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Acute Toxicities of Betel Nut: Rare but Probably Overlooked Events

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ABSTRACT

Background: Betel nut chewing has long been a social habit in Taiwan and other Asian and tropical countries. It produces various autonomic and psychoneurologic effects including tachycardia, flushing, warmth, cholinergic activation, alertness, and euphoria. Although the oral carcinogenic effects are well known, data concerning its acute toxicity are few. To better understand the toxicity of betel nut, cases reported to the Taiwan Poison Control Center as probable or possible betel nut-related toxicity (January 1988–June 1998) were reviewed. In the 17 cases suitable for review (14 males, 3 females, age 21 to 60 years), the most common manifestations were tachycardia/palpitations (7); tachypnea/dyspnea (6); hypotension and sweating (5); vomiting, dizziness, and chest discomfort (4); abdominal colic, nausea, numbness, and coma (3); and acute myocardial infarction and related manifestations (2). The reported quantity of betel nut used was low (1 to 6 nuts), except an extract of 100 betel nuts was used in 1 case and 66 chewed in another. Most cases recovered within 24 hours after the exposure. One patient developed probable acute myocardial infarction and ventricular fibrillation and died despite repeated cardiac defibrillation. Although betel nut chewing is widespread, significant toxicity as reported to a poison center is rare. Because most betel nut-related effects are transient and mild in nature, the incidence of such events is likely to be underreported. Nevertheless, betel nut chewing can produce significant cholinergic, neurological, cardiovascular, and gastrointestinal manifestations. It is possible that it may aggravate cardiac diseases in susceptible patients but this hypothesis must be further

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investigated. Treatment is symptomatic. With timely support, rapid and complete recovery is anticipated but a small risk of major complications cannot yet be discounted.

INTRODUCTION

Areca nut (frequently known as betel nut) is the ripe seed of the tall, slender palm tree *Areca catechu* that is widely cultivated in many tropical and subtropical areas, including India, Southeast Asia, East Africa, and New Guinea. Although betel-nut chewing has been associated with oral cancer for several decades, it is still a common masticatory in these countries (1–3). It was estimated in the early 1990s that 10% to 20% of the world's population chew betel quid daily (3,4). In Taiwan, an estimated 10% of the population, or some 2 million people, are current or ex-users of betel nut (5,6). The percentage of betel chewers, however, may be disproportionately higher in those of lower socioeconomic status and less education (6).

Betel nut can be chewed alone but is most commonly used with other ingredients known as a quid. A betel quid typically consists of three ingredients: areca nut, leaf of the betel pepper (*Piper betle*, a climbing shrub not related to the betel palm), and slaked lime paste obtained from shells, coral, or limestone (3). The constituents of a betel quid are fairly complex, and include several alkaloids such as arecoline, arecaidine, guvacine, and guvacoline (7). All of these are agonists at one or more subtypes of the muscarinic receptor. Arecoline is the most potent at M1-2-3 and arecaidine at M2 (8,9). In addition, arecoline possesses weak ganglionic nicotine agonism (10).

Users experience reinforcing effects including increased alertness, lesser fatigability, and a sense of well being (4,11,12). Chu and Chang, in a study of 170 volunteers, found betel nut–related adverse effects to be common (11). Among first-time users, dizziness was noted in 70%, followed by a sensation of warmth (60%), palpitations (45%), and increased alertness (15%). In contrast, alertness (70%), warmth (60%), palpitations (50%), sweating (40%), diarrhea (30%), and euphoria (20%) are reported among habitual users.

Despite the widespread use of betel nuts and the known pharmacological effects of their major alkaloids, acute betel nut poisonings are rarely reported in the literature. This common practice in eastern and tropical countries is becoming increasingly recognized among immigrant populations who bring their social habits with them to the new countries. Furthermore, availability of betel over the internet, among other ethnopharmaceuticals, increases the likelihood that such habits, otherwise geo-

graphically localized, will become more widespread. To better understand the clinical features and severity of acute betel nut intoxication, we reviewed the data regarding betel nut exposure reported to the Taiwan Poison Control Center (PCC).

METHODS

The Taiwan PCC handles calls from both health care professionals and the public. A case review was performed by identifying all telephone inquiries concerning betel nut–related toxicity received by the Taiwan PCC from January 1988 through June 1998. All available case and medical records for each identified betel inquiry were reviewed. Cases were identified for review by an exposure history that included the betel nut and a temporal connection between exposure and the occurrence of clinical manifestations. Nine cases were not included in the review because of inadequate general information or follow-up, or an uncertain exposure history. A case of a 2-year-old boy who was asymptomatic following the ingestion of 1 betel quid was also excluded from review. Cases were classified as “probable” or “possible” betel nut poisonings based on the clinical manifestations and the potential contribution of other coingestants or underlying diseases such as coronary heart disease. Probable poisoning was defined by the development of typical cholinergic manifestations such as diaphoresis, diarrhea, vomiting, bronchospasm, dizziness, hypotension, and facial flush, or CNS depression immediately following betel nut exposure in the absence of any potentially confounding coingestants or diseases. Possible poisoning was defined by development of nonspecific symptoms or signs temporally related to betel nut chewing, or there was evidence of potentially confounding diseases or coingestants.

Data selected for tabulation included age, gender, estimated number of nuts, reason for exposure, user status (first-time vs. habitual), coingestants, initial symptoms/signs, time of onset (if known), clinical severity, methods of management, outcome, duration of hospitalization, and cause of death if fatal exposure. The clinical severity of betel nut poisoning was classified as follows: *Mild*: Some transient, self-limited signs/symptoms (e.g., nausea, vomiting, and flush) were reported; *Moderate*: Signs/symptoms were more pronounced, more prolonged, or of a more systemic nature than mild poisoning



such as confusion and hypotension; *Severe*: Life-threatening manifestations such as shock, coma, and prolonged bronchospasm were reported or the manifestations resulted in significant disability; *Death*: The patient died as a result of betel nut exposure.

RESULTS

A total of 17 patients, all reported by physicians or other health care professionals, were identified from the approximately 42,000 calls received in that time period. There were 12 probable and 5 possible betel nut poisonings, displayed in Tables 1 and 2. These comprised 14 male and 3 female patients, ranging in age from 21 to 60 years (median 44 years). The circumstances of exposure were recreational/habitual use in 15 cases, attempted suicide in 1 case (number 3 in Table 2), and medicinal use in 1 case (number 8 in Table 1). Three were first-time

users and 9 were habitual users. User status was unknown in the other 5 patients.

The betel quid preparation was used by all but 1 patient. In general the number of nuts used was low, except in 2 cases. One drank an extract prepared by boiling 100 betel nuts for the treatment of constipation, and another chewed 66 betel nuts while drinking ethanol. Four patients were suspected of chewing the so-called “inverted nuts” similar in appearance to ordinary nuts, which grow upside down on the spadix, opposite the usual direction (cases 4, 7, 11, and 12 in Table 1). Inverted nuts are believed to be more potent than the normal betel nut. Recent studies confirm higher amounts of arecoline and other major alkaloids, but not of tannin or phenolic compounds (13,14). The arecoline concentration of betel nuts may also vary with the season and area of cultivation, and variance in potency could possibly explain the different manifestations of similar exposures.

Concomitant ethanol consumption was reported for 7 patients, although none were clinically intoxicated. Re-

Table 1
Demographic and Clinical Data of 12 Cases with Probable Betel Nut–Related Toxicity

Case No.	Age/ Gender	Amount/ Status†	Coingestant	Symptoms/Signs	Treatment and Severity*	Days of Hospitalization
1	29/M	1/N	—	Nausea, vomiting	Supportive; 1	1
2	39/M	1/N	Glyphosate	Dry mouth, oral numbness	Supportive; 1	1
3	45/M	5/U	—	Salivation, sweating, tremor	Supportive; 1	1
4	48/M	1/U	—	Dizziness, abdominal colic	Supportive; 1	1
5	50/M	1/U	—	Nausea, vomiting	Supportive; 1	1
6	32/M	66/H	—	Confusion, sweating, tachypnea, tachycardia, insomnia, difficulty voiding	Supportive; 2	1
7	42/F	1/H	—	Dizziness, palpitation, sweating, nausea, vomiting, transient hypertension	Supportive; 2	1
8	60/F	100/N	—	Abdominal colic & fullness, hypotension	Supportive; 2	1
9	53/F	1/H	Triphenyltin Acetate	Dizziness, facial flushing, vomiting, oculogyric crisis	Supportive; 2	3
10	21/M	6/H	Alcohol	Limb numbness & swelling, angioedema, tachycardia, hypotension, palpitation, bronchospasm with tachypnea	Diphenhydramine, steroid, supportive; 3	1
11	50/M	1/H	Alcohol	Hypotension, coma	Oxygen, inotropic agent, intensive care; 3	10
12	53/M	1/U	Alcohol	Dizziness, warm sensation of throat, sweating, hypotension, coma	Endotracheal intubation, oxygen, intensive care; 3	1

† Status of betel nut user: N = new user, H = habitual user, U = unknown user.

* 4: death; 3: severe poisoning; 2: moderate poisoning; 1: mild poisoning.



Table 2
Demographic and Clinical Data of 5 Cases with Possible Betel Nut–Related Toxicity

Case No.	Age/Gender	Amount/Status†	Coingestant	Symptoms/Signs	Treatment and Severity*	Days of Hospitalization
1	40/M	1/U	Alcohol	Headache, chest pain	Supportive; 1	1
2	28/M	1/H	Alcohol	Paroxysmal supraventricular tachycardia with chest discomfort, abdominal pain, palpitation, agitation, numbness, dyspnea	Verapamil, diazepam, supportive; 2	1
3	33/M	6–10/H	Sedatives	Coma, tachycardia, hypotension, tachypnea, pneumonia, fever, respiratory failure	Endotracheal intubation, oxygen, ventilator, antibiotics, intensive care; 3	8
4	45/M	3/H	Alcohol	Acute myocardial infarction with chest tightness and pain, tachycardia, tachypnea, ventricular tachycardia	Nitroglycerin, morphine, oxygen, β -blocker, ACE inhibitor, sedatives, aspirin, coronary angioplasty, intensive care; 3	9
5	44/M	1/H	Alcohol	Acute myocardial infarction with malaise, chest tightness, palpitation, diaphoresis, dyspnea, seizures, ventricular fibrillation	Oxygen, supportive, endotracheal intubation, inotropic agent, repeated cardiac defibrillation; 4	1 (death)

† Status of betel nut user: N = new user, H = habitual user, U = unknown user.
* 4: death; 3: severe poisoning; 2: moderate poisoning; 1: mild poisoning.

sidua of glyphosate herbicide or triphenyltin acetate molluscicide on the betel was reported in 2 patients but was judged not to contribute to the clinical features. A 33-year-old male coingested sedatives that resulted in coma, aspiration pneumonia, fever, and respiratory failure.

Most symptoms occurred within minutes of betel use and all occurred within 1 hour. Eleven patients developed symptoms of mild to moderate severity in the gastrointestinal, cardiovascular, or neurological systems, and 6 patients developed severe symptoms such as coma, hypotension, bronchospasm, respiratory failure, and acute myocardial infarction (AMI) with cardiac arrhythmias. Overall, the frequency of observed symptoms was tachycardia/palpitations (7); tachypnea/dyspnea (6); hypotension and sweating (5); vomiting, dizziness, and chest discomfort (4); abdominal colic, nausea, numbness, and coma (3); and AMI and related manifestations (2). One patient reported a similar episode of hypotension and coma (case 12 in Table 1) associated with betel nut chewing 8 years ago. Unique manifestations included oculogyric crisis, angioedema, and difficulty voiding.

Patients were treated with both gastric lavage and activated charcoal except the 2 patients with AMI and one with paroxysmal supraventricular tachycardia (PSVT). In these cases the treating physicians did not initially con-

sider that betel nut was involved. All patients received supportive treatment with intravenous fluid and electrolyte replacement therapy. Diphenhydramine and steroids were given to a patient with angioedema, and repeated doses of verapamil were administered to the patient with PSVT. Intensive care was needed in those manifesting severe toxicity.

There was full recovery in 16 of the 17 patients and none had sequelae at follow-up 1 month after the exposure. The only fatality was a 44-year-old previously healthy man who presented to the ED with chest tightness, diaphoresis, and dyspnea after chewing one betel quid. He developed ventricular fibrillation and died despite repeated cardiac defibrillation. No autopsy was performed but AMI with cardiac arrhythmia was considered to be the cause of death. There were no analyses of the arecoline concentrations in blood, urine, saliva or quids.

DISCUSSION

Although betel nut chewing is a very old habit in many countries, cases of acute betel nut poisoning have only rarely been reported, and its incidence is essentially unknown. The medical community is not generally aware



of the noncarcinogenic effects or complications of betel nut chewing since toxicity is usually mild and frequently overlooked. Arjungi, in his review of areca nut, noted that "the chewing of the nuts in excess is said to give rise to temporal giddiness, griping and strong intestinal irritations, followed by loose motions" (7). He further noted that amateur betel chewers usually experience a disagreeable combination of symptoms including esophageal constriction and sensations of heat in the head, facial flush, and dizziness. In an earlier paper, Burton-Bradley reported the neophyte user may experience dizziness, vertigo, nausea, cold perspiration, burning and acrid taste, a feeling of constriction of throat, and soreness of the tongue (15).

Reported adverse clinical manifestations following initial or heavy betel use include bronchoconstriction and aggravation of asthma, the cholinergic SLUDGE syndrome (salivation/sweating, lacrimation, urinary incontinence, diarrhea, gastrointestinal upset, and emesis), hypotension, possible cardiac arrhythmia and AMI in susceptible individuals, CNS depression, pulmonary edema, and death (3,16–19). Repeated use may result in habituation, addiction, and reversible toxic psychosis in predisposed patients; withdrawal symptoms are possible (11,20).

Many of the findings in this case review of poison center inquiries are in concordance with these previously reported pharmacological effects of betel nut chewing. Several unusual manifestations merit further comment.

Regarding the PSVT, sinus tachycardia, and hypertension, volunteer studies show a consistent sympathetic cardioacceleration in response to 1 or 2 quids. New chewers also exhibit elevated blood pressure which experienced users do not develop (21–23). These findings suggest that low doses of betel nut can result in sympathomimetic effect, while cholinergic effects will ensue at somewhat higher doses. Since sympathetic stimulation is a cause of atrioventricular tachycardia in susceptible patients (24), it is possible that betel nut-related supraventricular tachycardia was observed in this study.

In these reviewed cases, AMI occurred in 2 patients following the use of betel nuts. Case 4 in Table 2, who also smoked tobacco, was later found to have severe occlusion of both left anterior descending and right coronary arteries. The muscarinic alkaloids of betel can induce coronary vasospasm (10,18) and the concomitant ingestion of alcohol in these patients may also aggravate vasospasm hours after exposure (25). However, epidemiologic studies are needed to clarify whether there is any association between betel and AMI.

Angioedema has not been previously reported following betel nut chewing. It shares similar etiologies with

urticaria and both diseases are frequently managed as a single combined entity (26). It may develop after cholinergic stimulation in patients with cholinergic urticaria (27) but betel as inciting factor remains speculative.

Regarding oculogyric crisis, Deahl in 1989 reported betel nut-related extrapyramidal syndrome in 2 chronic schizophrenic patients who were treated with depot neuroleptics (28). Each developed rigidity and bradykinesia following a period of heavy betel nut consumption. Extrapyramidal manifestations including parkinsonian symptoms have also been reported following exposure to tacrine or organophosphate insecticides (29–31) in the absence of other neuroactive drugs or chemicals. Thus, it appears possible that the betel alone could induce this rare manifestation.

Despite the cholinergic basis for many of the effects, supportive measures and not specific antidote remain the cornerstone of treatment as atropine efficacy has not been documented in human poisonings. Given the short and frequently mild action of betel nut (21), complete and rapid recovery within 24 hours usually can be anticipated (3).

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