Highlights

1) New tool to monitor illicit substances used by injecting drug users in order to adapt prevention and harm reduction messages.
2) Assess if the drugs found in syringes are those injection drug users' (IDUs) think they use.
3) Compare adulterants found in syringe content and those found within drug seizures made by the police.

Abstract

Background: For the first time in Switzerland, an analysis of residual contents from used syringes collected from low threshold facilities was performed. This preliminary study is part of a wider project aiming to understand patterns of injecting drug use over time. Methods: Among the 100,000 syringes exchanged annually by the ABS foundation (Accueil Bas Seuil), 113 were collected following a purposive sampling method and analysed by gas chromatography coupled with mass spectrometry (GC–MS). Results: Four syringes (4% of the sample population) contained no substances take into consideration the limit of the method. Cocaine was the most commonly observed compound and was detected in 77 syringes (68%), whilst users reported syringes with cocaine among those analysed in this study. Heroin was detected in 49 syringes (43%) and reported by 53 users returning syringes; midazolam was detected in 31 syringes (27%) and reported as the medicine Dormicum1 in 22 occurrences. No new or unusual illicit drug was detected in the sample. Conclusion: The results show the presence of cocaine in more than half of the sample, an absence of new or unusual illicit drugs, as well as very few traces of methadone, which suggests that this substitution drug is rarely injected. This preliminary study also demonstrates the potential of this developed methodology for monitoring purposes. An ongoing and more systematic approach could allow to detect modifications in drug use patterns among the target population as well as the appearance of new and hazardous substances. Such systematic and timely results could allow an adaptation of harm reduction interventions.

Keywords: illicit drugs, needle exchange programs, injection drug users (IDUs), low threshold facilities (LTFs), GC-MS, harm reduction.

1. Introduction

The injection of illicit drugs is an important problem in Switzerland which culminated with the open drug scene in the 1980s and 1990s [1]. Since 1994, the Swiss Confederation has set up a drug policy based on "four pillars" [2]: prevention, treatment, harm reduction and repression (law enforcement). Low threshold facilities (LTFs) can be considered as the frontline of harm reduction programs [3] that the injection drug users (IDUs) can visit anonymously. They propose, among other things, needle exchange programs which were developed from the 1980s on to reduce the number of reused and shared syringes by IDUs for tackling the HIV/AIDS epidemic [4]. For over 20 years, the Institute of Social and Preventive Medicine (IUMSP) has been monitoring the number of syringes distributed in Switzerland and conducting periodic surveys in LTF structures to gather behavioral surveillance data from IDUs [1]. These data rely on the statements of the users and can be biased by the questionnaire or the responses provided. To have an objective picture of substances that are injected by IDUs, it has been proposed, for the first time in Switzerland, to analyse the residual contents of used syringes collected from two LTFs. In parallel, IDUs were to be questioned about the substances last used with the syringe. The results of the analysis were compared with the answers of the IDUs for evaluating their knowledge about what they are consuming. A study about residual content of used syringes had already been performed in Paris, where heroin (42%) was the most commonly observed substance followed by cocaine (41%), bupre-norphine (29%) and 4-methylethylcathinone (23%) [5]. The presence of 4-methylethylcathinone was surprising and allowed to assess and improve existing harm reduction strategies. The results of the present study could also be combined with other sources of data like the analysis of seizures made by the police [6] to compare, for example, the types of cutting agent involved. Cutting agents are compounds which are frequently used to increase the quantities of heroin and cocaine at various levels on the drug market. Two types of cutting agents exist, adulterants and diluents. The adulterants are pharmacologically active compounds whereas diluents are pharmacologically inactive compounds, such as sugars (glucose, lactose . . .) [7]. Some adulterants are known to be dangerous to IDUs' health. Their detection could allow one to adapt harm reduction message which could then lead to a better understanding of the illicit drug market.

2. Methodology

2.1 Sampling

Two major syringe exchange facilities from the ABS foundation in Lausanne, called Distribus (mobile) and Passage (stationary), were selected for this study. The syringes were collected during two weeks in March 2015. During this period, waste disposal boxes were placed on LTF, Distribus and Passage for the study. When an IDU brought multiple syringes, only one of them was placed in the study box, in order to maximize the number of participants and gathering the most reliable illicit drug use patterns. Each syringe providing IDU was asked to fill in a questionnaire with four questions about the last injection (What was the last product you injected? What was the injected dose? Did you purchase this product in Lausanne? Have you ever bought drugs on Internet?). The sampled syringes were kept at _20 _C to avoid degradation of compounds.

2.2 Chemicals and material

Methanol (MeOH) and acetic anhydride were purchased from Merck, acetonitrile, ethyl acetate from Sigma–Aldrich, N-methyl- N-(trimethylsilyl)trifluoroacetamide (MSTFA) from Macherey Negel and anhydrous pyridine from VWR prolabo. New disposable propylene syringes of 1 mL were purchased from Infochroma AG, and wheel filters (Nylon, 0.45 mm) from Titan. 300 mL vials with Silicone/PTFE caps were purchased from Agilent. Clean Pyrex test tubes were used.

2.3 Sample preparation

The sampled syringe was prepared by pumping 1 mL of MeOH five times consecutively. The MeOH mixed with the diluted compounds was then collected in a clean test tube, which was then vortexed for 1 min. This solution was equally divided into three test tubes. The first test tube was filtered into a vial with an insert and directly injected into a GC–MS ("Non derivatised sample") [5]. The second sample was first evaporated to dryness before silylation by adding 100 mL of a solution of anhydride acetic anhydrous and pyridine (3:2). This solution was heated at 80 _C in an oven for 30 min and evaporated to dryness. The residues were diluted with a 100 mL solution of ethyl acetate, filtered into a vial and injected into a GC–MS. The third sample was also evaporated to dryness before adding 100 mL of MSTFA. This solution was heated at 80 _C in an oven for 30 min and again evaporated to dryness. The residues present were diluted with 100 mL of a solution of MSTFA and acetonitrile (1:1), filtered into a vial and injected into a GC–MS. The sample preparation method is summarised in Fig. 1.

2.4 Analytical method

An Agilent gas chromatograph (6890N Network) interfaced with an Agilent mass selective detector (5973 Network) was used to perform the analyses. Separation was accomplished on a DB-XLB capillary column (30 m length, 0.25 mm in diameter and 0.25 mm film thickness). Injections were carried out in splitless mode using a general purpose split/splitless liner (Agilent Technologies 208122-10). One microliter of each sample was injected with Helium as carrier gas (constant flow mode, 1.2 mL/min). The temperature program starting at 70 _C was held for 1 min, then increased to 200 _C (at 15 _C/min) and to 300 _C (at 10 _C/min). At that temperature, the program was held for 7 min and then increased once more to 320 _C (30 _C/min), at which it was finally held for 3.67 min. The total run time was 31 min. Temperatures applied were 270 _C for the injector, 230 _C for the ion source and 150 _C for the quadrupole. The MS Data was acquired in full scan mode (10–400 m/z mass range for the first 7 min then 30–550 m/z mass range), with a sampling rate of 2 scans/s.

2.5 Software/data pre-treatment

The data was analyzed using MSD Enhanced ChemStation (Agilent Technologies) and compound characterization was performed using mass spectra computerized databases, such as NIST Version 2014 (National Institute of Standards and Technology), Wiley Edition 10, MPW Version 2011 (Maurer/Pfleger/Weber, Drugs/Poisons/Pesticides/Pollutants & Metabolites), DD Version 2014 (Drug Design & Discovery) and custom databases from the University Institutes of Legal Medicine of the Faculty of Medicine of Geneva (CURML). Compound characterisation was performed by a single macro in MSD Enhanced ChemStation in order to identify all the compounds present in the syringes using a screening method. The results were stored and handled in an Excel worksheet. The results of the analyses of the residues present in the used syringes were then compared to the

IDUs' answers in the first question which was "What was the last product that you injected". x2 tests were performed using the software R (ISBN: 3-900051-07- 0. R foundation for statistical computing, Vienne, 2015).

2.6 Comparison of cutting agent

Within this study, only adulterants were studied since diluents can originate from blood residues present in the syringes, which also contain sugars. For the interpretation, adulterant results were considered only when one psychoactive substance was present. Therefore this result was compared to the analysis of seizures made by the police [6].

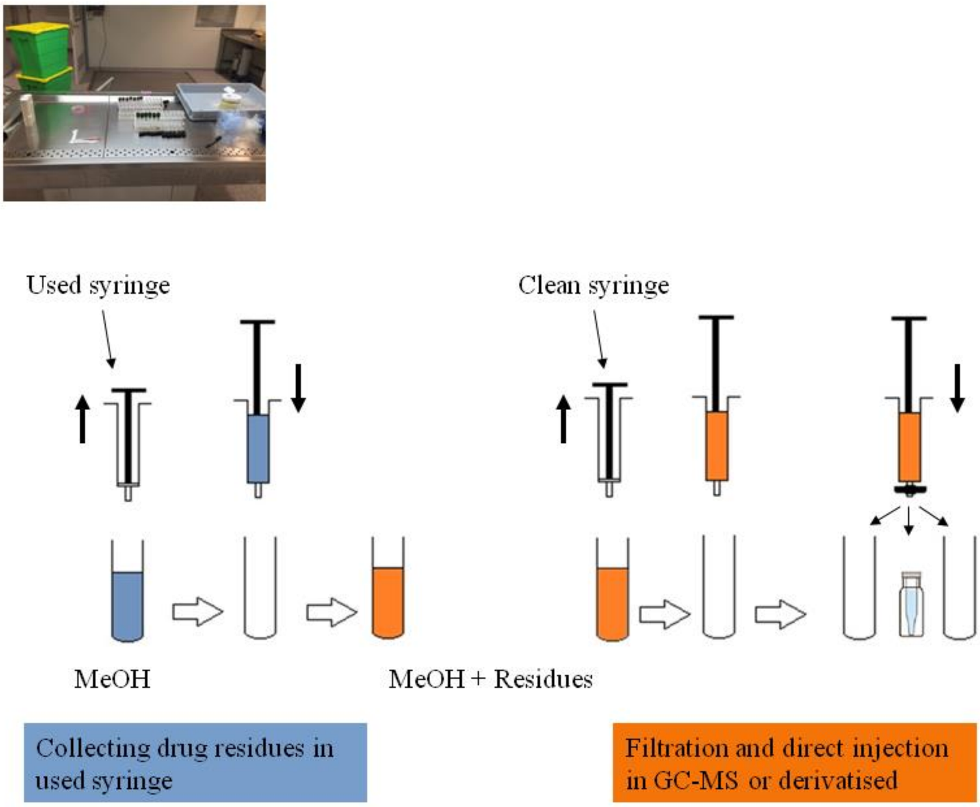

Figure 1 : Sample preparation method

3. Result

3.1 Participation rate and sample size

During this study, 111 contacts with IDUs were made at the Distribus. For 97 of these contacts, the IDU agreed to provide their used syringes for this study. Out of these 97 participants, 94 provided answers to the questionnaire. At the Passage, 22 contacts provided a used syringe. Of the 22 participants, 3 did not respond to the questionnaire.

A total of 113 syringe-questionnaire couples were considered (Table 1).

	Number of days	Number of contacts	Number of refuse	Number of questionnaires and syringe	Number of syringe without questionnaires
Distribus	9	111	14	94 (84%)	3
Passage	10	22	0	19 (86%)	3
Total		133	14	113 (85%)	6

Table 1: Number of samples per site

3.2 Illicit drugs detected and reported

One or more active substances were detected in 109 syringes from 113. In detail, one substance was detected in 64 syringes (57%), two substances in 32 syringes (28%) and three substances in 13 syringes (12%). No illicit drugs were detected in 4 syringes (4%).

Cocaine was the most quoted drug in the IDUs' questionnaire and also the most detected compound in this study. It was detected in 77 (68%) syringes, whilst participating IDUs reported it 73 times (65%) for the question about the last product injected.

Heroin was the second most used substance identified during this study in 49 (43%) syringes, whilst it was reported in 53 cases (47%). In third place, midazolam (a benzodiazepine used for reducing anxiety or anesthesia before certain medical procedures or surgery [8]) was detected in 31 syringes (27%), and corresponds to the announced prescribed drug Dormicum® (containing the active substance midazolam) in 22 IDU questionnaires (19%).

Finally, methadone was detected in three syringes, Δ-9-tetrahydrocannabinol (the main active molecule of cannabis) was detected in two syringes. Flurazepam (a benzodiazepine prescribed for short-term treatment of insomnia), zolpidem (a drug prescribed for insomnia) and methamphetamine were each detected in one syringe (Figure 2).

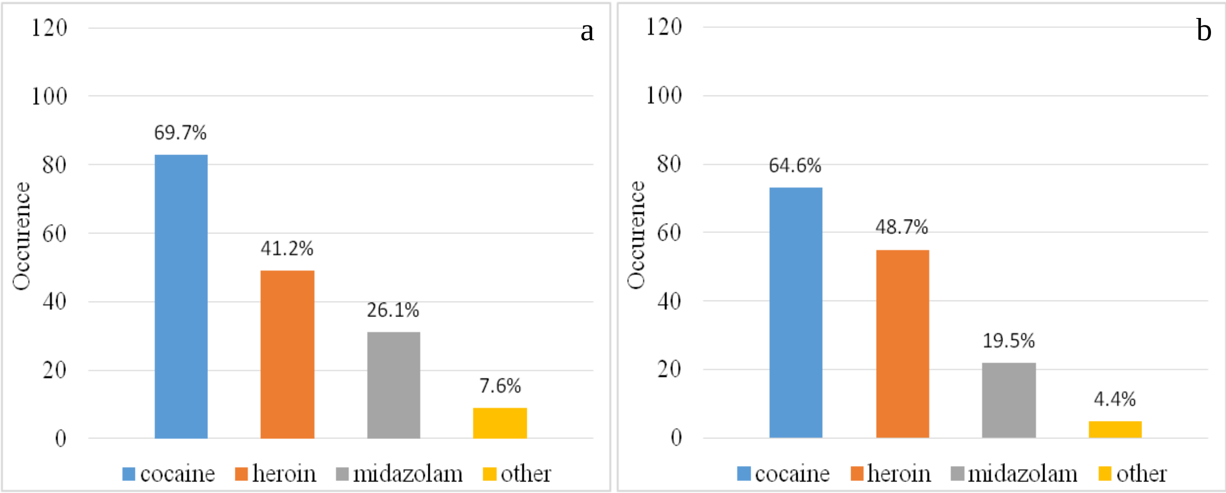

Figure 2: Occurrence and frequency (expressed as a percentage of the total number of specimens above each histogram) of the substances of abuse detected by GC-MS analysis (a) and reported by the UDIs (b)

3.3 Cutting agents

Three different groups were created according to the main drug detected. The first group was composed of syringes containing only cocaine (43 syringes), the second of those containing only heroin or midazolam and heroin (29 syringes) and the third group containing all other syringes (41) which consists of syringes contained heroin and cocaine, midazolam only and the empty syringe. Mixtures of drugs were not considered. However, no other adulterants were detected in the third group.

Cocaine

Among syringes containing only cocaine, phenacetin and caffeine were each detected in 32 (74%) samples, levamisole in 23 (53%), lidocaine in 14 (33%), hydroxyzine in six (14%), paracetamol in two (5%) and procaine in one (2%).

In three syringes (7%) containing cocaine, no adulterants were detected. One respective two adulterants were each detected in 6 syringes (14%), three adulterants in 18 syringes (42%), four adulterants in nine syringes (21%) and all adulterants were detected in one single syringe (2%). The most frequently detected combination was phenacetin with caffeine and levamisole, detected in eight syringes (19%) followed by the combination of phenacetine, lidocaine and caffeine in seven syringes (16%).

The frequency of each adulterant detected in the syringes which contained cocaine was compared to the frequencies of adulterants obtained from cocaine samples analysed in 2014 by the School of Criminal Sciences (ESC) in Lausanne [6] (Figure 4).

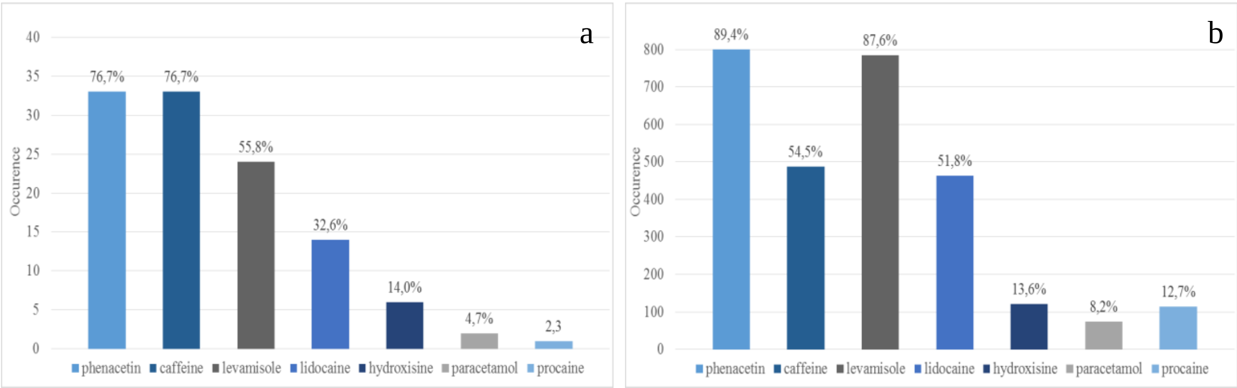

Figure 4: Occurrence and frequency (expressed as a percentage of the total number of specimens above each histogram) of adulterants detected in the syringes where cocaine was detected (a) and adulterants detected in cocaine street samples (b) (adapted from [6]).

The same types of adulterants were detected in these two set of data, however caffeine had a higher occurrence in this project and levamisole was most detected in cocaine seized by the police.

Heroin

In the heroin group, caffeine was detected in 28 syringes (97%), paracetamol in 27 (93%), levamisole in three (10%), griseofulvine in two (7%) and phenacetin (3%) in one.

The frequencies of each adulterant detected in syringes containing heroin or heroin/midazolam was compared to frequencies obtained for heroin samples seized by the police and analysed by the School of Criminal Sciences (Figure 5).

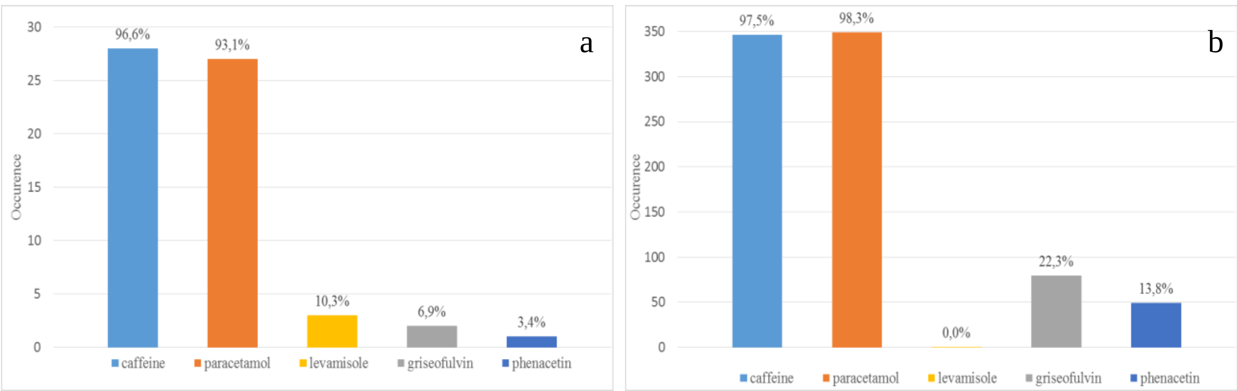

Figure 5: Occurrence and frequency (expressed as a percentage of the total number of specimens above each histogram) of the adulterants detected in the used syringes where heroin was detected (a) and adulterants detected in heroin street samples (b) (adapted from [6]).

Frequencies of caffeine and paracetamol were almost the same in this syringe group as well as the frequencies resulting from the heroin seizure.

4. Discussion

4.1 Participation

Among those people exchanging syringes in the two facilities, 89% accepted to participate in this study. Although authorization was granted for this study, only a small number refused to participate and many IDUs were even interested in knowing the contents of their syringes.

4.2 Analytical Strategy

For this first study, the analytical strategy was chosen in order to detect a large variety of psychoactive substances which could be used by IDUs. For this reason, a screening approach based on the analysis of the underivatised sample by the GC-MS was used. In fact, several mass spectra libraries including new psychoactive substances and illicit drugs are available for substance characterisation. In order to maximize, the number of substances that could be identified by GC-MS sample were also analysed after derivatisation. This procedure permits to reduce polarity and enhance volatility, increasing thermal stability and enabling a GC-MS analysis of a maximum of compounds [9].

The results presented in this study are a compilation of the three sample preparations. On the one hand, several substances detected in underivatised samples were confirmed by identification of each substance in the derivatised samples. On the other hand, some substances such as sugar and paracetamol were characterised on derivative samples only. The results after acetylating supplied no additional information compared to those obtained after sylilation, however peak resolution on the chromatograms was better after sylilation. For this reason, further studies using this strategy could be performed using direct injection and sylilation analysis.

This approach is qualitative. Due to the quality and heterogeneity of samples a quantitative analysis is not possible. However, differences in the intensity of the signal were observed, suggesting different amounts of substances in the different samples. Different reasons could explained these differences like the purity of the illicit drugs, the dilution of the injected materials, a contamination during the preparation of the injection or the reuse of syringes.

4.3 Illicit drugs announced versus illicit drugs detected

General

Based on the distribution of active substances, the difference between the illicit drugs announced during the survey and those detected by GC-MS was not statistically significant ($\chi 2$ test, p-value = 0.493 > 0.05) for the four groups, cocaine, heroin, midazolam (Dormicum®) and other. Moreover, no significant differences was observed between syringes collected during the different days of week ($\chi 2$ test, p-value = 0.642 > 0.05).

Cocaine

The most commonly observed compound measured during the sampling campaign was cocaine.

A good agreement was observed between the number of syringes for which IDUs announced cocaine injection (73 answered in the first question) and the number of syringes in which cocaine was detected (77 syringes).

In Europe, the use of cocaine by polytoxicomane has increased since 2009. This increase could reflect the use of cocaine in primary drugs as an opiate replacement as well as the use of cocaine among primary heroin users [10]. In the present study, cocaine frequency was higher than heroin frequency. Moreover, heroin and cocaine were detected in the same syringe which is in accordance with these trends.

In Switzerland since 2009, cocaine seizures have slightly increased (556 kg in 2009, 588 kg in 2015)., which is consistent with the increase of cocaine consumption [11,12].

Heroin

Heroin was the second most used substance in the sampled population (41% detected and 49% reported). When morphine was detected in presence of 6-monoacetylmorphine and/or diacetylmorphine (also called heroin), the result was expressed like heroin. In Switzerland, distribution of therapeutic heroin is only realised in the German part, therefore this practice doesn't exist in Lausanne [13]. For this reason it is supposed that when heroin was detected, it was not due to an opiate substitution therapy.

Since 2009, heroin seizures have decreased in Switzerland (200 kg in 2009, 151 kg in 2015), which is consistent with opiates replacement [11,12].

Midazolam

Midazolam is the third most occurring substance. It was detected in 31 syringes (26% of the sample population). Midazolam is an active compound found in medicine used for opiate addiction treatment, such as Dormicum®, beside substances use for opioid substitution treatment, such as methadone or buprenorphine. The Dormicum® is answered by 22 IDUs to be the last injected substance (19%). One can observe that IDUs did not use injectable midazolam solution but that they used a preparation based on Dormicum® pills for injection.

75% of the syringes in which midazolam was detected also contained heroin and 50% of the syringes where heroin was detected contained midazolam. Statements provided by the IDUs indicate that Dormicum® is sometimes used to increase the effect of heroin.

Previous studies have already shown that benzodiazepine was used to prolong the intensity and duration of the effect of opioid [14]. In Europe, the prevalence of benzodiazepine misuse with opioid substitution treatment was evaluated from 45% in France to 70% in Germany [15]. This practice was also described on heroin users which injected benzodiazepine with or without heroin [16–20]. In Australian's studies [21], users inject preferably temazepam, while in the present study only the use of midazolam was highlighted.

It's important to underline that simultaneous use of opiate with benzodiazepines and other central nervous system depressants, increase the risk of fatal overdose through respiratory depression [22].

Others

Only 2% of syringes contained methadone, a widely used opioid substitution treatment in Lausanne. This suggests that methadone is not injected by the sampled population, which could show the efficiency of prevention messages diffused by the public health sector [23].

No compounds were detected in 4 syringes (4%). It was assumed that these syringes had been cleaned or rinsed out, a process mentioned by one of the IDUs participating in the study. These syringes could have contained other psychoactive substances which were not detected within the other syringes collected..

Detection of several substances

The presence of several active substances detected in used syringes can be explained by various factors, such as the reuse or the sharing of syringes, simultaneous consumption of several compounds or contamination from materiel used before injection, or from the IDUs' blood due to a previous consumption of drugs. Indeed, 62% of the used syringes contained blood residues.

4.4 Cutting agents

Cocaine

All residual substances detected in the syringes are already known adulterants use to cut cocaine specimen [7]. Their relative frequencies observed in our sample of syringes reflect their presence in seized street samples of cocaine [6]. The caffeine frequencies in the present work could be higher than what the police seized because of blood interference as already discussed.

The detection of three different adulterants was detected more frequently on syringe contained only cocaine. Indeed 18 syringes containing only cocaine also contained three adulterants. The most detected combination was phenacetin with caffeine and levamisole (8 syringes 19%) [7].

Heroin

For more than 20 years, the mixture paracetamol and caffeine is used as a main adulterating mixture to cut heroin [7]. It is also these two substances that have been observed in the analysed syringes. In contrast to cocaine, heroin adulterants are almost exclusively identified as paracetamol and caffeine. Only 6 syringes contained other substances. The mixture paracetamol caffeine was only detected in 80% (23) of the syringes according to the limit of our method. This observation was already mentioned in precedent studies [6,7].

4.5 Data triangulation

Survey conducted in the Canton of Vaud

A precedent study was undertaken in 2012 in the Canton of Vaud. This study consists of a questionnaire among users of LTFs [4]. On this latter, all users of LTFs were interviewed, IDU and drug users consuming by other ways (inhalation route, sniff ...). The users questioned said they consumed primarily cocaine intravenously (37.5%), followed by heroin (30.2%). In the present work, only IDUs were considered which explains the higher rate. These observations support the hypothesis that no significant change in IDU consumption during the last three years occured

New Psychoactive Substances (NPS)

NPS are defined by the UNODC as "substances of abuse, either in a pure form or a preparation, that are not controlled by the 1961 Single Convention on Narcotics Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat." The EMCDDAs early warning system shows an important increase of this type of substances since 2010. NPS have become a global phenomenon and all regions of the world have detected them [12]. A study of residual content in used syringes from automatic injection kit dispensers in Paris detected a new psychoactive substance (NPS) – 4-methylethcathinone – in 23% of the syringes between the summer and winter of 2012 [5].

Within our study in Lausanne, no NPS were detected. This result is consistent with the low number of police records in Lausanne. Two hypotheses can be made to explain this finding. The first is that cocaine and heroin are readily available in Lausanne and that drug users do not need to turn towards new psychoactive substances whose effects are not well known.

The second hypothesis is that the absence of NPS is due to our sampling approach. Our targeted population was users of LTFs, people who may not be very likely to consume NPS [13]. Study participants also reported not buying drugs on the Internet, this being the place where most NPS are offered [20,24].

5. Conclusion

For the first time in Switzerland, an analysis of the residual contents of used syringes collected from low threshold facilities was performed. This study is part of a wider project aiming at understanding the illicit drug market and its evolution over time. Analyses of the content of used syringes inform about the actual composition of consumed illicit drugs among IDUs and thus provide opportunities to adapt harm reduction messages and interventions.

This study has shown that cocaine was the most commonly detected drug in the sampled syringes following by heroin. The third most consumed substance was midazolam, the active substance in Dormicum®. Only 2% of the sampled syringes contained opioids used in substitution treatment like methadone. No NPS were detected during this study.

The analysis of used syringes also allowed to identify adulterants. The samples in which cocaine was detected mainly contained phenacetin, caffeine and levamisole, in the same proportions as those observed among cocaine seizures analysed by the the School of Criminal Sciences (ESC) Lausanne. For specimens containing heroin, the main adulterants detected were paracetamol and caffeine. These observations are in agreement with current knowledge about cutting practices [7].

The analysis of the content in used syringes and surveys among IDUs provide a new insight into the composition of drugs that are used intravenously. A systematic analysis of used syringes offers a new tool to detect modification in patterns of drug consumption among a specific target population as well as to detect new substances that are injected. Such systematic and timely results could help to adapt harm reduction policies. An ongoing and more systematic approach could allow detections of modifications in drug use patterns among a larger population.

Reference

[1] F. Dubois-Arber, H. Balthasar, F. Zobel, S. Arnaud, S. Samitca, A. Jeannin, D. Schnoz, J.-P. Gervasoni, Trends in drug consumption and risk of transmission of HIV and hepatitis C virus among injecting drug users in Switzerland, 1993-2006, Euro Surveill. 13(21) (2008) 717–727.

[2] F. Zobel, R. Thomas, S. Arnaud, E. De Preux, T. Ramstein, B. Spencer, A. Jeannin, F. Dubois-Arber, Global Evaluation of the Confederation's Measures to Reduce Drug-Related Problems (ProMeDro) : Fourth Synthesis Report 1999-2002, Lausanne Inst. Univ. Médecine Soc. Préventive. (2003).

[3] J.-P. Gervasoni, H. Balthasar, T. Huissoud, A. Jeannin, F. Dubois-Arber, A high proportion of users of low-threshold facilities with needle exchange programmes in Switzerland are currently on methadone treatment: Implications for new approaches in harm reduction and care, Int J Drug Policy. 23(1) (2012) 33–39. doi:10.1016/j.drugpo.2011.05.015.

[4] S. Lociciro, S. Arnaud, G. Füglistaler, F. Dubois-Arber, J.-P. Gervasoni, Résultats de l'enquête 2011 auprès des usagers des structures à bas-seuil en Suisse, Raison Santé. 199a (2012) 2–64.

[5] T. Néfau, E. Charpentier, N. Elyasmino, C. Duplessy-Garson, Y. Levi, S. Karolak, Drug analysis of residual content of used syringes: A new approach for improving knowledge of injected drugs and drug user practices, Int. J. Drug Policy. 26(4) (2015) 412–419. doi:10.1016/j.drugpo.2014.09.010.

[6] J. Broséus, N. Gentile, F. Bonadio Pont, J.M. Garcia Gongora, L. Gasté, P. Esseiva, Qualitative, quantitative and temporal study of cutting agents for cocaine and heroin over 9 years, Forensic Sci. Int. 257 (2015) 307–313. doi:10.1016/j.forsciint.2015.09.014.

[7] J. Broséus, N. Gentile, P. Esseiva, The cutting of cocaine and heroin: A critical review, Forensic Sci. Int. 262 (2016) 73–83. doi:10.1016/j.forsciint.2016.02.033.

[8] J. Donzé, Brevimed : bréviaire clinique des médicaments - revmed, Ed. Médecine Hygiène. (2011). http://www.revmed.ch/rms/2011/RMS-296/Brevimed-breviaire-clinique-des-medicaments (accessed June 9, 2016).

[9] J. Drozd, Chemical Derivatization in Gas Chromatography, Elsevier, 1986.

[10] EMCDDA, Polydrug use: patterns and responses, (2009). http://www.emcdda.europa.eu/system/files/publications/534/EMCDDA_SI09_polydrug_use_187893.pdf (accessed June 20, 2016).

[11] Section Criminalité et droit pénal, Statistique policière de la criminalité (SPC). Rapport annuel 2009, (2009).

[12] Section Criminalité et droit pénal, Statistique policière de la criminalité (SPC). Rapport annuel 2015, (2015).

[13] D. Hiltebrand, M. Dickson-Spillmann, H. Bolliger, M. Schaub, Office fédéral de la santé publique - Traitement avec prescription de diacétylmorphine (héroïne), (n.d.). http://www.bag.admin.ch/themen/drogen/00042/00629/00799/index.html?lang=fr (accessed June 21, 2016).

[14] A. Casati, R. Sedefov, T. Pfeiffer-Gerschel, Misuse of Medicines in the European Union: A Systematic Review of the Literature, Eur. Addict. Res. 18 (2012) 228–245. doi:10.1159/000337028.

[15] EMCDDA, The misuse of benzodiazepines among high-risk opioid users in Europe, (2015). http://www.emcdda.europa.eu/system/files/publications/963/TDAT14001ENN.pdf (accessed June 9, 2016).

[16] S. Darke, J. Ross, M. Teesson, M. Lynskey, Health service utilization and benzodiazepine use among heroin users: findings from the Australian Treatment Outcome Study (ATOS), Addiction. 98 (2003) 1129–1135. doi:10.1046/j.1360-0443.2003.00430.x.

[17] M. Backmund, K. Meyer, K. Meyer, M. Soyka, J. Reimer, C.G. Schütz, Co-Consumption of Benzodiazepines in Heroin Users, Methadone-Substituted and Codeine-Substituted Patients, J. Addict. Dis. 24 (2006) 17–29. doi:10.1300/J069v24n04_02.

[18] J. Ross, S. Darke, W. Hall, Benzodiazepine use among heroin users in Sydney: patterns of use, availability and procurement, Drug Alcohol Rev. 15 (1996) 237–243. doi:10.1080/09595239600185971.

[19] M. Vogel, B. Knöpfli, O. Schmid, M. Prica, J. Strasser, L. Prieto, G.A. Wiesbeck, K.M. Dürsteler-MacFarland, Treatment or “high”: Benzodiazepine use in patients on injectable heroin or oral opioids, Addict. Behav. 38(14) (2013) 2477–2484. doi:10.1016/j.addbeh.2013.05.008.
[20] UNODC, World Drug Report 2014, U. N. Publ. 14(7) (2014). http://www.unodc.org/documents/wdr2014/World_Drug_Report_2014_web.pdf (accessed June 9, 2016).
[21] C.L. Fry, R.B. Bruno, Recent trends in benzodiazepine use by injecting drug users in Victoria and Tasmania, Drug Alcohol Rev. 21 (2002) 363–367. doi:10.1080/0959523021000023225.
[22] M. Warner-Smith, S. Darke, M. Lynskey, W. Hall, Heroin overdose: causes and consequences, Addict. Abingdon Engl. 96 (2001) 1113–1125. doi:10.1080/09652140120060716.
[23] T. Huissoud, C. Gumy, J.-P. Gervasoni, F. Dubois-Arber, Analyse de la statistique des traitements à la méthadone dans le canton de Vaud. Période 2001-2008., Raisons Santé. 175 (2010). https://www.iumsp.ch/Publications/pdf/rds175_fr.pdf (accessed June 17, 2016).
[24] EMCDDA, European Drug Report 2014: Trends and developments, (2014). http://www.emcdda.europa.eu/publications/edr/trends-developments/2014 (accessed June 9, 2016).