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Methamphetamine Washout Syndrome: More than Just Catecholamine Depletion?

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ABSTRACT

Methamphetamine (MA) use continues to increase on a global scale. Patients using MA utilize emergency department and hospital resources at a higher rate than other patients due to serious associated medical conditions, including blunt and penetrating trauma, stroke, myocardial infarction, cardiomyopathy, and rhabdomyolysis. Mental health resources are also utilized at a high rate stemming from MA-associated agitation, aggression, psychosis, self-harm, and suicidal ideation. Patients presenting with MA toxicity frequently require a combined team effort of clinicians, nurses, psychiatric workers, and social services prior to final disposition. The phenomenon of "Methamphetamine Washout Syndrome" (MAWS) has been used to describe a period of MA-induced hypersomnolence greater than eight hours at our institution. During this period the patient cannot easily be awakened or interviewed, and they continue to occupy a hospital bed. The etiology of MAWS was initially thought to simply be a result of catecholamine depletion followed by a period of synthesis and restoration. In this report, we investigate this theory and other potential causes of MAWS such as MA neurotoxicity from microglial activation and cytokine release, mitochondrial dysfunction, energy supply disruption, and apoptosis. The effect of MA on sleep is also detailed, and potential treatment options to optimize patient outcome and decrease length of stay are discussed.

Introduction

Methamphetamine (MA) use continues to escalate worldwide, with parallel increases in emergency department utilization and hospital admissions[1–4]. Acute and chronic users of MA frequently present with serious medical conditions, including blunt and penetrating trauma, stroke, myocardial infarction, cardiomyopathy, and rhabdomyolysis[2,5]. Mental health issues are also commonly encountered in this patient subgroup, and include agitation, aggression, psychosis, self-harm, and suicidal ideation[6–8]. Acute medical care of MA users experiencing toxicity often begins with sedation and restraint, and this aspect of patient care has garnered the most interest in past literature[9]. However, post-treatment prolongation of hospital length of stay due to hypersomnolence greater than eight hours has been noted. Chronic users of MA term this phenomenon "crashing" and attribute it to sleep deprivation from a side effect of the drug itself[10]. In our institution we have termed this period of hypersomnolence as the "Methamphetamine Washout Syndrome" (MAWS), during which time the patient cannot easily be awakened to be interviewed by psychiatric and social service workers, and, as a result, they cannot be legally discharged.

Crowding of emergency departments and lack of hospital beds is a worldwide problem projected to worsen as the population increases and ages[11,12]. Patient flow and length of stay have become important metrics as hospital utilization increases each year. Patients presenting with MA toxicity frequently require a combined team effort of medical, trauma, nursing, psychiatric, and social services care prior to final disposition. Patients with MAWS further add to this complexity and total length of stay. In a study of MA users presenting to an urban emergency department, one-quarter experienced sleep disturbance[13]. Another study compared emergency department flow times, and MA users had the highest length of stay compared to other substance-using patients[14]. Improving care and appropriate disposition of MA patients while decreasing length of stay is a challenging task, but understanding the potential mechanisms behind MAWS is an important step. In 1992 Sporer and Lesser were the first to describe "cocaine washed-out syndrome" followed by Trabulsy in 1995.[15,16] The etiology was initially thought to be a result of catecholamine depletion followed by a period of synthesis and restoration. Unlike cocaine, this syndrome has not been detailed for MA. In this report, we investigate this theory and other potential causes of MAWS and evaluate treatment options to optimize patient outcome and decrease length of stay.

Methamphetamine Pharmacology

Methamphetamine use results in increased sympathetic nervous system activation through a variety of mechanisms. Due to its high lipid solubility, MA traverses the blood-brain-barrier and penetrates the central nervous system (CNS). Methamphetamine is an indirect agonist at norepinephrine, dopamine, and serotonin receptors, and thus stimulates releases of these monoamines in the CNS and peripheral nervous system[17]. Methamphetamine increases extracellular monoamines through non-exocytotic mechanisms and direct interaction with monoaminergic cells. Due to its structural similarity to dopamine, MA is transported to the cytosol via the dopamine transporter in exchange for intracellular dopamine. The norepinephrine transporter is similarly affected. The dopamine transporter exchange of extracellular MA for intracellular dopamine increases extracellular dopamine. Methamphetamine impairs vesicular monoamine transporter2 function, which is responsible for monoamine storage into synaptic vesicles. At a certain threshold, MA diffuses into the cytosol and synaptic vesicles. This results in the release of stored vesicular dopamine into the cytosol, which is ultimately transferred to the extracellular space via dopamine transporter reverse transport. This induces a short-developing tolerance termed tachyphylaxis[18]. The vesicles become depleted of monoamines, and MA is released into the synaptic cleft and acts as a "false neurotransmitter." Methamphetamine increases tyrosine hydroxylase activity while decreasing monoamine oxidase activity, thus adversely affecting monoamine synthesis and metabolism. The half-life of MA is over 10 hours, and while the euphoric effect usually recedes by four hours, MA-induced tachycardia and hypertension may persist for over 24 hours.

Methamphetamine and Sleep

The disruptive effect of MA on sleep has been recognized since its advent over a century ago[19]. There are four sleep stages, the non-rapid eye movement (NREM) sleep stages N1, N2, and N3 (also known as slow-wave sleep), as well as rapid eye movement (REM) sleep. Disruption of REM sleep associated with MA use was first noted in 1964 by Rechtschaffen and Maron[20]. Paradoxical hypersomnolence in MA users admitted to the hospital was first reported by Gossop in 1982[10]. More recent primate studies also demonstrated MA decreases N2, slow-wave (N3), and REM sleep duration[21,22]. There is also a MA dose-dependent increase in sleep latency and wake time after sleep onset with second night rebound effects. An important factor in MA-associated sleep disruption is the role of the dopaminergic system on the sleep-wake cycle and circadian rhythm. The sleep-wake cycle is comprised of the sleep-promoting circuits of substantia nigra, and the wake-promoting circuits of the ventral tegmental area and dorsal raphe nucleus. Circadian activity involves modulation of the circadian pacemaker in the suprachiasmatic nucleus, and suppression of melatonin release from pineal gland[23]. Different neurotransmitters, cytokines, and neuropeptides are involved in sleep regulation. These include monoamines (dopamine, norepinephrine, and serotonin), adenosine, acetylcholine, γ-aminobutyric acid (GABA), and histamine[24]. Cytokines such as tumor necrosis factor (TNF) and interleukin-1β (IL1β), and neuropeptides such as orexin (hypocretin) are associated with sleep[25]. The disruption of normal sleep patterns by MA can be linked to its deleterious effects on these various systems.

MONOAMINES

Methamphetamine increases extracellular dopamine secretion primarily from inhibition of the vesicular monoamine transporter2 and dopamine transporter at dopaminergic terminals, stimulates the mesolimbic system, and disrupts sleep. Depletion of monoamine stores and down-regulation of monoamine receptors from acute and

chronic MA use results in hypersomnolence[26]. Decreased dopamine transporter and dopamine D2/D3 receptor availability has been shown not only in MA users but drug-free individuals with acute sleep deprivation[27]. The dopamine D4 receptor has a role in regulating circadian rhythms, and its associated gene is affected by MA use[28]. Another monoaminergic mechanism involved in sleep is regulation of growth hormone-releasing hormone. Dopamine receptors in the hypothalamus inhibit release of growth hormone-releasing hormone, which promotes sleep[29]. Early studies showed a link between MA use, monoamine depletion, and sleep disruption. In a 1957 animal study, the nexus between MA and the monoaminergic system highlighted tachyphylaxis and alteration of epinephrine within the reticular activating system from electroencephalogram and sleep observations[30]. Watson and associates in 1972 showed MA discontinuation in human subjects resulted in increased REM sleep and decreased excretion of 3-methoxy-4-hydroxy-phenylglycol, a marker of synthesis and metabolism of norepinephrine in the CNS[31]. Conversely, the authors found 3-methoxy-4-hydroxy-phenylglycol excretion increased during active MA use.

The increased dopamine concentration in the synaptic cleft induced by MA is responsible for its physical, psychological, and addictive effects[17]. This increase also results in neurotoxicity from monoamine oxidase metabolic and oxidative reactions, such as production of dopamine quinones, superoxide anions, hydrogen peroxide, and hydroxyl radical species[32]. These in turn lead to mitochondrial dysfunction and damage. Reactive oxygen and nitrogen species are by-products of normal CNS metabolism, but excessive production of these reactive species from MA use can damage cellular components, such as cell membranes, the blood brain barrier, proteins, and nucleic acids from peroxidation[33]. Autophagy is the process in which the organism breaks down and recycles its own cellular components, such as damaged nucleic acids, proteins, organelles, and cellular debris. Autophagy and "mitophagy" (specific to mitochondria) are important for maintenance of neuronal function, homeostasis, and survival, and MA inappropriately accelerates this process[34]. This results in damage to the CNS dopaminergic system with similar mechanisms and symptoms of Parkinson's disease. High doses of MA increase expression of autophagy markers, Beclin-1, LC3-II, and DNA damage-inducible transcript 4[35].The monoamine melatonin has been shown to protect against MA-associated escalation of autophagy and mitophagy[36].

The monoamine serotonin is also involved in sleep regulation[37]. In 1955 Brodie and associates found that brain serotonin depletion by reserpine induced sleep[38]. In addition to modulating sleep-vigilance cycles, serotonin regulates appetite, mood, thermoregulation, locomotion, and sexual behavior. Serotonin is especially important for NREM sleep, but its role has been clarified over time such that it promotes wakefulness and suppresses NREM sleep[37]. Blockade of serotonin 5-HT2 receptors has been shown to increase NREM sleep in animal and human studies[39].

MICROGLIAL IMMUNE RESPONSE AND CYTOKINES

The CNS is an immune privileged area with a distinct immune system. Microglia are the resident macrophages of the CNS and act as the first-line immune defense. Damage to the CNS from infection and trauma results in activation of microglia, which migrate to the damaged sites and secrete proinflammatory cytokines, such as interleukins and TNF. Prostaglandins, nitric oxide, and reactive oxygen and nitrogen species are also released during this immune defense process, and astrocytes are then activated by the process of reactive gliosis to initiate repair and restore energy and ion balance to the damaged CNS areas[40]. Microglial activation is initiated by MA use, and this process was initially believed to take days to complete but instead has been shown to occur minutes after MA exposure[41]. However, MA-activated microglia release a variety of reactants that damage neurons, and this process could be the source of virtually all saboteurs implicated in MA-induced neurotoxicity, such as reactive oxygen and nitrogen species[42]. Abnormal microglial activation is also a factor in the pathogenesis of Parkinson's disease, Alzheimer's disease, and multiple sclerosis[43].

Methamphetamine elevates expression of the sleep-promoting cytokine, IL1β, in the CNS. Animal studies demonstrated activation of the interleukin-1 receptor (IL1R) is responsible for the increase in the depth and amount of sleep that occurs after MA-induced wakefulness[44]. This occurs at different doses of MA and chronicity of use. Low doses of MA trigger homeostatic IL1R-dependent increases in sleep as seen with sleep deprivation. Chronic MA use and higher neurotoxic doses of MA result in depletion of CNS monoamines[45]. Exposure to MA increases IL1β in the CNS even after the drug is metabolized. Tumor necrosis factor is another important cytokine that shares these characteristics. Neurons that are immunoreactive for IL1β and TNF are located in brain regions involved in regulation of sleep-wake behavior, such as the hypothalamus, hippocampus, and brainstem[37]. Diurnal levels of IL1β and TNF vary with the sleep-wake cycle and are highest at the onset of sleep[46].

GLUTAMATE AND ADENOSINE

Methamphetamine induces excitotoxicity and sleep disturbance from glutamate release and glutamate receptor activation, including N-methyl-D-aspartate and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor subtypes[47]. Stimulation of these receptors increases intracellular calcium with activation of kinases, proteases, lipases, and free radicals. Cell membrane, nucleic acid, protein, and cytoskeleton damage ensues. Adenosine inhibits glutamate transmission in several brain regions from the inhibition of presynaptic calcium influx. Interleukin-1 indirectly suppresses glutamate transmission by promoting endogenous adenosine release[48].

GLUCOSE, MITOCHONDRIA, AND ATP PRODUCTION

Glucose levels in the CNS depend on two opposing factors: metabolic use by brain cells, and delivery across the blood brain barrier via glucose transporter protein facilitated diffusion. Although MA stimulates glycolysis and lactate production, it also stimulates insulin release in

the pancreas decreasing blood glucose while increasing free fatty acid concentration[49,50]. Methamphetamine causes blood brain barrier dysfunction and diminishes CNS glucose uptake from impairment of glucose transporter, further exacerbating neurotoxicity[51,52]. Mitochondria are bioenergetic organelles that utilize glucose for energy in the form of adenosine triphosphate (ATP) to maintain normal cell function. The Krebs cycle and electron transport chain are the essential metabolic pathways for producing ATP. Methamphetamine can diffuse into mitochondria, where it inhibits ATP synthesis and accumulation[53]. Increase in reactive oxygen and nitrogen species precipitated by MA results in mitochondrial edema, permeability, nucleic acid damage, and inhibition of electron transport chain[54]. This mitochondrial dysfunction may lead to apoptosis[55].

OREXIN

Orexin, also known as hypocretin, is a neuropeptide with two forms, orexin-A and orexin-B. Orexin is expressed in the hypothalamus then is widely distributed throughout the brain, ventral tegmental area and nucleus accumbens[22]. Orexin is associated with sleep, appetite, reward, motivation, and addiction[56]. Orexin stimulates glutamate and dopamine release in these areas. Increased orexin activation at night has been shown to result in sleep impairment[57]. Previous studies found MA enhanced Fos expression in orexin neurons and decreased orexin in MA users in acute withdrawal[58]. Administration of the orexin receptor antagonist almorexant and suvorexant countered the negative effects of MA in primate studies[59].

Etiology of Methamphetamine Washout Syndrome

Perhaps the simplest theoretical explanation for MAWS is it represents a necessary period of hypersomnolence and low energy utilization for restoration of catecholamine stores after MA-induced depletion. Catecholamine synthesis begins with adrenocorticotropic hormone-dependent tyrosine hydroxylase, which converts tyrosine to dihydroxyphenylalanine through cyclic adenosine monophosphate-dependent phosphorylation. After dihydroxyphenylalanine is decarboxylated to dopamine, it is transported into chromaffin granules and further hydroxylated to form norepinephrine. In the adrenal medulla, norepinephrine is converted to epinephrine and is also stored in granules. As intracellular catecholamines accumulate, a negative feedback mechanism inhibits further synthesis, whereas extracellular catecholamines represent a depleted reserve and stimulate synthesis[60]. This process may take a few hours to complete and coincides with the clinical time frame of MAWS[61]. Patients who use MA are often deficient in their dietary intake and malnourished[62]. A low energy state of sleep allows limited energy supplies in the form of glucose and free fatty acids to be prioritized for catecholamine replenishment.

Metabolism of MA over several hours may represent another important component of MAWS, as it aligns with the clinical time frame of MA cessation and is also an energy-intensive process. It is further possible MAWS may reflect concomitant reactive microgliosis, in which a state of hibernation occurs to minimize energy utilization for teleological but unwarranted immune defense and repair within the CNS. During this period, cytokines TNF and IL1β may be elevated and have a soporific effect. Theoretical reversal of damaged cellular and mitochondrial nucleic acids may be prioritized during this period of hypersomnolence by upregulation of nucleic acid repair genes, such as the base excision repair pathway[35]. Repair of damaged cells, mitochondria, and autophagy may also occur during this period of rest.

Treatment of Methamphetamine Washout Syndrome

Agitated MA patients frequently require sedation in the early stages of their emergency department stay, and the most commonly used agents are the dopamine D2 antagonists haloperidol, droperidol, olanzapine and GABA agonist benzodiazepines such as midazolam, lorazepam, and diazepam[9]. The pharmacotherapeutic effect and half-life of these drugs is usually less than MA, thus MAWS becomes more likely when hypersomnolence lasts greater than eight hours. Theoretical treatment options to shorten MAWS in the emergency department exist but are unproven. As MAWS may represent a form of MA withdrawal, medications used for this indication, such as mirtazapine, modafinil, melatonin, and bupropion are worth considering but are not utilized in routine practice[63,64]. As such, this section shall focus on readily available therapy found in any emergency department.

CARBOHYDRATES AND ENERGY REPLETION

Restoration of MA-depleted monoamine stores and metabolism of MA are energy-intensive processes requiring copious amounts of ATP. Reversal of MA neurotoxicity through microglial activation and astrocyte reactive gliosis are further energy-intensive processes. The blood brain barrier function is also maintained at the expense of significant energy consumption. The blood brain barrier glucose transporter protein 1 facilitates glucose transport from the circulation into the CNS, which is critical for survival of glial and neuronal cells. It has been shown MA impairs glucose transporter protein 1 function to deprive glucose uptake, further exacerbating this issue on inadequate energy supply[52]. Human studies demonstrated MA use results in a hypoglycemic state from direct influence on pancreatic insulin release[49]. Depletion of hepatic glycogen stores by MA may result in short- and long-term liver damage[45]. Positron emission tomography studies of MA users revealed significant loss of cerebral dopamine transporters and abnormalities of cerebral glucose metabolism[65]. These deleterious processes are likely involved in the development of MAWS, during which time the patient attempts to conserve energy through a form of mini hibernation. To counteract this low energy state, the provision of carbohydrates in the form of food and/or fruit juice to MA-using patients provides substrate for restoration of glycogen and intracellular energy storage. From a practical standpoint, the MAWS patient may need to be physically awakened, sat upright, and assisted by hospital staff to actively eat and drink.

HYDRATION

Methamphetamine is eliminated by both hepatic metabolism and renal excretion, with over 50% of MA recovered unchanged in the urine[66]. The renal excretion

rate for MA is highly dependent on urinary pH, and acidification of urine increases MA excretion[67]. Patients with MAWS can lay for hours with no oral fluid intake, thus intravenous hydration is important for rehydration and increasing renal perfusion for effective excretion of unmetabolized MA and its metabolites. To lower urinary pH and augment MA excretion, normal saline should be the crystalloid of choice as it has a pH of 5.5 compared to lactated ringers (pH of 6.5) and plasma-lyte (pH of 7.4)[68]. For oral hydration, most readily available fruit juices are acidic and may help lower urinary pH[69].

COOLING

Brain and body hyperthermia results from MA-induced vasoconstriction and loss of heat dissipation, as well as heat generation from increased physical and metabolic activity. Cutaneous blood flow and adipose tissue thermogenesis are also involved[70]. Hyperthermia also affects the permeability of the blood brain barrier, allowing water, ions, and potentially neurotoxic substances from blood plasma to enter the CNS[71]. Microglial activation, with release of pro-inflammatory cytokines causing neuronal damage, is enhanced by hyperthermia[72]. Elevation of ambient temperature is associated with enhanced production of IL1β or TNF[73]. Brain cells are extremely temperature-sensitive, and irreversible changes in neurochemical processes, cell structure and function occur starting at 40°C, which is just three degrees above normal[74]. The toxicity of MA increases at higher environmental temperature and is diminished at low ambient temperatures[75]. Since MAWS may represent a period of necessary CNS monoamine and energy store recovery, maintaining body temperature at or below normal could lessen MA toxicity and time to restoration. In the emergency department, this may be accomplished by close attention to the patient's temperature, removal of blankets, use of fans, misting, or cooling packs to the head and neck if hyperthermia is present.

CAFFEINE

Caffeine (1,3,7-trimethylxanthine) is a well-known psychostimulant that is readily available in natural sources such as coffee, tea, and cacao. Caffeine antagonism of adenosine receptors is responsible for its effect on sleep and wakefulness. However, adenosine exerts a neuroprotective effect in the CNS during MA use[76]. In addition to adenosine antagonism, caffeine produces a significant increase in the extracellular concentration of dopamine in the CNS and may potentiate MA-induced neurotoxicity[77]. Based on these interactions, the administration of caffeinated beverages to MAWS patients in the emergency department is not recommended despite ease of access.

ANTI-INFLAMMATORY AGENTS

As mentioned earlier, microglial activation, cytokine release, and neurotoxicity are one of the most serious consequences of MA use. Attenuation of microglial activation may help protect against MA neurotoxicity as it has been shown for Parkinson's and Alzheimer's disease[43]. Anti-inflammatory drugs commonly used in the ED such as acetaminophen, ibuprofen, and indomethacin have been used to mitigate microglial activation and neuronal damage in prior animal studies[78,79]. Although theoretical, there may be improved patient outcomes and less hypersomnolence from administration of an anti-inflammatory agent in patients with MAWS as the risk-benefit ratio is low.

Conclusion

This report represents the first time the phenomenon of MAWS has been described and analyzed from a clinical and molecular standpoint. The protracted hypersomnolence that is the highlight of MAWS represents a challenge to clinicians, nurses, psychiatric specialists, and social workers trying to optimize patient care and hospital throughput. In addition to the aforementioned proposed treatments to counter MAWS, further research is needed to determine how treatment of MA use, addiction, and acute toxicity may be optimized for the benefit of the patient, and society.

Conflict of Interest Statement:

The author has no conflict of interest to declare.

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