Etiology of Xerostomia and Dental Caries among Methamphetamine Abusers

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Abstract: This study reviews the peripheral effects of methamphetamine on the salivary acini, the pathogenesis of methamphetamine-induced xerostomia, and its anecdotal relationship to dental caries. Methamphetamine is a sympathomimetic central stimulant which is abused for its euphoric effects. Its pharmacological action is exerted indirectly by sustaining high levels of catecholamines in the synaptic cleft and directly by binding to the postsynaptic adrenergic receptors. Methamphetamine abusers report subjective perception of xerostomia, which cannot be explained by the direct peripheral action of methamphetamine on the secretory acini. The drug may cause a decrease in salivary flow rate by centrally inhibiting salivatory nuclei via stimulation of alpha-2 receptors in the brain. Drug mediated dehydration state may influence the perception of dry mouth in abusers. The decreased salivary flow rate, either due to a central inhibitory action of methamphetamine or generalised dehydration, likely contributes to the increased occurrence of dental caries.

Five cases of methamphetamine abuse are presented, three of whom experienced rampant dental caries. A direct association between methamphetamine abuse and the occurrence of rampant caries was not clear.

Keywords: methamphetamine, xerostomia, dental caries, sympathetic, meth

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Methamphetamine is classified as a mixed sympathomimetic agent that exerts a predominantly indirect action upon adrenergic receptors (Abel and Piascik, 2004b). There are 33 million methamphetamine addicts worldwide, 75% of whom live in Asian countries (Ahmad, 2003). Methamphetamine use has reached an epidemic proportion in the United States; particularly in Hawaii, the Southwest and the Central Plains (Slobo-

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da, 2002). Surveys have shown that 5.3% of adults over the age of 12 have tried methamphetamine at least once in their lifetime. The drug is popular among blue collar workers, truck drivers, medical students, athletes and housewives (Meeks and Stevens, 2004).

Methamphetamine mediates psycho-stimulant effects similar to cocaine; however it is preferred by the abuser due to its long duration of action and lower cost. The popularity of this drug may be explained, in part, by its ability to cause increased mental alertness, decreased fatigue and loss of appetite when taken in low doses. Amphetamine-like stimulants are also employed in the treatment of narcolepsy and in children suffering from attention deficit and hyperactivity disorder (ADHD) (Derlet and Heischober, 1990). In addition to auditory and visual hallucinations, in high doses methamphetamine causes intense euphoria. The abuser develops rapid tolerance to the euphoric

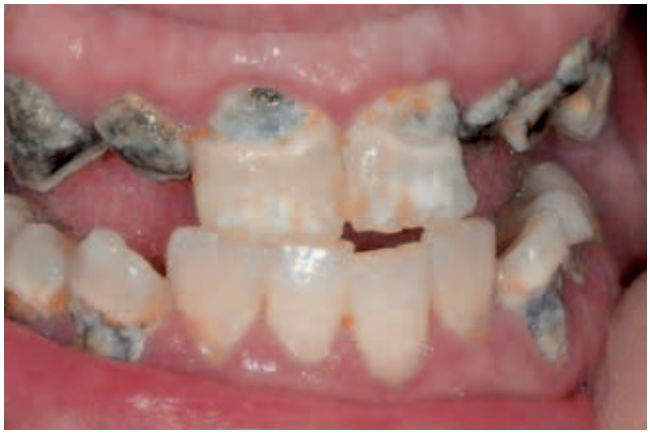

Fig 1 Case 1: Generalised marginal gingivitis and rampant dental caries involving all quadrants.

action of the drug resulting in repeated binges, which may last for days, characterised by a continuous escalation of dosage to sustain the euphoric state ('tweaking'). This often leads to extreme frustration, violent behavior and intense insomnia followed by bouts of prolonged sleep ('crashing') (Ray and Ksir, 1990).

Methamphetamine can be smoked, snorted, ingested orally or administered intravenously. It is a lipid soluble agent which diffuses rapidly across the blood brain and placental barriers. The pharmacological effects manifest immediately after inhalation or intravenous administration and 40 minutes after oral ingestion (Bailer, 2002).

A number of clinical effects of interest to the dental profession have been attributed to chronic methamphetamine abuse. These include xerostomia, tongue ulcerations and dental attrition (Bockman and Abel, 2004). The occurrence of rampant dental caries involving the buccal and proximal surfaces has also been reported (Shaner, 2002).

We report five cases of methamphetamine abusers, three of whom developed rampant dental caries. The pathogenesis of methamphetamine-induced xerostomia and its relationship to an increased incidence of dental caries is discussed.

CASE REPORTS

Case 1

A 22-year-old white male reported to our Dental School Clinic with a chief complaint that he was losing all of his teeth. A review of the patient's medical history revealed a five-year history of methamphetamine abuse. Initially he would smoke the methamphetamine, but later he switched to intravenous injection and snorting. He had discontinued abusing methamphetamine 18 months prior to presenting to our clinic. The patient indicated that while using the methamphetamine, he often felt hot and sweaty and experienced a dry mouth. During this period, he would consume up to two litres of carbonated beverages per day to relieve the dryness of the mouth. The patient also reported nocturnal bruxism and a daytime clenching habit, both of which were more pronounced during periods of drug abuse. He indicated that he tried to brush his teeth one time per day, but often was unable to due to dental pain. Intraoral examination revealed a plaque index of 95% and rampant caries involving multiple tooth surfaces (Fig 1). His DMFT score was 31.

Case 2

A 27-year-old white male presented to our Acute Care Clinic with several fractured teeth. The patient volunteered that he had a six-year history of methamphetamine abuse and a 13-year history of marijuana and alcohol abuse. With the exception of marijuana, the patient had reportedly discontinued drug use six months earlier. The patient was under psychiatric treatment and was taking quetiapine, 50 mg tid, for delusional psychosis. The patient brushed his teeth every other day and flossed less than one time per week. He consumed up to two litres of carbonated beverages per day. Intraoral examination revealed a plaque index of 90%, generalised calculus deposits, and rampant caries (Fig 2). His DMFT score was 31.

Case 3

A 31-year-old white male presented with a chief complaint of badly broken down teeth. Medical history revealed an eight-year history of methamphetamine and cocaine abuse, both of which had been administered by intravenous injection. Current medications included sertraline hydrochloride, 100 mg per day, for severe depression. The patient reported that during the period of drug abuse he bruxed and consumed large amounts of fruit juice

and carbonated beverages to relieve his dry mouth. Intraoral examination revealed a 45% plaque index, generalised gingival hyperplasia and rampant dental caries involving both interproximal and cervical surfaces. The patient's DMFT score was 32.

Case 4

A 34-year-old white female presented with a chief compliant of loose teeth and receding gums. A review of the patient's medical history revealed a 10-year history of methamphetamine abuse which she discontinued one year ago. She brushed her teeth once per day and reported a high consumption of carbonated beverages. Intraoral examination revealed a plaque index of 70%, generalised calculus, and moderate pit and fissure caries. Her DMFT score was 7.

Case 5

A 19-year-old white female who presented for a routine dental examination admitted a five-year history of daily methamphetamine abuse. Initially the route of administration was daily intravenous injection, however after two years the patient switched to the inhalation route. While abusing methamphetamine, the patient stated that she noted a chalky feeling in her mouth, which she relieved by brushing her teeth, sometimes up to 6 times per day. In addition she also noted a feeling of dry mouth, which was remedied by chewing gum and drinking fruit juices. She stated she avoided carbonated beverages because they upset her stomach. Intraoral examination revealed a DMFT score of 5. Interestingly, only pit and fissure caries were noted.

DISCUSSION

Methamphetamine is considered a mainly indirect mixed sympathomimetic agent because of a predominance of indirect rather than direct effects on the adrenergic receptors in sustaining the levels of the catecholamines norepinephrine, serotonin and dopamine in the synaptic cleft (Williams and Turner, 2005). Methamphetamine stimulates the release of these neurotransmitters from the presynaptic vesicles by reversing the direction of vesicular monoamine transporter activity, which is responsible for concentrating catecholamines in the synaptic vesicles. It blocks the norepinephrine transporter, thereby preventing the reuptake of neurotransmitter from the synaptic cleft (Galanter and Wartenberg, 2005). In addition, methamphetamine blocks the metabolic breakdown of norepinephrine by presynaptic mitochondrial monoamine oxidase. Methamphetamine also binds directly to peripheral alpha-1 and beta-1 adrenoreceptors located in the postsynaptic cell membrane of target cells. However, this action is minimal in magnitude compared to its indirect effect at the presynaptic level (Forster, 1998).

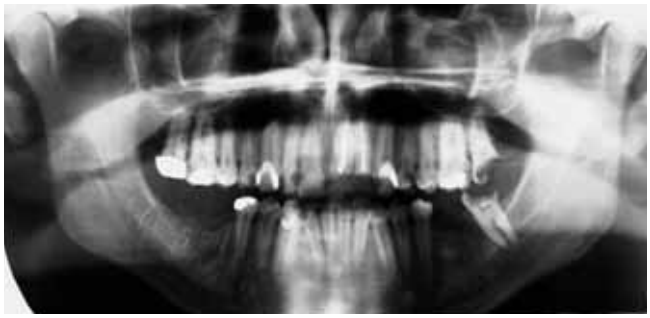

Fig 2 Case 2: Panoramic view demonstrating rampant dental caries involving all quadrants.

Compared to other sympathomimetic agents of the amphetamine category, methamphetamine demonstrates a higher ratio of effects on the central nervous system than the peripheral nervous system (Forster, 1998). Dopamine release in the nucleus accumbens (a critical component of the 'reward center') and the lateral cerulus-mediated release of norepinephrine in the central nervous system explain some of the psycho-physiologic effects of methamphetamine such as mental alertness, stereotypic repetitive behaviors, purposeless movements, as well as its reinforcing effects (Galanter and Wartenberg, 2005).

An apparent association between methamphetamine abuse and dental caries has been reported in the literature. Di Cugno et al (1981) observed that patients who were abusing amphetamine alone or in combination with marijuana had four times more decayed, extracted or teeth requiring extraction than control subjects. Duxbury (1993) noted the frequent occurrence of cervical caries in patients abusing ecstasy (3,4-methylenedioxy-methamphetamine). Howe (1995) observed that children treated with methamphetamine for ADHD or narcolepsy developed labial and proximal caries in

the mandibular anterior teeth, an unusual location for dental decay. Venkar (1999) described the concomitant occurrence of rampant cervical caries and an increased incidence of bruxism-related occlusal wear in methamphetamine abusers. Shaner (2002) stated that rampant caries is one of the hallmarks of chronic methamphetamine abuse, characterised by a distinctive involvement of the buccal and proximal surfaces of anterior teeth.

Many postulations have been proposed to explain the apparent higher incidence of dental caries among patients abusing methamphetamine and amphetamine-like agents. Richards and Brofeldt (2000) studied tooth wear among chronic methamphetamine abusers and, judging from the published clinical photos, erroneously recorded dental caries as an example of 'dietary erosion/wear'. The authors noted higher dental hard tissue damage in anterior teeth compared to posterior teeth in abusers who snorted methamphetamine as compared to subjects ingesting or inhaling the drug. They proposed that drug delivery through the nasal pathway caused vasoconstriction of the anterior and middle superior alveolar arteries, leading to 'weakening of the tooth structure due to restriction of vascularity'. However, it has been documented in the endodontic literature that the loss of vascular supply to teeth, in and of itself, does not lead to weakening of tooth structure (Messer and Wilson, 1996). Moreover, their postulation does not adequately explain the apparent increased incidence of caries in the mandibular anterior teeth.

An association between xerostomia and the use of amphetamine-like agents has also been reported (Shaner, 2002). The exact mechanism of methamphetamine-induced xerostomia is not known. It may be related to the central inhibitory action of methamphetamine, especially with regards to its effect on unstimulated salivary flow rates. Additionally, xerostomia could be related to a generalised state of dehydration due to a loss of total body water secondary to a methamphetamine-induced increase in the metabolic rate.

Xerostomia is best viewed as a subjective sensation of oral dryness. Developing objective clinical criteria for measuring and quantifying xerostomia is problematic. Salivary hypofunction can be defined as a 50% percent reduction in the salivary secretion (an unstimulated salivary flow rate of less than 0.1 ml/minute) (Dawes, 1987; Edgar and O'Mullane, 1990). Bushfield et al (1961) found no correlation between subjective reporting of dry mouth and an actual reduction in salivary flow. Overall dryness is less important as a subjective perception of dryness than regional differences in mucosal hydration. In other words, areas such as the anterior hard palate that are devoid of minor salivary glands are more prone to developing a sensation of dryness following a decrease in salivary flow (Milosevic et al, 1999).

Di Cugno et al (1981) report a 73% reduction of stimulated parotid salivary secretion in amphetamine users and a 59% reduction in the stimulated parotid secretion in subjects abusing both amphetamine and marijuana compared to healthy controls. They noted that the perceived oral dryness following the ingestion of amphetamine could be relieved by the ingestion of milk or water, in preference to sweet or citric acid-containing drinks. This is in contrast to other studies (Shaner, 2002) that have reported a high ingestion of carbonated beverages by methamphetamine abusers, purportedly in an attempt to relieve xerostomia. Milosevic et al (1999) noted that their ecstasy-abusing subjects used chewing gum to counteract xerostomia, implying that salivary flow could be stimulated in this group. This suggests that methamphetamine-related xerostomia is characterised primarily by a reduction in the unstimulated salivary flow rate.

Salivary secretion is mediated by the autonomic nervous system via parasympathetic and sympathetic pathways. There are interspecies differences in the neuroantomical characteristics of the salivary glands, intracellular signaling pathways and glandular transport systems. Therefore, interspecies extrapolations of findings should be approached with caution. In humans, the sublingual and minor salivary glands respond primarily to parasympathetic stimulation (Dowd, 1999). This dominant parasympathetic pathway facilitates stimulation of muscarinic receptors present on the salivary acini by binding to the neurotransmitter acetylcholine. It also regulates the concentration of electrolytes and the volume of water in the salivary fluid (Garant, 2003). The parasympathetic pathway would not be expected to play a role in methamphetamine-induced xerostomia because this class of drug affects only the sympathetic system.

The influence of the sympathetic pathway on secretory acini is minimal. In humans, the parotid gland acini are devoid of secretory sympathetic fibers (Abel and Piascik, 2004a). The secretory sympathetic system modulates the composition of saliva rather than adding fluid volume. Norepineph-

rine responsive sympathetic adrenoreceptors include the alpha-1, beta-1, beta-2 and alpha-2 receptors. The latter has an inhibitory role on the release of norepinephrine from the presynapse. The stimulation of the adrenergic beta-1 acinar receptors initiates a cascade of signal transduction via activation of cyclic adenosine phosphate (cAMP), resulting in exocytosis of acinar granules and generation of protein-rich saliva (Izutsu, 1989). The alpha-1 receptors play a minor role in response to norepinephrine stimulation; primarily by influencing the secretion of water and electrolyte potassium ions. This effect is similar to what is seen following muscarinic receptor stimulation (Abel and Piascik, 2004b). Moreover, the distribution of alpha-1 adrenergic receptors in the cell membrane of acinar cells is far less than the concentration of beta-1 adrenergic receptors (Garrett and Kidd, 1993).

Although methamphetamine can bind directly to adrenoreceptors of some target cells, the direct binding to acinar adrenoreceptors has not been demonstrated. Peripheral stimulation of beta-1 acinar receptors by methamphetamine would be expected to result in hypersecretion of amylase, kallikrein and peroxidase (Garant, 2003). In contrast, stimulation of alpha-1 acinar receptors would cause secretion of water and electrolytes only. Therefore, the increased incidence of xerostomia among methamphetamine abusers cannot be explained by peripheral sympathomimetic activity on beta-1 or alpha-1 acinic receptors.

The net result of catecholamine-mediated autonomic stimulation of acinar cells is the mobilization of intracellular calcium ions from the rough endoplasmic reticulum and the calciosomes. Elevated concentrations of cytosolic calcium ions open the intramembranous gated channels and move chloride and sodium ions from the interstitial fluid to the acinar lumen. The build up of an osmotic gradient in the lumen of the acini aids in the influx of water molecules. The newly formed saliva is isotonic to plasma. Sodium ions are subsequently reabsorbed by the water-impermeable cells of the striated duct, resulting in hypotonic saliva (Garant, 2003).

The vascularity and vasomotor tone of the salivary glands is under sympathetic control (Garrett, 1987). This system plays an important role in the production of saliva by regulating the extracellular fluid volume from which saliva is derived. Adrenergic stimulation of alpha-1 receptors in the salivary gland vasculature leads to localised vasoconstriction, thereby reducing the fluid content of excreted saliva. One would anticipate that methamphetamine-induced vasoconstriction should be generalised in nature. Consequently a similar reduction in the rate of secretion from other exocrine gland secretions should be seen. However, it has been demonstrated that the glandular secretions of the gastrointestinal tract are not decreased in methamphetamine abusers (Smith and Chamberlin, 1937). Anatomically, a rich capillary network surrounds the striated ducts of the salivary glands and branches from this network extend and loop to form an arcade around the secretory acinar end units (ten Cate, 1998). Theoretically, methamphetamine-mediated vasoconstriction of the capillary network that surrounds the striated ducts should result in cellular hypoxia, restricting the reabsorbtion of sodium ions from the lumen of the duct, leading to the secretion of hypertonic saliva. To our knowledge, evidence of such a change in osmolarity has not been reported in the saliva of methamphetamine abusers.

A state of stress and anxiety is usually characterised by the presence of oral dryness, due to a central inhibitory modulation of the superior and inferior salivatory nuclei, which was previously thought to be due to inhibitory peripheral sympathetic stimulation. It has been shown that norepinephrine stimulation of inhibitory alpha-2 receptors in the brain causes inhibition of salivary secretion (Moreira et al, 2002). One could speculate that methamphetamine may also exert its influence on salivary secretion in a similar fashion.

Physical changes in methamphetamine abuse include an increased basal metabolic rate, physical overactivity, excessive sweating and hyperthermia, all of which contribute to a state of generalised dehydration. The degree of dehydration plays a significant role in regulating salivation. When the water content of the body is reduced by 8% percent the salivary flow is nearly decreased to zero (Holmes, 1964). We would, therefore, expect that the generalised dehydration experienced by methamphetamine abusers is likely to play a role in the perceived sensation of oral dryness.

As previously mentioned, there are anecdotal reports of frequent sipping of carbonated beverages (soft drinks) by methamphetamine abusers in an attempt to alleviate oral dryness. These soft drinks usually contain high levels of phosphoric and citric acid, leading to a pH-mediated loss of dental hard tissues (Jarvinen et al, 1991). This is aggravated

by a concomitant decrease in unstimulated salivary flow rates.

Even though methamphetamine is excreted in saliva (Cook et al, 1993), the pH of this drug apparently is not enough to play a significant role in caries induction. The mean reduction of salivary pH after ingestion of 100 milligrams of ecstasy has been shown to be 0.6 pH units lower than the predose pH of 7.4 (Navarro et al, 2001). Although there is a reduction of pH, the resultant pH is above the critical pH of 5.5 at which tooth dissolution occurs (Newburn, 1983).

Newburn (1983) stated that prolonged use of amphetamine may cause dryness of the mouth and dental caries. A low unstimulated salivary flow rate is usually accompanied with reduction of the buffering capacity of saliva (Abelson and Mandel, 1981), lowering of the salivary pH (Shannon and Prigmore, 1960), decreased rate of clearance of sugars from the oral cavity (Edgar, 1998) and alteration of the composition and volume of the dental plaque (Newburn, 1983). All these factors, in combination with frequent ingestion of acid and sugar-containing beverages, lack of oral hygiene and fear or lack of access to dental treatment increase the incidence of dental caries among the drug abuser (Scheutz, 1984).

All of our patients reported that they were no longer abusing methamphetamine. The abstinence period among our patients varied from six to 18 months. Two were currently under psychiatric care for psychosis and depression. Many drug classes, including antimuscarinic anticholinergics, first generation histamine receptor antagonists, tricyclic antidepressants and centrally acting antihypertensives are known to produce a sensation of dry mouth by reducing salivary flow (Dowd, 1999). One patient was taking quetiapine, a dibenzothiazepine derivative, for delusional psychosis; which is commonly seen in the recovering methamphetamine addict (Ray and Ksir, 1990). The other patient had been taking sertraline for the last four months for the treatment of severe depression. Both of these medications are known to produce xerostomia (Wynn et al, 1999) but it is highly improbable that in such a short period they could have had any role in the rampant decay seen in these two patients.

Three patients in this series who abused the drug for five to eight years had a generalised heavy build up of dental plaque and rampant caries (DMFT above 30). The decreased salivary flow rate, either due to a central inhibitory action of methamphetamine or generalised dehydration, likely contributed to the increased occurrence of dental caries. Two patients had low DMFT values (5-7). One of these who abused the drug for five years reported that she obsessively brushed her teeth (up to six times daily) in an attempt to relieve a sensation of perceived oral chalkiness. Stereotype repetitive behavior is common among chronic methamphetamine abusers. This patient also mentioned that she used a straw when drinking cariogenic beverages. Even though the drug profile of these two patients were similar to the three patients with high caries rate, the regularity of oral hygiene measures was the only distinguishing factor which may explain low caries incidence.

Preventive dental management of these patients has been described previously and is similar to other high caries risk patients, particularly those with severe xerostomia (Shaner, 2002). In addition to promoting daily, regular oral hygiene measures, preferably using an electric toothbrush with a built-in two-minute timer, patients are counseled on restricting carbonated beverage consumption to mealtime only, avoiding between meal sipping. Sugarless chewing gum is strongly encouraged and patients are advised to chew a piece for a minimum of three times a day for at least five and preferably 20 minutes. Daily fluoride supplementation using rinses, trays, brush-on gel/toothpaste should be prescribed along with the use of an aggressive fluoride varnish application regimen. Compliance with these recommendations is an obvious concern due to the high recidivism among recovering methamphetamine abusers necessitating a more frequent recall interval to monitor their oral health status.

We conclude that the most significant contribution to an increased caries rate in methamphetamine abusers is related to a lack of oral hygiene and a reduced unstimulated salivary flow rate. The compulsive methamphetamine abuser is generally not motivated to practice oral hygiene measures, resulting in a high caries rates. A comprehensive control study is needed to establish direct relationship between dental caries and methamphetamine abuse.

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