A DIGOXIN-LIKE IMMUNOREACTIVE SUBSTANCE AND ATRIOVENTRICAL BLOCK INDUCED BY A CHINESE MEDICINE “KYUSHIN”

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The attempted suicide by 2 women with a kyushin overdose is reported. Kyushin caused them to produce a significant elevation of a serum digoxin-like immunoreactive substance (2.35 and 1.84 ng/ml) and symptoms of nausea, vomiting and general malaise. Their blood biochemistry and electrolytes were normal. In one patient, an electrocardiogram revealed a second degree Wenckebach atrioventricular block and T-wave change. Toad venom, a kyushin ingredient, is possibly responsible for the development of these clinical features and electrocardiographic changes.

**KYUSHIN** (Kyushin Seiyaku Co., Tokyo, Japan) is a commonly used Chinese medicine in Taiwan. It consists of 7 different ingredients: toad venom (Ch’an-su), oriental bezoar (Niu-Huang), musk (She-Hsiang), ginseng, rhinoceros horn (Hsi-Chiao), pearl (Chen-Chu), and borneol (Lung-Nau). Its effect is not well known. However, toad venom has been reported to have cardiotoxic effects, a central nervous system-stimulating action and a local anesthetic effect.

Our previous study showed that oral administration of kyushin to dogs will produce a digoxin-like immunoreactive substance (DLIS) in the serum. However, whether this reaction also occurs in human beings was not previously known. Here we describe 2 cases of attempted suicidal kyushin overdoses, who presented a high serum DLIS concentration and an electrocardiographic change.

Case report 1

A 65-year-old woman who attempted suicide was admitted to Yu Min Hospital 5 hours after ingesting about half a bottle (100 pills/bottle) of kyushin. On one previous occasion she had required hospitalization for impaired liver function and at that time her electrocardiogram was normal (Fig. 1-A). On admission following the suicide attempt she was conscious but looked acutely ill. Her blood pressure was 140/70 mmHg and heart rate was 60 beats/min. Nausea, vomiting and frequent diarrhea appeared on admission. She also complained of abdominal pain and general malaise. After supportive treatment, these symptoms improved on the second hospital day, and subsided 3 days after admission. The electrocardiogram on admission showed a second degree Wenckebach atrioventricular block (Fig. 2-A) and a flat T-wave (Fig. 1-B). These changes returned to normal

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Fig. 1. Electrocardiograms of case 1 taken previous admission (panel A), and on the first day of attempted suicide admission (panel B) and the second day of admission (panel C). Note the flat T-wave change of panel B compared with panels A and C.

Fig. 2. Electrocardiograms of case 1 taken on the first day of admission (panel A) and the second day of admission (panel B). Note that the second degree Wenckebach atrioventricular block in panel A became normal in panel B. Arrows indicate the P-wave.

on the second hospital day (Fig. 1-C and 2-B). Two blood biochemistry tests were normal, except for slight increases in glutamic-oxalacetic transaminase (40 IU/l) and glutamic-pyruvic transaminase (45 IU/l). Her serum electrolytes were Na: 145 mmol/l, K: 4.4 mmol/l, Cl: 114 mmol/l, Ca: 9 mg/dl and P: 4.1 mg/dl.

The serum DLIS concentration checked 24 hours after ingestion of kyushin by fluorescence polarization immunoassay using a commercial kit (Digoxin II, Abbott Laboratories Inc., North Chicago, IL), revealed a very high concentration of 2.35 ng/ml. This high blood level declined gradually and had almost completely subsided 5 days after the kyushin ingestion (Fig. 3). The patient was discharged in fair condition on the eighth day.

Case Report 2

A 34-year-old female presented to the Chung Shan Medical College Hospital Emergency Department because of attempted suicide with about half a bottle (100 pills/bottle) of kyushin. She developed nausea, vomiting and general malaise 2 hours after she took the drug. On admission, her heart rate was 64 beats/min and blood pressure was 110/70 mmHg. Her blood biochemistry was normal and serum electrolytes were Na: 137 mmol/l, K: 3.8 mmol/l, Cl: 106 mmol/l, Ca: 8.7 mg/dl, P: 4.3 mg/dl. Her serum DLIS level measured 10 hours after she took the drug was 1.84 ng/ml. This abnormal serum level decreased to 0.67 ng/ml on the second day of admission (Fig. 3). The symptoms of intoxication subsided on the second day of admission after supportive treatment and then she was discharged. Her electrocardiograms during hospitalization were all normal.

Discussion

Serum digoxin concentration monitoring is

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Kyushin-induced DLIS and AV Block

Fig.3. Time course of serum digoxin-like immunoreactive substance concentrations after the patients started to take kyushin at hour zero. A concentration of less than 0.2 ng/ml is considered negative.

essential in evaluating the optimal dose for a digitalized patient. Because the optimal therapeutic range for serum digoxin concentration is narrow, at between 0.8 and 2.0 ng/ml, the accuracy of the digoxin concentration measurement is very important. The appearance of serum DLIS is an important factor which may interfere with serum digoxin measurement. Serum DLIS has been found in neonates, pregnant women, and in patients with renal insufficiency and in those receiving spironolactone treatment. In our previous animal study, serum DLIS was found in very high concentrations after oral kyushin administration. To our knowledge, the present report is the first to confirm this finding in human beings. The exact amount of kyushin taken by these 2 patients is not known, but the serum DLIS concentrations in their first blood samples were very high (2.35 and 1.84 ng/ml). The high serum DLIS concentration observed in case 1 decreased gradually and subsided 5 days after ingestion of the drug. In our previous study, we suggested that the appearance of serum DLIS after kyushin administration is possibly due to the similarity in chemical structures between toad venom, a kyushin ingredient, and digoxin, resulting in cross-reactivity of toad venom with the digoxin immunoassay antibody.

The electrocardiographic changes in case 1 presented a second degree Wenckebach atrio-ventricular block and a T-wave change (Figs. 1-B and 2-A). These electrocardiographic changes suggest, at least in part, that kyushin has a cardiotoxic effect. Case 2 presented with no electrocardiographic changes and less severe symptoms than Case 1, something which is possibly due to her relatively small kyushin intake and lower resultant DLIS concentration. The electrocardiographic changes and the symptoms of nausea, vomiting and general malaise which developed after ingestion of kyushin are similar to the effect of digitalis intoxication. Among the 7 ingredients of kyushin, toad venom has been found to have a cardiotoxic effect and to produce DLIS in the serum of dogs. Its toxic symptoms are nausea and vomiting, suggesting that these patients' clinical features were induced mainly by the toad venom.

Kyushin is a commonly used nonprescription drug in Taiwan. Thus, the clinician must be aware of the potential for kyushin to cause falsely elevated apparent digoxin concentrations and intoxication signs in a significant number of patients.

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