Ecstasy: Pharmacodynamic and Pharmacokinetic Interactions

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At “raves,” young people dance and ingest illicit drugs, the most common of which is MDMA (N-methyl-3,4-methylenedioxymethamphetamine) or “ecstasy.” This drug is metabolized principally through the cytochrome P450 (CYP450) 2D6 enzyme. Pharmacokinetic drug-drug interactions can occur if MDMA is combined with other recreational or therapeutic drugs that are 2D6 inhibitors. Ecstasy concentration may increase to cause toxicity. Since ecstasy is pro-serotonergic, it may also be involved in pharmacodynamic drug-drug interactions when other pro-serotonergic drugs are combined with it, leading to a central serotonin syndrome. Some drugs are both pro-serotonergic and CYP450 2D6 inhibitors and, if co-administered with ecstasy, may cause both pharmacokinetic and pharmacodynamic drug-drug interactions.

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Since the 1980s, all-night dance parties known as “raves” have been popular among young people throughout the world. Often held in poorly ventilated surroundings and accompanied by the ingestion of illicit substances, individuals vigorously dance while listening to electronic music or viewing laser shows. Rave pills often have embossed logos that purport to identify particular drugs. In fact, they may contain inert substances or an entirely different drug, or the “true” drug may be laced with other contaminants. Without careful laboratory testing, the actual contents of an ingested drug may be impossible to determine.

The most commonly used rave drug, MDMA (N-methyl-3,4-methylenedioxyamphetamine), is structurally similar to both methamphetamine and mescaline. This drug—also known as ecstasy, E, Adam, Ecky, X, Bicky, or yaoto-wang—is illicitly compounded in tablets, capsules, or powder and may be embossed with a logo (e.g., Calvin Klein CK, Mitsubishi, 007, Coco Channel CC, Nike, or Rolex). Studies in the field have shown that tablets contain between 80 to 150 mg of MDMA, but they commonly contain inert substances and other drugs as well.1

Emergency room physicians have become experts in the treatment of rave drug intoxications, but other medical specialists are less knowledgeable about these drugs and their potential for interactions with prescribed or recreational substances. Unfortunately, large gaps exist in our understanding of this subject because few clinical studies have been done of rave drug interactions. Therefore, we must rely on case reports, in vitro studies of the metabolism of rave drugs, and knowledge of other drugs’ metabolism...
and their potential for cytochrome P450 (CYP450) inhibition/induction to examine the pharmacodynamic and pharmacokinetic interactions of MDMA.

MDMA Metabolism

Most of MDMA is demethylenated to 3,4-dihydroxymethamphetamine (DHMA) by CYP450 2D6, but other enzymes contribute (e.g., 1A2, 2B6, and 3A4). A smaller portion of MDMA is also N-demethylated via CYP450 1A2 and 2D6 to 3,4-methylenedioxyamphetamine (MDA). MDMA's further phase II metabolism is poorly understood. MDMA or one of its metabolites has been shown to be a 2D6 inhibitor in vitro, but whether this is also true in vivo is not known. This speculation would be consistent with the observation that small increases in dosing of MDMA lead to large increases in blood concentration, i.e., nonlinear kinetics.

Mechanism of Action

The mechanism of action of MDMA is incompletely understood, but it is believed to inhibit the reuptake of serotonin (5-HT), to facilitate serotonin release, and to a lesser extent cause dopamine and noradrenaline. The serotonin boost can produce a sense of emotional closeness, elation, and sensory delight. MDMA acute adverse effects may include increased heart rate and blood pressure, tremor, sweating, bruxism, and life-threatening hyperthermia that may be further complicated by rhabdomyolysis, disseminated intravascular coagulation, and acute renal failure. Because MDMA users are aware of its toxic potential, they often drink fluids to prevent hyperthermia. (A teen told one of the authors [J.R.O.] that profits from bottled water can top money made on MDMA at some raves.) MDMA users also carry lollipops or pacifiers to alleviate the bruxism side effect.

Metabolic Pharmacogenetics of MDMA

Since the CYP450 2D6 enzyme is the primary metabolic pathway, individuals with genetic variations of this enzyme (e.g., slow metabolizers or ultra rapid metabolizers) will have variable concentrations of the parent compound and metabolites. Even extensive 2D6 metabolizers will be vulnerable to increased blood concentration of MDMA when a potent 2D6 inhibitor is added, since large increases in the blood level can occur because of nonlinear kinetics.

Pharmacokinetic Drug-Drug Interactions With MDMA

Potent 2D6 inhibitors block the most important metabolic pathway of MDMA. An in vitro study showed that fluoxetine, paroxetine, and cocaine all inhibited MDMA metabolism, and one can predict that these and other co-administered drugs that are potent 2D6 inhibitors may substantially increase the concentration of MDMA in vivo, such as bupropion, haloperidol metabolites, methadone, quinidine, ritonavir, pimozide, and others.

However, drugs that inhibit most or all of the CYP450 pathways (e.g., 1A2, 2B6, 3A4) will likely have even a more profound effect. For instance, it is well known that the acute usage of ritonavir inhibits 2B6, 2C9, 2C19, 2D6, and 3A4. Several cases have been reported of life-threatening interactions or death in individuals who ingested MDMA while taking ritonavir. In one case, it was estimated that the blood concentration was 10-fold higher than what might have been expected from the dose of MDMA ingested. Although not as potent as 2D6 inhibitors, other protease inhibitors that also inhibit 2D6 and 3A4 may be similarly implicated in increasing MDMA concentrations when co-administered. Like ritonavir, fluoxetine is a potent CYP450 2D6 inhibitor, and it also inhibits 2B6, 2C9, 2C19, and 3A4 to some extent. Amiodarone is a potent inhibitor of CYP450 1A2, 2C9, 2D6, and 3A4, and it may be potentially dangerous in co-administration.

Pharmacodynamic Drug-Drug Interactions With MDMA

MDMA's pro-serotonergic effects can be augmented by ingestion of other pro-serotonergic drugs. These drugs may be ingested inadvertently as contaminants of MDMA (e.g., amphetamines, MDA) or taken to enhance MDMA effects (e.g., cocaine, dextromethorphan). Pro-serotonergic drugs (e.g., fluoxetine, amphetamines, St. John’s wort, tramadol, venlafaxine, lithium, clomipramine, and others) prescribed for medical disorders may increase the likelihood and severity of MDMA's serotonin effects. A florid central serotonin syndrome involving autonomic, cognitive, and neuromuscular symptoms may develop. Moderate symptoms manifest as sweating, shivering, hyperreflexia, and agitation; severe symptoms include myoclonus, diarrhea, and fever. The most serious cases of central serotonin syndrome can develop with drugs that block both serotonin “exits”—reuptake and monoamine oxidase. Cases of toxicity or death have been reported from MDMA interactions with the monoamine oxidase inhibitor phenel-
Med-Psych Drug-Drug Interactions

Some MDMA users will “pre-load” with citalopram or another serotonin reuptake inhibitor (SRI) because they believe that co-administration will protect against possible toxic CNS effects. It has been shown that co-administered SRIs can block the subjective effects and increases in blood pressure and heart rate of MDMA but not the effects of hyperthermia. Unfortunately, combined pharmacokinetic and pharmacodynamic drug-drug interactions can ensue when some SRIs that are also potent CYP450 2D6 inhibitors (e.g., fluoxetine, paroxetine) increase both the concentration of MDMA (pharmacokinetic) and serotonergic activity (pharmacodynamic). MDMA users may also consume other drugs at the same time to enhance their experience. Cocaine is both an SRI and a moderate 2D6 inhibitor and may have similar effects as fluoxetine and paroxetine. Some MDMA users will “pre-load” with citalopram or another serotonin reuptake inhibitor (SRI) because they believe that co-administration will protect against possible toxic CNS effects. It has been shown that co-administered SRIs can block the subjective effects and increases in blood pressure and heart rate of MDMA but not the effects of hyperthermia. Unfortunately, combined pharmacokinetic and pharmacodynamic drug-drug interactions can ensue when some SRIs that are also potent CYP450 2D6 inhibitors (e.g., fluoxetine, paroxetine) increase both the concentration of MDMA (pharmacokinetic) and serotonergic activity (pharmacodynamic). MDMA users may also consume other drugs at the same time to enhance their experience. Cocaine is both an SRI and a moderate 2D6 inhibitor and may have similar effects as fluoxetine and paroxetine.8

Other Common Drug Combinations With MDMA

There are two other drugs that are commonly ingested with MDMA: alcohol and sildenafil. A clinical study has shown that the MDMA plasma concentrations increase 9%–15% when taken with alcohol. More important, the combination leads to a longer-lasting feeling of euphoria and the false impression that one’s performance of a task has improved when it has actually been impaired.24 This discrepancy may fuel potentially dangerous actions. Sildenafil is sometimes combined with MDMA (termed “sexstasy”), but since the former is a CYP450 3A4 substrate, no additional interactive pharmacokinetic or pharmacodynamic effects occur.

Conclusion

MDMA became a popular rave drug because of its intense effects and because it was believed to have few toxic effects. This has proven to be false. Ingested alone, it has the potential for serious acute toxicity. Taken with other therapeutic and recreational drugs, it has the potential for complicated pharmacokinetic and pharmacodynamic drug interactions.

References