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Internet pseudoscience: Testing opioid containing formulations with tampering potential

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ABSTRACT

Drug tampering practices, with the aim to increase availability of drug delivery and/or enhance drug effects, are accessible on Internet and are practiced by some portion of recreational drug users. Not rarely, recreational misuse may result in toxic and even fatal results. The aim of the present study was to assess the tampering risk of medicaments containing different formulations of an opioid in combination with paracetamol or dexketoprofen, following the procedures reported in dedicated forums on the web. Tablets and suppositories containing codeine, tramadol and oxycodone were extracted following the reported "Cold water extraction"; dextromethorphan was extracted from cough syrup following the procedure reported as "Acid/base extraction" and fentanyl was extracted from transdermal patches according the procedure reported in Internet. The tampered products and opportunely prepared calibrators in water were analysed by liquid chromatography coupled to tandem mass spectrometry (LC–MS/MS). The separation of the analytes was carried on Agilent ZORBAX Eclipse Plus C18 (RRHT 2.1 mm × 50 mm, 1.8 μm) by the gradient elution of 0.01% formic acid in water and 0.01% formic acid in methanol. Acquisition was by MRM mode considering at least two transitions for compound. Declared recoveries for these home-made extractions claimed to exceed 99% for the opioid and to complete remove paracetamol, often associated to liver toxicity and thus to obtain a "safer" preparation. In this study, the authors demonstrated that rarely the recoveries for the opioid reached 90% and that up to 60% of the paracetamol amount remained in solution. Thus, high risks for health remained both for the potential lethality of the opioid content, but also for the sub-lethal chronic use of these mixtures, which contained still uncontrolled, ignored, but often important amounts of paracetamol.

1. Introduction

Prescription opioids, such as oxycodone, fentanyl, codeine, tramadol and dextromethorphan, are used in the management of pain, both acute and chronic. These drugs are available in various forms, such as immediate-release (IR), extended-release (ER) and controlled-release (CR) oral preparations, or skin patches, or suppositories. Prescription opioids offer a therapeutic option for the management of pain, but they can also lead to physical and psychological dependence and therefore be misused and abused, resulting in harms such as addiction, overdose and even death. In fact, in recent years, an increase in the rates of deaths involving controlled prescription opioids, including fentanyl, has been recorded in the European countries [1,2] as well as in United States [3–6]. Abuse and misuse of psychotropic pharmaceuticals have been defined according to "The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)" as "use of pharmaceutical drugs ... that deviate from accepted medical practice and/or scientific knowledge" and 'the intentional or unintentional use ... contrary to directions, regardless of whether a harmful outcome occurs' [7], respectively. Such misuse and abuse include borrowing

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or stealing medications from friends or relatives, deliberately using higher-than-recommended doses, hoarding medications, tampering with the medication or altering the route of delivery and using opioids together with alcohol or other medications that have a sedating effect. Although no statistics appear to be available on the number of individuals who attempt to alter opioid formulations, there is growing evidence that "drug/formulation tampering" is widely prevalent. Pharmaceutical drugs are formulated in many different compositions targeted for specific routes of administration or bioavailability scope and though opioid formulations with tamper-resistance or abuse-deterrent features are developing, physical or chemical modifications of original formulation to enhance drug availability and/or eliminate undesirable excipients are still attempted by drug users. On this regard, Internet offers several home-made tampering procedures that can be exploited by old opioids consumers, which need to artificially increase the amount of ingested drug as well as by new opioids consumers, who can easily provide medications by family members or friends. The risk of using more than one medication simultaneously or to involuntarily exceed the "dose" is associated to drug abuse and fatal poisoning cases [8]. On this regard, a case of fatal codeine intoxication originating from a homemade extraction attempt has been recently experienced and described by the authors [9]. It is not strange that for this reason, starting from the last decade the interest of the scientific society about this topic has been gradually increasing, although limited to codeine formulations, with the publication of papers in which the investigation of Internet procedures for codeine extraction has been carried out [10,11]. The aim of the present study was to assess the tampering potential of medicaments containing an opioid (tramadol, codeine, oxycodone, dextromethorphan) in combination with an analgesic (paracetamol or dexketoprofen) in different formulations, following the procedures reported in dedicated forums [12–14]. Medicaments containing dexketoprofen, although not described in forums, were also included in the study for the availability in drug stores and for the suspected renal and liver toxicity on rats [15]. Experiments on fentanyl transdermal patches have also been performed, based on the possibility of fentanyl misuse both exploiting new and used patches. In many cases, the online statements on recoveries for these home-made extractions claim to exceed 99% for the opioid and, where present, to complete remove the analgesic, associated to liver toxicity, to obtain a "safer" preparation. In this study, the authors will demonstrate that rarely the recovery for the opioid reaches 90% and that up to 60% of the paracetamol original amount remains into solution that is then used for abuse. Thus, high risks for health remain both for the possibility to increase the number of starting tablets/suppositories/liquid/patches containing the opioid, reaching fatal doses, but also in the sub-lethal chronic use of these mixtures, which contain still uncontrolled, ignored, but often important amounts of paracetamol. Paracetamol is usually linked to serious hepatotoxicity after exposure to high-doses, but evidences of toxicity are available also for chronic pain patients at regular doses [16]. Moreover, in this work, the abuse potential of dextromethorphan containing syrup and fentanyl patches will be also evaluated in the frame of tampering potential. The results of this study offer experimental evidence of a widely widespread phenomenon of over-the-counter drugs misuse possibly affecting both the clinical and the forensic toxicologists, who could be involved in the evaluation of intoxication and even death events. Furthermore, investigations on medicine misuse and tampering potential for medicines on the market should have an important role in the pharmacovigilance system thus to help to identify strategies for risk reduction to be exploited by medicine regulators and pharmaceutical industry.

2. Methods

2.1. Materials

Water, methanol and formic acid were LC–MS grade from Honeywell (Morris Plains, NJ, USA). Tablets and suppositories containing an opioid and paracetamol or dexketoprofen (codeine/paracetamol, codeine/dexketoprofen, tramadol/paracetamol, oxycodone/paracetamol), cough syrup (dextromethorphan/paracetamol) and fentanyl patches were purchased in drug stores or pharmacies. Unbleached coffee filters (Finum, Riensch & Held GmbH & Co.KG, Germany) and whisky at 35% v/v alcohol were purchased at the supermarket. Paper filters were from Merck KGaA, (Darmstadt, Germany). For the extractions, hexane and isopropanol were both from Sigma-Aldrich (Merck KGaA, Darmstadt, Germany) and solutions of 0.1 M of NaOH and 0.1 HCl were freshly prepared, all from Honeywell. For quantitative analysis a solution of certified reference nalorphine (Cerilliant, Round Rock, Texas, USA) at the concentration of 2 μg/mL in methanol was prepared.

2.2. Analytical method

2.2.1. Chromatographic conditions

The separation of the analytes was carried on an Agilent 1290 LC system (Santa Clara, CA, US) equipped with a binary pump and a thermostatic auto-sampler. An Agilent ZORBAX Eclipse Plus C18 (RRHT 2.1 mm × 50 mm, 1.8 μm) was used by the gradient elution of 0.01% formic acid in water as mobile phase A and 0.01% formic acid in methanol as phase B: 0–0.5 min, 5% B; 0.5–7 min, 5–30% B; 7–12 min, 30–90% B; 12–15 min, 90% B; 15.1–17 min, 5%B. The mobile phase was delivered at a flow rate of 0.4 mL/min and the injection volume was 3 μL. The autosampler tray temperature was set at 8 °C, while the column temperature was 30 °C.

2.2.2. Mass spectrometric conditions

Analyses were performed on a 6460 Triple quadrupole spectrometer (Agilent technologies, Santa Clara, CA, US). The applied ESI ion source conditions were set as follows: drying gas 230 °C, drying gas flow 10 L/min, capillary voltage 2000 V, nozzle voltage 1500 V, nebulizer flow 35 psi, sheath gas temperature and flow were 375 °C and 12 L/min, respectively. Acquisition was in multiple reaction monitoring (MRM) and transitions for each compound are reported in Table 1. Data acquisition and processing were carried out using MassHunter software (Agilent Technologies, Santa Clara, CA, US) with Qual and Quan browsers.

2.3. Methodologies

The tampered products and opportunely prepared calibrators in water were analysed by liquid chromatography coupled to tandem mass spectrometry (LC–MS/MS). At this scope, a method for the simultaneous determination of codeine, tramadol, oxycodone, fentanyl, dextromethorphan, paracetamol, dexketoprofen was developed and preliminarly validated in terms of precision and linearity (Fig. 1). Intra and inter-day precision were always below 10% for all compounds while non-including origin, weighted (1/x) linearity, assessed between the 10% and 100% of the declared compound amount, showed residuals to be randomly scattered without displaying any systematic patterns. Prior to analysis, samples and calibrators were diluted to fall into the instrumental linearity range (i.e. 1: 100000) and added of I.S. at the concentration of 60 ng/mL.

All material was prepared according the procedures found in Internet in dedicated forum following the research with keywords "opioids and extraction" or "opioids and tampering" or "fentanyl and patches". Tablets and suppositories containing codeine; tra-