Concentrations of mephedrone in cases of fatal and non-fatal clinical intoxications

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Introduction

Mephedrone (4-methylmethcathinone, 4-MMC) has become established as a permanent illicit drug in the dynamic new psychoactive substances (NPS) scene.

Objectives and Aims

The aim of this work is to collect published data on the mephedrone concentrations in biological samples from cases of acute intoxications (fatal and non-fatal) and compare with results from human pharmacokinetics studies, wastewater and anonymous pooled urine analysis

Methods

The PubMed® database complemented with Google Scholar® were systematically searched from database inception until February 15, 2017, to find published cases of mephedrone intoxications and concentrations in biological samples.

Results

Over the studied period, a total of 437 articles were identified for the general search “mephedrone OR 4-methylmethcathinone”, only publications including specific toxicokinetics criteria were included to review consideration.

A total of 97 fatal cases and 57 non-fatal intoxication providing mephedrone concentrations in human biological matrices and attributed directly or indirectly to mephedrone were found. Mephedrone mean blood concentrations from fatal cases were 2,663 ng/mL (range 51-22,000 ng/mL), and from non-fatal cases mean were 166 ng/mL (range, 13-412 ng/mL) (Table 1, Table 2). These were in a similar range from data found in controlled studies of mephedrone pharmacokinetics non reporting acute toxicity (135 ng/mL, range 52-218 ng/mL) (Table 3). Forensic epidemiology studies based on wastewater and anonymous pooled urine analysis point towards similar variations in use (nightclub scene) to those self-reported in surveys and questioners.

Table 1. Mephedrone concentrations in human biological samples from fatal cases

Subjects	Blood		Clinical presentation
	Mephedrone (ng/mL)	Other drugs	
N=1	500	ND	Unresponsive
N=1	22000	Diazepam, nordiazepam, amphetamine	Method validation
N=1	3300	NT	
N=1	5700	NT	
N=1	1200	NT	
N=1	980 (femoral)	Atropine, naloxone,	Collapsed
N=1	2240 (femoral)	Atropine, 3-TFMPP	Shake and twitch, sweaty and acting strangely
N=1	130 (femoral)	Methadone, diazepam, nordiazepam, olanzepine, chlorpromazine metabolite	Unresponsive
N=1	230 (femoral)	NR	Traffic collision
N=1	51	NR	Metabolism study
N=1	5100(femoral)	Cocaine, benzoylecgonine, methylecgonine, MDMA, oxazepam, midazolam	Fury
N=42	1483 (10-22.000)	Positive /negative	NPSAD data record
N=1	500 (blood heart post-mortem)	GHB (blood heart post-mortem)	Unconsciousness
N=12	160 (3-650)	Positive	Sudden death
N=1	5500	NT	Critical state
N=1	1300	Methcathinone, ethanol	No signs of life
N=1	1330	Ethanol, cocaethylene	Found death
N=1	2600	Methylone	Death in bed
N=1	692	Pentedrone	Death
N=1	200	Heroin, butylone, venlaflaxine, zopiclone, diazepam, quetiapine	Cardiorespiratory arrest
N=21	720	Positive/negative	NPSAD, EU-MADNESS data record (incomplete)
N=1	--	Alpha-PVP	Found death (carbon monoxidetoxication)

NR: not reported
NT: not tested

Table 2. Mephedrone concentrations in human biological samples from non-fatal cases

Subjects	Blood		Clinical presentation
	Mephedrone (ng/mL)	Other drugs	
N=1	150	Negative	Palpitations, blurred tunnel vision, chest pressure, sweating, unwell feeling
N=1	193	THC, 11-OH-THC, 11-nor-9-carboxy-THC	Unconsciousness
N= 1	NR	NR	Method validation
N=10	NR	NR	Method validation
N=32	210 (10-740)	Negative/Positive	Agitation, hyperactivity, twitching movements, sweat and chew the inside of cheeks, no eye contact, lack of coordination, slurred speech, field impairment tests test failed… Appearance of highly intoxicated
N=1	39	Diazepam, nordiazepam, temazepam	Unsteady on feet, dilated pupils, drunkenness, slow speech
N=1	40	None	Slumped across steering wheel, drooling, difficult to wake, dilated pupils
N=1	56	THC	Thirst, drowsiness and hyperactivity
N=1	110	MDA, MDMA, cocaine, THC	Drowsiness, thirst, hyperactivity
N=1	350	None	Dilated pupils
N=1		MDMA	Chewing gums, twitchy, fidgety, dilated pupils, hyperactivity, thirst
N=1	412	THC ,11-OH-THC, THCCOOH, amphetamine	Delayed reaction time, deranged sensation of time, deficiency in concentration and pupil abnormalities
N=1	NT	NT	Method validation
N=1	NT	NR	
N=1	52	THC, THCCOOH	Talkative, accelerated heart rate and sluggish pupil reaction to light
N=1	13	3-MMC	NR
N=1	NR	NR	Delirious, tachycardia

NR: not reported
NT: not tested

Table 3. Mephedrone concentrations in human biological samples (clinical trial)

Subjects	Oral dose (mg)	Blood (ng/mL)	Setting	Clinical findings
N=12	200	135	Clinical Trial Unit	Prototypical acute effects/ Method validation
N=12	200	159		
N=6	150	123		
N= 3	100	22		
N= 3	50	42		

Conclusions

Mephedrone blood concentrations in cases of fatal intoxications were higher than in non-fatal cases. In both, great variability in mephedrone concentration were found that could be explained by interindividual differences in pharmacokinetics-pharmacodynamics, dose and routes of administration and concomitant poly-drug use.

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