Human Pharmacology of MDMA

Pharmacokinetics, Metabolism, and Disposition

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Abstract: MDMA (3,4-methylenedioxymethamphetamine, ecstasy) is a widely misused psychostimulant drug abused among large segments of the young population. Pharmacologically it displays effects related to amphetamine-type drugs and a set of distinctive effects (closeness to others, facilitation to interpersonal relationship, and empathy) that have been named by some authors "entactogen" properties. MDMA is a potent releaser and/or reuptake inhibitor of presynaptic serotonin (5-HT), dopamine (DA), and norepinephrine (NE). These actions result from the interaction of MDMA with the membrane transporters involved in neurotransmitter reuptake and vesicular storage systems. The most frequent effects after MDMA/ecstasy administration are euphoria, well-being, happiness, stimulation, increased energy, extroversion, feeling close to others, increased empathy, increased sociability, enhanced mood, mild perceptual disturbances, changed perception of colors and sounds, somatic symptoms related to its cardiovascular and autonomic effects (blood pressure and heart rate increase, mydriasis), and moderate derealization but not hallucinations. Acute toxic effects are related to its pharmacologic actions. The serotonin syndrome (increased muscle rigidity, hyperreflexia, and hyperthermia), among others, is characteristic of acute toxicity episodes. MDMA metabolism is rather complex and includes 2 main metabolic pathways: (1) O-demethylenation followed by catechol-O-methyltransferase (COMT)-catalyzed methylation and/or glucuronide/sulfate conjugation; and (2) N-dealkylation, deamination, and oxidation to the corresponding benzoic acid derivatives conjugated with glycine. The fact that the polymorphic enzyme CYP2D6 partially regulates the O-demethylenation pathway prompted some expectations that subjects displaying the poor metabolizer phenotype may be at higher risk of acute toxicity episodes. In this metabolic pathway a mechanism-based inhibition of the enzyme operates because the formation of an enzyme–metabolite complex that renders all subjects, independently of genotype, phenotypically poor metabolizers after the administration of 2 consecutive doses. Therefore, the impact of CYP2D6 pharmacogenetics on acute toxicity is limited. One of the interesting features of MDMA metabolism is its potential involvement in the development of mid- to long-term neurotoxic effects as a result of progressive neurodegeneration of the serotonergic neurotransmission system.

Key Words: MDMA, ecstasy, metabolism, pharmacokinetics, toxicity

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CHEMISTRY AND MECHANISM OF ACTION

MDMA (3,4-methylenedioxymethamphetamine, ecstasy) is a ring-substituted amphetamine structurally similar to methamphetamine and mescaline. MDMA, as do other amphetamines, has a chiral center with a pair of enantiomers (the racemic mixture is the one consumed) that show different pharmacologic activities, stereoselective metabolism, and body disposition. The *S*(+) isomer of MDMA is responsible for psychostimulant and empathic effects, as compared with hallucinogenic-type properties of the *R* isomer.

MDMA is a potent releaser and/or reuptake inhibitor of presynaptic serotonin (5-HT), dopamine (DA), and norepinephrine (NE). These actions result from the interaction of MDMA with the membrane transporters involved in neurotransmitter reuptake and vesicular storage systems. MDMA reverses the direction of the membrane transporter, facilitating the efflux of NE, DA, and 5-HT to the synaptic cleft, with increased activation of postsynaptic receptors. MDMA is a mild inhibitor of monoamine oxidase (MAO) and reuptake but also has some direct actions in several types of receptors including the 5-HT_2 receptor, the M_1 muscarinic receptor, the α_2-adrenergic receptor and the histamine H_1 receptor. MDMA inhibits tryptophan hydroxylase, the rate-limiting enzyme of serotonin synthesis, decreasing the formation of serotonin.[1,2]

ACUTE PHARMACOLOGIC AND ADVERSE EFFECTS

The acute effects of ecstasy in humans have been extensively described in retrospective studies, surveys, and cases of

intoxication, and more recently after the controlled administration of MDMA to recreational users in experimental conditions.[2–4] Psychological and adverse effects reported in retrospective studies and surveys are similar to those described in laboratory conditions. The most frequent effects after MDMA/ecstasy administration are euphoria, well-being, happiness, stimulation, increased energy, extroversion, feeling close to others, increased empathy, increased sociability, enhanced mood, mild perceptual disturbances, changed perception of colors and sounds, somatic symptoms related to its cardiovascular and autonomic effects (blood pressure and heart rate increase, mydriasis), and moderate derealization but not hallucinations. Acute side effects most often reported are (in order of frequency) lack of appetite, jaw clenching, dry mouth, thirst, restlessness, palpitations, impaired balance, difficulty in concentration, dizziness, feeling and sensitivity to cold, drowsiness, nystagmus, hot flashes, trismus, muscular tension, weakness, insomnia, confusion, anxiety, and tremor. MDMA can also produce panic attacks, delirium, and brief psychotic episodes that usually resolve rapidly when the drug action wears off. Short-term side effects (up to 24 hours after ecstasy consumption) most often reported are (in order of frequency) fatigue, heavy legs, dry mouth, loss of appetite, insomnia, drowsiness, weakness, muscular tension, lack of energy, difficulty concentrating, and headache. Late short-term residual side effects (up to 7 days after ecstasy use) include fatigue, irritability, anxiety, lack of energy, fatigue, depressed mood, insomnia, drowsiness, and muscular tension. Some effects of MDMA such as closeness to others, facilitation of interpersonal relationships, and empathy have been referred to by some authors as "entactogen" properties. In humans MDMA increases cortisol, prolactin, ACTH, dehydroepiandrosterone (DHEA), and antidiuretic hormone (ADH, vasopressin) secretion. MDMA has been shown to induce a transient immune dysfunction related to its plasma concentrations, with a decrease in circulating CD4 T-helper lymphocytes, an increase in NK cells, and impaired lymphocyte mitogen-induced proliferation.[5–7] The effects of repeated administration of MDMA seemed to potentiate the immune dysfunction and extend it over time.

OVERDOSE

The acute toxic effects of MDMA are related to its pharmacologic actions.[2,3] Mild toxicity signs include nausea, vomiting, mydriasis, dry mouth, sweating, restlessness, tremor, hyperreflexia, irritability, pallor, bruxism, trismus, and palpitations. Moderate intoxication signs include hyperactivity, confusion, aggression, panic attack, psychosis, muscle tension, tachycardia, hypertension, and increase in body temperature. Severe intoxication can include delirium, coma, seizures, hypotension, tachydysrhytmias, hyperthermia (>40°C), and renal failure associated with rhabdomyolysis. A serotonin syndrome (increased muscle rigidity, hyperreflexia, and hyperthermia) and intracranial hemorrhage have been described. Hyperthermia may result from a direct action of the drug on the CNS temperature-regulating center and vasoconstriction of skin vessels and can be related to muscular activity associated with dance or tremor and rigidity, high ambient temperatures in crowded places, and dehydratation. Heat stroke is a severe complication that can cause death; it includes hyperthermia, rhabdomyolysis, myoglobinuria, disseminated intravascular coagulation, and renal failure. Hyponatremia is an uncommon complication associated with an excessive water intake; the syndrome of inappropriate antidiuretic hormone (SIADH) is usually present. Fulminant hepatitis and hepatic necrosis have been described.[2,3]

METABOLISM OF MDMA

MDMA metabolism has 2 main metabolic pathways: (1) O-demethylenation followed by catechol-O-methyltransferase (COMT)-catalyzed methylation and/or glucuronide/sulfate conjugation; and (2) N-dealkylation, deamination, and oxidation to the corresponding benzoic acid derivatives conjugated with glycine (see Fig. 1). MDMA N-demethylation gives rise to 3,4-methylenedioxyamphetamine (MDA). The parent compound and MDA are further O-demethylenated to 3,4-dihydroxymethamphetamine (HHMA) and 3,4-dihydroxyamphetamine (HHA), respectively. Both HHMA and HHA are subsequently O-methylated by the enzyme catechol-O-methyltransferase (COMT) mainly to 4-hydroxy-3-methoxymethamphetamine (HMMA) and 4-hydroxy-3-methoxyamphetamine (HMA), respectively. These metabolites are mainly present in plasma and in urine as their glucuronide or sulfate conjugates.[8–11] The successive degradation of the side chain gives rise to N-dealkyl (MDA) and deaminooxo metabolites. MDMA is subsequently metabolized to glycine conjugates of the corresponding 3,4-disubstituted benzoic acids.[8] A similar metabolic disposition has been described for MDEA (3,4-methylenedioxyethylamphetamine).[12] Demethylenation in vitro shows biphasic kinetics with high- and low-affinity components. The low-affinity component seems mainly regulated by CYP2D6,[13–15] and the high-affinity component is regulated mainly by CYP1A2 and to a lesser extent by CYP2B6 and CYP3A4. It has also been described that O-demethylenation may occur spontaneously.[14] N-Dealkylation velocity is nearly 1 order of magnitude lower than for O-demethylenation, and it is characterized by apparently monophasic kinetics. The most important isoenzyme of cytochrome P450 regulating this reaction appears to be CYP2B6.[15]

PHARMACOKINETICS AFTER A SINGLE ADMINISTRATION

There are few studies of the controlled administration of MDMA in humans. The pharmacokinetics parameters for MDMA and metabolites are presented in Table 1. In Figure 2, plasma concentration-versus-time curves of MDMA and main

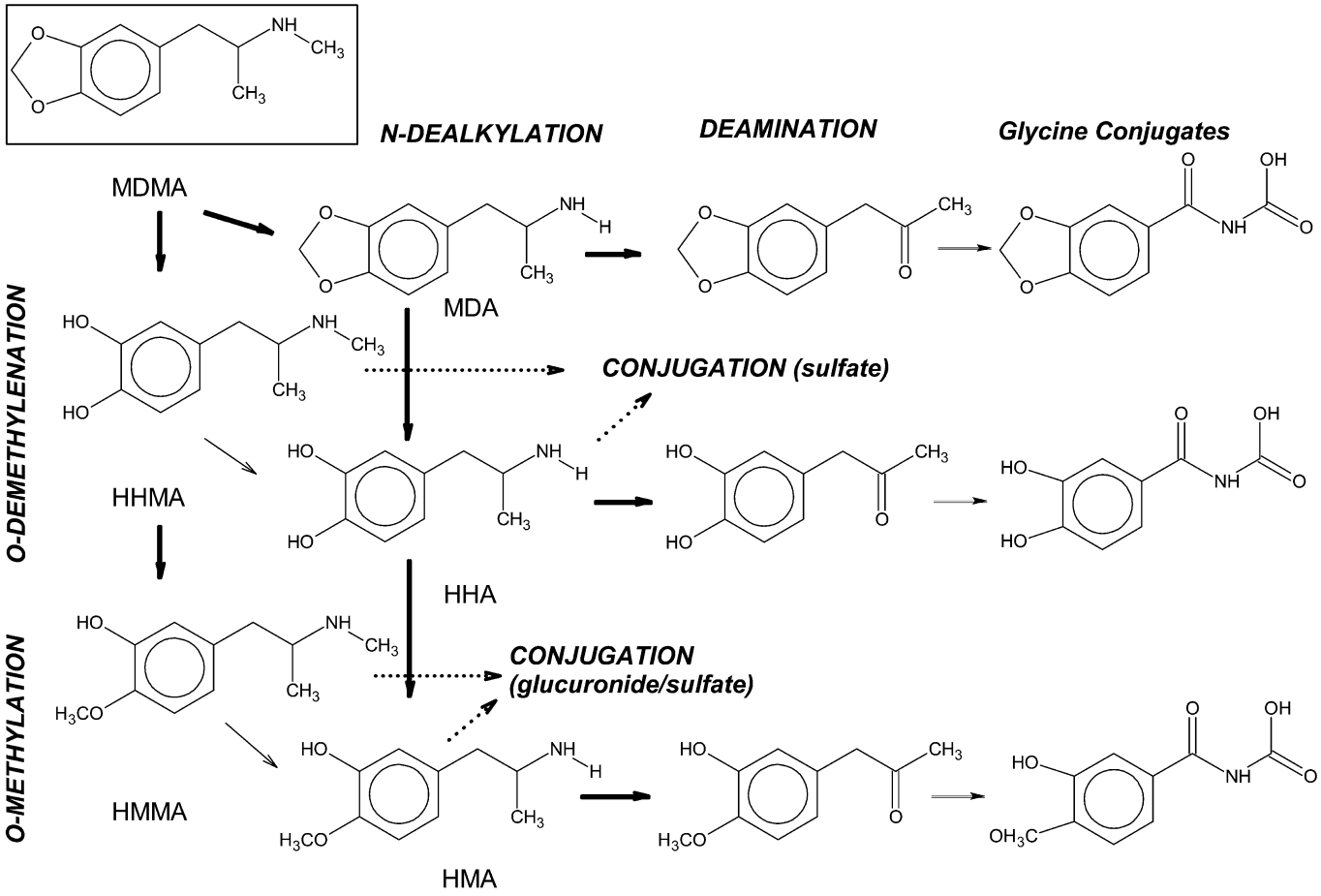

FIGURE 1. Metabolic pathways of MDMA hepatic disposition.

metabolites are represented. After MDMA administration, t_{max} is attained at 2 hours.[9,10,16,17] Binding to plasma proteins has only been investigated in dog plasma and has been estimated to be 34% for MDMA and 40% for MDA,[18] data that are close to estimations made for methamphetamine. Apparent volume of distribution was calculated as 453 L. The elimination half-life of MDMA (100 mg dose) is about 8–9 hours, similar to that reported after 50, 75, and 125 mg. These values are lower than those published for methamphetamine (10–12 hours) or amphetamine (12–15 hours). Nonlinear pharmacokinetics of MDMA has been suggested on the basis of results from several doses administered to healthy volunteers[9,19] and is most probably mediated by the formation of an enzyme–metabolite complex with CYP2D6.[20,21] It is postulated that the methylenedioxy group present in the chemical structure of MDMA is responsible for the autoinhibition of its metabolism (Fig. 1). Indeed, methylenedioxy groups form intermediate metabolite–enzyme complexes that quasi-irreversibly inactivate cytochrome P450 in both animals[22] and plants.[23] MDA appears to be a minor metabolite, representing 8–9% of the concentrations of MDMA (AUC comparisons) for all the doses tested. This finding is further supported by the fact that MDA urinary recovery is about 1% of the dose administered, whereas for methamphetamine the N-demethylated product (amphetamine) is about 10%. Nevertheless, the proportion between MDMA and MDA recovered in urine approaches the 10% reported for methamphetamine. Urinary concentrations in a series of 34 nonrelated cases (spot urines) were 0.38–96.2 mg/L (mean 13.4 mg/L) for MDMA and 0.15–8.6 mg/L for MDA (mean 1.6 mg/L).[24] HHMA and HMMA are the main metabolites of MDMA either in plasma or in urine.[25] The t_{max} for HHMA precedes the one corresponding to MDMA and HMMA, suggesting a quite relevant first-pass hepatic metabolism and also that HMMA formation is subsequent to HHMA, as previously hypothesized. HHMA and HMMA cannot be found in their free form but only conjugated to glucuronic acid (HMMA) or sulfate (HHMA and partially HMMA), which makes enzymatic/acid hydrolysis of the plasma samples necessary for their determination. Urinary recovery of these metabolites (MDMA 100 mg) is about 40% of the dose in 24 hours, whereas MDMA recovery is 15% (see Table 1). Higher recoveries are observed with lower MDMA doses, whereas the

TABLE 1. Pharmacokinetic parameters for MDMA and metabolites (MDMA 100 mg administered to 8 subjects)

	C_{max} (ng/mL)	t_{max} (h)	k_a[b] (h^{-1})	$t_{1/2}$ (h)	Urinary excretion[c] [µmol (%)]
MDMA					
Mean	222.5	2.3	2.7	9.0	77.8 (15.0%)
±SD	26.1	1.1	1.5	2.3	25.4
MDA					
Mean	13.1	6.7	0.6	24.9	7.8 (1.5%)
±SD	4.5	2.6	0.3	14.5	3.0
HHMA[a]					
Mean	154.5	1.2	5.3	13.4	91.8 (17.7%)
±SD	76.6	0.3	2.9	8.1	23.8
HMMA					
Mean	236.7	2.3	2.3	11.2	117.4 (22.7%)
±SD	87.1	0.9	0.9	2.9	40.0
HMA					
Mean	7.5	8.2	0.4	37.4	7.0 (1.35%)
±SD	4.0	1.7	0.1	17.9	1.6

[a]n = 4 for HHMA.
[b]Formation constant rate in the case of MDA, HHMA, HMMA, or HMA.
[c]Recoveries (0–24 hours) as amount (µmol) and percentage of the administered dose (%); C_{max}, peak plasma concentration; t_{max}, time of peak plasma concentration; AUC_{0-24}, area under the curve from 0 to 24 hours; k_a, absorption constant; $t_{1/2}$, elimination half-life.

contrary is observed at higher doses. These findings are consistent with the nonlinear pharmacokinetics phenomenon described above. Body clearance of HHMA and HMMA are a bit longer than that described for MDMA, as estimated elimination half-lives are longer than 11 hours. HMA is a minor MDMA metabolite, as it is for MDA, its metabolic precursor. Urinary recovery of HMA is very low, about 1.5% of the dose. Its elimination half-life presented in Table 1 is probably overestimated, and additional samples should be collected after 24 hours for a better estimation.

The time-course of blood concentrations of MDMA and its pharmacologic effects (eg, hormone secretion, cardiovascular effects) rise and fall with a similar profile. Both peak concentrations and peak effects were obtained between 1 and 2 hours and decreased to return to baseline values 4–6 hours after drug administration for most pharmacologic effects.[17]

A further aspect to be considered in MDMA pharmacokinetics is its enantioselective disposition. The O-demethylenation regulated by CYP2D6 exhibits some degree of enantioselectivity toward the *S* enantiomer. In an experiment in which MDMA racemate (40 mg) was administered to healthy volunteers, plasma concentrations of (*R*)-MDMA exceeded those of the *S* enantiomer [ratio *R*:*S* of the area under the curve (AUC), 2.4 ± 0.3], and the plasma half-life of (*R*)-MDMA (5.8 ± 2.2 hours) was significantly longer than that of the *S* enantiomer (3.6 ± 0.9 hours). The majority of the recovered material in urine was excreted within 24 hours after dosing, with the recovery of (*R*)-MDMA (21.4% ± 11.6%) being significantly greater than that of (*S*)-MDMA (9.3% ± 4.9%).[26] The stereoselectivity of MDMA disposition has been confirmed in fatal poisoning cases where other fluids and tissues were examined for MDMA and MDA concentrations.[27] Some preliminary results from analyses of MDMA and HMMA in urine samples nevertheless suggest that differences in the disposition of enantiomers of metabolites that maintain the 3 substituents in the α-carbon that define the chiral center are lost, most probably because of the autoinhibition of CYP2D6 discussed previously.[28]

MDMA can be easily detected in biologic matrices other than urine and plasma. Studies have being performed showing its detection and kinetics in saliva,[29,30] sweat,[31] and hair.[32]

PHARMACOKINETICS AFTER REPEATED DOSES

Ecstasy users are known to often take more than 1 dose per session. This practice could have serious implications for the acute and mid- to long-term toxicity of MDMA because of MDMA's inhibition of its own metabolism. In a randomized, double-blind, crossover, placebo-controlled trial conducted in 9 healthy male subjects, MDMA 100 mg or placebo was administered in 2 successive doses separated by an interval of 24 hours. Following the second dose, the plasma concentration of MDMA increased (AUC 77% and C_{max} 29%) in comparison to the first. The increase is greater than that expected by simple accumulation and indicates metabolic inhibition, further supporting the concept of nonlinear pharmacokinetics of MDMA. Results from this study suggest that CYP2D6 inhibition lasts at least 24 hours. Further experiments need to be conducted to evaluate the duration of the CYP2D6 inhibition phenomenon. The toxicologic consequences of this inhibition imply that subjects consuming MDMA are not conscious that long after its consumption, CYP2D6 is inhibited, and substrates of this enzyme may be at the origin of pharmacokinetic interactions leading to acute toxic effects (see also Pharmacogenetics section).[33]

PHARMACOGENETICS

Two enzymes involved in MDMA disposition in humans, CYP2D6 and COMT, exhibit genetic polymorphisms. CYP2D6 is highly polymorphic, and many of the gene variations affect the expression or activity of the CYP2D6 enzyme to various extents. Approximately 7–10% of European whites present a metabolic deficiency and are termed poor metabolizers (PMs).[34] A single nucleotide polymorphism in the catechol-O-methyltransferase (COMT) gene encodes for high- and low-activity forms of the enzyme. Approximately 25% of the white population present lower COMT activity.[35]

The genetic polymorphisms associated with individual differences in CYP2D6 activity created some expectations that

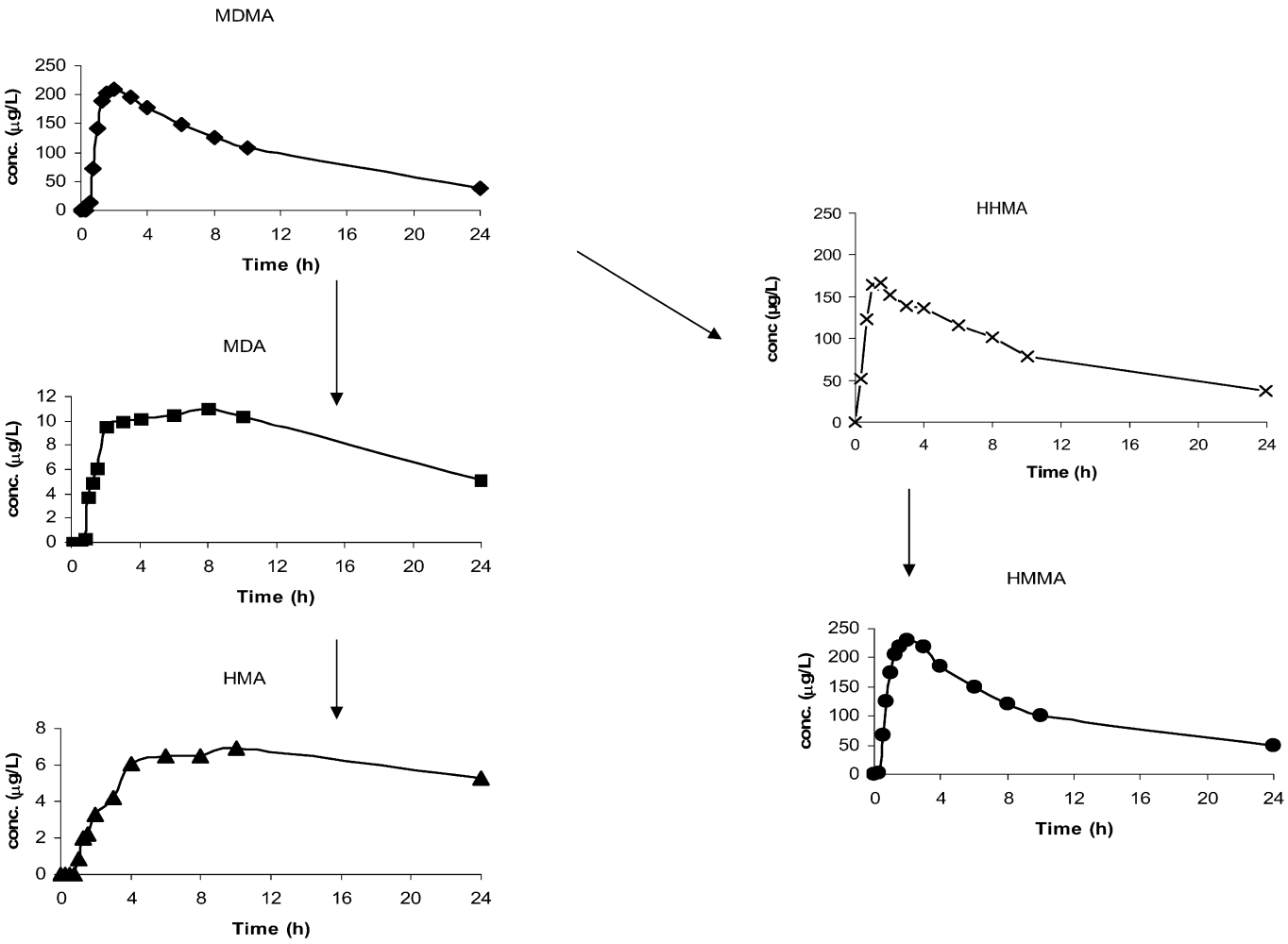

FIGURE 2. Concentration time course for MDMA (dose 100 mg PO) and its main metabolites (mean values of 8 subjects). MDMA and MDA are present in plasma in their free form. Plasma concentrations of HMA, HHMA, and HMMA can only be determined after samples are submitted to an enzymatic hydrolysis with β-glucuronidase/aryl sulfatase because they are mainly present as conjugates.

subjects exposed to these types of drugs who were genotypically classified as PM would be more susceptible to acute toxic effects of these drugs or to a higher abuse liability.[36] Toxicologic data do not seem to fully support these expectations because in a series of acute intoxications, no bias was observed toward an overrepresentation of genotypes leading to the PM phenotype.[37] In addition, CYP2D6 may also be the source of a number of drug–amphetamine interactions because it regulates the biotransformation of many therapeutic drugs. There have been several reports on the manipulation of MDMA preparations by spiking with dextromethorphan.[38] Because dextromethorphan is a CYP2D6 substrate, a pharmacokinetic interaction was anticipated. To date, no clinical cases have been reported, suggesting that such an interaction with a toxicologic impact has occurred. Antiretroviral drugs and MAO inhibitors have been reported to be the main cause of life-threatening interactions with MDMA.[36,39–41] The phenomenon of CYP2D6 inhibition as well as the fact that other isoenzymes of cytochrome P450 may contribute to MDMA disposition may explain why the contribution of CYP2D6 genetic polymorphism to acute toxicity is probably less relevant than expected.

The COMT enzyme is responsible for the transformation of HHMA to HMMA. This enzyme is of interest because studies in vitro have shown that HMMA is even more potent than MDMA in releasing vasopressin.[42] The inappropriate secretion of antidiuretic hormone has been implicated in life-threatening cases of hyponatremia in acute MDMA poisoning.[43] Variability of COMT activity as a result of genetic polymorphisms may account for interindividual differences in vasopressin secretion after MDMA consumption.

INTERACTION STUDIES

A limited number of interaction studies in humans have been performed, but only a few of them were designed to study pharmacokinetic interactions. Two clinical trials studying the pharmacologic interaction of MDMA with alcohol and paroxetine included pharmacokinetic evaluation of MDMA and its main metabolites. Nine male healthy volunteers received single oral doses of 100 mg of MDMA plus 0.8 g/kg ethanol, 100 mg of MDMA, 0.8 g/kg of ethanol, or placebo in a double-blind, double-dummy, randomized crossover trial. MDMA–ethanol interaction leads to dissociation between subjective and objective sedation. Subjects feel euphoric and less sedated and may have feelings of better performance, but actual performance ability continues to be impaired by the effect of alcohol. Plasma concentrations of MDMA showed a 13% increase after the use of alcohol, whereas plasma concentrations of alcohol showed a 9% to 15% decrease after MDMA administration. Changes observed may be related to hemodynamic alterations induced by both drugs rather than to a metabolic interaction.[44]

In a double-blind, randomized clinical trial, the influence of paroxetine (a selective serotonin reuptake inhibitor and a potent inhibitor of hepatic CYP2D6 isoenzyme) on the pharmacologic effects and the pharmacokinetics of MDMA was evaluated. A group of 10 recreational users of MDMA were included. Subjects were randomized to receive paroxetine (20 mg once a day) or matched placebo over 3 days. Three hours after the last paroxetine/placebo administration, subjects were given a pharmacologic challenge with MDMA (100 mg oral). Paroxetine produced a slight increase of MDMA plasma concentrations (a 30% increase in AUC) but reduced by half the formation of 4-hydroxy-3-methoxymethamphetamine (HMMA).[45] Paroxetine was chosen because it bears in its chemical structure the same methylenedioxy grouping of MDMA. MDMA and paroxetine are both substrates and inhibitors of CYP2D6 in vitro and in vivo[20,46] and display nonlinear pharmacokinetics in humans. The formation of a metabolite–intermediate complex leading to a quasi-irreversible inhibition of CYP2D6 has been proposed as the most likely mechanism of enzyme inhibition for both drugs.[21,47] From these studies it has been postulated that the contribution of CYP2D6 to MDMA disposition is around 30%.

A number of clinical trials have been conducted to study neurotransmitters and receptors responsible for the effects of MDMA in humans, using citalopram, haloperidol, and ketanserin as pharmacologic tools.[48] Unfortunately, these studies did not include sampling to study possible pharmacokinetic interactions. It was found that pretreatment with 40 mg IV citalopram significantly reduced the psychological and physiologic effects of MDMA, but effects lasted longer. Citalopram reduced the cardiovascular response and acute vegetative effects of MDMA. Pretreatment with haloperidol (1.4 mg IV) significantly reduced MDMA-induced positive mood and euphoria but had no effect on cardiovascular stimulation. In another study, pretreatment with ketanserin (50 mg PO) significantly reduced MDMA-induced perceptive changes, emotional excitability, and vigilance.

MDMA METABOLISM AND NEUROTOXICITY

MDMA consumption is associated with acute and mid- to long-term neurotoxic effects in animals. Mid- to long-term toxicity has been associated with a neurodegeneration of the serotonergic system. The impact of this neurodegeneration on subjects consuming MDMA is the most worrisome issue of its misuse. In clinical terms it has been related to a gradual loss of some cognitive functions (memory, performance of complex tasks), a higher impulsivity (may be translated into aggressiveness) and to some extends a larger incidence of psychopathology among users of such substances (depression among others).[1,2]

There are a large number of animal studies that demonstrate significant long-term neurochemical and morphologic changes in 5-HT neurons in response to administration of the methylenedioxy analogues that have been the object of several good reviews.[49–51] The mechanism underlying this neurotoxicity has not yet been determined, although a role for MDMA-induced hyperthermia and free-radical formation have been proposed. However, it is unclear whether neurotoxicity results from a direct action of MDMA or through its metabolites. Both MDMA and its active metabolite MDA are serotonergic neurotoxins. Nevertheless, when injected directly into the brain they are not neurotoxic; they only induce monoamine release.[52] This observation suggests that a previous metabolic activation of both substances is needed for the development of neurotoxicity.[53,54] The administration of major MDMA metabolites—HMMA, HHMA, HHA, and HMA—into the brain did not reproduce MDMA/MDA neurotoxicity. These observations prompted an investigation of the pharmacologic/toxicologic profile of several minor metabolic pathways. One of the most interesting hypotheses concerning putative toxic metabolites involved in the development of MDMA neurotoxicity is the formation of thioether adducts (with glutathione, cysteine) with HHMA and HHA.[55,56] Such metabolites [2,5-bis(glutathione-S-yl)-α-methyldopamine, 5-(glutathione-S-yl)-α-methyldopamine, and 5-(N-acetylcystein-S-yl)-α- methyldopamine] are able to reproduce behavioral alterations comparable to those observed after the administration of MDA or MDMA, induce a rise in serotonin and dopamine concentrations in the striatum, hippocampus, and cortex when administered intracerebroventricularly, and cause a long-lasting serotonergic neurodegeneration. This hypothesis has been supported by indirect evidence, but its formation in vivo both in animals and in humans is still pending.

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