

A case of imipramine induced toxicity with Brugada electrocardiographic pattern in a toddler

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= Abstract =

Imipramine, a tricyclic antidepressant (TCA), is used for the treatment of non-polar depression and nocturnal enuresis in children in whom an organic pathology has been excluded, anxiety disorders, and neuropathic pain. Clinical toxicity following the treatment of TCAs, including imipramine, is well known. The anticholinergic effects initially present include a dry mouth, ileus, dilated pupils, urinary retention, and mild sinus tachycardia. The central nervous system toxicity includes delirium, agitation, restlessness, hallucinations, convulsions, and CNS depression or coma. However, the most life-threatening toxicity remains the development of cardiac dysrhythmias. Conduction delays such as QRS and corrected QT prolongation, wide QRS complex tachycardia, and the Brugada electrocardiographic pattern have been reported. Sodium bicarbonate decreases QRS widening and suppresses dysrhythmias by providing excess sodium to reverse the TCA-induced sodium-channel blockade and possibly by binding directly to the myocardium. There are no pediatric case reports on imipramine or other TCA associated toxicity in Korea. Here, we describe a patient who presented with convulsions, tachycardia with a wide QRS complex, a Brugada electrocardiographic pattern, and anuresis associated with an accidental overdose of imipramine and the outcome of treatment with sodium bicarbonate. (*Korean J Pediatr* 2008 51 :1232-1235)

Key Words : Tricyclic antidepressant, Imipramine, Brugada electrocardiographic pattern

Introduction

Tricyclic antidepressants (TCAs) include imipramine, desipramine, amitriptyline, nortriptyline, doxepin, trimipramine, protriptyline, and clomipramine¹⁾. Among these, imipramine was first synthesized in 1948. However, it was not until 1958 that its antidepressant effects in humans were recognized. Since then, it has been the prototype TCA. Imipramine is used for the treatment of non-bipolar depression²⁾, nocturnal enuresis in children, in whom an organic pathology has been excluded³⁾, anxiety disorders, and neuropathic pain⁴⁾. The TCAs, including imipramine, may cause fatal toxicity in children with an initial adult dose of 25-100 mg (one or two pills) once a day⁵⁾. Herein, we describe a patient that

presented with convulsions, and tachycardia with a wide QRS complex, a Brugada electrocardiographic pattern (BEP), and anuresis associated with imipramine ingestion and was successfully treated with sodium bicarbonate.

Case report

A 3-year-old boy presented to the emergency department with clonic movements of four extremities, fever and vomiting. On presentation the body temperature was 38.0°C with a pulse rate of 136 beats/min, a respiratory rate of 26 breaths/min, and a blood pressure of 100/70 mmHg. The patient was alert. The history was significant for the ingestion of four imipramine tablets (one tablet contains 25 mg, 7.69 mg/kg) obtained from a kindergarten friend, 15 hours previously. The patient did not have a history of cardiac disease, dysrhythmias or other medical problems.

The results of the laboratory studies were as follows: hemoglobin 12.4 g/dL, white blood cell count 12,400/mm³ and a platelet count of 188,000/mm³. The cardiac enzymes were CKMB 5.8 U/L and Troponin-I 0.04 ng/mL. The am-

Received : 4 June 2008, Revised : 25 August 2008,

Accepted : 4 September 2008

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monia, lactate and creatinine kinase results were 69 $\mu\text{g/dL}$, 1.7 mmol/L and 99 U/L, respectively. The C-reactive protein was 5.8 mg/dl, the renal and liver function tests were within normal range.

The patient was successfully treated with intravenous diazepam, one dose, for the clonic movement of four extremities. An electrocardiogram (ECG) displayed a wide QRS complex tachycardia, with a down sloping ST segment elevation and a prominent J wave in lead V2 (Fig. 1). This ECG findings were characteristic of the BEP found in the Brugada syndrome. However, the patient did not have a history of cardiac disease or dysrhythmias. A 2-D echocardiography was performed for the evaluation of underlying heart disease; the heart was structurally normal with good function. The patient was treated with a sodium bicarbonate infusion. The QRS duration narrowed gradually from 129 ms to 108 ms, six hours after admission. However, the BEP persisted (Fig. 2). Further shortening of the QRS duration

was noted 12 hours after admission, and the BEP was unchanged. A repeat ECG showed no electrocardiographic ischemic changes. Three days after admission the BEP resolved (Fig. 3). The urinary retention, present for three days, also resolved with bladder massage. The patient had a complete clinical recovery, and was discharged to home on the seventh hospital day. In the outpatient department, all signs and symptoms had resolved. The ECG showed a normal sinus rhythm with a heart rate of 108 beats/min, a QRS duration of 75 ms and normal ST segment.

Discussion

Imipramine is well absorbed from the gastrointestinal tract after oral administration, and undergoes extensive first-pass metabolism in the liver. About 40% of the ingested dose, mostly free and conjugated metabolites, is excreted within 24 hours in the urine. Only 0.3% of a dose is excreted

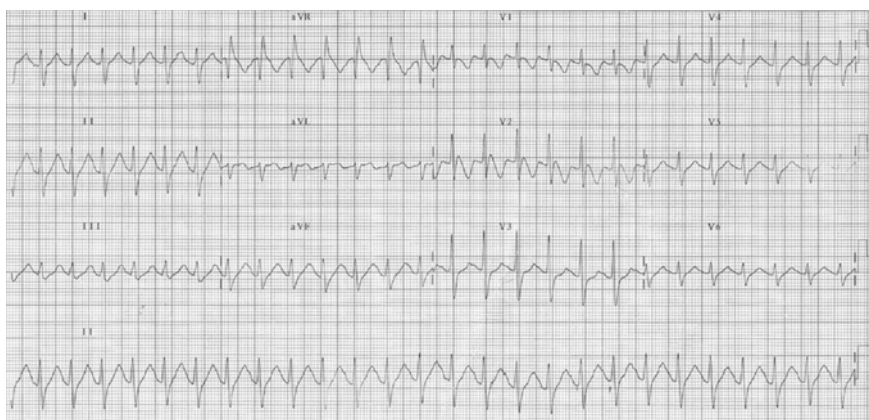


Fig. 1. On presentation, the electrocardiogram shows tachycardia with a wide QRS duration, 129 ms, and the characteristic downsloping ST segment elevation in lead V2, a pattern consistent with the Brugada electrocardiographic pattern.

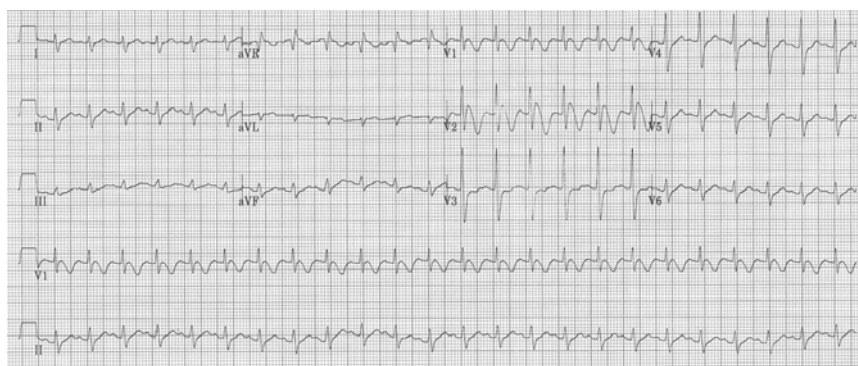


Fig. 2. The electrocardiogram shows tachycardia with a shorter QRS duration, 109 ms, persistence and clarification of the Brugada electrocardiographic pattern after sodium bicarbonate administration.

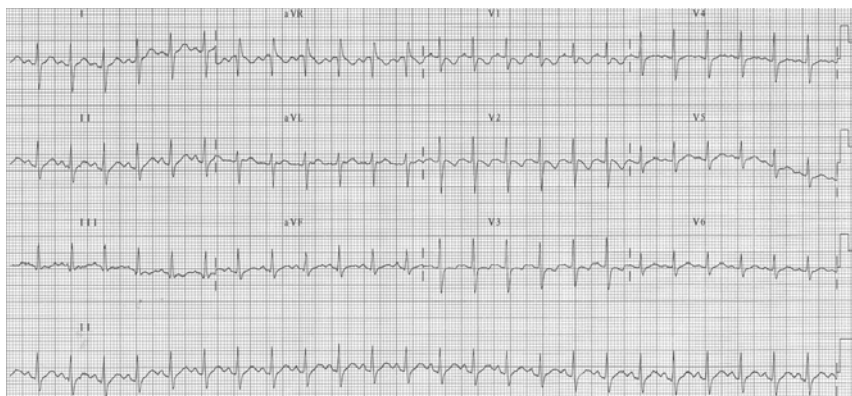


Fig. 3. The electrocardiogram, on the third day of admission, shows resolution of the Brugada electrocardiographic pattern and a normal QRS duration.

unchanged. Acidification of the urine results in a higher imipramine excretion. About 20% of an ingested dose is eliminated in the stool. The elimination half-life of imipramine is eight to 20 hours in adults, but is increased in children, the elderly and in cases with an overdose⁶.

The side-effects and toxicities associated with imipramine therapy are the same as for all TCAs. The clinical toxicity of TCAs becomes evident by six to eight hours with an overdose and peaks within 24 hours^{7, 8}. The anticholinergic effects initially present as a dry mouth, ileus, dilated pupils, urinary retention, and mild sinus tachycardia. The central nervous system (CNS) effects may be seen at any time post-ingestion and include delirium, agitation, restlessness, hallucinations, convulsions, and CNS depression or coma. Generalized seizures most often develop within 12 hours of presentation; however, the most life-threatening toxicity remains cardiac dysrhythmias^{1, 10, 11}. The ECG is not sensitive or specific enough to be used alone for the diagnosis or prediction of the outcome of a TCA overdose. However, the characteristic ECG changes seen with TCAs serve to confirm TCA toxicity^{7, 8, 11}. Conduction delays such as QRS and corrected QT prolongation appear to be associated with seizures⁹. A study by James evaluated 45 children admitted for TCA ingestion, to validate adult guidelines for the evaluation and monitoring of TCAs, and found that ECG changes accompany seizures. However, this study did not demonstrate a relationship between the serum concentration and the conduction delay nor the conduction delays and serious cardiac dysrhythmias¹². For patients with a wide complex tachycardia, studies have shown the efficacy of sodium bicarbonate treatment in both adults and children^{13, 14}. Sodium bicarbonate decreases QRS widening and suppresses dysr-

hythmias by providing excess sodium to reverse the TCA-induced sodium-channel blockade and possibly by binding directly to the myocardium¹⁰. In addition, the intervention that has been clearly beneficial in children is alkalinization¹³.

The Brugada syndrome, first described in 1992, has a characteristic ECG pattern similar to a right bundle branch block with down sloping ST segment elevation in leads V1 through V3. The Brugada syndrome is associated with sudden death and is thought to be mediated by dysfunction of the myocardial sodium channels leading to a slow inward current^{15, 16}. The Brugada syndrome has been reported after TCA overdose^{17, 18}. However, the ECG is not sensitive or specific enough to be used alone for the diagnosis or the prediction of outcome in patients with a TCA overdose. Nevertheless, the characteristic EKG changes seen with TCAs serve to confirm TCA toxicity^{1, 7, 8, 11}. The sodium channel mediated Brugada electrocardiographic pattern remained unchanged in this case of TCA overdose despite narrowing of the QRS complex after sodium bicarbonate administration¹⁹.

Rosenbaum *et al*²⁰ reported that fatalities involving amitriptyline, desipramine and imipramine occurred with doses equal to or greater than 15 mg/kg, and most were over 30 mg/kg. Therefore, They recommended that if the history clearly establishes a dose of a TCA that is less than 5 mg/kg (i.e., the exact amount and number of pills can be quantified without any doubt) in a completely asymptomatic child, this would suggest that conservative treatment with observation at home may be safe. Another study reported that the lowest fatal dose of imipramine was 15 mg/kg, in a 6-year old child⁵. Though exposures of 5-6.67 mg/kg also may be safe, this report recommended greater caution with

these exposures until further data are available; therefore, these children should be carefully monitored by a physician. If the exact amount of ingested TCA is unknown or there are any symptoms of toxicity, the child should be evaluated immediately. The amount of TCA ingested will determine the likely toxicity, not the serum levels. Therefore, any question about the amount swallowed should be considered to be potentially above the threshold requiring evaluation and close monitoring²⁰⁾.

Although the ingestion of TCAs can be fatal with doses equal to or greater than 15 mg/kg, TCAs, including imipramine, are widely used. Therefore, children can be exposed to TCAs, which can be fatal with an accidental overdose. This is the first case in Korea of a pediatric overdose of imipramine. Imipramine toxicity included convulsions, tachycardia with a wide QRS complex, BEP, and anuresis. The patient was successfully treated with sodium bicarbonate.

한 글 요약

Brugada 심전도 양상을 포함한 이미프라민에 의한 독성 부작용 1예

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삼환계 항우울제의 하나인 이미프라민은 우울장애와 야노증, 불안장애, 신경성 통증에 쓰인다. 그러나 이미프라민을 포함한 삼환계 항우울제는 많은 부작용이 관찰되는 데, 항콜린성 작용으로 초기에 입이 마르고 동공산대, 소변 정체, 동성빈맥을 보인다. 또한 중추신경계에 작용하여 섬망, 불안, 초조, 환각, 경련, 혼수를 야기할 수 있다. 그러나 앞에서 말한 부작용 보다도 치명적인 것인 삼환계 항우울제에 의해 소듐 채널 차단으로 인한 부정맥이다. QRS파의 연장과 QTc 연장, 넓은 QRS파 빈맥, Brugada 심전도 양상이 나타나며 이런 현상은 중탄산 나트륨을 통해 나트륨을 대량으로 공급하여 회복시킬 수 있다. 이미프라민을 포함한 삼환계 항우울제에는 아직도 널리 쓰이고 있지만 지금까지 소아에서 부정맥이 부작용으로 나타난 증례에 대한 보고가 없었다. 따라서 저자들은 이미프라민 과량복용 후 경련, 넓은 QRS파를 보이는 빈맥, Brugada 심전도 양상, 무뇨를 보인 환아를 경험, 치료하여 이를 보고한다.

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