Research Article ISSN 2689-1050

Chemical & Pharmaceutical Research

Toxicological Aspect of Fatal Methamphetamine

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Received: 27 March 2021; **Accepted:** 15 April 2021

Citation: Alqallaf M. Toxicological Aspect of Fatal Methamphetamine. Chem Pharm Res. 2021; 3(1): 1-5.

ABSTRACT

Drug addiction has become a worldwide problem and the leading cause of death. The global problem of addiction and drug abuse is responsible for hundreds of deaths every year. It affects not only individual users, but also their families and communities.

The current study, presents the fatality of some cases caused by the complications brought about the presence of methamphetamine and other abused drugs. It has been a drug of abuse in the past and is still gaining popularity as a recreational drug because of its much longer excitatory duration of more than three hours and its biotransformation to amphetamine, the active metabolite. In present postmortem cases methamphetamine and other combined drugs have issue in cardiac major health problems and poisoning-related deaths. Many postmortem cases found positive to methamphetamine and amphetamine or combined with other drugs include different narcotics/ stimulants drugs such as : benzodiazepines, THC, opium, and lyrica. The toxic effects of methamphetamine can explain increasing reports of heart failure and consequently death in young abusers. As this recognition may prove to be of some forensic value to clarify the death in methamphetamine abusers.

Keywords

Methamphetamine, Postmortem, Toxicity, Randox immunoassay, Q-exactive foucs Orbitrap LC/MS/MS.

Introduction

Methamphetamine is a potent central nervous system (CNS) stimulant drug, and a member of the phenethylamine family. The N-methyl derivative of amphetamine, is commonly used in the treatment of obesity, and to treat attention-deficit hyperactivity disorders (ADHD), narcolepsy, and sleep disorder.

Crystal methamphetamine is a form of drug that looks like glass fragment, bitter-tasting, shiny, bluish-white rocks. Methamphetamine is produced in several different forms, and so it can be used and abused in many ways depending on what is available to the person using the drug and base on personal preference [1-3].

The most common ways of abused methamphetamine as follow:

- *Smoking:* is very common between addicts which is done using a pipe or "flute" and doesn't require mixing with any other substances, smoking methamphetamine causes the drug to enter the bloodstream immediately, which gives an intense high or "rush", which is increase the risk of addiction and overdose.
- *Snorting:* is often done by new users, that lead to damage the sinus cavities. A chronic runny nose can be the result and continued use might even lead to a hole being worn into the septum. Snorting methamphetamine generally produces feeling of euphoria as it is absorbed into the body, even though the effects take several minutes to feel high.
- *Injecting:* is done by diluting crystal methamphetamine from powder to a liquid and injecting it directly into the bloodstream. It is extremely risky and is linked with diseases like HIV and hepatitis as a result of sharing needles.
- *Swallowing:* is the slowest acting way to use the drug, and it may take 15-20 minutes to feel the effects [4].

Chemistry and Pharmacology of Methamphetamine

Chemistry of methamphetamine

Methamphetamine also known as N-methylamphetamine, and exists in two stereoisomer, L- and D- forms. D-methamphetamine,

or the dextrorotatory enantiomer, is a more powerful psychostimulant, with 3-5 times the central nervous system (CNS) activity as compared to L-methamphetamine, or the levorotatory enantiomer, both enantiomers influence dopamine release and can induce stereotypy and psychosis at high doses. Illicitly, methamphetamine may be sold as pure D-methamphetamine (dextromethamphetamine) or in racemic mixture, and presents as powder or crystalline form, the latter commonly referred to as "ice" or "crystal meth" [3].

Pharmacology and Pharmacokinetics of Methamphetamine

Methamphetamine is a potent central nervous system stimulant which affects neurochemical mechanisms responsible for regulating heart rate, body temperature, blood pressure, appetite, attention, mood and responses associated with alertness or alarm conditions. At high doses, methamphetamine activated the cardiovascular system that lead increased heart rate and blood pressure that can cause death.

In the brain, a primary action of methamphetamine is to elevate the levels of extracellular monoamine neurotransmitters (dopamine, serotonin, norepinephrine) by promoting their release from the nerve endings.

Methamphetamine is largely metabolized in the liver, resulting in metabolites including amphetamine, 4-hydroxymethamphetamine, norephedrine, hippuric acid, 4-hydroxyamphetamine, 4-hydroxynorephedrine. It is then excreted by the kidneys, with the majority excreted as unchanged methamphetamine (30-50%), followed by up to 15% as 4-hydroxymethamphetamine, and 10% as amphetamine. Approximately 70% of a single oral dose is excreted in the urine within 24 hours. With repeated dosing, methamphetamine can accumulate in the urine, and observed at 3-4 days interval [5,6].

Toxicology of Methamphetamine

Abuse of the illegal psycho-stimulant, methamphetamine has become an international public health problem with million users worldwide. Immediately after taking the drug, users experience a sense of euphoria, increased productivity, hypersexuality, decreased anxiety and increased energy. These effects can last for several hours because the elimination half-life of methamphetamine ranges from 10-12 h. methamphetamine abuse is also associated with a number of negative consequences in humans. These include acute toxicity, altered behavioral and cognitive functions, and neurological damage. Methamphetamine users might experience agitation, aggression, tachycardia, hypertension, and hyperthermia. Ingestions of large doses of the drug can cause more serious consequences that include life-threatening hyperthermia above 41 ºC, renal and liver failure, cardiac arrhythmias, heart attacks, cerebrovascular hemorrhages, strokes and seizures. Chronic abuse of methamphetamine contributes to anxiety, depression, aggressiveness, social isolation, psychosis, mood disturbances, and psychomotor dysfunction [7-11].

Methods

Cases

A complete postmortem examination was performed on three cases including analysis and identification of samples of postmortem blood, and urine where a full survey was done to all samples and specimens received for each case in toxicology lab.

Systematic toxicological analysis was performed in each case, starting with a screening of urine and blood by means of immunoassay (Randox technology), as a routine analysis for the following substances: Benzodiazepines, barbiturates, tramadol, cannabinoids, amphetamine, methamphetamine, cocaine, opiates, tricyclic antidepressants, and synthetic cannabinoids. The positive results cases were confirmed by High-Resolution Accurate- Mass (HRAM) Orbitrap LC/MS/MS detection.

The cases were identified for drugs abuse in general and for specific methamphetamine, and one or more drugs abuse were found and confirmed. The risk of methamphetamine is more when taken with other drugs which can produce unwanted increases in heart rate and blood pressure, which may leads to acute circulatory failure that followed to death according to pathologist investigation.

Immunoassay Screening

Randox Screening (urine and blood): Randox immunoassay testing offers rapid separation of presumptive positive and negative specimens, prior to more costly and time consuming chromatographic confirmation. Evidence investigator biochip array technology is used to perform simultaneous detection of multiple analytes from a single sample. The core of the technology is the randox biochip; a solid state device with array of discrete testing regions containing immobilized antibodies specific to different drugs of abuse compound classes. The Randox DoA V Urine kit (Randox laboratories Limited, 55 Diamond Road, Crumlin, County Anntrim, UK) used in this paper employs a competitive chemiluminescent immunoassay, where the drug in the specimen and drug labeled with Horse Radish Peroxidase (HRP) are in direct competition for the antibody binding sites. Increased levels of drug in a specimen will lead to reduced binding of drug labeled with HRP and thus a reduction in the chemiluminescent signal emitted. The light signal generated from each of the test regions on the biochip is detected using digital imaging technology and compared to that from a stored calibration curve. The cutoff concentration of a drug or its metabolites in the matrix established for assigning negative and positive specimens. In an immunoassay, cutoff concentrations can be selected at the assay's optimal sensitivity, selectivity, and efficiency reducing the number of false positive and false negative specimens [12,13].

LC/MS/MS Confirmation

A Q-ExactiveTM Hybrid Quadrupole-OrbitrapTM Mass Spectrometer (Thermo Fisher Scientific, Bremen, Germany) was used to confirm the results generated from the screening test of the biological urine and blood samples. The Q Exactive system provides very good analytical performance in terms of

reproducibility, linearity, and signal-to-noise, and addresses an extremely wide range of masses.

The mass spectrometer is a Benchtop LC/MS/MS system that combines quadruple precursor ion selection with High-Resolution, Accurate-Mass (HRAM) Orbitrap detection. Samples (5 µL) were injected in a 2.6 mm AccucoreTM Phenyl-Hexyl column (100 mm × 2.1 mm) and the LC column was heated to 40°C. Analytes were resolved at 0.5 mL/min using a mobile phase consisting of two solvents. The Mobile phases for LC-Screening are (Phase A: H2O, [NH4]+[HCOO]- 2 mM, 0.1% HCOOH), for 1 L mobile phase A use 1 L of water and add 126 mg of ammonium formate and 1 mL of formic acid. (Phase B: [NH4]+[HCOO]- 2 mM, MeOH/ACN 50:50, 0.1% HCOOH, 1% H2O), for 1 L of mobile phase B use 495 mL of methanol, 495 mL of acetonitrile, 10 mL of water, and add 126 mg of ammonium formate and 1 mL of formic acid.

Results and Discussion

All cases in this study were investigated under authority of the general department of criminal evidence in Kuwait (Forensic Toxicology Lab) including performance of all toxicology tests, in addition to Pathology Lab in Forensic Medicine Department that is deal with the autopsy and samples provided. Both screening and confirmation results of the three postmortem cases were summarized in Table 1. In all cases positive results of methamphetamine and its major metabolites were confirmed, although the amphetamine also can be found as a result of captagon tablets, where captagon is metabolized into amphetamine (24.5 % of oral dose) and theophylline (13.7 % of oral dose).

In postmortem case number one both amphetamine, methamphetamine, pregabalin and tetrahydrocannabinoids (THC) were confirmed in screening and confirmation tests in both biological samples, the second postmortem case was only having amphetamine and methamphetamine in both urine and blood. The third one has the most danger combine drugs that results positive to opium, benzodiazepine, amphetamine, methamphetamine and pregabalin.

The effects of these drugs depend on the general heath issue of the user before death and also the history of the addiction (short or long) which can be critical to contribute and to enhance the possibility of risk of death.

All biological samples were screen tested of full survey of all drugs abuse; the positive sample will be furthered confirmed by LC/MS/MS for all other drugs found. In this study, toxicity of methamphetamine is critical point, either it causes death in direct or indirect way, also addiction of methamphetamine alone or with combination with other drugs. Table 2 summarized these combinations where there is high risk of cardiovascular, brain problems and other adverse effects in user's body.

The cardiovascular complications associated with methamphetamine use can occur with all of the major routes of administration :(intranasal, oral, smoking, and injection). While, there is no evidence to suggest that any one route of methamphetamine administration should be more strongly associated with cardiotoxicity than another, the risk of complications may be higher with patterns of use that are associated with frequent use and taking higher doses, such as injecting and smoking crystalline methamphetamine.

The high level of methamphetamine increases synaptic levels of the monoamine neurotransmitters dopamine, serotonin (5-HT), and norepinephrine, and has α and β-adrenergic agonist effects. Amphetamine also interferes with vesicular monoamine transporter-2 (VMAT-2) function, impairing the active transport of the monoamines into synaptic vesicles, where they are stored. The increase in dopamine levels induced by amphetamines

Table 1: Screening and Conformation Results for Postmortem Cases.

Case Number	Samples	Screening Results (ng/mL)	Conformation Results
	Urine	THC: +145.2 PGB: +2000 MAMP: +500 AMP: +85.55	THC-COOH, THC-COOH glucuronide Pregabalin Methamphetamine Amphetamine
1	Blood	THC: +80.45 PGB: +1200 MAMP: +870 AMP: +125.5	THC-COOH glucuronide Pregabalin (Lyrica) Methamphetamine Amphetamine
	Urine	MAMP: +1000 AMP: +845.4	Methamphetamine Amphetamine
2	Blood	MAMP: +68.21 AMP: +300	Methamphetamine Amphetamine
	Urine	BENZ: +495.0 OPT: +1000 MAMP: +2000 AMP: + 654.2 PGB: +500	Alprazolam, Diazepam, Nordiazepam Morphine, Morphine-3-glucuronide Methamphetamine Amphetamine Pregabalin
3	Blood	BENZ: +340.4 OPT: +875.0 MAMP: +1650 AMP: +420.6	Diazepam, Oxazepam, Nordiazepam Morphine-3-glucuronide Methamphetamine Amphetamine

Table 2: Combination of Methamphetamine and other Drugs.

Drug	Combined Drug	Effect
	Benzodiazepines	Using methamphetamine with benzodiazepines such as Xanax (Alprazolam) in high dose puts the body under incredible stress. The combination puts immense strain on the heart, which can lead to cardiac arrest, stroke, hospitalization and possible death. Methamphetamine as stimulant causes anxiety, extreme euphoria, and abnormal energy. Xanax is benzodiazepine typically prescribed to treat anxiety or panic attacks. Benzodiazepines work in almost the exact opposite way of methamphetamine.
Methamphetamine	Opium	Combination of morphine and other opium derivative with methamphetamine can create a " speedball", which is combination of opioid (depressant) and stimulant (methamphetamine). Speedball can cause negative side effects such as confusion, incoherence, blurred vision, stupor, drowsiness, paranoia, and mental impairment because of lack of sleep. The combination can also result in uncontrooled and uncoordinated skills, and also the risk of death from stroke, heart attack, aneurysm, or respiratory failure.
	THC	Methamphetamine and cannabis are commonly abused together. Mixing crystal methamphetamine and marijuana can cause significant brain damage. They have opposing actions on the CNS. Although some addicts take THC to calm, relax and to feel sleepy after methamphetamine dose, and reduce the side effect of methamphetamine.
	PGB	Pregabalin is an anticonvulsant medication used to treat epilepsy. PGB usually mixed with opiates, cocaine, cannabis, benzodiazepines. No interactions were found between PGB and methamphetamine.

leads to an increase in its oxidative metabolism, which generate free radicals that may induce cyto-toxicity. Dopamine mediates locomotor stimulation, psychosis, and perception disturbances, whereas changes in norepinephrine levels are associated with alerting, anorectic, locomotor, and sympathomimetic effects and 5-HT is responsible for delusions and psychosis. Toxicity of methamphetamine may lead to renal and liver failure, hyperthermia, cardiac arrhythmias, heart attack, cerebrovascular hemorrhages, stroke, seizures, and death. The lethal dose of methamphetamine in human is usually within 140-1650 mg [14-17].

The results of toxicological analyses of fatal or non-fatal overdose poly drugs (exposure to one or more drugs in one use) is associated on the pharmacological properties and with the amounts of substances consumed. The high risk of methamphetamine is that it increases catecholamine activity in the branch of the peripheral nervous system responsible for modulating heart rate and blood pressure. Excessive catecholamine activity is the primary mechanism underlying the cardiotoxic effects of methamphetamine. High catecholamine levels are known to be cardiotoxic, causing narrowing and spasm of the blood vessels, rapid heart rate, high blood pressure and possible death of heart muscle. Thus, low level use of methamphetamine does not appear to be associated with major acute complication, such as myocardial infarction, or chronic cardiovascular disease. The long term and combined drugs users appear to be most at risk of cardiovascular damage, such as premature, accelerated coronary artery disease. As such, methamphetamine toxicity is more to have a fatal outcome with chronic use.

Conclusion

Methamphetamine causes health hazards in many vital organs. Long-term methamphetamine users appear to be most at risk of cardiovascular damage, such as premature, accelerated coronary artery diseases. As such methamphetamine toxicity is more likely to have a fatal outcome with chronic use.

Further research is needed to establish the risk of serious cardiac events among methamphetamine users, whether there is evidence of a dose response relationship between methamphetamine use and cardiotoxicity in humans, and also the relative contribution of methamphetamine over other concurrent risk factors such as: alcohol, tobacoo, and other drugs of abuse, and pre-existing cardiac pathology.

Acknowledgement

I would like to thank the Forensic Toxicology Laboratory for all techniques, samples and standards provided. Also, I would like to express our gratitude to the forensic medicine and pathology division for their remarks in postmortem cases.

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