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New designer drug of abuse: 3,4-Methylenedioxypyrovalerone (MDPV). Findings from apprehended drivers in Finland

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ABSTRACT

Starting in 2008 a new designer drug, 3,4-methylenedioxypyrovalerone (MDPV) appeared among users of illegal drugs in Finland. Since then there have been several seizures of MDPV by police and customs and it has been connected to many crimes of different types. In this study the incidence and impact of the use of MDPV in drivers suspected of being under the influence of drugs (DUID) in Finland was assessed.

Since autumn 2009, blood samples from drivers suspected of DUID in Finland have been analysed for the presence of MDPV. A new LC–MS/MS method for the determination of MDPV in serum was established. In order to assess the impact of MDPV on driving performance, drug and alcohol findings of positive MDPV cases were compared with data from the clinical examination carried out while the suspect was under arrest. In a period of one year there were 259 positive MDPV cases from apprehended drivers (5.7% of all confirmed DUID cases). In 80% of the cases in which MDPV was found, amphetamine was also present. Benzodiazepines were also frequently found together with MDPV, which was to be expected since in Finland, in our experience, stimulants are very often used together with benzodiazepines.

In most cases it remained unclear whether the observed psycho-physical achievement deficiency was induced by MDPV because the concentrations of other drugs, especially other stimulants, were often high. However, in some subjects, MDPV, or MDPV in combination with other substances was the most probable cause of the impairment. The concentrations of MDPV varied from 0.016 mg/L to over 8.000 mg/L.

Little is known about the pharmacology of MDPV. However, based on our findings it is clear that MDPV has a serious impact on traffic safety in Finland.

1. Introduction

MDPV (Fig. 1) is a so-called "designer drug" with stimulant effects similar to cocaine and amphetamine. It is an analogue of pyrovalerone, a psychostimulant that was used to treat lethargy and chronic fatigue in the 1970s, but was later withdrawn from the market because of problems with abuse and dependency [1,2]. MDPV structurally resembles cathinone, found in Khat, and has thus been referred to as a synthetic cathinone derivative [3].

MDPV has no medical use and is said to have exceptionally high dependency potential and high risk of psychosis. At higher doses some users report extremely unpleasant "come-down" effects [4]. Police reports indicate that people under the influence of MDPV very often act violently and unpredictably. MDPV is most often sold as powder, but capsules have also been reported. A wide range of dosage forms and routes of administration are used: oral (capsules or powder dissolved in water), IV, rectal [4].

Very recently, Ojanperä et al. published their results about MDPV findings from the urine of opioid-dependent patients [5], which is, other than our results, the only published study about MDPV in clinical samples. There are, however, some data on the pharmacology and toxicology of other structurally similar designer drugs of pyrrolidinophenone or cathinone types available [6–9]. Also some reports on the structure and determination and *in vitro* metabolism of MDPV have been published recently [10–13].

Since the first seizure of MDPV in Finland in 2008, there have been several deaths where involvement of MDPV was suspected by the police (personal communication). Whether the actual cause of these deaths really was MDPV or perhaps some other drug used in combination with it is still not settled. It seems that MDPV is a major phenomenon only in Finland. There have been some reports

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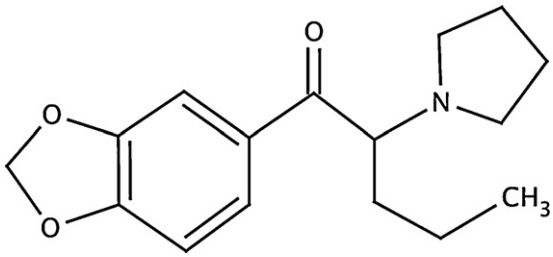

Fig. 1. 1-(3,4-Methylenedioxyphenyl)-2-pyrrolidinylpentan-1-one (methylenedioxypyrovalerone, MDPV).

of cases also in other countries (United Kingdom, Ireland and Sweden) but not on the scale seen in Finland [14–16].

In our laboratory, screening of MDPV was initiated at the request of the Forensic Laboratory of the Finnish National Bureau of Investigation (NBI), after there had been several seizures of MDPV by police. The drug screening procedures currently used by the police in Finland (e.g. DrugWipe, Securetec/Afiniton, Williamsport, PA, USA), fail to detect MDPV, as is true for most other designer drugs. Since August 2009 blood samples from drivers suspected of being under the influence of drugs (DUID) have been analysed for the presence of MDPV. Initially, a qualitative screening method using LC–MS/MS was developed. After a commercial reference standard came available, it became possible to convert this assay into the quantitative confirmation method for the determination of MDPV described in this paper.

In many DUID cases in Finland the suspect is given a psycho-physical achievement test by a physician after the arrest. The requirement for the test is determined by the severity of the suspected crime. The test includes specific psychomotor and cognitive tasks and questions. Based on the results of the tests the physician describes the overall functional impairment of the subject using a three-step scale: within the normal range, mild aberrations, moderate or greater aberrations. Although such tests provide evidence of drug effects on the arrested driver, they do not specifically demonstrate driving impairment [17]. Furthermore, due to the possible impact of acute and chronic tolerance, blood concentrations do not necessarily reflect the degree of impairment observed in the psycho-physical achievement test. These issues lead to difficulty in establishing guidelines for the concentrations of drugs that are dangerous or impair driving. In Finland, the authorities do not need to prove actual driving impairment when a suspect of DUID is taken into custody; a suspicion of DUID is a sufficient reason for the arrest. The psycho-physical achievement deficiency test provides additional information that can be used in setting penalties: higher penalties in cases with aberrations.

The aim of this study was to report on the prevalence and significance of MDPV among drivers apprehended for DUID in Finland. In MDPV positive cases, drug and alcohol findings were compared with data from the clinical examination carried out while the suspect was under arrest. The psycho-physical achievement deficiency information was used to evaluate the significance of the presence of MDPV in DUID cases. We also report concentrations of MDPV in the blood of DUID offenders.

2. Materials and methods

2.1. Chemicals and reagents

The reference standard of MDPV (purity 98%) used for the quantitative determination and the (±)-3,4-methylenedioxyethylamphetamine-d5 (MDEA-d5) used as internal standard were obtained from LGC Standards (Wesel, Germany). For the qualitative analysis that was used before the availability of a reference standard made a quantitative assay possible, a seized MDPV sample (VARA-4108, purity 4%) supplied by NBI Forensic Laboratory, Vantaa, Finland was used to develop the assay and check reproducibility. HPLC grade methanol, water, ammonia 32% p.a. and acetic acid p.a. were purchased from Baker (Griesheim, Germany) and formic acid 98–100% from Merck (Darmstadt, Germany). As the solid phase column an OASIS HLB 1 cc 30 mg from Waters (Eschborn, Germany) was used.

2.2. Sample preparation

The first step of sample preparation consisted of adding 0.8 mL 0.1 M acetic acid and 20 μL of an internal standard solution to 0.2 mL of test material (serum or control). The internal standard solution contained 500 ng/mL MDEA-d5 in methanol. Spiked samples were vortex mixed for 10 s and centrifuged at 13 000 rpm for 3 min.

Sample cleanup was performed by solid phase extraction (SPE) using OASIS HLB cartridges with 30 mg sorbent. The SPE cartridges were conditioned with 1 mL of methanol and 1 mL of deionised water. Supernatants were loaded on the cartridges and drawn through under gravity flow. The cartridges were washed with 1 mL of a mixture of deionised water, methanol and ammonia (93:5:2, v/v/v) and 1 mL of a mixture of deionised water, methanol and ammonia (78:20:2, v/v/v). The cartridges were dried for 10 min in order to remove washing solutions. The analytes were then desorbed with 1 mL methanol and acetic acid (95:5, v/v). The eluted solutions were evaporated under a nitrogen stream at 45 °C, and the residue was reconstituted with 0.5 mL of a mixture of methanol and 10 mM NH_4 acetate in 0.1% formic acid (80:20, v/v). After vortex mixing, 5 μL sample was injected into the LC–MS/MS system.

2.3. LC–MS/MS conditions

The LC–MS/MS system consisted of a Shimadzu LC 20A LC-system and a triple quadrupole mass spectrometer (API 4000, SCIEX) with Turbo Ion Spray. Chromatography with a total runtime of 5.5 min was performed using a phenyl–hexyl 50 mm × 3.0 mm 3 μm column from Phenomenex operated in gradient mode at 0.5 mL/min. Solvent A consisted of methanol and Solvent B of 10 mM NH_4 acetate in 0.1% formic acid. The column oven temperature was set to 40 °C. Multiple reaction monitoring (MRM) was created for the analyte and internal standard (MDPV m/z 276/126 and m/z 276/135, MDEA-d5 m/z 213/163) in positive ion mode at the ionisation voltage of 4200 V, the source temperature being 550 °C.

Integration of peak areas and standard calibration for the MRM transitions were performed using the quantification tool of Analyst 1.5.1 software (SCIEX). Confirmatory analysis was performed based on the ratio of two MRM transitions detected for each analyte.

The validation of the method was performed according to the guidelines of the GTFCh (Gesellschaft für Toxikologie und Forensische Chemie) for limit of detection, limit of quantification, precision, recovery, selectivity and matrix effect [18]. No interference was found with any of the 38 most commonly occurring stimulants, sedatives and opioids that were analysed together with MDPV. The procedure also included verification of isobar mass transitions from the literature [19,20]. The calculations for the limit of detection were performed according to the German standard specification DIN 32645 [21].

The limit of detection (LOD) for MDPV was 0.003 mg/L and the limit of quantification 0.011 mg/L. The calibration was linear over the range 0.010–0.500 mg/L. For sample concentrations exceeding the calibration range the curve was extended and an approximate value was given as a result. The extraction recovery was determined at the lowest and highest point of the calibration in blank serum, and was found to be 67.9% at 0.200 mg/L and 89.8% at 0.020 mg/L. The matrix effect, measured in 6 different samples, was 21.5%. Precision was measured at two different concentrations, 0.015 mg/L and 0.400 mg/L, by performing two analyses on 8 different days. The standard deviation (CV) of within- and between-day repeatability was between 9.5% and 11.8%. Accuracy ranged between 3.9% and 5.2%.

LC–MS/MS chromatograms of a blank, a spiked sample and a real sample are presented in Figs. 2–4.

3. Results and discussion

Prior to development of the quantitative assay, the screening assay was used to determine whether samples were positive or negative for the presence of MDPV, i.e., above or below the limit of detection for MDPV, 0.003 mg/L. After the quantitative assay became available, samples were initially screened using the non-quantitative assay and for those found to be positive the quantitative assay was performed using a separate aliquot of serum.

In Finland, the number of cases per year of driving under the influence of drugs or alcohol in which a blood sample is taken is over 12 500. In approximately 4570 of them a drug analysis was requested. MDPV is, however, not screened from every sample. Between 28 August 2009 and the end of August 2010, blood

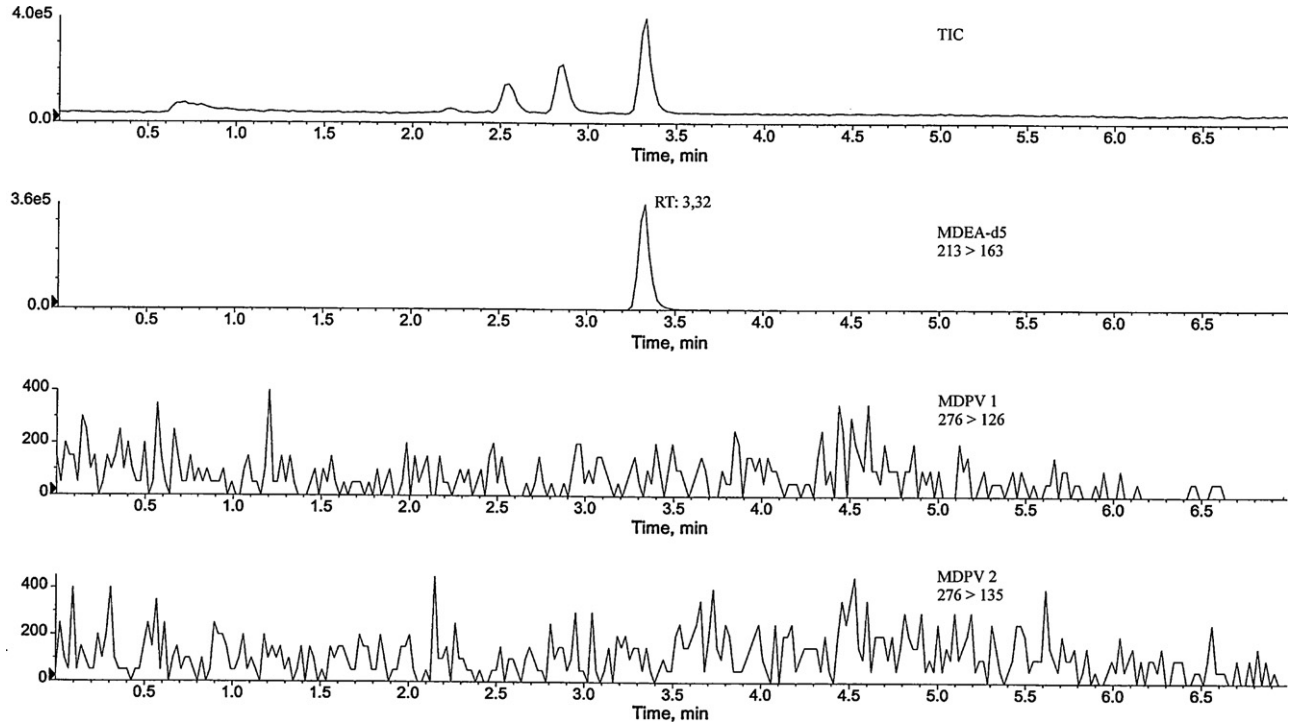

Fig. 2. Total ion chromatogram (TIC) and extracted ion chromatograms (XTC) of a blank sample with 0.050 mg/L of internal standard (±)-3,4-methylenedioxyethylamphetamine-d5 (MDEA-d5).

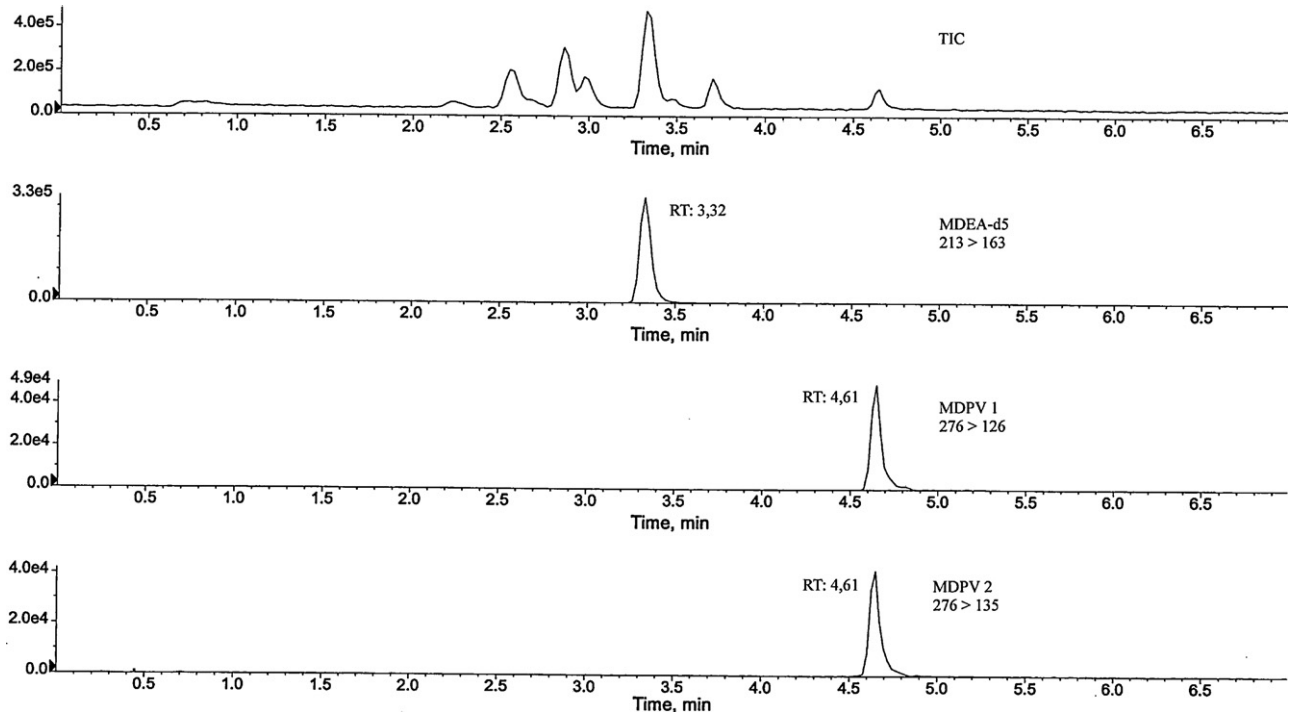

Fig. 3. Total ion chromatogram (TIC) and extracted ion chromatograms (XTC) of a blank sample spiked with a concentration of 0.015 mg/L of methylenedioxypyrovalerone (MDPV) and with 0.050 mg/L of internal standard (±)-3,4-methylenedioxyethylamphetamine-d5 (MDEA-d5).

samples from about 3000 drivers apprehended on suspicion of DUID were analysed for the presence of MDPV. These cases were not selected randomly and are not necessarily representative of the overall DUID population. They were selected partly on the basis of the needs of and information provided by the police, e.g., drivers admitted use of MDPV or amphetamine-like drugs, failure to detect other drugs which could explain aberrant behaviour. A positive immunological blood screening test for amphetamines was also an indication for an MDPV analysis, even though MDPV does not show in that test.

Of the samples screened for MDPV in this one year period, 259 (8.6%, $n = 3000$) were found to be positive. This represents approximately 5.7% of all confirmed DUID cases excluding alcohol-only cases ($n = 4570$) in Finland over the same time

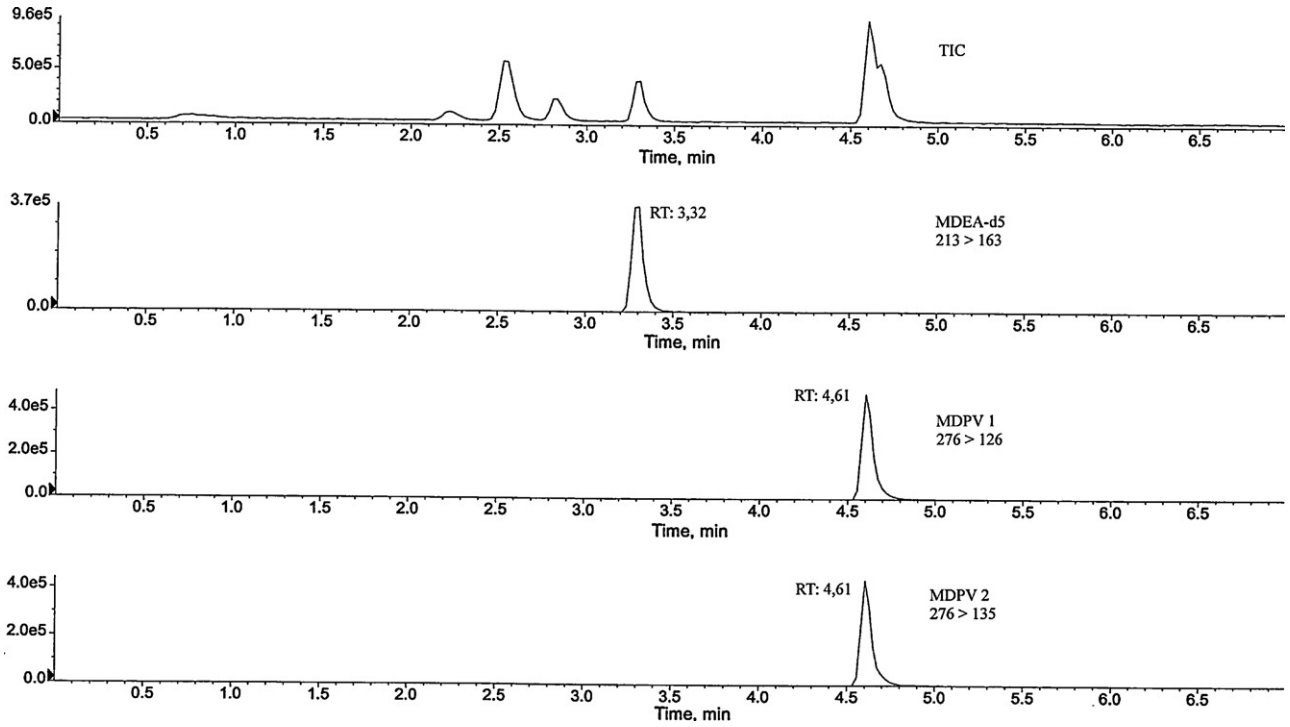

Fig. 4. Total ion chromatogram (TIC) and extracted ion chromatograms (XTC) of a representative positive sample from an apprehended driver containing 0.164 mg/L of methylenedioxypyrovalerone (MDPV) and 0.050 mg/L of internal standard (±)-3,4-methylenedioxyethylamphetamine-d5 (MDEA-d5).

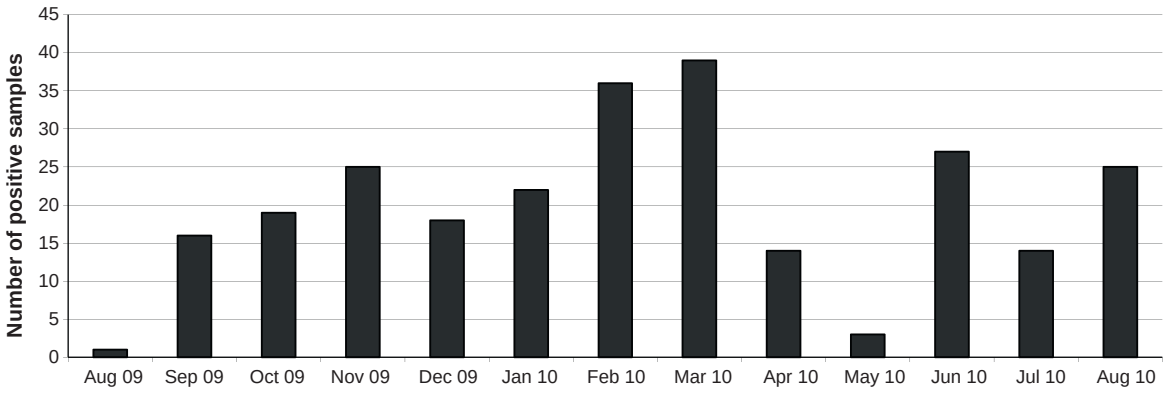

Fig. 5. The numbers of positive methylenedioxypyrovalerone (MDPV) samples among apprehended drivers in Finland between 28 August 2009 and the end of August 2010.

period. The monthly numbers of positive MDPV samples between August 2009 and August 2010 are illustrated in Fig. 5. 87% of the MDPV positive drivers were male, 96% were from Southern Finland and 76% were between 25 and 44 years.

Of all the 259 MDPV positive cases, in 80% amphetamine and in 67% benzodiazepines were also present. A combination of MDPV, amphetamine and benzodiazepines was found in 54% of the cases. Interestingly, MDPV was often found together with phenazepam, which is a widely abused benzodiazepine that has not been approved for prescription use in Finland. Alcohol was present in only 22 cases (8.5%) and in 18 of them was below the level (0.5 g/L) that defines intoxication in Finland. Surprisingly, the levels of benzodiazepines and most other drugs were often low compared to levels associated with major behaviour effects. However, the levels of other stimulants found together with MDPV were in most cases high. The high percentage of multi-drug findings among the positive MDPV samples is generally typical of DUID cases in Finland [22]. In 8 cases were no other compounds besides MDPV found.

The concentrations of MDPV in samples from a typical month, August 2010, are shown in Fig. 6. The concentration range is very similar to the range of amphetamine concentrations that we see in the DUID samples in Finland. There were two remarkable outliers (2.4 mg/L and 8.4 mg/L) in these samples. Unfortunately, no data

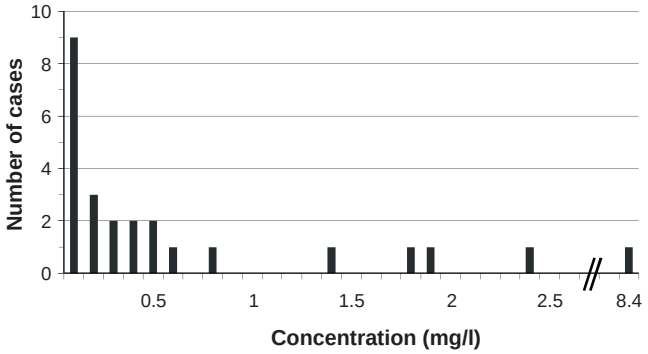

Fig. 6. Concentrations of methylenedioxypyrovalerone (MDPV) found in the 25 blood samples from apprehended drivers selected for analysis in August 2010.

Table 1
Concentrations of methylenedioxypyrovalerone (MDPV) and other drugs in positive samples from August 2010.

Sample	MDPV (mg/L)	Benzodiazepines[a]	Stimulants[b]	Cannabis[c]	Other findings	Clinical examination
1-08/2010	0.430	±	++		Ethanol	Normal
2-08/2010	1.700	±	++			Aberrations monitored, no overall functional disorder
3-08/2010	1.310	+	++			Aberrations and functional disorder monitored
4-08/2010	2.400					
5-08/2010	0.049	±	++			Aberrations monitored, no overall functional disorder
6-08/2010	0.330	++	++		Methadone	Aberrations and functional disorder monitored
7-08/2010	0.020		++	+		Aberrations and functional disorder monitored
8-08/2010	0.142		+			
9-08/2010	0.020	±	++			
10-08/2010	0.860	±	++	±		Normal
11-08/2010	0.270	+	+		Methadone	Aberrations monitored, no overall functional disorder
12-08/2010	0.050		++			
13-08/2010	0.031	+	++		Zolpidem	
14-08/2010	0.020	±	+		Buprenorphine, tramadol	Aberrations monitored, no overall functional disorder
15-08/2010	0.090		++		Methylphenidate	
16-08/2010	0.380	±	+			Aberrations and functional disorder monitored
17-08/2010	0.550	+	+			
18-08/2010	8.400		++		Methadone	
19-08/2010	0.120	+	++			Aberrations monitored, no overall functional disorder
20-08/2010	0.450	+	++			Aberrations monitored, no overall functional disorder
21-08/2010	0.240	+	++	±		Aberrations and functional disorder monitored
22-08/2010	0.044		++			Normal
23-08/2010	0.044	+	++			
24-08/2010	1.900	±	+			Normal
25-08/2010	0.110		+	+		

[a] ±One or more benzodiazepines with insignificant concentrations.
+One or more benzodiazepines at concentrations up to those seen at prescribed doses.
++One or more benzodiazepines with concentration above those seen at prescribed doses.
[b] +Amphetamine, methamphetamine or MDMA concentration <0.100 mg/L.
++Amphetamine, methamphetamine or MDMA concentration ≥0.100 mg/L.
[c] ±No THC, but THC–COOH positive.
+THC positive.

either on history of drug use or clinical examinations are available in these two cases.

The psycho-physical achievement deficiency test was performed on 208 MDPV positive cases. Functional impairment was found in 84% of these 208 cases but in only 7% was the impairment rated as moderate or greater. Typically the observed aberrations included difficulty in defining the current time, walking in a straight line, turning around and speech. As already mentioned, this evaluation does not demonstrate driving impairment directly, but does give some insight into the impact the drugs had on the subject at the time of the examination. In particular, the impaired judgement and increased willingness to take risks that are associated with the use of stimulants do not necessarily show in the clinical examination.

A summary of the levels of MDPV and other drugs and findings in the clinical tests of the 25 positive samples from August 2010 is illustrated in Table 1. In most MDPV positive cases there was also a considerable amount of amphetamine present in the blood of the suspect. However, there have been some cases where there was reason to believe that the impairment was mainly caused by MDPV. Overall, in 60 of the 259 MDPV positive cases, the analyses showed no other substances, or, the substances found were not at levels sufficient to explain the driving impairment that lead to the arrest. In most of such cases no clinical examination was performed. We introduce one case as an example, where the clinical examination was indeed performed and the concentrations of other drugs beside MDPV were relatively low (case 16-08/2010 in Table 1). The samples of this case were received from the police in Helsinki in the middle of August 2010. The suspected DUID offender was a 28-year old male who had been driving a van at night and had been reported to the police by a citizen. The reason for the report is not known. A roadside drug test was performed on the suspect and it showed positive results for benzodiazepines and amphetamines. The suspect showed aberrations in the clinical examination, including: unstable gait, balance problems in Romberg's test, his thinking was not clear, depressed and apathetic mood and pupil reaction to light was delayed. In the opinion of the examining physician, the suspect also attempted to disguise his impairment in order to give a misleading impression of normal functioning. The overall functional impairment was, however, estimated to be moderate. The drug analysis of the suspect's blood showed 0.380 mg/L MDPV, low concentrations of benzodiazepines (alprazolam 0.002 mg/L, nordiazepam 0.020 mg/L and oxazepam 0.094 mg/L) and relatively low concentrations of other stimulants (amphetamine 0.092 mg/L and methamphetamine 0.023 mg/L). These other findings were considered to be insignificant in respect to the suspected driving impairment.

There were 219 seizures of MDPV by Finnish Police between 1 January and 31 June 2010 (Fig. 7), accounting for about 45% of all designer drug seizures. Samples of the seized materials were analysed in NBI Forensic Laboratory, Vantaa, Finland. Some samples were found to contain MDPV alone but others contained various mixtures which combined MDPV with benzodiazepines (especially phenazepam) and with other stimulants (especially amphetamine). MDPV confiscated by the Finnish customs has been of Chinese origin.

In the view of the fact that in the past 10 years over 100 new psychotropic substances have appeared on the illicit drug market all over the world, the incidence of MDPV among drivers in Finland is exceptional [23]. MDPV was first reported as new psychoactive substance to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and Europol in 2009 [24]. In Finland MDPV was classified as an illegal drug in June 2010. It has been shown that law enforcement is not a particularly effective deterrent and does not necessarily decrease the prevalence of a particular drug among drivers [25]. However, prior to June 2010 MDPV distributors had the advantage that the drug was not illegal. Presumably, its new designation as an illegal drug will make it less

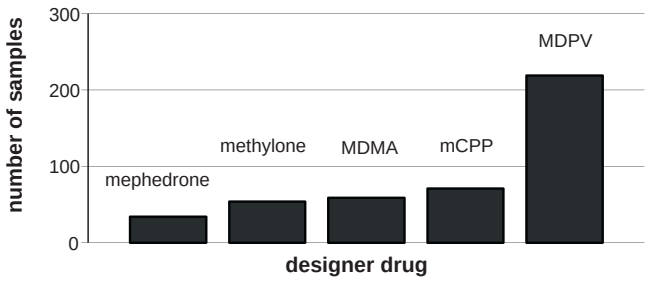

Fig. 7. Most abundant designer drugs seized in Finland between 1 January and 31 August 2010 and analysed by the Finnish National Bureau of Investigation Forensic Laboratory, Vantaa, Finland.

attractive to distributors and result in reduced availability of MDPV.

4. Conclusions

Given the non-random sample selection process and the fact that clinical evaluation and quantitative MDPV data was only available for a sub-set of the samples, the results must be interpreted with particular caution. Nevertheless, it can be concluded that the incidence of MDPV in confirmed DUID cases (excluding alcohol-only cases) is at least 5.7% and could be higher. This is a remarkable number considering that MDPV is a relatively new substance that has only been in Finland for about 2 years. The preponderance of males among MDPV positive cases is typical of all kinds of DUID cases and the 25–44 age range is typical of non-alcohol DUID cases, in our experience. The very high percentage of MDPV positive cases from Southern Finland is somewhat unusual and may reflect a limited distribution of the drug in Finland at this time. The data strongly suggest that MDPV is responsible for at least a portion of the behavioural abnormalities and driving difficulties observed. Since MDPV is most often found together with other psychoactive drugs, it is difficult to determine whether the observed driving impairment was indeed caused by MDPV exclusively, or rather by the combined effect of several substances. However, the results of this study show that MDPV use is a significant problem in DUID cases in Finland. Since at this point it has only been a few months since the legislative change in respect to MDPV, more time is needed to determine whether a decline in the incidence of the drug among Finnish drivers will be achieved. In addition, further studies are needed in order to gain more information on the pharmacology and toxicology of MDPV and to be able to determine what concentrations are dangerous.

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