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The designer drug situation in Ibiza

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Abstract

A total of 137 urine samples and 46 serum samples, corresponding to 154 self-confessed designer drugs consumers in Ibiza island, were analyzed for the presence of designer drugs: amphetamine and amphetamine derivatives (methamphetamine, methylenedioxymethamphetamine (MDMA), methylenedioxyethylamphetamine (MDEA), methylenedioxyamphetamine (MDA), *p*-methoxymethylamphetamine (PMMA), *p*-methoxyamphetamine (PMA), etc.), ketamine and γ-hydroxybutyric acid. Among this population, coming both from the forensic clinic and from the emergency room of a hospital, a total of 99 cases were found positive for some designer drug. This study shows the prevalence of methylenedioxymethamphetamine (MDMA) among designer drug users, sole or in association with other drugs. Also, the mixture of MDMA with other designer drugs, ethanol and/or cocaine is shown to be more likely to produce toxic symptoms requiring clinical attendance in a hospital emergency room. These findings along with the consumption history, the concentrations of drugs and metabolites in urine and serum and the toxicological significance for the interpretation of some MDMA metabolites such as 4-hydroxy-3-methoxymethamphetamine (HMMA) are discussed in this study.

Keywords: Designer drugs; MDMA metabolites; Amphetamine derivatives

1. Introduction

It is well known that recreational life is a characteristic of Ibiza island, specially in summer time, when the arrival of visitors from other countries becomes massive. In 1999, 700,000 English tourists visited Ibiza between January and September and the island with a population of 80,000 people attended the visit of 1,500,000 tourists [1]. Ibiza is undoubtedly the most popular place in Europe for its night clubs; the association between disco music and drug consumption, specially designer drugs in young people, has been known for long. In 1986 ecstasy started to be used in this island as the most suitable substance to accompany the kind of music performed in these ''discos'' [2]. From then on Ibiza's popularity has increased enormously helped by cheap international flights and cheap holiday packages specially directed to young people. Other designer drugs such as ketamine and γ-hydroxybutyric acid (GHB, called by users ''liquid ecstasy'') appeared as novelties later on in this scenery. They are substances which have become popular in recreational life, and are easily accessible because of their reasonable cost. Given the illicit source of these substances, it is unknown to the individual whether a given tablet contains amphetamine, methamphetamine, methylenedioxymethamphetamine(MDMA), methylenedioxyamphetamine (MDA), methylenedioxyethylamphetamine (MDEA), ephedrine or any other compound. The names employed among the users to identify the tablets, generally refer to the logo of the tablet (Mitsubishi, Superman, etc.) but do not give any idea of its chemical composition [3]. The ingestion of tablets is often accompanied by the intake of alcohol or other drugs.

Due to all these facts Ibiza island represents an ideal frame for the study of designer drugs and so we were asked by our authorities to collaborate in a multiple study among designer drugs users in Ibiza in order to evaluate the drugs

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more frequently used in the island and the extent of use of methylenedioxymethamphetamine (MDMA). Two different categories of users were included in the study: users of designer drugs, who had been arrested when committing some offence and designer drug users who were admitted to the emergency room of a hospital with some toxic symptoms.

There are not many data from MDMA users concerning concentrations of MDMA and its metabolites although some MDMA studies have been performed in healthy volunteers. Methylenedioxyamphetamine (MDA) was firstly reported as the main metabolite of MDMA in one case after the ingestion of a single dose [4]. Many fatal cases have been published giving both MDMA and MDA concentrations [5–9]. 4-Hydroxy-3-methoxymethamphetamine (HMMA) and other metabolites were reported first in rats [10] and then in human urine in one post-mortem case [11]. Pharmacokinetic and metabolic studies have been performed on patients in controlled clinical studies, generally with a small number of individuals and relatively low doses [12,13]. These studies have provided important information on the metabolic pathways of MDMA and have shown great variety among individuals [14,15]. The large interindividual variations were also reported by Kunsman et al. in an interesting study attempting to give MDMA/MDA ratios in urine [16]. Many other studies focus on the crossreactivity of the different commercial immunoassays for the detection of MDMA in urine, not dealing with real samples, but with spiked ones [17]. Yet there is no literature available that provide MDMA, MDA and HMMA data in urines of street users, where the concentrations found may account for the last tablet ingested but also for the summing up of other doses in different stages of metabolism.

We present a compilation of the toxicological data from all the positive samples collected in Ibiza from June 2000 to October 2000, in which some ‘‘designer drug’’ was detected. The purpose was to determine the designer drugs more frequently used, the extent of use of MDMA, the association between drugs and the differences between users without apparent symptoms (group of people under arrest) and users with toxic symptoms (received at the emergency room of a hospital). In the cases where MDMA was found, we tried to assess metabolites previously published [11–13], study their concentration range in urine and serum and report some observations made upon these findings.

2. Specimen acquisition

The material consists of two categories, viz urine samples collected at the forensic clinic of 96 designer drugs users who had been arrested for committing some offence (drug trafficking, robbery, etc.) and who voluntarily confessed the recent intake of some designer drug and agreed to provide an urinary sample. The second category consists of samples (urine and in some cases serum) of 58 subjects who were admitted to the emergency room of the Can Misses Hospital (Ibiza) presenting toxic symptoms after the intake of some designer drug.

At the time of the sample collection, data concerning history of addiction, last drug consumed, time elapsed since the last consumption and pattern of consumption, were gathered in a specified questionnaire constructed for the study. Samples were refrigerated until analysis.

3. Toxicological analysis

3.1. Screening of urines

A preliminary immunoassay was performed on a Hitachi 902 Automatic analyzer, using original CEDIA reagents for opiates, cocaine, cannabis, lysergic acid diethylamide (LSD) and amphetamines (monoclonal). The sensitivity of the immunoassay was as given by the manufacturer: 300 ng/ml for opiates, 150 ng/ml for cocaine, 25 ng/ml for cannabis, 2.5 ng/ml for LSD and 1000 ng/ml for amphetamine.

3.2. Methodology

As it is well known, amphetamine reagent has different crossreactivity for the different amphetamine derivatives, thus giving false negatives for some of them depending on the concentration. For that reason, regardless of the results of the amphetamine immunoassay, all the samples were analyzed for amphetamine derivatives: to 2 ml of urine, the internal standards (amphetamine-d5 and methylenedioxymethamphetamine-d5 in all the cases; benzoylecgonine-d3 and/or morphine-d3 and/or methylphenidate if the results of the inmunoassay were positive for cocaine, opiates and amphetamine respectively) were added and the pH was adjusted to 9 with borate buffer. The samples were vortex mixed for 10 min, and poured into a Chemelut column (Varian, Middelburg, The Netherlands). After 10 min, the elution was carried out with 10 ml of 2-propanol-dichloromethane (10:90). The eluates, spiked with 10 μl of ClH, were evaporated under nitrogen. The extracts, reconstituted in methanol, were analyzed by high-performance liquid chromatography (HPLC) with diode array detection. The same extracts of the samples used for HPLC, were derivatized with pentafluoropropionic anhydride (PFPA) and hexafluoroisopropanol (HFIP) and subjected to gas chromatography–mass spectrometry (GC–MS) for the detection of amphetamine derivatives and confirmation of other findings. The quantification of MDMA and metabolites was performed by CG–MS using adequate calibration curves with the deuterated internal standard. When the amount of MDMA exceeded 1 μg/ml, the quantification was performed by HPLC, using methylphenidate as internal standard for the quantification. The combination of the HPLC screening [18] and GC–MS confirmation [19,20] in the aliquot of urine accounted for the results in amphetamine

derivatives, opiates, cocaine and other basic drugs such as ketamine.

For conjugated metabolites of MDMA, hydrolysis with β-glucuronidase (Sigma, St. Louis, Mo. USA) was performed in the urine prior to the extraction.

For LSD and its main metabolite 2-oxo-3-hydroxy-LSD, another aliquot of the urine was extracted following the method published by Foltz and co-workers [21], using GC–MS for quantification with LAMPA as internal standard.

When γ-hydroxybutyric acid (GHB) was suspected, another aliquot of the urine was analyzed using the method published by Couper and Logan [22] using GHB-d6 as internal standard for quantification.

When alcohol was suspected, the urine ethanol analysis was performed by gas-chromatography with flame ionization detection (FID) and automatic head space injection, using propanol as internal standard for quantification.

Cannabis main metabolite in urine, 11-nor-Δ^9-tetrahydrocannabinol carboxylic acid was analyzed by GC–MS using 1 ml of urine and its corresponding deuterated standard for quantification.

Unfortunately, not all the cases had sufficient amount of urine to perform all the analysis. In some cases (mainly in the emergency room group), not even the immunoassay could be performed, and thus priority was given to the analysis of amphetamine derivatives. In other cases, the volume of urine was larger but the results of the immunoassay were positive for many of the drugs (LSD, cannabis, etc.) so priorities were to be decided for the confirmation of the other drugs. Our criteria for these priorities was: (1) as said, amphetamine-derivatives in an aliquot which, as explained, could also be used for opiates, cocaine and other basic drugs analysis; (2) immunoassay; (3) LSD if the immunoassay was positive for this drug; (4) other drugs reported used in the questionnaire (alcohol, GHB). When MDMA was positive and the amount of urine was sufficient, enzymatic hydrolysis with β-glucuronidase was performed in other aliquot in order to study the conjugated metabolites. Last, when urine was still left, analysis of THC was performed on a 1 ml aliquot.

Serum samples were always scarce and in a few cases, it was the only sample available. Priorities were given as for the urine but unfortunately, some drugs such as alcohol could not be analyzed. The extraction procedure for serum was as follows: to 1 ml of serum, the internal standards amphetamine-d5, methylenedioxymethamphetamine-d5, benzoylecgonine-d3 and morphine-d3 were added. The extraction was performed as for urine but the dry extract, derivatized with PFPA and HFIP, was directly taken to GC–MS for the analysis of amphetamine derivatives, opiate metabolites and cocaine metabolites.

3.3. Accuracy and precision of the methods

Under the chromatographic conditions used, there was no interference with all drugs or deuterated internal standards by any extractable endogenous materials in the control urines and serum. The calibration curves for determination of the drugs and metabolites were constructed by analyzing the extracted and derivatized control specimens spiked with the standard solutions of these drugs and the corresponding internal standard. The calibration curves for MDMA, MDA, HMMA, BE and morphine were linear over the concentration range 0.010–1 μg/ml in serum and 1–50.00 μg/ml in urine with correlation coefficients of $r = 0.998$ and 0.999, respectively. For LSD and its metabolite the linearity range was 0.1–50 ng/ml and for GHB it was 25–500 μg/ml with correlation coefficients of $r = 0.989$ and 0.991, respectively. The coefficients of variation of the analysis ($n = 6$) for control urines spiked with standard solutions of MDMA, MDA, HMMA, BE and morphine at 0.10 and 1.00 μg/ml were in the range of 3.2–12.05%. The coefficient of variation for control urines spiked with standard solutions of LSD at 1 ng/ml and 2-oxo-3-hydroxy-LSD at 20 ng/ml were in the range of 15 and 10%, respectively. The coefficient of variation for GHB at 30 and 250 μg/ml were in the range of 7–10%.

4. Results and discussion

Results are presented in three different tables. They show the consumption history (usual kind of consumption, last tablet ingested, time elapsed since and scene of consumption) as reported by the individual and the toxicological findings in urine and plasma. They have been separated in Tables 1 and 2 (arrestees) and Table 3 (emergency room cases) so as to compare the toxicological findings in these groups more easily. The only difference between Tables 1 and 2 is whether urine hydrolysis was performed or not. Due to the importance of MDMA, the cases are presented in increasing order of MDMA concentration in urine. Cases without MDMA appear at the end of each table.

Tables 1 and 2 present the results of 70 of the 96 arrested people, who were found to contain some designer drug. Out of these, 54 cases contained MDMA as sole designer drug; other 14 cases contained MDMA together with another designer drug such as amphetamine, ephedrine, MDEA, 2-chloro-4,5-methylenedioxymethamphetamine (Cl-MDMA), MDMA, metamphetamine or ketamine. In comparison, only two cases contained amphetamine as sole designer drug. These are real data that confirm that the compound MDMA is the most abused designer drug in Ibiza.

Regarding other drugs, cocaine was found in 39 of the 70 cases and cannabis was found in 41 cases. Ethanol was analyzed in 26 cases and only one was found positive.

In all the cases where MDMA was found, the concentration of the parent drug and the concentration of MDA and HMMA are given. For this metabolite, in cases where hydrolysis was performed (Table 2), the concentration of total HMMA is given in brackets besides the concentration of the free metabolite.

Table 1
Arrestees (hydrolysis not performed)

Identification no.	Consumption history				Results in urine		
	Kind of consumption of the designer drugs	Time elapsed	Scene	Tablet (shape/colour/logo)	Designer drugs		Other drugs
					MDMA/MDA/HMMA	Other designer drugs	
7827	Weekend	Unknown	Leisure area	Unknown	0.01/Neg/Neg		BE 0.65 Ethanol NP
7817	Weekend	48 h	Leisure area home work	Round/blue/“Versace”	0.02/Neg/Neg		Ethanol NP
7805	Sporadic	30 days	Leisure area	Round/white/star	0.05/Neg/Neg		THC 0.14 Ethanol NP
7801	Sporadic	Unknown	Leisure area	Round/white/“EURO”	0.05/Neg/Neg		Ethanol NP
7793	Sporadic	4 days	Leisure area	Unknown	0.13/0.05/0.01		Ethanol NP
7808	Weekend	Unknown	Home leisure area	Triangle/white/“Mitsubishi”	0.14/0.34/0.04		BE 9.67 THC 0.14 Ethanol Neg.
10286	Sporadic	Unknown	Leisure area	Unknown	0.23/0.03/0.37		THC 0.04 Ethanol NP
7795	Weekend	>72 h	Leisure area	Triangle/grey/“Mitsubishi”	0.34/0.12/1.28		BE 1.93 Ethanol NP
10308	Sporadic	3 days	Leisure area home	Unknown	0.49/0.50/0.15		BE 1.37 THC 0.08 Ethanol NP
6581	Unknown	Unknown	Unknown	Unknown	0.77/0.04/0.02		BE 2.83 Ethanol NP
7800	Weekend	4 days	Leisure area	Round/beige	1.78/0.90/0.18		BE 77.85 THC 1.26 Ethanol Neg.
7782	Weekend	<24 h	Leisure area	Round/white/heart	1.88/0.28/0.11		BE 7.20 Cocaine 0.76 THC 0.17 Ethanol Neg.
7788	Sporadic	Unknown	Leisure area	Unknown	2.06/0.49/0.03	Amphetamine 0.45	Ethanol NP
7797	Weekend	24–48 h	Leisure area	Round/white/“Mitsubishi”	2.21/1.03/0.36		BE 0.50 THC 0.30 Ethanol NP
7799	Habitual	20 h	Leisure area	Round/white/“Rolex”	2.34/0.04/0.54		Ethanol NP
7798	Weekend	7 days	Leisure area	Unknown	2.57/1.09/0.06		BE 0.31 THC 0.48 Ethanol Neg.
7807	Habitual	Unknown	Home	Round/brown/“XL”	3.30/1.02/0.34	Norephedrine 0.01 Amphetamine 1.37 Metamphetamine 0.03	THC 0.58 Ethanol Neg.
7802	Weekend	Unknown	Leisure area	Round/white/star	3.26/0.6/0.06		BE 0.26 THC 1.13 Ethanol Neg.

Table 1 (*Continued*)

Identification no.	Consumption history				Results in urine		
	Kind of consumption of the designer drugs	Time elapsed	Scene	Tablet (shape/colour/logo)	Designer drugs		Other drugs
					MDMA/MDA/HMMA	Other designer drugs	
7811	Sporadic weekend	Unknown	Leisure area	Round/white/radioactive	5.61/1.11/0.90		BE 0.48 THC 0.50 Ethanol Neg.
7810	Sporadic	12 h	Leisure area	Round/white/radioactive	7.34/1.35/0.17		BE 0.15 Ethanol NP
7815	Sporadic	48 h	Leisure area	Capsule/white/–	8.32/2.54/0.33		BE 4.30 Ethanol NP
7796	Weekend	18 h	Leisure area	Round/green/"Versace"	9.86/0.97/0.13	Ephedrine 0.27 Amphetamine 1.37	BE 1.17 THC 0.02 Ethanol Neg.
7778	Sporadic	Unknown	Leisure area	Unknown	11.53/2.26/0.18		BE 0.59 Ethanol Neg.
7777	Weekend	Unknown	Leisure area	Unknown	11.78/2.55/0.27		THC 0.02 Ethanol NP
7812	Weekend	1 day	Leisure area	Round/white/radioactive	11.88/1.78/1.37		BE 0.19 Ethanol NP
7780	Habitual	24 h	Leisure area street home	Unknown	14.24/2.25/0.18	MDE 0.10 Ephedrine 0.04	BE 0.25 Ethanol NP
6584	Unknown	Unknown	Unknown	Unknown	16.29/1.53/0.90		THC 0.82 Ethanol NP
7809	Weekend	12 h	Leisure area	Round/white/radioactive	21/1.46/0.23		BE 25.31 THC 0.27 Ethanol Neg.
6562	Sporadic	Unknown	Leisure area	Unknown	21/2.10/0.14	MDE 6.74 Ephedrine 1.10 Norephedrine 0.06 Pseudoephedrine 0.18 Cl MDMA 0.84	BE 4.13 Ethanol 0.84
7784	Weekend	24 h	Leisure area	Round/yellow/"M"	24.55/3.74/0.36	MDE 0.05 Ephedrine 3.13 Norephedrine 1.37 Pseudoephedrine 0.34	THC 0.41 Ethanol NP
7794	Habitual	48 h	Leisure area work	Round/blue/"Versace"	26.35/4.27/0.18		BE 0.06 THC 0.37 Ethanol Neg.
7803	Weekend	6 days	Leisure area	Round/white/bird	27.38/2.27/0.13	Ephedrine 0.06	BE 14.54 THC 0.33 Ethanol Neg.
7791	Weekend	24 h	Leisure area	Unknown	29.61/2.36/0.40		Ethanol NP
7813	Weekend	12 h	Leisure area	Round/white	84.59/5.54/0.91		BE 21.18 Cocaine 0.94 THC 0.35 Ethanol NP

Table 1 (*Continued*)

Identification no.	Consumption history				Results in urine		
	Kind of consumption of the designer drugs	Time elapsed	Scene	Tablet (shape/colour/logo)	Designer drugs		Other drugs
					MDMA/MDA/HMMA	Other designer drugs	
7814	Sporadic weekend	5 days	Leisure area	Round/white/"TT"	101.64/16.03/1.38		Ethanol NP
7787	Weekend	Unknown	Leisure area	Unknown	108.31/7.26/0.32	Ephedrine 0.25 Norephedrine 0.08 Amphetamine 6.62 Metamphetamine 3.40	THC 0.44 Ethanol NP
7783	Weekend	<12 h	Leisure area	Round/white	128.24/7.00/0.32	Ephedrine 1.03 Amphetamine 1.10 Ketamine 1.34 LSD 13.2 Oxo-LSD 42.7	BE 30.84 Cocaine 0.3 THC 0.32 Morphine 0.06 Ethanol NP
7826	Habitual	7 h	Leisure area	Round/white/"Liberty statue"	149/5.97/0.66		BE 0.31 Ethanol NP
10302	Habitual	Unknown	Home	Unknown	175.00/11.00/0.27		BE 36.14 Morphine 0.05 Dihydrocodeine 4.06 Ethanol NP
7790	Weekend	48 h	Leisure area	Round/white/smiling face	225.4/11.8/0.94	Ephedrine 0.03	Ethanol NP

NP: not performed; DD: demethyldiazepam; THC: 11-nor-Δ^9-tetrahydrocannabinol carboxilic acid; BE: benzoylecgonine; Neg: negative result; CocEt: cocaethylene; Oxo-LSD: 2-oxo-3-hydroxy-LSD; all the concentrations are given in μg/ml except LSD and 2-oxo-3-hydroxy-LSD which are in ng/ml and ethanol in g/l.

In all 40 cases of MDMA where hydrolysis was not performed (Table 1) the parent drug MDMA was the major product found in urine. Its concentration ranged from 0.01 μg/ml (Case 7827) to 225.4 μg/ml (Case 7790). Curiously, this latest extraordinary amount corresponds to an individual who reports an elapsed time of 48 h since his last intake. This discrepancy between last intake reported and concentration of MDMA in urine occurs in some other cases. If this is due to an erroneous information, to an accumulation of several doses of drug or to an unique intake of a great number of tablets, remains unknown.

MDA is the second metabolite found in urine followed by the not conjugated demethylenated metabolite HMMA (free-HMMA). Both metabolites are found in 37 cases. Only three cases of this group (7799, 10286 and 7795) have free-HMMA concentration greater than its corresponding MDA concentration and even greater than MDMA concentration in two of them.

In 28 cases where hydrolysis was performed (Table 2) MDMA concentration ranges from 0.05 to 397.48 μg/ml. The ranking: concentration MDMA > concentration MDA > concentration total HMMA was found in 11 cases (cases where MDMA concentration was relatively high). In six cases, total HMMA was greater than its corresponding MDA concentration but lower than MDMA concentration; in eight cases total HMMA was the first metabolite and in two cases (6583 and 10310) only total HMMA was found. The inversion in the concentration ranking seems to occur generally when MDMA concentration in urine is relatively low, probably because the time elapsed since the last intake was quite long.

Total HMMA concentration in the cases where hydrolysis was performed range from 0.03 μg/ml (Case 6583) to 12.62 μg/ml (Case 10304) with MDMA concentrations ranging from 0.05 μg/ml (Case 10311) to 397.48 μg/ml (Case 7792); this narrow range of concentration for total HMMA, as compared to MDMA range of concentration, could be the confirmation, in real cases, of the inhibition of MDMA demethylenation to produce HMMA when MDMA overpasses certain concentration [14]. Also, the persistence of HMMA when very low concentrations of MDMA are still in urine and its presence in two cases in the absence of MDMA and MDA (6583 and 10310) points to a longer clearance of HMMA.

Fig. 1 shows the concentrations of HMMA, both total and free for each of the cases where hydrolysis was performed. As

Table 2
Arrestees (hydrolysis performed)

Identification no.	Consumption history				Results in urine		
	Kind of consumption of the designer drugs	Time elapsed	Scene	Tablet (shape/colour/logo)	Designer drugs		Other drugs
					MDMA/MDA/HMMA	Other designer drugs	
6583	Habitual	Unknown	Unknown	Unknown	Neg/Neg/0.02(0.03)		THC 0.69 Ethanol NP
10310	Sporadic	Unknown	Leisure area	Unknown	Neg/Neg/0.03(0.16)		BE 19.38 THC 1.65 Ethanol Neg.
10311	Sporadic	Unknown	Leisure area	Unknown	0.05/Neg/0.01(0.06)		BE 12.52 THC 0.35 Ethanol NP
10292	Weekend	7 days	Leisure area	Round/white/"EURO"	0.06/Neg/2.38(3.45)		THC 0.03 Ethanol Neg.
6591	Unknown	24 h	Unknown	Round/beige/"Mitsubishi"-clover	0.08/0.06/0.04(0.14)	Ephedrine 0.80 Amphetamine 0.50	BE 13.20 THC 0.01 Ethanol Neg.
10309	Sporadic	Unknown	Leisure area	Unknown	0.09/0.05/Neg(0.04)		BE 0.04 THC 0.34 Ethanol NP
10293	Weekend	Unknown	Leisure area	Round/white/heart	0.17/0.10/0.14(0.70)		THC 0.12 Ethanol Neg.
10300	Habitual	24 h	Leisure area	Unknown	0.23/0.17/0.04(0.60)		THC 0.06 Ethanol NP
10301	Sporadic	4 days	Leisure area	Unknown	0.23/1.17/0.03(0.60)		THC 0.10 Ethanol NP
10280	Sporadic	3 days	Leisure area home	Unknown	0.38/0.05/0.02(0.32)		THC 0.10 Ethanol NP
10303	Unknown	Unknown	Unknown	Unknown	0.42/0.09/Neg(0.06)		Ethanol NP
6593	Weekend	24 h	Unknown	Round/white/"Mitsubishi"	1.47/0.54/0.16(3.11)		BE 2.65 THC 0.06 Ethanol Neg.
10279	Sporadic	4 days	Leisure area	Round/pink/"007"	1.55/0.5/0.02(0.39)		Ethanol NP
10283	Sporadic	48 h	Leisure area	Round/pink/–	2.36/0.67/0.03(0.50)		DD Ethanol NP
10307	Habitual	Unknown	Leisure area workplace	Unknown	2.75/0.63/0.04(3.15)	Amphetamine 1.14	BE 1.58 Ethanol NP
6563	Party	Unknown	Leisure area	Unknown	3.39/1.46/1.79(5.03)	Ephedrine 0.68 Norephedrine0.40	Ethanol Neg.
10306	Sporadic	Unknown	Leisure area	Round/red-white/"Superman"	4.30/1.95/0.17(2.33)		BE 1.58 Ethanol NP
10305	Weekend	48 h	Leisure area	Round/brown/"007"	6.55/3.36/0.48(2.68)		BE 1.50 THC 0.94

Table 2 (*Continued*)

Identification no.	Consumption history				Results in urine		
	Kind of consumption of the designer drugs	Time elapsed	Scene	Tablet (shape/colour/logo)	Designer drugs		Other drugs
					MDMA/MDA/HMMA	Other designer drugs	
7789	Weekend	24 h	Leisure area	Round/white/"CK"	13.18/1.28/2.94(6.55)		THC 0.04 Ethanol NP
10278	Habitual	48 h	Leisure area home	Mushrooms	15.2/1.2/3.63(4.97)		THC 0.50 Ethanol NP
10298	Sporadic	24 h	Leisure area	Unknown	31.5/2.63/0.67(2.74)		THC 0.41 Ethanol NP
10296	Unknown	10 h	Leisure area home	Round/white/arrow	48.17/8.43/0.17(3.14)		BE 117 COC 1.07 COCET 2.98 Ethanol Neg.
6590	Weekend	48 h	Work	Round/blue-grey/star-Liberty statue	49.01/10.05/3.08(10.13)	Amphetamine 0.62	THC 0.01 Ethanol Neg.
10295	Habitual	10 h	Home	Round/beige/"Armani"	53.3/7.5/0.19(2.05)		BE 70 THC 0.40 Ethanol Neg.
6592	Habitual	60 h	Unknown	Round/beige/"Mitsubishi"	79.50/23.84/3.07(12.41)		BE 1.89 Ethanol Neg.
10297	Habitual	10 h	Leisure area	Round/yellow/"Versace"	127.68/9.73/0.44(3.78)		BE 0.44 Ethanol Neg.
10304	Habitual	Unknown	Leisure area	Unknown	172.5/16.0/1.35(12.62)		BE 7.16 THC 0.05 Ethanol Neg.
7792	Weekend	24 h	Leisure area	Round/white/"CK"	397.48/13.50/1.57(2.38)		THC 0.09 Ethanol Neg.
7781	Weekend	3 days	Home	Round/white	–	Amphetamine 0.06	Ethanol NP
7779	Sporadic weekend	Unknown	Leisure area	Unknown	–	Amphetamine 0.85	BE 1.56 THC 0.03 Ethanol NP

NP: not performed; DD: demethyldiazepam; THC: 11-nor-Δ^9-tetrahydrocannabinol carboxilic acid; BE: benzoylecgonine; Neg: negative result; CocEt: cocaethylene; the numbers in brackets correspond to total HMMA.; all the concentrations are given in μg/ml except LSD and 2-oxo-3-hydroxy-LSD which are in ng/ml and ethanol in g/l.

it can be seen, there is a great variability from one case to another; in some cases the difference between free-HMMA and total HMMA is big as compared with cases where this difference is insignificant. No quantitative relationship could be established, but some very interesting observations can be concluded as regards the toxicological significance of HMMA: HMMA is the specific metabolite of MDMA and as such, it should be investigated in all the cases. As a free form, it can be found in non hydrolyzed urines but if it is not found, hydrolysis should be performed in order to detect it. As for each individual case, it is irrelevant if this HMMA is the free or the total amount, provided it is detected in some of the forms as the unequivocal proof of MDMA consumption.

As regards other metabolites, 4-hydroxy-3-methoxy-amphetamine (HMA) was detected in all the cases of hydrolyzed urines but it could not be quantitated as we did not have a reference standard. In the analytical conditions applied for the determination of MDMA and all its mentioned metabolites, other metabolites described by other authors such as 3,4-dihydroxy-methamphetamine (HHMA) and 3,4-dihydroxy-amphetamine (HHA) were not found in the urines [23].

Table 3
Emergency room

Identification no.	Consumption history					Results					
	Kind of consumption of the designer drugs	Time elapsed	Scene	Taken to Emergency room by	Ingested substance	Drugs in urine			Drugs in serum		
						MDMA/ MDA/ HMMA	Other designer drugs	Other drugs	MDMA/ MDA	Other designer drugs	Other drugs
10418	Weekend	48 h	Unknown	Ambulance	Ecstasy alcohol	0.10/0.06/2.73	–	–	N.D.	–	–
10414	Sporadic	1 h	Leisure area	Himself	Cannabis	0.27/0.27/0.22	–	BE 1.35 THC 0.10	N.D.	–	–
10423	Weekend	12 h	Leisure area	Himself	Ecstasy alcohol	0.94/0.14/2.32	–	BE 15.5	0.55/0.03	–	–
10391	Sporadic	8 h	Leisure area	himself	Cocaine alcohol	1.6/0.17/0.32	MDE 0.25	BE 59.16	N.D.	–	–
6572	Habitual	10 h	Street	Himself	Ecstasy tablet liquid LSD	3.53/0.39/4.20	–	LSD 3.32 Oxo LSD 42.6	0.13/0.01	–	–
6574	Habitual	7 h	Leisure area	Unknown	Ecstasy tablet cocaine speed ketamine	3.53/0.29/ 0.14 (3.25)	Ketamine 6.5 Norephedrine 2.87	Cocaine 4.38 BE 5.84 CocEt 0.68 Ethanol 1.55	0.05/0	Ketamine 0.05	BE 0.07
10413	Habitual	3 d	Leisure area	Ambulance	Ecstasy	5.28/1.11/7.54	–	–	N.D.	–	–
10394	Sporadic	5 h	Unknown	Ambulance	Liquid ecstasy	10.44/0.36/2.52	Ketamine 6.23 Norketamine		N.A.	–	–
7819	Sporadic	2 h	Leisure area	Friends	Alcohol ecstasy tablet	12.45/0.82/0.39	–	Ethanol 1.65	0.29/0	–	–
7824	Sporadic	2 h	Leisure area	Friends	–	13.23/1.14/0.09	MDE 1.46	–	N.A.	–	–
7823	Sporadic	3 h	Leisure area	Ambulance	Alcohol ecstasy tablet	13.65/0.51/ 29.78(36.91)	–	Ethanol 0.5	0.10/0	–	–
10396	Habitual	48 h	Home street leisure area	Himself	Cocaine ecstasy	14.95/6.70/7.60	–	BE 218 Ethanol 0.42 THC 0.15	0.34/0.08	BE 0.11	–
10419	Sporadic	24 h	Unknown	Unknown	Ecstasy alcohol	15.2/2.39/0.71	–	–	N.D.	–	–
10398	Habitual	2 h	Leisure area	Himself	Ecstasy alcohol	18.54/5.32/2.88	–	Ethanol 2.3	0.31/0.09	–	–
6575	Habitual	15 h	Street	Ambulance	Ecstasy tablet cocaine liquid GHB	20.13/2.05/6.03	–	BE 3.00 THC 0.07	0.35/0.04	–	BE 0.04
10397	Unknown	1 h	Leisure area	Ambulance	Ecstasy alcohol	22.92/0.50/1.61	–	Ethanol 0.95 THC 0.06	0.22/0	–	–

Table 3 (*Continued*)

Identification no.	Consumption history					Results					
	Kind of consumption of the designer drugs	Time elapsed	Scene	Taken to Emergency room by	Ingested substance	Drugs in urine			Drugs in serum		
						MDMA/ MDA/ HMMA	Other designer drugs	Other drugs	MDMA/ MDA	Other designer drugs	Other drugs
6573	Unknown	Unknown	Leisure area	Himself	Ecstasy tablet LSD	24.69/1.60/6.30	–	LSD 4.8 Oxo LSD 49.88 THC 0.06	0.29/0.02	–	–
10404	Sporadic	5 h	Leisure area	Ambulance	Liquid ecstasy	30.32/2.35/3.11	–	Ethanol 2.46	0.32/0	–	–
7818	Unknown	Unknown	Leisure area	Ambulance	Liquid ecstasy	89.29/7.87/ 1.22 (10.64)	Ephedrine 4.23 Norephedrine 0.81 GHB 34.30	–	0.38/0.04	–	–
10425	Habitual	Unknown	Leisure area	Ambulance	Ecstasy alcohol	289.9/35.4/11.93	–	Ethanol 2.85 THC 0.04	N.A.	–	–
10393	Weekend	2 h	Leisure area	Friends	Liquid ecstasy	404.92/37.7/5.54	Ketamine 1.57 Norketamine Mb Ketamine	THC 0.02	0.85/0.7	Ketamine 0.10	–
10417	Unknown	2 h	Unknown	Unknown	Tablet	–	N.A.	–	0.2/0	–	BE 0.04
7820	Weekend	11 h	Leisure area	Ambulance	Cannabis ecstasy tablet	–	N.A.	–	0.30/0.13	–	BE 0.05
10410	Unknown	4 h	Unknown	Himself	Liquid tablet	–	N.A.	–	0.31/positive	–	–
10416	Unknown	Unknown	Unknown	Unknown	Unknown	–	N.A.	–	0.36/positive	–	–
6568	Sporadic	9 h	Leisure area street	Ambulance	Tablets “ Superman”	–	N.A.	–	0.57/0.06	–	–
10422	Unknown	Unknown	Leisure area	Unknown	Liquid tablet	–	N.A.	–	0.90/0.12	–	–
10392	Sporadic	2 h	Leisure area	Ambulance	Ketamine alcohol	–	Ketamine 0.5 Norketamine	–	–	Ketamine 0.12 Norketamine	–
10399	Unknown	2 h	Unknown	Ambulance	Liquid ecstasy	–	GHB 313 μg/ml	BE 0.3	N.D.	–	–

UNA: urine not available; ND: not detected; BE: benzoylecgonine; LSD: lysergic acid diethylamide; Oxo-LSD: 2- oxo-3-hydroxy-LSD; THC: 11-nor-Δ^9-tetrahydrocannabinol carboxilic acid; CocEt: cocaethylene; GHB: γ-hydroxybutyric acid.

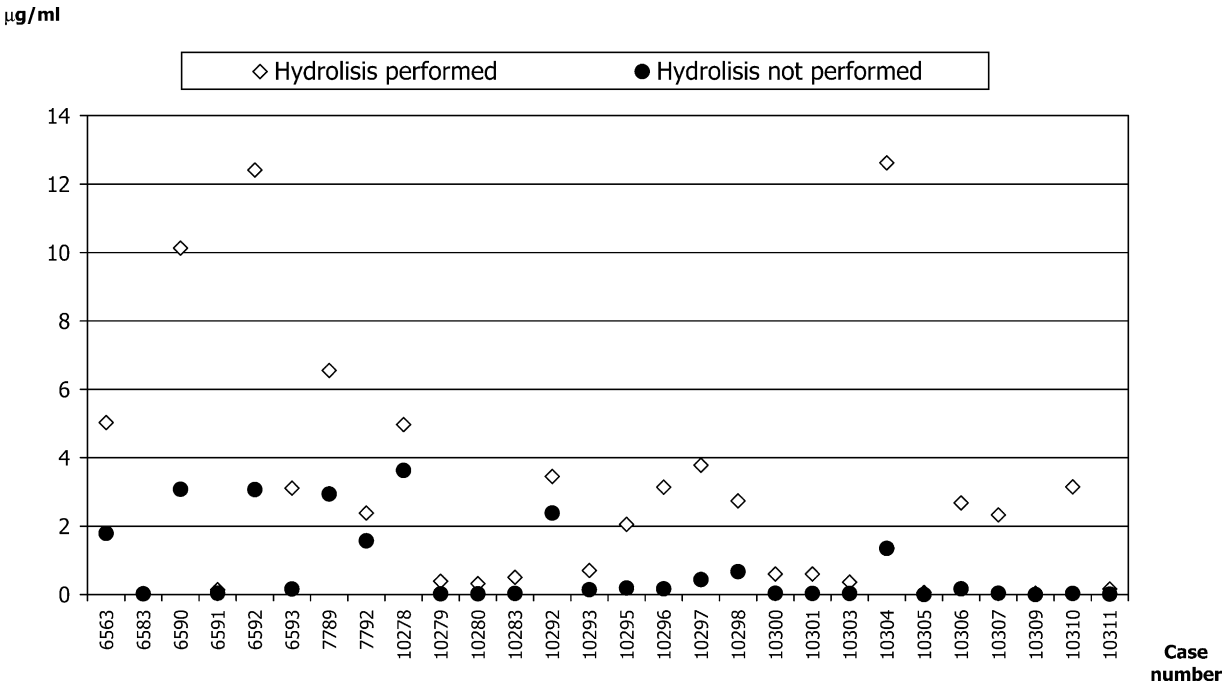

Fig. 1. Cases of the arrestee group where hydrolysis was performed: (◇) concentration of total HMMA and (●) concentration of free-HMMA.

Table 3 presents the 29 cases of self reported "tablet consumers" who were attended in the emergency room. The toxicological findings in urine in this group (23 cases) have similarities with the cases in Tables 1 and 2 but some differences, which may account for the toxicity symptoms, can be pointed out: MDMA as sole designer drug was found in 15 cases: seven of them with alcohol, four with cocaine and two with LSD. In the other eight cases, MDMA was found together with MDEA (two cases), ketamine (three cases) and GHB (one case). It can be concluded that, in this group, the mixture of several designer drugs between them and with alcohol and/or cocaine is the characteristic pattern, and so these mixtures appear to be responsible for the toxic symptoms requiring emergency room attendance.

The concentration of MDMA in urine in this group ranged from 0.10 to 404 µg/ml, quite similar to the ranges of Tables 1 and 2 groups. Unfortunately, only three urines in this group could be hydrolyzed, so no comparison could be done with total HMMA from Table 2; yet, the higher amount of total HMMA was found in this group (36.91 µg/ml in Case 7823) with a level of MDMA of 13.65 µg/ml.

The concentration of MDMA in serum ranged from 0.05 to 0.90 µg/ml with MDMA concentration always exceeding MDA concentration; it will be hazardous to draw conclusions on toxic concentrations in serum as only four cases had MDMA solely and even in these cases the complete analysis as regards alcohol and other drugs could not be performed. Yet, comparing with the cases with MDMA and other drugs which could be held responsible for the toxicity symptoms, the MDMA concentrations in serum do not differ significantly.

5. Conclusion

This study, with real cases of designer drug users both with toxic symptoms (emergency room group) and without them (arrested people group), provide useful data on consumption habits in young European people visiting Ibiza island in holidays. The prevalence of MDMA as designer drug, its association with other drugs, mainly cocaine and alcohol, the latest producing toxic symptoms, should be underlined. The information provided here on concentrations of MDMA and its metabolites in urine, the toxicological significance of HMMA and the serum levels of MDMA supplied may prove useful for the forensic interpretation of cases related to abuse of amphetamine derivatives.

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