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Toxicology of Nutmeg Abuse

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ABSTRACT

Background: Unpleasant and frightening side effects associated with the abuse of nutmeg occasionally generate emergency department referrals. We report a young patient’s first-time experience with nutmeg and review the mechanisms of its toxicity. Case Report: A 13-year-old female ingested 15–24 g of nutmeg over a 3-hour period and smoked and shared 2 joints of marijuana. To facilitate ingestion, the nutmeg was put into 00–000 gelatin capsules. Bizarre behavior and visual, auditory, and tactile hallucinations developed. She also experienced nausea, gagging, hot/cold sensations, and blurred vision followed by numbness, double, and “triple” vision, headache, and drowsiness. Nystagmus, muscle weakness, and ataxia were present. Her vital signs and laboratory tests were normal. She received 50 g of activated charcoal and except for complaints of dizziness and visual changes, her 2-day admission was uneventful. The central nervous system activity of nutmeg is often postulated to result from biotransformation of its chemical components to amphetamine-like compounds, but this has not been proven. Nutmeg contains several compounds with structural similarities to substances with known central nervous system neuromodulatory activity.

INTRODUCTION

Nutmeg is best known as the kitchen spice derived from the seed of the nutmeg tree, Myristica fragrans. Toxicologically, it is best described as a substitute psychotomimetic substance of abuse. Historically, epidemics of nutmeg intoxication were described around the turn of the century, with few subsequent cases until a resurgence of use in the mid-1960s. Since then, nutmeg has been relegated to the role of a natural or legal high, that is periodically rediscovered by adolescents. Widespread and repeated abuse of nutmeg is not a
common problem since the side effects are typically unpleasant and frightening and occasionally generate self referral for medical treatment. We report a young patient’s first-time experience with nutmeg and examine proposed mechanisms of its psychotropic effects.

Case Report

On the advice of a friend, a 13-year-old female ingested 19 gelatin capsules containing an unknown “cinnamon-colored vegetable material.” She began taking the capsules at 2000 hours, with 10 capsules taken between 2200 and 2300 hours. She also shared a pipe containing the contents of 2 capsules, which left a bad aftertaste, and smoked most of 2 joints of marijuana. She began “butting heads” with a friend who had taken 4 capsules. At 2400–0100 hours, she described seeing things, like coats and clothing flying at her. Her vision was blurred, she felt hot and cold sensations, and she kept answering the phone even though her friends kept telling her it was not ringing. She awoke at 0700 hours after dreaming she had centipedes crawling on her, although she wasn’t sure she had been asleep. She was afraid and asked her mother to take her to the hospital.

The patient presented to an emergency department at 0800 hours, and a call placed to the patient’s friend identified the substance as nutmeg. He obtained the recipe for encapsulation from another teenager, who had found it in a book. The patient complained of drowsiness, num

inness, headache, and double and triple vision. The temperature was 36.9°C, blood pressure 110/60 mm Hg, pulse 88/min, and respiration 18/min. Nystagmus was present and she was weak and unstable upon standing. She complained of left lower quadrant abdominal tenderness. Cranial nerves were intact and an electrocardiogram (ECG) was unremarkable with a sinus rate of 78/min, PR 150 msec, QRS 66 msec, and QT/QTc 362/412 msec. The serum electrolytes, renal and liver function tests, urinalysis, hematology, and a pelvic ultrasound were normal. She was given activated charcoal 50 g with sorbitol, trimethobenzamide for nausea, and intravenous fluids.

Table 1

Summary of Common Clinical Effects of Nutmeg Abuse

<table>
<thead>
<tr>
<th>Category</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Nervous</td>
<td>euphoria, giddiness, anxiety, hallucinations: (visual, auditory, tactile), apprehension, detachment, headache, dizziness, drowsiness, confabulation</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>tachycardia, hypotension, flushing</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>xerostomia, nausea, pain gagging, vomiting, ileus</td>
</tr>
<tr>
<td>Peripheral, other</td>
<td>parasthesias, numbness, blurred vision, hypothermia, sweating</td>
</tr>
</tbody>
</table>

Table 2

Composition of Oil of Nutmeg: Terpenic Fraction*

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Relative Quantity %</th>
<th>Reported Effects*</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Pinene</td>
<td>36.2</td>
<td>convulsant</td>
</tr>
<tr>
<td>Sabinene</td>
<td>12.8</td>
<td></td>
</tr>
<tr>
<td>1,8-α-Menthadiene</td>
<td>12.8</td>
<td>anticholinesterase, sedative</td>
</tr>
<tr>
<td>β-Pinene</td>
<td>6.2</td>
<td>convulsant</td>
</tr>
<tr>
<td>1,4-α-Menthadiene</td>
<td>3.5</td>
<td>anticholinesterase</td>
</tr>
<tr>
<td>Camphene</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>1-Methene-4-OL</td>
<td>2.9</td>
<td>anticholinesterase</td>
</tr>
<tr>
<td>Borneol</td>
<td>2.6†</td>
<td>CNS stimulant</td>
</tr>
<tr>
<td>p-Cymene</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Furfural</td>
<td>1.5†</td>
<td></td>
</tr>
<tr>
<td>Furfurol</td>
<td>1.5†</td>
<td></td>
</tr>
<tr>
<td>1,4(8)-p-Menthadiene</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>1-Menthene-8-OL</td>
<td>0.4</td>
<td>anticholinesterase</td>
</tr>
<tr>
<td>1,8-Cineole</td>
<td>0.4†</td>
<td>anesthetic, anti-</td>
</tr>
<tr>
<td>α-Terpinene</td>
<td>0.3†</td>
<td>cholinesterase, sedative</td>
</tr>
<tr>
<td>Geranyl acetate</td>
<td>0.2</td>
<td>sedative</td>
</tr>
</tbody>
</table>

*Adapted from reference 10. †Maximum concentrations in nutmeg seed; other compounds at less than 1% concentration include β-myrcene, α-phellandrene, α-thujene, cis-p-ment-2-enol and cis-piperitol; ‡Adapted from reference 43.
had a history of an eating disorder and admitted to occasional use of marijuana, but denied ethanol use. One year earlier, she had taken an overdose of ibuprofen. Urine toxicology was negative for barbiturates, acetone, ethanol, isopropanol, methanol, salicylates, tricyclic antidepressants, acetaminophen, methaqualone, meprobamate, phenytoin, glutethimide, and ethchlorvynol. On the second day, the patient continued to complain of dizziness and needed assistance out of bed, despite normal blood pressure, and she continued to complain of triple vision. On the morning of the third day of admission, she still complained of dizziness but was dismissed home that afternoon.

DISCUSSION

Based on the patient’s description, we estimated that the capsule size was 00 or 000, containing 0.8 and 1.3 grams per capsule, respectively, yielding a total oral dose of approximately 15–25 g. This dose and the patient’s narrative and presentation were similar to previous reports. Table 1 summarizes the clinical effects of nutmeg abuse. The encapsulation method surmounted the main difficulty of palatability of the large dose. This method of administration and the concurrent use of marijuana may explain the absence of vomiting.

There is a wide variability in the clinical signs and symptoms and psychopharmacological response associated with nutmeg intoxication. The concentrations of its active components (Table 2) are influenced by the botanical source, quality, and storage of commercial nutmeg and the methods used for their isolation and analysis.

As with other psychoactive drugs, variations in interindividual response may be due to the baseline neurobiological state of the user and may be influenced by social setting, even though prisoners in isolation have reported typical effects.1

The limited research on nutmeg components and their psychopharmacology accompanied its popularity in the mid-1960s, with no recent investigations. Major clinical toxicology references continue to cite an early hypothesis of the amination/transamination of nutmeg’s aromatic compounds to amphetamine-like compounds,

Figure 1. Proposed and actual pathways for the biotransformation of myristicin.10,23
Figure 2. Biotransformation of eugenol in man.²
e.g., mescaline in the case of elemicin and 3,4-methylenedioxy-5-methoxyamphetamine in the case of myristicin (Figure 1). This mechanism was originally proposed in the 1960s by Alexander Shulgin,¹⁰−¹² who may be described as the “Father of Nutmeg Toxicology,” but even Shulgin doubted its relevance in vivo.¹¹

Few animal studies provide evidence of the amination of nutmeg components in vitro and in vivo,¹⁶ and no studies exist in humans. The pathways defined in animals are inconsistent with human biotransformation of xenobiotics in general¹⁹ and the amine donor compounds identified as necessary cofactors in animal studies¹⁷ are not known to exist endogenously in humans. The majority of investigations in animals²⁰−²² and humans²⁴,²⁵ (Figure 2) exclude amination and are more consistent with established biotransformation pathways for xenobiotics in humans.¹⁹

Although alpha-keto acid intermediates (substrates for “transamination”²⁶) are generated during the biotransformation of nutmeg’s aromatic compounds (Figure 2), such foreign alpha-keto acids are generally quickly reduced to their corresponding alcohol moieties.¹⁹ Similarly, there is no evidence for reversal of the metabolic pathways for endogenous neurotransmitter amines (e.g., vanillylmandelic acid to norepinephrine or homovanillic acid to dopamine).²⁷ A possible scenario may be that nutmeg compounds and their metabolites may interfere with endogenous neurotransmitter pathways which generate central neurotransmitters. However, this would be anticipated to produce imbalances in neurotransmitter concentrations (e.g., depletion, accumulation of false neurotransmitters) which would require chronic abuse. We were unable to locate any data that support any of these processes.

Perpetuation of a transamination mechanism is likely due to the association of psychoactivity to the presence of a nitrogen-containing functional group²⁸; however, absence of a nitrogen functional group does not always preclude psychoactivity (see below).

As with other naturally derived chemicals, evidence for the direct effects of the major components of nutmeg has also been limited (Tables 2 and 3). The focus usually centers on the aromatic fraction because nutmeg, devoid of its volatile components, lacks central nervous system (CNS) activity.¹³ Human studies with pure myristicin have been equivocal¹³ and behavioral studies in animals with pure nutmeg compounds²⁹ and their metabolites³⁰ suggest CNS depressant activity. Although commonly cited, there is also limited evidence regarding MAO inhibition by some components.³¹ The complex psychiatric effects indicate a contribution from the terpenic fraction of nutmeg (see below) and its other components, with synergism as an additional consideration.

The structural similarities of nutmeg compounds to mescaline and methylenedioxyamphetamine (Figure 3) which, along with other classical hallucinogens that are known to act at the 5-HT2A and 2C class of serotonin (5-HT) receptors, seems relevant.³² Despite the absence of a nitrogen group, elemicin and myristicin demonstrate activity at 5-HT receptors (Table 3). The aromatic nutmeg compounds are structurally related to other nonaminated botanically-derived chemicals, such as mangostin (containing the common substituted phenylpropene fragment), from the mangosteen tree (Garcinia mangostana).

### Table 3

<table>
<thead>
<tr>
<th>Composition of Oil of Nutmeg: Aromatic Fraction*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compounds</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Myristicin</td>
</tr>
<tr>
<td>Elemicin</td>
</tr>
<tr>
<td>Safrole</td>
</tr>
<tr>
<td>Methyleugenol</td>
</tr>
<tr>
<td>Eugenol</td>
</tr>
<tr>
<td>Methylisoegenol</td>
</tr>
<tr>
<td>Methoxyeugenol</td>
</tr>
<tr>
<td>Isoeugenol</td>
</tr>
<tr>
<td>Isolemicin</td>
</tr>
<tr>
<td>Toluene</td>
</tr>
</tbody>
</table>

*Adapted from reference 10. †Adapted from reference 43.
which is also active at 5-HT2 receptors and the psychoactive myristicin analogues apiole and dillapiole (Figure 3).

The structure–activity relationships of other botanical compounds may help to explain the central activity of nutmeg compounds. Magnolol and honokiol (which contain the common phenylpropene fragment), from Magnolia officinalis, share the central depressant/sedative effects. The kava extract ingredients, methysticin and kavain (substituted myristicin analogues), inhibit voltage-operated sodium channels, a possible mechanism for the local anesthetic (membrane-stabilizing) effects of some nutmeg compounds (Table 3).

Compounds from the terpenic fraction of nutmeg are structurally related to known CNS stimulants, such as homocamin (a veterinary stimulant), camphor, and thujone (an inhibitor of type A GABA receptors), and act as in vitro inhibitors of CYP2B1 monooxygenase (Figure 4). The calcium antagonist and antiarachidonate activity of several components (Table 3) and their possible influence on central neurotransmitter release and activity of intracellular second messengers and on anandamide disposition and central cannabinoid receptors need to be explored.

There are several reasons why nutmeg abuse is not a major issue. These include the need for a large unpalatable dose (unless encapsulated as in this case), a high risk(unpleasantness)-to-benefit ratio, lack of effectiveness as compared to other hallucinogens, and an unpredictable response. Nutmeg, however, is easily obtainable and legal and its use is perpetuated in easy access resources such as the Internet. Reevaluation of the mechanism of action of nutmeg components may shed light on the activities of other natural substances and herbal drugs of increasing use. Future areas of research should examine the effects of these compounds on central
Figure 4. Structures of nutmeg components* (terpenic fraction) and related compounds (see text for details).

neurotransmitter synthesis and disposition and on their receptors and transporters.

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REFERENCES

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