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Short report

Portable gas chromatography–mass spectrometry in drug checking: Detection of carfentanil and etizolam in expected opioid samples

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ABSTRACT

Background: There has been a recent increase in adulteration of opioids with low concentration actives such as fentanyl analogues and benzodiazepines. As drug checking projects using vibrational spectroscopy continue to seek confirmatory lab-based testing, the concern and reality of missing these potentially harmful substances in point-of-care testing is prevalent.

Methods: A portable GC-MS was used to analyze select opioid samples acquired at a drug checking service in Victoria, Canada (n = 59). Certified reference standards of several fentanyl analogues and benzodiazepines were measured to guide targeted analysis of these samples. Results were compared with those obtained using a lab-based paper spray mass spectrometer.

Results: Portable GC-MS was able to identify 62% of samples containing carfentanil and 36% of samples containing etizolam. In the case of etizolam, the success rate was higher for more potent samples: 78% of etizolam-containing samples were identified when the etizolam concentration was above 3% by weight. In comparison, infrared spectroscopy was able to detect etizolam in only 9% of the etizolam-containing samples, and is not sensitive enough to detect carfentanil at relevant concentrations.

Conclusions: Portable GC-MS has potential in identifying low concentration substances in a point-of-care setting, without relying on subsequent off-site confirmatory testing.

Introduction

Drug checking is increasingly being adopted within public health responses to the North America-wide opioid overdose crisis (Laing et al., 2018). Fentanyl test strips have become mainstream harm reduction responses which are relatively low cost, simple to use, provide rapid results and have high sensitivity (Peiper et al., 2019). At the same time fentanyl test strips have significant limitations as they; only detect a range of fentanyl analogues and not other possibly active ingredients or cuts and buffs, do not report on the amount of the fentanyl (or analogue), and, do not distinguish between fentanyl analogues such as carfentanil (Green et al., 2020; Park et al., 2021; Weicker et al., 2020). Fentanyl strip tests are becoming less relevant for testing opioids in localities where fentanyl is assumed and has essentially replaced heroin as an option (Green et al., 2020; Long et al., 2020; Park et al., 2021). Recognizing this, analytical instruments such as spectrometers are also being pursued within public health and harm reduction responses with the goal of providing the complete composition of drug mixtures and go beyond simple yes/no results provided by test strips (Ti et al., 2020a). However, there are many types of instruments available and it is not yet clear which ones are best suited for responding to the crisis. In addition, unregulated drug markets can cause the drug supply to evolve and vary significantly between communities. In general, it seems that the illicit opioid markets are becoming increasingly complex, which further challenges drug checking efforts (Palamar et al., 2020; Ti et al., 2020b; Tobias et al., 2020). For example, low concentration substances and complex mix-

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tures pose significant challenges for techniques like Fourier-transform infrared (FTIR) spectroscopy and immunoassay test strips. Some examples include fentanyl analogues such as carfentanil (Bergh et al., 2021), and a number of adulterants found in opioids or other expected drugs, such as xylazine (Tobias et al., 2020), benzodiazepines (Laing et al., 2021), and synthetic cannabinoids (Ti et al., 2020b).

Laboratory-based analytical instruments are highly sensitive and can be expected to report on the full composition of a sample. However, there is an interest in portable instruments which are better suited to provide more immediate, point-of-care test results, and can be more easily integrated within supervised consumption sites and overdose prevention services. Many drug checking services seek out confirmatory laboratory testing to address any substances that may be undetectable using portable technologies such as FTIR. Mass spectrometry (MS), typically coupled with a separation technique such as gas chromatography (GC), is considered a gold standard technique for the analysis of illicit drugs (Borden et al., 2020a). This is, in part, due to its ability to confirm the presence of components based on molecular ion and/or fragment mass, without the strict requirement of library searching. Despite its excellent sensitivity and discrimination for drug identification, gas chromatography-mass spectrometry (GC-MS) is typically less considered for on-site testing due to its large size, site requirements (electricity, pump ventilation, carrier gas availability), long run-time, and dependence on significant technical knowledge and experience for operation (Harper et al., 2017). Portable GC-MS instruments mitigate these challenges and therefore enable field use. Their development has allowed for more accurate and immediate testing in a broad range of applications such as the detection of chemical warfare agents, forensics, and environmental analysis (Leary et al., 2016; 2019). Their use is also geared towards individuals who may not have a significant background in science or analytical techniques, such as emergency responders, military personnel, and law-enforcement (Leary et al., 2016; 2019). Portable GC-MS therefore holds significant promise as a portable drug checking technology. However, its effectiveness has yet to be explored within harm reduction applications.

This short report is aimed at demonstrating the use and potential benefits of portable GC-MS in the detection of several important compounds increasingly appearing in the illicit opioid drug market linked to unprecedented rates of overdose. Opioid samples for which laboratory-based mass spectrometry identified carfentanil and/or etizolam were analyzed with portable GC-MS in order to determine whether the portable instrument was able to detect the same compounds. We also comment on the suitability of GC-MS for point-of-care drug checking with a focus on harm reduction, analogous to how FTIR is currently used.

Methods

Samples were received as a part of an ongoing drug checking project established in 2018 in Victoria, Canada (Wallace et al., 2021). Ethical approval was provided by the Health Research Ethics Board at Island Health Authority (J2018-069). For this study, a subset of samples received at the drug checking service between December 2020 and February 2021 were tested on a portable GC-MS and portable FTIR, where the presence of etizolam and/or carfentanil was identified by paper spray mass spectrometry (PS-MS) (Borden et al., 2020b, 2021). Instrument descriptions, sample preparation techniques, and compound identification details appear in the Supplementary Information.

Results

During the study period, $n = 59$ samples that received quantitative testing using PS-MS were found to contain etizolam and/or carfentanil. In many of these samples, other notable substances were also detected. Table 1 presents a comparison of the substances positively identified through PS-MS analysis and those detected with portable GC-MS. In 36% of the samples, all of the substances identified by PS-MS were also detected by GC-MS analysis. If we rearrange the data according to component rather than the individual samples (Table S1), we find that 100% of the samples containing heroin or cocaine, 95% of samples containing fentanyl, 62% of samples containing carfentanil, and 36% of samples containing etizolam were identified using portable GC-MS.

When the samples are arranged according to etizolam concentration as determined from a PS-MS analysis (Table S2), this reveals that the portable GC-MS demonstrated no evidence of etizolam within the lowest concentration bracket (0.14–0.70%). As the concentration of etizolam increases, the reliability of detecting etizolam by GC-MS also improves. However, there remains a significant unpredictability, especially within the mid concentration range (0.70–3.0%). Above 3%, the portable instrument was able to detect 78% of the etizolam samples that were confirmed by PS-MS. Portable GC-MS detected carfentanil at much lower concentrations (0.13–0.63%). We note that 3% by weight in a typical 100 mg (one “point”) opioid sample corresponds to an etizolam dose of 3 mg, approximately 3–6 times greater than a typical therapeutic dose. If we again consider a 100 mg sample, this concentration range translates to 130–630 μg of carfentanil. While dosing for opioids widely varies, this dose is equivalent to roughly 1300–6300 mg of morphine. Current prescribing practices for opioid agonist treatments (OAT) with slow-release oral morphine are in the range of 235–791 mg/day (Use and Health, 2017). For comparison, a simple IR analysis was done on the same samples and the detection of the compounds is summarized in Table S1. In 3% of cases, all target substances (as detected by PS-MS) were correctly identified by IR analysis. Notably, 9% of samples containing etizolam were detected with IR. No instances of carfentanil, ANPP, or heroin were detected.

Discussion

The ability to perform on-site MS analysis enables results to be delivered directly to people who use drugs at the time of testing and detect actives at concentrations well below the limits of detection offered by other mobile technologies, such as portable FTIR. As services begin to explore quantification with spectroscopic methods as an indication of sample strength, there is the additional concern of misleading information when potent analogues such as carfentanil are going undetected. Given the preliminary data presented here, there is evidence that portable GC-MS may address many of these concerns, and further optimization and method development is encouraged.

An important consideration is the intrinsic value of the component separation that GC provides, prior to the MS analysis. Techniques such as IR and Raman spectroscopy rely on mixture analysis to deconvolute the spectral signatures of all components present in the drug sample, significantly limiting accurate discrimination of low concentration actives like fentanyl analogues. Prior separation using either GC or LC has two advantages. First, it simplifies the subsequent MS analysis tremendously as components can be analyzed individually, increasing the accuracy of library searching routines. Second, the retention time of sample components is characteristic of the molecule, and so identification is often possible without analysis of the mass spectrum, simply based on comparison of the retention time with reference standards. Having a mass spectrometer as the detector enables further confidence in the result, as well as immediate characterization of substances with novel retention times. The inherent trade-off is speed. Samples must first be prepared for GC-MS (dissolution in methanol, occasional centrifugation, sampling with CME fibre) and then the GC run takes on the order of 5–10 min. Additional time must be allotted for cleaning the CME fibre between runs to avoid carry-over. The GC column itself is also susceptible to carry-over from components that are strongly retained. Finally, as the sample preparation typically involves placing the sample in a solvent, the detection of components is ultimately limited by their initial solubility and later volatility.

Many of the challenges described above are characteristics of GC-MS in general, and are not specifically associated with portable instruments.

Table 1
Breakdown of components detected in $n = 59$ samples with portable GC-MS where target substances were identified by PS-MS.

Substances detected by PS-MS	Substances detected by portable GC-MS[a]	n
ANPP, Caffeine, Cocaine, Etizolam, Fentanyl	Caffeine, Cocaine, Etizolam, Fentanyl	1
ANPP, Caffeine, Etizolam, Fentanyl, Heroin	All Detected	1
ANPP, Etizolam, Fentanyl	All Detected	1
ANPP, Caffeine, Etizolam, Fentanyl	All Detected	4
	ANPP, Caffeine, Fentanyl	6
	Caffeine, Fentanyl	2
Caffeine, Carfentanil	Caffeine	1
Caffeine, Carfentanil, Cocaine, Etizolam, Fentanyl	Caffeine, Carfentanil, Cocaine, Fentanyl	1
	Caffeine, Cocaine, Fentanyl	1
Caffeine, Cocaine, Etizolam, Fentanyl	Caffeine, Cocaine, Fentanyl	1
Caffeine, Etizolam, Fentanyl	All Detected	9
	Caffeine	2
	Caffeine, Fentanyl	14
Caffeine, Etizolam, Fentanyl, Heroin	All Detected	1
	Caffeine, Fentanyl, Heroin	4
Caffeine, Fentanyl, Carfentanil	All Detected	2
Caffeine, Carfentanil, Etizolam, Fentanyl	All Detected	3
	Caffeine	1
	Caffeine, Carfentanil, Fentanyl	2
	Caffeine, Fentanyl	2

[a]For substances without an analytical standard (Cocaine, Caffeine, ANPP, Heroin), when the substance is reported as detected a top hit has been obtained in NIST database searching as described for non-targeted analysis. Any additional detected substances via portable GC-MS, such as pre-cursors, cutting agents, or breakdown products have been excluded for this comparison.

Operators of drug checking services need to evaluate their capacity for operating GC-MS on-site, in terms of technician training, instrument calibration, optimization, and maintenance. The results we have presented above demonstrate significant variability in detecting trace components using portable GC-MS. Other projects may face the same challenges as a result of: (a) the heterogeneity of the samples, (b) the lack of analytical balances at many harm reduction sites, resulting in differences in the amount of sample measured; (c) a potentially multi-component sample matrix that results in interference for certain compounds; (d) adjustments of GC-MS parameters during performance validation, and baseline fluctuations due to cleanliness of the injection port and/or CME syringe influencing the limits of detection; and (e) inconsistent sampling volume due to the capillary mechanism in the CME syringe. Many of these challenges may be addressed with further method development, including optimization of instrument parameters (temperature programming, inlet parameters, detector settings) and exploration of techniques such as selective ion monitoring. Sample preparation steps such as the use of internal standards, solvent extractions, or derivatization of less volatile compounds could also be explored further. It is worth noting that this process of developing reliable methods relies on both access to analytical standards, as well as technicians with a comprehensive background in GC parameter optimization and validation.

Conclusions

The illicit opioid market continues to increase in complexity and unpredictability including low levels of carfentanil and etizolam. Our study illustrates how a portable GC-MS performs on street opioid samples including those containing carfentanil and etizolam. It is useful in mitigating some of the challenges associated with the detection of low concentration actives within the framework of an on-site drug testing service. MS with chromatographic separation simplifies the analysis of complex mixtures and offers increased sensitivity and specificity necessary in these cases, albeit with variable results depending on the compound. Drug checking faces ongoing challenges as an overdose intervention to both provide immediate point-of-care results (typically utilizing portable instruments) while seeking to report at extremely low-levels of detection of these notable components.

Declarations of Interest

None.

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.drugpo.2021.103409.

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