prevalence is an expected finding due to the intrinsic nature of 'emerging' rather than 'established' drugs. Nevertheless, PMMA is a highly toxic methamphetamine derivative that has been sold on the drug market as MDMA (3,4-methylenedioxy-methamphetamine) substitute.[8] The drug has been reported to have caused up to 90 fatalities worldwide over the years, including eight fatalities in Taiwan.[8,17] In particular, PMMA-associated fatalities have also been reported recently in Hong Kong.[6]

On the other hand, TFMPP is a piperazine derivative with mild hallucinogenic effects and, when taken with another piperazine derivative benzylpiperazine (BZP), causes ecstasy-like effects.[18] Piperazine derivatives are known to cause dissociative and sympathomimetic toxicity.[19] The drug TFMPP was first reported in Hong Kong in 2010[4] and has been identified as an emerging drug in Ireland in recent years.[15]

FIG 4. Comparison of the drugs detected in urine samples collected under the rehabilitation (white bars) and acute (dark bars) settings
* P<0.001
† P<0.05 but ≥0.005

Another emerging DOA detected in the study, methcathinone, gained popularity from the 1970s to 1990s, and was recently reported as a 're-emerging' DOA in Sweden.[14] It is an amphetamine-like stimulant and is among a group of synthetic cathinone compounds, commonly known as "bath salts", that have been associated with numerous fatalities worldwide.[20] Other highly toxic cathinone derivatives include mephedrone and MDPV (methylenedioxypyrovalerone),[9,10] both of which are also covered in the analytical method but were not detected in the current study.

Of the conventional DOA, the opiates, methamphetamine, and ketamine were among the most frequently detected in this study. This is consistent with the data on reported drug abusers that was published by the local Central Registry of Drug Abuse.[21] Since this manuscript focuses on screening for emerging DOA, detailed analysis of conventional drug use such as gender and age differences was not performed. However, an interesting finding was the observation that significantly higher proportions of South Asian drug abusers used opiates such as heroin, methadone, and codeine compared with Chinese; Chinese drug abusers were much more likely to use ketamine, cocaine, zopiclone, and diazepam. This highlights the ethnic differences in drug use and indicates that alternative approaches may be required for the clinical and social management of ethnic minorities in Hong Kong.

It is of interest to note the particularly high percentage of ketamine and cocaine detected in urine samples collected at A&E departments and toxicology clinic compared with the other collection sites. This may indicate that these drugs carry a more acute and severe toxicity profile relative to the other drugs with a consequent need of hospitalisation. A previous study on drug driving in Hong Kong also reported ketamine as the most prevalent drug detected in driver casualties who presented to the A&E department.[22] Comparison of hair analysis results was not made here, since the main focus was on the difference between acute and non-acute cases; hair specimens would be less helpful since this biological matrix does not reflect recent exposure to drugs (see below for further discussion).

The present study showed a broadly similar pattern in urine and hair matrices in terms of the conventional DOA detected. Cocaine, dextromethorphan, and zolpidem were detected at higher rates in hair compared with urine, and may indicate the relatively high deposition efficiency of these drugs in hair matrix. It should be noted, however, that the metabolites of zolpidem were not included in the current assay, and may decrease its sensitivity for detection in urine. Urine and hair specimens have different 'detection windows', that is, they reflect different time frames of drug intake.

Detection in urine indicates recent intake (within hours/days); thus this matrix is useful for the management of acute toxicity and drug overdose. The detection window of hair is much longer (weeks/months), enabling this matrix to be used for monitoring long-term drug use or abstinence.

When interpreting the results of the current study, it should be noted that some drugs may have been taken for therapeutic reasons, for example codeine, methadone, phentermine, or the tranquilizers/benzodiazepines. It was not possible in this study to differentiate medical use from abuse. It should also be noted that some drugs may be present as metabolites of others, for example temazepam and oxazepam (both of which are diazepam metabolites) and the emerging drug mCPP (metabolite of the antidepressant trazodone). Morphine is also the metabolite of codeine and heroin; it was only reported here as a drug in the absence of either codeine or heroin in the same sample.

Effective control of novel drugs depends on their early identification. A number of means to monitor emerging DOA have been proposed, such as conducting population surveys, analysing online test purchases, or wastewater analysis.[3] Population surveys suffer the potential drawback of obtaining inaccurate data, since the actual identity of the drugs may differ from the claimed ingredients, for example, BZP being sold as 'MDMA' tablets.[23] Analysing drug items purchased online is a costly approach due to the vast number of products available. Wastewater analysis may be used for monitoring conventional DOA, but the approach may not be easily adapted to the surveillance of emerging drugs due to the anticipated minute levels (ng/L range) in wastewater.[24] All the above approaches require a considerable amount of financial and manpower resources. We propose the integration of emerging DOA surveillance into the routine drug monitoring of patients using the established analytical method. This surveillance approach is accurate, readily attainable, and is also achieved with minimal extra cost and effort since it is a convenient by-product of the routine drug monitoring of patients. Additionally, its applicability in A&E department patients allows the early identification of highly toxic novel drugs.

The proposed analytical method is LC-MS/MS–based, and offers several advantages over traditional DOA testing by immunoassay methods. First, development of an immunoassay is a lengthy process (in terms of years) involving the generation of antibodies. Immunoassay analysis also depends solely on the availability of commercial kits. These features do not favour early detection of new compounds given the protean nature of emerging drugs. In contrast, LC-MS/MS–based methods are much more versatile, permitting in-house enhancement of the method to allow detection of

new compounds as soon as they enter the market. Second, although immunoassay methods require minimal capital investment, their running costs are high due to the generation of antibodies. On the other hand, LC-MS/MS methods require a high initial investment in analysers, but the running cost is lower in the long term as the reagents involved are relatively inexpensive. Lastly, unlike immunoassay methods that are only preliminary in nature and require further confirmatory testing, mass spectrometry analysis is already confirmatory with accurate and definitive results.

In addition to laboratory analysis, the emerging DOA surveillance team requires the expertise of medical doctors to keep a close watch on emerging drugs on the market, especially those with high clinical toxicity. Based on this 'toxico-intelligence', scientists should then enhance the analytical method to include such emerging substances. Hence, the effective control of emerging drugs will require a team of trained medical doctors and scientists, as well as versatile technology that enables the continual expansion of analytical coverage. In view of the resource requirements, specialised toxicology centres may be better suited for the purpose.

The present study has proven the concept that a locally developed analytical method is a valid tool to monitor emerging DOA whilst simultaneously performing regular DOA testing in patients. Implementation of the method in the routine drug monitoring of abusers will enable the continued and proactive surveillance of novel drugs in the population with minimal extra cost and effort. This surveillance gathers important information so that society can be prepared in terms of legislation, as well as social and clinical management of these potentially dangerous drugs. Further expansion of the analytical coverage will help keep abreast of the rapid and constant change in the designer drug scene.

Acknowledgements

Declaration

No conflicts of interests were declared by authors.

Appendix

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