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Methylphenidate disintegration from oral formulations for intravenous use by experienced substance users

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ABSTRACT

Background and aims: Methylphenidate (MPH) is a prescription stimulant used to treat attention-deficit hyperactivity disorder. MPH is currently the preferred substance among most intravenous (i.v.) substance users in Iceland. Four types of MPH preparations were available in Iceland at the time of study: Immediate-release (IR), sustained-release (SR), osmotic controlled-release oral delivery (OROS) tablet and osmotic-controlled release (OCR). MPH OROS has previously been rated the least desirable by i.v. users and we hypothesized that this was associated with difficulty of disintegrating MPH from OROS formulation. The aim of the study was to measure the amount of MPH and the viscosity of the disintegrated solutions that were made from the four MPH formulations by four i.v.-users and non-users.

Methods: A convenience sample of four i.v. substance users and 12 non-users. Non-users imitated the methods applied by experienced i.v. substance users for disintegrated MPH formulations.

Results: Both groups managed to disintegrate over 50% of MPH from IR and SR formulations but only 20% from OROS ($p < 0.0001$). The viscosity of the disintegrated MPH was significantly higher for MPH OROS and MPH OCR and the preparation was significantly more time-consuming than for the other MPH samples. No differences were observed between users and non-users.

Conclusions: To our knowledge, this is the first investigation of viscosity and the amount of disintegrated MPH from prescription drugs for i.v. use. The results indicate that the ease of disintegration, amount of MPH and viscosity may explain the difference in popularity for i.v. use between different MPH formulations.

1. Introduction

Methylphenidate (MPH) is a sympathomimetic psychostimulant which shares similar pharmacological features with other psychostimulants such as amphetamine and, in particular, cocaine. In recent years, MPH has been considered first line treatment for adult attention deficit hyperactivity disorder (ADHD) (National Institute for Health and Care Excellence, 2008). In the past decade, the incidence of diagnosis has increased resulting in a steep rise of MPH prescriptions worldwide, particularly in Iceland where the prescription rate is currently among the highest in the world (INCB, 2015a). Only MPH and atomoxetine are approved as first line treatments for ADHD in Iceland and at the time of this study, four MPH preparations were available: Ritalin© (MPH immediate-release (IR)), Ritalin Uno© (MPH sustained-release (SR)), Concerta© (MPH osmotic controlled-release oral delivery (OROS)) and Methylphenidate Sandoz© (MPH osmotic-controlled release (OCR)). Historically, MPH has generally been considered to have lower abuse potential than other psychostimulants (Volkow and Swanson, 2003; Volkow et al., 1995; Kollins, 2003; Kollins et al., 1998). Nevertheless, both oral and intravenous (i.v.) misuse has been reported (Benson et al., 2015; Frauger et al., 2016) and MPH has recently been shown to be the leading substance for i.v. use in a nationwide cohort (Bjarnadottir et al., 2015). It is thought that the pharmacological technology of MPH OROS lowers its abuse potential since it is more difficult to manipulate MPH from the tablets (López and Leroux, 2013; Schapperer et al., 2015). This is in line with a study where MPH OROS was reported to be the least preferred i.v. substance among i.v. MPH abusing patients (Bjarnadottir et al., 2016).

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The primary aim of this study was to measure the amount of MPH that i.v. substance users can disintegrate from four different MPH preparations as well as to measure the viscosity of the samples since it may explain why certain MPH preparation are more likely to be chosen for i.v. abuse than others. A secondary aim was to compare the amount of MPH and the duration of MPH disintegration from the different tablets between i.v substance users and non-users in order to investigate how easily the preparation can be learned.

2. Material and methods

2.1. Study design and participants

A convenience sample of four i.v. MPH substance users and 12 non-users. Substance i.v. users were recruited from halfway homes allowing substance use in Reykjavik. Employers at the halfway homes reached out to eligible participants and each potential participant got an introduction letter about the study. Four males out of five eligible agreed to participate and signed an informed consent. Because the study could induce craving for substance use and participants were not allowed to use their preparations afterwards, they received a compensation of $60 each for their time and effort. **Non-users**: Twelve clinical staff members from the Mental Health Services of the National University Hospital in Iceland were also recruited. They all had a university degree but none had a degree in chemistry or pharmacology.

2.2. Settings and procedure

The study was conducted at the outpatient addiction clinic of the National University Hospital of Iceland.

2.2.1. Disintegration of MPH formulations

Participants were provided with one formulation, in the highest dosage, of each available MPH medication in Iceland: MPH IR (10 mg), MPH SR (40 mg), MPH OROS (54 mg) and MPH OCR (54 mg) and the equipment requested by the i.v. substance users was provided. Participants were asked to prepare each formulation to make it ready for injection. A stopwatch was used to observe how much time it took to crush and dissolve the tablets and capsules. There was no time limit for participants to finish preparing the formulations. The i.v. users' procedure was written down step by step for each preparation by one of the investigators. The non-users received written instructions and each of them was randomly assigned to imitate one of the i.v. substance users' methods to prepare the MPH formulations for injection. The samples were subsequently measured in the Department of Pharmacology and Toxicology, University of Iceland (Fig. 1).

2.2.2. MPH viscosity

Two of the non-users prepared a total of 6 samples of each MPH formulation in order to measure viscosity at the Department of Pharmacology and Toxicology.

2.3. Equipment requested by the i.v. substance users

Needles (0.45 × 13 mm and 0.5 × 16 mm), 2 mL and 5 mL syringes, mortar, egg beakers, knife, scissors, towel paper, cigarette filters, cotton, soda caps and tap water.

2.4. Laboratory equipment for measurement of disintegrated

The high-performance liquid chromatography system consisted of an Agilent 1100 (Phenomenex, UK). A Synergi 4 μm MAX-RP 80A® column (150 mm × 4.6 mm, 4 μm particle size) (Phenomenex, UK) was used as stationary phase and a mixture of pH7, 10 mM, 30% KH_2PO_4, 35% acetonitrile, MeOH 35% was degassed by ultra-sonication and delivered at the flow rate of 1.0 mL/minute. The samples were dissolved in mobile phase. A diode array detector was used and samples were analyzed at 220 nm. Chromatography was carried out at ambient (27 °C) temperature. Data processing was performed using Chromoleon 7 (Thermo Scientific,USA). Certified reference material was acquired from Sigma (Sigma Aldrich, Germany).

2.5. Laboratory equipment for measurement of MPH viscosity

The viscosity of the solutions was measured using a DV2T viscometer (Brookfield Ametek, USA) at the speed of 9 RPM and 50 RPM at a temperature 25 °C ± 2 °C which was controlled with a water bath. Brookfield viscosity standard (Brookfield Ametek, USA) was used as a certified reference material, viscosity of 4.90 cP, temperature 25 °C ± 2 °C.

2.6. Statistics

All data was coded and analyzed using SPSS 11 (PC, SPSS Inc. Chicago). When comparing two continuous variables, an independent two-tailed *t*-test was used between groups. Volume, concentration of active MPH (mg/mL) and the total milligrams of each tablet was used to calculate the percentage of disintegrated MPH. One–way Anova and Tukey's post hoc test was performed to compare viscosity values. In all analyses, statistical significance was declared at p values < 0.05.

2.7. Missing values for MPH disintegration

Three out of four i.v. substance users had never used MPH OCR (Methylphenidate Sandoz©) and therefore could not prepare that formulation as easily as the other formulations. Only four out of twelve non-users succeeded to manipulate MPH OCR in order to disintegrate MPH. Therefore, we did not include MPH OCR when calculating the amount of disintegrated MPH.

2.8. Missing values for MPH viscosity

Two out of 6 MPH OCR measurements were not measurable but reached at least over 306.60 cP while the average was 4.65 cP. Those two samples were excluded in the calculations since the exact viscosity was unknown.

2.9. Ethics

The study was approved by the Icelandic Bioethics Committee (VSN12-038-V3) and reported to the Icelandic Data Protection Authority (2012/272). The information disclosed during the procedure was confidential and did not affect current or future treatments. Three out of four i.v. users had used i.v. MPH on the day of the study. The participants could omit any question and withdraw at any time.

3. Results

All i.v. substance users were males with a mean age of 39 years (SD ± 9.84, range 26–50). Three of them most commonly used i.v. MPH SR but the fourth one i.v. MPH IR. The mean duration of i.v. substance use was 15 years (SD ± 12.57, range 2–32). Non-users were 10 males and two females and their mean age was 42 years (SD ± 12.94, range 24–60).

The mean of disintegrated MPH per milliliter (mg/mL) for all participants (n = 16) was highest for MPH SR, 9.14 ± 2.30 (7.91–10.37 CI95%) which was statistically different ($p < 0.001$) from MPH IR and MPH OROS (2.62 ± 1.03 and 3.73 ± 1.37, respectively).

On average, both the i.v. substance users and non-users managed to disintegrate roughly half of the total amount of MPH IR (53%) and MPH SR (58%). For MPH OROS, both groups managed to disintegrate on average only 20% which was statistically less than for both MPH IR and