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Severe toxicity due to injected but not oral or nasal abuse of methylphenidate tablets

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Summary

BACKGROUND: Non-medical use of methylphenidate is increasing. Little is known about potential acute medical complications associated with recreational use of methylphenidate.
STUDY AIM: To identify medical problems associated with methylphenidate abuse.
METHODS: Retrospective case series of methylphenidate abuse cases presenting to an inner city emergency department.
RESULTS: We identified 14 cases of methylphenidate abuse between 2003 and 2010. Ten of these patients abused methylphenidate alone while four co-ingested other drugs, mainly alcohol. The route of ingestion was oral in nine patients, nasal in one and intravascular in four. Severe toxicity was exclusively observed in users who injected the drug. Two cases involved accidental intra-arterial injection and resulted in tissue necrosis leading to the amputation of a forearm and of fingertips, respectively. Clinical findings in the non-serious cases included mild to moderate symptoms and signs of sympathetic nervous stimulation such as agitation, tachycardia, hypertension, anxiety, hallucination, headache, tremor and dizziness. Nine of the fourteen patients were taking methylphenidate as a prescribed drug. Eight patients were former or current multiple substance abusers.
CONCLUSION: Methylphenidate misuse is not a significant burden for emergency departments in Switzerland. Oral and nasal administration of methylphenidate did not result in severe toxicity. However, injection of crushed methylphenidate pills lead to serious local toxicity. Most patients with methylphenidate abuse had a prescription for the drug indicating deviation from medical use. A history of multiple substance use may be a risk factor for non-medical use of methylphenidate.

Key words: *methylphenidate; intoxication; abuse; misuse*

Introduction

Methylphenidate (MPH) is an amphetamine-like psychostimulant drug approved for the treatment of attention-deficit-hyperactivity-disorder (ADHD) and narcolepsy. An increase in MPH abuse has been observed in the United States in recent years [1, 2]. In Switzerland, frequent recreational use of MPH was also noted in the Zurich party scene [3] and the number of reports of MPH intoxications to the Swiss Toxicological Information Centre (STIC) has increased in recent years [4]. MPH is abused for recreational purposes with the aim of inducing feelings of euphoria: However, the use of MPH as so-called cognitive enhancer to boost performance has become a focus of concern [5]. Little is known about the medical problems associated with MPH abuse and the characteristics of acute MPH toxicity. Data from poison centres suggest only mild or moderate toxicity in most cases of MPH abuse [2, 4, 6]. Of 530 children and adolescents with abuse of MPH, only one developed major toxicity, while 55% experienced minor and 44% moderate toxicity [2]. In another study, about 6% of the MPH abuse cases were reported to have major toxicity and no fatalities were reported [6]. Consistently, in a series of cases reported to the STIC, we found that none of the abusers who used MPH alone had a major or fatal medical outcome [4]. However, information based on reports to poison centres is limited for several reasons. Analyses of hospital data from emergency physicians may therefore offer a more valid description of the characteristics of MPH toxicity. We are not aware of any systematic data on the clinical picture of MPH toxicity from emergency care facilities. There are only a few single case reports describing MPH abuse via the intranasal route [7–9], including a report of intranasal MPH use at a party associated with a fatal cardiopulmonary arrest [8]. We therefore report a retrospective series of MPH abuse cases presenting to a Swiss emergency department.

Methods

The study was approved by the ethics committee of the cantons of Basel. A retrospective study design was used with standardised data recording. We performed an electronic full text search in the electronic hospital patient chart system for consultations related to MPH use seen in the emergency department between January 2002 and

December 2010. Search terms used were methylphenidate, Ritalin, Concerta, Medikinet and miss spellers. All patient records identified were manually reviewed and included in the study if the definition for MPH abuse was met. MPH abuse was defined as intake without prescription, use of a higher dose than the one prescribed or non-oral administration. Laboratory confirmation of methylphenidate was not available and methylphenidate use was confirmed by medical history. Information on clinical symptoms and signs and characteristics of MPH abusers were then taken from the ED records and entered into a structured data base. Additional information on medical history, e.g. psychiatric disease and prescription of MPH was also taken from former patient's records. Severity of intoxication was graded according to the Poison Severity Score of the European Association of Poison Centres and Clinical Toxicologists (EAPCCT) [10]. Moderate toxicity is defined as the presence of pronounced or longer acting signs and symptoms as a result of substance exposure but is not life-threatening and does not result in residual disability whereas severe (major) toxicity is defined as being life threatening or resulting in major residual disability [10].

Results

Characteristics of MPH abusers

There were 14 patients with self-reported methylphenidate abuse admitted between 2002 and 2010. Patient characteristics are listed in table 1. There were nine female and five male patients. The median age was 31 years (range 17–51 years). Nine (57%) patients used MPH as a prescribed drug. Four of these patients were diagnosed with ADHD. In the other five patients the indication for MPH prescription was unknown. Four of the 14 patients were multiple substance abusers and one had a diagnosis of borderline syndrome.

Oral doses of MPH ranged from 30 to 400 mg. Nine patients administered MPH orally, one nasally, and one intravenously. Three patients intended intravenous injection but then injected MPH intra-arterially by accident. Two of these injections were into a forearm artery and one into an inguinal artery. Nine patients took MPH alone, two used it together with alcohol, one used MPH together with a benzodiazepine, one used MPH together with methadone and one used MPH with alcohol and a benzodiazepine. Drug screens were done in nine patients and were negative except for one case with a positive screen for cocaine. No screens were performed in the four patients with parenteral use and in one patient with chronic use and no history of other drug use. No laboratory confirmation of MPH was available.

One female patient used her sister's prescribed MPH. In the remaining four patients who abused MPH without prescription the source of MPH was not known. Eight patients were known as multiple substance abusers. Of the 14 admissions, eleven concerned acute MPH abuse, two concerned chronic MPH abuse (presentation at the ED more than 8 h after ingestion) [2], and one patient took more than the prescribed dose during several months. This patient presented to the emergency department because she ran out of MPH and needed a renewal of the prescription. One patient nasally administered 80 mg of MPH following intake of daily doses of 40–60 mg orally over three weeks while her prescribed dose was 20 mg per day. One patient was admitted one week after an inguinal injection when she noted painful swelling and warmth at the injection site. One patient took 30 mg of MPH orally before a school examination to improve performance. One patient took 270 mg of MPH orally with suicidal intentions.

Clinical features of MPH toxicity

Of the patients with oral MPH abuse, one had no effects, six exhibited minor and three exhibited moderate toxicity. Toxicity was mostly due to sympathetic nervous system stimulation. Marked sinus tachycardia with a heart rate of 170/min and hypertension with a systolic blood pressure of 160 mm Hg was seen in one patient and mild tachycardia with a heart rate of 116/min was noted in another patient. Neuropsychiatric symptoms included agitation in four patients and anxiety in two patients. Hallucinations, headache, dizziness and tremor each occurred in one patient. One patient, who also ingested a benzodiazepine, experienced multiple absence seizures. In the patient with nasal MPH administration the main symptom was anxiety. Three patients with intra-vascular MPH injection suffered from severe ischaemia and necrosis of a forearm and of fingertips, respectively, and of an inguinal abscess at the injection site.

Treatment and outcome

Most of the sympathetic nervous stimulation symptoms were self-limited and were monitored at the emergency department for several hours. Patients admitted in the late evening usually stayed overnight. Two patients were monitored overnight in the intensive care unit due to agitation and absence epilepsy. Two patients were treated with benzodiazepines. Two patients were transferred to a psychiatric clinic following monitoring, including the suicidal patient. The patient with the inguinal abscess was transferred to the general internal medicine ward for intravenous antibiotic treatment. In one of the patients with intra-arterial MPH injection, the distal right hand was cyanotic at admission. Intra-arterial lysis with urokinase and a continuous intravenous infusion with iloprost and heparin were started and resulted in restoration of blood flow. However, demarcation of three fingertips developed after 30 days and amputation was necessary.

In the other patient with MPH injection into a radial artery, no radial pulse and ultrasound Doppler flow signal was detected and the hand was cold, white and painful. Initial therapy consisted of intravenous phentolamine and heparin infusions. Additionally, blockage of stellatum ganglion and urgent fasciotomy were performed. Despite these measures, amputation of the forearm became necessary after nine days.

Discussion

There were 14 cases of MPH abuse during the retrospective 8-year study period of the present case series. The main finding was that oral or nasal MPH abuse was associated

with only minor to moderate sympathomimetic toxicity, which was mainly self-limited and was treated with sedatives in some cases. Evaluations of reports to poison control centres showed that exposures to MPH similarly resulted in mild to moderate toxicity in most cases [2, 4, 6]. A recent case report described a girl who ingested 1134 mg of modified release MPH without sequelae [11]. Of note, no cases of severe toxicity associated with MPH exposure including injection use were reported to the STIC [4]. However, in our study, intravenous MPH abuse was associated with serious local ischaemic and inflammatory complications. Complications of parenteral injection of dissolved MPH tablets have previously been reported and included local infection, cutaneous foreign body reactions, endocarditis of the tricuspid valve, pulmonary granulomatous disease and pulmonary hypertension due to obstruction of the pulmonary vasculature [12–14]. Accidental injection of dissolved tablets into an artery might have lead to vasospasm, endothelial-damage and microembolisation followed by thrombosis, ischaemia and ultimately necrosis in our cases. One of these cases has been described previously [15].

In our study, all injection MPH abusers had a diagnosis of multiple substance abuse including intravenous drug abuse. The present study was too small to detect any trends in the number of presentations over time. The number of calls to the STIC relating to MPH exposures has been increasing, starting in 2004 [4]. In addition, the number of reported MPH exposure cases has even exceeded the number of reports related to ecstasy exposures in 2009 and was second only to reports on cocaine. An increase in MPH abuse has been reported by the annually monitoring report on the state of drugs and addiction in the town of Zurich, Switzerland [3]. The report states that MPH is mostly administered by the nasal route and used in the "hip-hop-dance scene" [3].

MPH is an inhibitor of the neuronal dopamine and norepinephrine reuptake transporters similar to cocaine [16, 17]. Similar subjective and physiological effects of MPH and cocaine were described by subjects receiving both drugs intravenously [17] or orally [18]. The subjective and cardiovascular stimulant as well as the behavioural effects of oral MPH (doses of 5–60 mg) were also similar to those of oral amphetamine or methamphetamine (doses of 2.5–30 mg) in human laboratory studies [19, 20]. In addition, reinforcing effects of oral MPH (40 mg) were similar to those of amphetamine (10–20 mg) indicating equal abuse potential [21]. Effects of intranasal MPH have also been studied under laboratory conditions. MPH insufflation of doses of 10–30 mg produced dose-dependent subjective stimulant-like, cardiovascular and reinforcing effects similar to other abused stimulants [22]. Although the effects of nasal MPH were not directly compared with other stimulants, the response to 30 mg of nasal MPH was reported to be similar to the effects of an intermediate (45 mg) dose of intranasal cocaine [22, 23].

The subjective drug high depends not only on the kind of drug but also on its concentration and time to reach maximal concentrations in the brain. Higher and more rapid drug exposures are associated with more pronounced subjective rewarding effects and increased abuse liability [24]. Oral controlled release formulations produce lower peak plasma levels than regular formulations of MPH while intravenous administration results in higher peak drug levels and faster exposure to the drug [25]. The oral bioavailability of the active d-MPH is limited to 22% because of extensive presystemic metabolism [25]. Bypassing presystemic elimination in the gut and liver by nasal administration may result in increased and more rapid plasma and brain exposure to MPH. Approximately 20% of MPH abusers were reported to use the nasal route [2]. It is not known whether the preparations derived from crushed tablets do indeed result in higher MPH exposure. In fact, some more tamper-resistant extended-release formulations do not produce psychotropic effects when snorted [26]. A subject reported in the present study used 80 mg by nose and experienced mild effects. We previously reported five exposures to nasally snorted MPH and all experienced symptoms of minor toxicity [4]. Taken together, the limited data available indicate

Table 1: Patient characteristics.

Patient	Sex/age	Route	Dose (mg)	Main symptoms	Diagnosis	Medical history	MPH prescription	Severity of intoxication
1	f/30	oral	unknown	no	chronic MPH abuse	ADHD	yes	no symptoms
2	f/21	oral	unknown	agitation	MPH/alcohol intoxication	ADHD	yes	mild
3	m/51	oral	unknown	sedation	MPH/methadone intoxication	MSA	yes	mild
4	m/33	oral	30	tachycardia	MPH abuse		no	mild
5	f/17	oral	100	headache, tremor, dizziness	MPH abuse	sister with ADHD	no	mild
6	m/47	oral	100	agitation	alcohol/MPH abuse	former MSA	no	mild
7	f/39	ia	unknown	anxiety	accidental inguinal intra-arterial injection	MSA	yes	mild
8	f/29	nasal	80	anxiety	intended MPH overdosing	MSA	yes	mild
9	f/33	oral	300–400	disorientation, agitation	MPH abuse	ADHD, MSA	yes	moderate
10	m/28	oral	270	agitation, tachycardia, hypertension, hallucination	MPH intoxication with suicidal intent	ADHD	yes	moderate
11	f/25	oral	320	multiple absences	MPH/benzodiazepine/alcohol intoxication	borderline-syndrome	yes	moderate
12	f/28	ia	6	pain, necrosis of forearm	amputation of forearm	MSA	no	severe
13	m/37	ia	unknown	pain, necrosis of finger tips	amputation of finger tips dig II, III, IV	MSA	yes	severe
14	f/41	iv	unknown	inguinal erythema, fever	inguinal abscess	MSA	no	severe

MPH: methylphenidate, MSA: multiple substance abuser, m: male, f: female, ia: intra-arterial, iv intravenous, ADHD: Attention deficit and hyperactivity disorder

that oral and nasal MPH abuse both result in overall similar mild to moderate toxicity.

Nine of the 14 MPH abusers (56%) in the present study had a prescription for MPH. Similar deviation from the intended medical use was observed in 40% of the MPH exposures reported to the STIC [4] and reported in 14–22% of patients treated with MPH for ADHD, typically in those with additional substance abuse [27, 28]. Abuse of prescribed MPH clearly needs attention. Although acute toxicity of MPH abuse is rarely severe, our study shows that prescribers should be aware of the potential deviational use of MPH. For example, prescription of abuse-deterrent damper-resistant formulations of MPH may prevent parenteral MPH abuse [29].

Our study has several limitations. Firstly, the number of cases was very small and included only adult patients. Secondly, data collection was done retrospectively and identification of MPH abuse cases relied on identification by full text search of medical records. This might have led to an underestimation of MPH cases, predominantly among multiple substance abusers in whom co-use of MPH might have gone unrecorded. Thirdly, MPH exposure was not confirmed by laboratory analyses (MPH is not detected by routine toxicological drug screens) and we relied solely on patient reports and clinical signs and symptoms of sympathetic stimulation. However, drug of abuse screens excluded amphetamine and cocaine use in eight patients.

In summary, we found that oral and nasal MPH use was associated with mild to moderate toxicity while intravenous and intra-arterial injection of crushed MPH tablets resulted in severe complications.

Treatment guidelines

An evidence-based guideline for out-of-hospital management of MPH overdose has been published [30]. Patients can be discharged from the ED if they ingested MPH more than three hours previously and show no signs of toxicity. No ED referral (observation) is needed if patients ingested less than 2 mg/kg (or 60 mg) of MPH of an immediate release formulation or less than 4 mg/kg (or 120 mg) of a modified release formulation. Patients with hallucinations, abnormal muscle movements or chest pain should be referred to an ED. Intensive care may rarely be indicated in cases of severe sympathomimetic toxicity, co-morbidity or polydrug use.

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References

1 Kroutil LA, Van Brunt DL, Herman-Stahl MA, Heller DC, Bray RM, Penne MA. Nonmedical use of prescription stimulants in the United States. Drug Alcohol Depend. 2006;84:135–43.

2 Klein-Schwartz W, McGrath J. Poison centers' experience with methylphenidate abuse in pre-teens and adolescents. J Am Acad Child Adolesc Psychiatry. 2003;42:288–94.

3 Kostka R, Monego R, Rüegg S, Suter D, Zeltner C. Monitoringbericht Drogen und Sucht 2010. Zurich, Switzerland: Stadt Zürich, 2010.

4 Bruggisser M, Ceschi A, Bodmer M, Wilks MF, Kupferschmidt H, Liechti ME. Retrospective analysis of stimulant abuse cases reported to the Swiss Toxicological Information Centre during 1997–2009. Swiss Med Wkly. 2010;140:w13115.

5 McCabe SE, Knight JR, Teter CJ, Wechsler H. Non-medical use of prescription stimulants among US college students: prevalence and correlates from a national survey. Addiction. 2005;100:96–106.

6 Forrester MB. Methylphenidate abuse in Texas, 1998–2004. J Toxicol Environ Health A. 2006;69:1145–53.

7 Coetzee M, Kaminer Y, Morales A. Megadose intranasal methylphenidate (ritalin) abuse in adult attention deficit hyperactivity disorder. Subst Abus. 2002;23:165–9.

8 Massello W, 3rd, Carpenter DA. A fatality due to the intranasal abuse of methylphenidate (Ritalin). J Forensic Sci. 1999;44:220–1.

9 Garland EJ. Intranasal abuse of prescribed methylphenidate. J Am Acad Child Adolesc Psychiatry. 1998;37:1242–3.

10 Persson HE, Sjoberg GK, Haines JA, Pronczuk de Garbino J. Poisoning severity score. Grading of acute poisoning. J Toxicol Clin Toxicol. 1998;36:205–13.

11 Klampfl K, Quattlander A, Burger R, Pfuhlmann B, Warnke A, Gerlach M. Case report: intoxication with high dose of long-acting methylphenidate (Concerta((R))) in a suicidal 14-year-old girl. Atten Defic Hyperact Disord. 2010;2:221–4.

12 Elenbaas RM, Waeckerie JF, McNabney WK. Abscess formation as a complication of parenteral methylphenidate abuse. JACEP. 1976;5:977–80.

13 Hahn HH, Schweid AI, Beaty HN. Complications of injecting dissolved methylphenidate tablets. Arch Intern Med. 1969;123:656–9.

14 Lewman LV. Fatal pulmonary hypertension from intravenous injection of methylphenidate (Ritalin) tablets. Hum Pathol. 1972;3:67–70.

15 Thalhammer C, Aschwanden M, Kliem M, Sturchler M, Jager KA. Acute ischemia after intraarterial drug injection. Dtsch Med Wochenschr. 2004;129:2405–8.

16 Hannestad J, Gallezot JD, Planeta-Wilson B, Lin SF, Williams WA, van Dyck CH, et al. Clinically relevant doses of methylphenidate significantly occupy norepinephrine transporters in humans in vivo. Biol Psychiatry. 2010;68:854–60.

17 Volkow ND, Ding YS, Fowler JS, Wang GJ, Logan J, Gatley JS, et al. Is methylphenidate like cocaine? Studies on their pharmacokinetics and distribution in the human brain. Arch Gen Psychiatry. 1995;52:456–63.

18 Rush CR, Baker RW. Behavioral pharmacological similarities between methylphenidate and cocaine in cocaine abusers. Exp Clin Psychopharmacol. 2001;9:59–73.

19 Martin WR, Sloan JW, Sapira JD, Jasinski DR. Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man. Clin Pharmacol Ther. 1971;12:245–58.

20 Sevak RJ, Stoops WW, Hays LR, Rush CR. Discriminative stimulus and subject-rated effects of methamphetamine, d-amphetamine, methylphenidate, and triazolam in methamphetamine-trained humans. J Pharmacol Exp Ther. 2009;328:1007–18.

21 Rush CR, Essman WD, Simpson CA, Baker RW. Reinforcing and subject-rated effects of methylphenidate and d-amphetamine in non-drug-abusing humans. J Clin Psychopharmacol. 2001;21:273–86.

22 Stoops WW, Glaser PE, Rush CR. Reinforcing, subject-rated, and physiological effects of intranasal methylphenidate in humans: a dose-response analysis. Drug Alcohol Depend. 2003;71:179–86.

23 Lile JA, Stoops WW, Allen TS, Glaser PE, Hays LR, Rush CR. Baclofen does not alter the reinforcing, subject-rated or cardiovascular effects of intranasal cocaine in humans. Psychopharmacology. (Berl) 2004;171:441–9.

24 Mumford GK, Evans SM, Fleishaker JC, Griffiths RR. Alprazolam absorption kinetics affects abuse liability. Clin Pharmacol Ther. 1995;57:356–65.

25 Srinivas NR, Hubbard JW, Quinn D, Korchinski ED, Midha KK. Extensive and enantioselective presystemic metabolism of dl-threo-methylphenidate in humans. Prog Neuropsychopharmacol Biol Psychiatry. 1991;15:213–20.

26 Jaffe SL. Failed attempts at intranasal abuse of Concerta. J Am Acad Child Adolesc Psychiatry. 2002;41:5.

27 Wilens TE, Gignac M, Swezey A, Monuteaux MC, Biederman J. Characteristics of adolescents and young adults with ADHD who divert or misuse their prescribed medications. J Am Acad Child Adolesc Psychiatry. 2006;45:408–14.

28 Bright MG. Abuse of medications employed for the treatement of ADHD: results from a lage-scale community survey. Medscape J Med. 2008;10:111.

29 Ciccone PE. Attempted abuse of concerta. J Am Acad Child Adolesc Psychiatry. 2002;41:756.

30 Scharman EJ, Erdman AR, Cobaugh DJ, Olson KR, Woolf AD, Caravati EM, et al. Methylphenidate poisoning: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol. (Phila) 2007;45:737–52.