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Intoxication by star fruit (*Averrhoa carambola*) in 32 uraemic patients: treatment and outcome

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Abstract

Background. Clinical symptoms and outcomes of uraemic patients ingesting star fruit are quite variable and may progress to death. The purpose of the present report was to discuss the neurotoxic effects of star fruit intoxication in uraemic patients and to present the efficacy of different therapeutic approaches.

Methods. We studied a total of 32 uraemic patients who had ingested star fruit. Before the intoxication episodes, 20 patients were on regular haemodialysis, eight were on peritoneal dialysis and four were not yet undergoing dialysis. Two patients were analysed retrospectively from their charts, 17 were directly monitored by our clinic and 13 were referred by physicians from many areas throughout the country, allowing us to follow their outcome from a distance. Intoxicated patients were given different therapeutic approaches (haemodialysis, peritoneal dialysis and supportive treatment), and their outcomes were analysed.

Results. The most common symptoms were persistent and intractable hiccups in 30 patients (93.75%), vomiting in 22 (68.7%), variable degrees of disturbed consciousness (mental confusion, psychomotor agitation) in 21 (65.6%), decreased muscle power, limb numbness, paresis, insomnia and paresthesias in 13 (40.6%) and seizures in seven (21.8%). Patients who were promptly treated with haemodialysis, including those with severe intoxication, recovered without sequelae. Patients with severe intoxication who were not treated or treated with peritoneal dialysis did not survive.

Conclusions. Haemodialysis, especially on a daily basis, is the ideal treatment for star fruit intoxication. In severe cases, continuous methods of replacement therapy may provide a superior initial procedure, since rebound effects are a common event. Peritoneal dialysis is of no use as a treatment, especially when consciousness disorders ensue.

Keywords: *Averrhoa carambola*; hiccups; neurotoxicity; star fruit intoxication; treatment; uraemia

Introduction

Certain patients with renal failure display behavioural and cognitive alterations compatible with neurologic effects after ingesting star fruit (*Averrhoa carambola*; Figure 1). In 1998, we reported that the ingestion of star fruit led to neurological disturbances, including hiccups and mental confusion, and death in one patient after presenting with convulsions [1]. Recently, Chang *et al*. [2], in a retrospective study, reported the same neurologic symptoms in all 20 patients after they ingested star fruit, with death occurring in eight patients. These eight patients had presented mental confusion and seizures, and died in spite of supportive treatment and haemodialysis.

Star fruit is believed to have originated in Ceylon and the Moluccas, but it has been cultivated in southeast Asia and Malaysia for many centuries. It is commonly grown in southern China, Taiwan and India. The fruit was introduced in Southern Florida before 1887 [3,4]. It is rather popular in the Philippines and Queensland (Australia), and moderately so in some of the South Pacific islands, and there are some subspecies in the Caribbean islands, in Central America and in tropical west Africa. It is also common in Brazil, where it is served as a fresh beverage, *in natura*, or as an industrialized juice, as it is also served throughout the world. It is widely used in restaurants for decorative purposes. In India, ripe fruit is administered to halt haemorrhages and to relieve bleeding haemorrhoids.

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Fig. 1. Star fruit (*A. carambola*).

In Brazil, carambola is recommended as a diuretic for kidney and bladder complaints [3].

The aim of the present study was to discuss the neurotoxic effects of star fruit intoxication in mostly dialysed patients with chronic renal failure. We studied 32 cases, which included seven deaths, and analysed their outcome after different therapeutic approaches had been used to treat the neurotoxic signs and symptoms of star fruit ingestion.

Subjects and methods

From August 1996 to June 2001, we added 26 patients to six who had been described previously [1], giving a total of 32 uraemic patients observed after ingestion of star fruit. Two of the patients who had died in 1993 and 1997 were analysed retrospectively by their charts, 17 were monitored in our hospitals in Ribeirão Preto (Brazil) and 13 had their clinical conditions reported to us by physicians from many areas throughout the country, so that their outcomes could be followed from a distance. Before the intoxication episodes, 20 patients were on regular haemodialysis, eight were on peritoneal dialysis [six on continuous ambulatory peritoneal dialysis (CAPD), one on automated peritoneal dialysis (APD), one on intermitent peritoneal dialysis (IPD)] and four were not yet undergoing dialysis. The mean age of the patients (18 males and 14 females) was 49.0 years. The mean duration of dialysis for the 28 patients was 34.5 months (range 2–144 months). The causes of renal failure were diabetic nephropathy in eight patients (25.0%), unknown

aetiology in seven patients (21.8%), glomerulonephritis in six (18.7%), hypertension in five (15.6%), tubulointerstitial nephritis in four (12.5%) and polycystic kidney disease in two (6.2%). All patients were in a stable clinical condition before the intoxication episodes, except for two patients on supportive treatment who had presented with signs and symptoms of uraemia at the time of intoxication.

Once the intoxication syndrome was detected, patients were submitted to different therapeutic approaches (haemodialysis, peritoneal dialysis and supportive treatment) and the outcomes were analysed.

Results

Clinical manifestations and outcome

The amount of fruit ingested, time of symptom onset and treatment and time of recovery are listed in Table 1 for the 19 patients followed by us, and in Table 2 for the 13 patients referred to our clinic. For the 32 patients as a whole, the time from ingestion to onset of symptoms ranged from 30 min to 6 h, with no difference between the patients who died or survived. The amount of fruit ingested varied among the 32 patients, from half a fruit (~25 ml of juice) to 10 fruits (~500 ml), and we found a poor association between the amount ingested and the severity of symptoms. The most common symptoms in all 32 patients included persistent and intractable hiccups in 30 (93.7%), vomiting in 22 (68.7%), disturbed consciousness of variable degrees (mental confusion, psychomotor agitation) in 21 (65.6%), decreased muscle power, limb numbness, paresis, insomnia and paresthesias in 13 (40.6%), seizures in seven (21.8%) and haemodynamic instability (hypotension and shock) in three (9.3%). The major difference between the two groups in Tables 1 and 2 was the more severe symptoms found in the cases referred to our clinic. Nevertheless, most of these patients improved following treatment suggested by our staff. Of the four patients who died in Table 2, one received supportive treatment and the case was reported after he died, and three other cases were reported later. Of the three patients who died in Table 1, patient 19 was treated by CAPD, and the other two were analysed retrospectively and were not submitted to dialysis.

Of the 17 patients who survived, nine were on regular haemodialysis, and when they had presented with moderate to severe mental confusion they were admitted to a hospital for treatment (two in Table 1 and seven in Table 2). One of these nine patients had seizures and another had haemodynamic instability. All nine patients had a good outcome. Most of the patients with severe mental confusion (seven out of nine) improved after being submitted to daily haemodialysis, and the remaining two patients, with less severe mental confusion, improved after intermittent haemodialysis. The other eight patients, treated on an outpatient basis, had less severe symptoms. Patients on regular haemodialysis (three times per week) with persistence of symptoms, rebound effects or both were assigned to daily dialysis, ranging from up to 5 or 7 h, depending on the severity of symptoms. Importantly,

Table 1. Symptoms, time of onset, amount of ingested fruit, treatment and outcome of 19 patients followed in our clinic after ingestion of star fruit (*A.carambola*)

Patient	Amount of ingested fruits (U or ml of juice)	Onset of symptoms (h)	Symptoms[a]	Previous renal substitutive treatment	Treatment	Recovery (days)
1	300 ml	1.5	1, 2, 7	HD	HD daily	4
2	3	6	5, 6	HD	HD cv	7
3	4 in 2 days	?	1, 3, 4, 7	HD	HD cv	3
4	2 everyday/5 days	?	1, 5, 6	HD	HD cv	7
5	300 ml	2	1, 2	HD	HD cv	3
6	5	2	1, 2	HD	HD daily	6
7	4	2	1, 2	HD	HD cv	4
8	2	2	1	HD	HD cv	1
9	1	4	1, 2, 5	HD	HD daily	3
10	1	1.5	1	CAPD	IPD	1
11	1	2	1	CAPD	IPD	1
12	8	1.5	1, 2, 5, 7	CAPD	IPD	5
13	3	5	1, 2, 6	Supportive	Symptomatic	4
14	300 ml/day during 4 days	?	1, 2	Supportive	Symptomatic	3
15	3	1	1, 2	Supportive	HD daily	4
16	Half fruit	2	1, 2	Supportive	Symptomatic	1
17[b]	4	2.5	2, 7, 9	HD	Symptomatic	Death in 13 h
18[b]	300 ml prior to haemodialysis	6 h after dialysis	1, 7, 9	HD	Symptomatic	Death in 4 days
19[b]	2	1.5	1, 2, 7, 8, 9	HD	CAPD	Death in 36 h

HD, haemodialysis; HD cv, conventional or every other day haemodialysis; HD daily, haemodialysis every day.
[a]Symptoms: 1, hiccups; 2, vomiting; 3, asthenia; 4, paresis, paresthesias; 5, psychomotor agitation; 6, insomnia; 7, mental confusion; 8, hypotension; 9, convulsions.
[b]Patients who died.

Table 2. Symptoms, time of onset, amount of ingested fruit, treatment and outcome of 13 referred patients after ingestion of star fruit (*A.carambola*)

Patient	Amount of ingested fruits (U or ml of juice)	Onset of symptoms (h)	Symptoms[a]	Previous renal substitutive treatment	Treatment	Recovery (days)
1	4	4	1, 2, 5, 7	HD	HD daily	5
2	6	?	1, 5, 6, 7	HD	HD daily	7
3	200 ml	?	1, 2, 5, 7	HD	HD cv + HD daily	7
4	3	3	1	HD	HD cv	2
5	4	1	1, 2, 3, 4, 5, 7	HD	HD daily	6
6	?	?	1, 2, 5, 7, 9	HD	HD cv + CVVHD (15 h) + HD daily	8
7	1	1	1, 2, 4, 7	HD	HD daily	3
8	200 ml/day during 5 days	?	1, 2, 3, 4, 5, 7, 8	HD	CAVHD (36 h) + HD daily	12
9	4	½	1, 3, 7	CAPD	HD daily	3
10[b]	500 ml	?	1, 2, 7, 9	IPD	IPD + CAVHAD	Death in 10 days
11[b]	3	5	1, 2, 7, 9	CAPD	IPD	Death in 5 days
12[b]	4	4	1, 2, 7, 8	HD	Symptomatic	Death in 36 h
13[b]	1	3	1, 2, 3, 5, 7, 9	CAPD	CAPD + 2 h of HD	Death in 24 h

HD, haemodialysis; HD cv, conventional or every other day haemodialysis; HD daily, haemodialysis every day.
[a]Symptoms: 1, hiccups; 2, vomiting; 3, asthenia; 4, paresis, paresthesias; 5, psychomotor agitation; 6, insomnia; 7, mental confusion; 8, hypotension; 9, convulsions.
[b]Patients who died.

one patient (number 6 in Table 2) improved after a first approach treatment of 15 h of continuous replacement therapy [(continuous venovenous haemodialysis (CVVHD)], and patient 8 (Table 2), with haemodynamic instability, was given continuous arteriovenous haemodialysis (CAVHD) as a first approach treatment for 36 h. Of the seven patients with convulsive activities, only patient 6 (Table 2) survived. Patients 6 and 8 required orotracheal intubation for artificial respiration. After improvement of clinical conditions, both patients were submitted to daily haemodialysis and discharged without sequelae. Patients with mental confusion completely recovered over a mean period of 6.1 days (range 3–12 days) compared with 4.2 days (range 1–7 days) in patients without mental confusion. Four patients submitted to CAPD (three patients in Table 1 and one patient in Table 2) were hospitalized even though two of them had only hiccups, and two showed mental confusion. Three of these patients were treated by IPD and improved. Patient 9 (Table 2) was given daily haemodialysis for 3 days and was discharged from the hospital without sequelae. Patient number 12 (Table 1) improved more slowly than the other three. Most of the symptoms lasted 5 days, and diplopia continued for 6 weeks after the patient had been discharged; this patient resumed her CAPD treatment. Patients 13–16 (Table 1) were on previous supportive treatment. Three of them improved with symptomatic treatment and one improved following haemodialyis treatment.

Most of the patients had rebound effects after dialysis, with symptoms starting a few hours after the end of the dialytic procedures. These rebound effects included persistence of hiccups (patient 6 in Table 1) or the consciouness disturbances described previously.

Seven patients died after intoxication episodes (three in Table 1 and four in Table 2). The mean age of these patients was 58.8 years, which was higher than the group as a whole (49.0 years). The principal characteristics of these patients were convulsive activities in six patients and severe mental confusion in all patients. Most of these patients were treated by peritoneal dialysis or did not receive any kind of treatment. Interestingly, patient 18 (Table 1) drank 300 ml of juice before a haemodialysis session and showed no symptoms until 6 h after the session when he presented with hiccups, mental confusion and convulsive activities followed by death. This patient received only symptomatic treatment for 4 days in the hospital. Of the other six patients that died, one had been monitored in the Intensive Care Unit (ICU; patient 17 in Table 1) with suspected stroke. The patient submitted to spinal fluid examination that yielded normal results. He died 13 h after star fruit ingestion. Patient 12 (Table 2), also with a suspected stroke, was examined by a neurologist. According to the doctor reporting the case, the patient did not present seizures and had laboratory tests showing expected patterns for uraemic dialysed patients. The patient died of circulatory shock. Patient 10 (Table 2) was continuously monitored in an ICU outside Ribeirão Preto, and we were told that her metabolic parameteres were well controlled. Although the patient was initially given IPD for 7 days and then continuous arteriovenous haemodiafiltration (CAVHAD), she died after 10 days in *status epilepticus*. Patient 11 (Table 2) was treated by IPD and died 5 days later. Patient 19 (Table 1) was examined by a neurologist and a brain computed tomography (CT) scan was negative. He was continued on CAPD treatment but died 36 h later after showing

convulsive activity and circulatory shock. We did not detect hyperkalaemia, excessive increases in urea or creatinine levels, or changes in acid–base balance in any of the patients.

Described below is the clinical picture of a 'typical case' of star fruit intoxication in a patient that improved with treatment (patient 6; Table 1), and another 'typical case' in a patient that died after ingesting star fruit (patient 13; Table 2).

Patient 6 (Table 1)

A 25-year-old female had been enrolled in a regular haemodialysis programme for 6 years. She ate one star fruit at 08:00 and developed hiccups 2 h later. At 14:00 she ate four more fruits and showed intractable hiccups at 14:30, followed by vomiting at 16:30. The patient went to the University Hospital and was given haemodialysis for 2 h. The hiccups and vomiting disappeared after 1 h of dialysis. She returned home but the hiccups began again 2 h later and persisted up to the next day, when she was again given 4 h of haemodialysis, which stopped the hiccups. Upon returning home, the hiccups started again, and she was not able to sleep even though she experienced 10 min intervals that were free of symptoms. On the following morning the hiccups 'crises' worsened and she was again treated with 4 h of dialysis. After this session, the hiccups persisted while the patient was at home, but the 10 min hiccup-free intervals increased in length. On the next day, after an additional 4 h haemodialysis, the hiccups finally disappeared after a total of 14 h of dialysis. The patient had no sequelae. There had been no laboratory tests during these 7 days of follow-up.

Patient 13 (Table 2)

A 55-year-old female who enrolled in a regular CAPD programme had been on dialysis for 27 months. She ingested a star fruit and developed hiccups, vomiting, asthenia and mild psychomotor agitation 3 h later. At the emergency room, she was medicated with chlorpromazine and metoclopramide and was discharged. Seven and a half hours after star fruit ingestion, she presented with mental confusion and was admitted to the hospital. The laboratory tests showed: blood urea nitrogen = 52 mg/dl, creatinine = 6.8 mg/dl, K = 3.4 mEq/l, pH = 7.27, HCO_3 = 14.4 mEq/l and base excess (BE) = −11.3. She was admitted to an ICU with moderate mental confusion and, 12 h after fruit ingestion, presented with convulsive activity. She was seen by a neurologist who prescribed hydantoin 400 mg i.v., phenobarbital and diazepam. The convulsive activities progressed to *status epilepticus*. At 22 h after fruit ingestion, she showed haemodynamic instability with low blood pressure, and was given dopamine. She was continued on dialytic treatment (CAPD, now increased to every 4 h) and was given haemodialysis 22 h after fruit ingestion, but died 2 h later during this procedure.

Discussion

Our clinical findings, including continuous observations following our initial report, have allowed us to classify the neurotoxic effects of star fruit into three levels of intoxication that may provide a useful guideline for institution of proper treatment: (i) mild intoxication: hiccups, vomiting and insomnia; (ii) moderate intoxication: psychomotor agitation, numbness and paresthesias of the limbs, and mild mental confusion; and (iii) severe intoxication: moderate to severe mental confusion progressing to coma, seizures progressing to *status epilepticus*, and haemodynamic instability progressing to hypotension and shock. The severe cases may be difficult to diagnose, since the symptoms mimic either strokes, brain stem strokes, or may even resemble 'metabolic' or uraemic disturbances. Certain cases of mild intoxication progress to severe symptoms if patients are not properly treated, and the velocity of progression is extremely variable, depending on the characteristics of each patient. Some patients may die shortly after intoxication if they are not treated. Therefore, any patient with a suspected star fruit intoxication should not be discharged and should be observed very closely. With proper treatment, many patients will avoid progression to severe symptoms. Nevertheless, mild symptoms such as hiccups may persist for several days and upon stopping treatment the hiccups may continue, with the symptoms disappearing slowly. These variations differ among individuals and might be explained by individual biological responses, patient age, the amount of toxin content in each fruit, various star fruit subspecies, and the detoxification, excretion, or both, of this toxin from the bloodstream.

In most of our intoxication cases, attempts to treat intractable hiccups with chlorpromazine and metoclopramide, drugs that are most extensively used for this symptom [5], were unsuccessful. In contrast, we observed that only haemodialysis improves this symptom. In the study by Chang *et al.* [2], 20 intoxicated patients, including one who had not yet begun dialysis, developed muscle weakness, intractable hiccups, various degrees of consciousness disturbance and seizure. Eight out of 10 patients with disturbed consciousness died despite additional haemodialysis treatment. In Tables 1 and 2, it is clear that haemodialysis, given on a daily basis, removed the neurotoxic activity in most patients, allowing them to recover without sequelae within 1–12 days. Interestingly, two surviving patients with severe intoxication, presenting with seizures and haemodynamic instability, were given continuous renal replacement therapy (CVVHD and CAVHD) as first choice treatment. On the basis of these data, we conclude that patients presenting with severe intoxication who are not treated, that are treated by peritoneal methods, or by late haemodialysis, will die with most of them in *status epilepticus*.

Although star fruit, like other fruit, probably has a high potassium content, we did not detect any

alterations in serum potassium in the patients that were measured. This was also reported by Chang *et al*. [2]. In addition to causing neurotoxic symptoms such as hiccups and seizures [1,2], star fruit has a high oxalic acid content that may cause acute reversible nephrotoxic effects [6,7]. Importantly, there has been a growing number of new cases of star fruit intoxication in our hospitals in the last few years. This may be because this type of intoxication in renal patients has been underestimated. Our first report [1], combined with presentations at nephrology meetings in Brazil, have alerted many nephrologists about this danger throughout the country. These presentations caused many nephrologists to seek our help and to refer patients to our clinic in order to gain from the experience of our staff in treating neurologic disturbances, especially in patients undergoing dialysis.

To our knowledge, there are no reports of star fruit neurotoxicity in people with normal renal function. However, Chang *et al*. [2] found that certain uraemic patients failed to develop neurologic symptoms following star fruit ingestion. This was also observed in the initial report of star-fruit-induced hiccups in dialysis patients [8]. In this report, 10 out of 18 patients on dialysis ingested star fruit and eight of these developed intractable hiccups. Although we have not yet confirmed Koch's postulates [9] identifying the offending toxin, attempts at purification and the establishment of experimental models are currently under way. Preliminary experimental assays in our laboratories have shown that intracerebroventricular injection of the fruit extracts in rats or mice induce immmediate and persistent convulsions of the tonic-clonic type. The putative excitatory neurotoxin that induces convulsion may act specifically by increasing GABA uptake in rat cerebral cortex synaptosomes (our unpublished data).

In conclusion, we documented 32 cases of neurologic symptoms following star fruit ingestion in uraemic patients. All patients who were promptly and properly treated recovered without sequelae. Haemodialysis, especially daily dialysis, is the ideal treatment, and in severe cases continuous treatment methods may provide a superior initial procedure, since rebound effects are a common event. Peritoneal dialysis is of no use, especially when disturbance of consciousness ensues. These observations, which confirm our first report and reports from others, serve to warn physicians and dietitians that star fruit intoxication may be harmful and even life threatening in uraemic patients on supportive or dialytic treatment. Hiccups and vomiting, which are common symptoms, could be used as an indication of star fruit intoxication in renal patients presenting with neurological and consciousness disturbances that have no apparent cause.

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References

1. Neto MM, Robl F, Netto JC. Intoxication by star fruit (*Averrhoa carambola*) in six dialysis patients? (Preliminary report). *Nephrol Dial Transplant* 1998; 13: 570–572
2. Chang JM, Hwang SJ, Kuo HT *et al*. Fatal outcome after ingestion of star fruit (*Averrhoa carambola*) in uremic patients. *Am J Kidney Dis* 2000; 35: 189–193
3. Morton JF. *Fruits of Warm Climates*. Flair Books, Miami, FL; 1987: 125–128
4. Margen S. *The Wellness Encyclopedia of Food and Nutrition*. Health Letter Assoc, New York, NY; 1992: 271–282
5. Kolodzik PW, Eilers MA. Hiccups (singultus): review and approach to management. *Ann Emerg Med* 1991; 20: 565–573
6. Chen CL, Fang HC, Chou KJ *et al*. Acute oxalate nephropathy after ingestion of star fruit. *Am J Kidney Dis* 2001; 37: 418–422
7. Fang HC, Chen CL, Wang JS *et al*. Acute oxalate nephropathy induced by star fruit in rats. *Am J Kidney Dis* 2001; 38: 876–880
8. Martin LC, Caramori JST, Barreti P *et al*. Soluço intratável desencadeado por ingestão de carambola (*Averrhoa carambola*) em portadores de insuficiência renal crônica. *J Bras Nefrol* 1993; 15: 92–94
9. Evans AS. Causation, disease: the Henle–Koch postulates revisited. *Yale J Biol Med* 1976; 49: 175–195

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