Fluid Retention and Cardiomegaly Associated with Carbamazepine in an Epileptic Child

Semra Atalay, M.D.,* Ayse Öner, M.D.,** Y.K. Yavuz Gürer, M.D.,*** and Selmin Karademir, M.D.****

SUMMARY

Carbamazepine (CBZ) has been reported to have an antidiuretic action, though it is not known how it produces this effect. This is a well recognized complication of CBZ therapy in adults. However this syndrome has been rarely observed in childhood. We present an epileptic child with fluid overload due to CBZ treatment who was referred with chest pain and cardiomegaly. Our patient developed fluid retention with cardiomegaly during treatment with CBZ alone at a normal dose and for a short time. To our knowledge this is the first case of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) due to CBZ therapy which has been observed to be associated with cardiomegaly. (Jpn Heart J 34: 239–243, 1993.)

Key Words: Carbamazepine therapy SIADH and cardiomegaly

Carbamazepine has been used as an anticonvulsant since 1962. Various side effects such as drowsiness, dry mouth, nausea, vomiting, generalized erythema, photosensitivity, cardiac conduction disturbance and systemic lupus erythematosus have been documented.1)-3) In addition to these side effects, hyponatremia and low plasma osmolality have been reported in CBZ-treated patients.4)

In this report, we present an epileptic child who developed fluid overload while receiving CBZ treatment. To our knowledge, this is the first case of the syndrome of inappropriate antidiuretic hormone secretion due to CBZ therapy which has been observed to be associated with cardiomegaly.

CASE REPORT

A 13-year-old boy was referred to Dr. Sami Ulus Children's Hospital,
Pediatric Cardiology Unit on December 23, 1991 with a complaint of chest pain. The history revealed that this patient had suffered from epilepsy for 10 years and had been treated with CBZ 200 mg 3 times a day for only the last 3 months.

The physical examination upon admission revealed a minimal degree of peripheral edema, a heart rate of 90/min, and a blood pressure of 130/80 mmHg. His weight was 61 kg (1 month ago his weight was 60 kg). Skin turgor was normal. Gallop rhythm and murmur were not heard on auscultation. Minimal neck vein distention was noticed. Central venous pressure was 13 cmH2O. Neurologic examination was normal. Electroencephalogram showed slow waves in the left temporal region. Chest x-ray demonstrated cardiac enlargement (Fig. 1) and his electrocardiogram was normal. Two-dimensional and Doppler echocardiographic examinations were performed. The main cardiac structures were normal. Left ventricular end-diastolic dimension was increased (53.4 mm). The laboratory findings were as follows; plasma sodium 128 mEq/l, plasma potassium 4.07 mEq/l, plasma urea 20 mg/dl, plasma creatinine 0.8 mEq/l, urine sodium 180 mEq/l, urine creatinine 100 mEq/l, plasma osmolality 268 mOs/kg, urine osmolality 880 mOs/kg and plasma CBZ level 4.30 μg/ml (normal therapeutic range 5–10 μg/ml). Based upon the laboratory findings, we thought that this patient’s condition might be explained by inappropriate secretion of arginine vasopressin (AVP) caused by CBZ. Unfortunately, it was not possible for us to measure plasma AVP levels because radioimmunoassay is not available in our hospital. Daily plasma and urine sodium values and
Table I. Daily Plasma and Urine Sodium Values, Osmolality and Withdrawal Doses of Carbamazepine

<table>
<thead>
<tr>
<th>Date</th>
<th>Plasma Na (mEq/l)</th>
<th>Osmolality (mOsm/kg)</th>
<th>Urine Na⁺ (mEq/l)</th>
<th>Osmolality (mOsm/kg)</th>
<th>Withdrawal dose of carbamazepine (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 Dec 1991</td>
<td>128</td>
<td>268</td>
<td>180</td>
<td>880</td>
<td>500</td>
</tr>
<tr>
<td>26 Dec 1991</td>
<td>129</td>
<td>—</td>
<td>140</td>
<td>—</td>
<td>400</td>
</tr>
<tr>
<td>27 Dec 1991</td>
<td>132</td>
<td>—</td>
<td>70</td>
<td>—</td>
<td>200</td>
</tr>
<tr>
<td>28 Dec 1991</td>
<td>135</td>
<td>288</td>
<td>40</td>
<td>460</td>
<td>discontinued</td>
</tr>
</tbody>
</table>

Fig. 2. December 31, 1991. Control telecardiogram showing cardiothoracic ratio returned to normal limits (carbamazepine was stopped 3 days previously).

osmolality are shown in Table I. CBZ was tapered rather more rapidly than the classic method and then discontinued. Furosemide 2 mg/kg was given for 5 days. The plasma and urine sodium concentrations returned to normal ranges within 3 days. Four days later, his weight was 60.2 kg, central venous pressure was 11.5 cmH₂O and blood pressure was 120/75 mmHg. After tapering CBZ, the cardiac findings disappeared completely and returned to normal within 7 days (Fig. 2).

**DISCUSSION**

CBZ is one of many drugs that have been associated with inappropriate antidiuresis. Its mode of action is not clearly understood, though it may stimulate vasopressin secretion from the pituitary or potentiate the action of AVP on
the renal tubules. There are some reports on the incidence of CBZ-induced hyponatremia in epileptic patients.

Because of the development of chest pain, the patient was referred to our hospital for evaluation. There was not any reasonable explanation for the cause of cardiomegaly based upon physical examination and echocardiography. During a routine laboratory examination, we had found an unexpectedly low serum sodium concentration. Furthermore, there was low plasma osmolality and high urine osmolality with normal renal function. Hyponatremia with corresponding hypoosmolality of the serum, continued renal excretion of sodium, absence of clinical evidence of fluid volume depletion, osmolality of the urine greater than appropriate for the concomitant tonicity of the plasma and normal renal and adrenal function are cardinal findings of SIADH. Although we could not measure the ADH level, we made a diagnosis of SIADH on the basis of these typical laboratory and clinical findings. The improvement in clinical features and laboratory values following the withdrawal of CBZ and the initiation of diuretic treatment confirmed our diagnosis. This syndrome is well described in adults receiving CBZ therapy. However, this entity has been rarely observed in children. The youngest patients reported in the literature were 13 and 15 years old.

Perucca et al noted that there is a negative correlation between plasma sodium concentration and both the dose and serum concentration of CBZ as described by Henry et al. There have been some reports of severe water intoxication when the CBZ serum concentration reaches toxic levels. Likewise, we could not find a positive correlation between plasma sodium concentration and serum concentration of CBZ. Smith et al described a case with CBZ-induced water intoxication who had a normal plasma CBZ level (6 μg/ml), as did our case.

Perucca et al observed that hyponatremia was more frequent in those patients on monotherapy. They postulated that the other coadministered antiepileptic drugs may prevent the antidiuresis induced by CBZ. Kalff et al have reported that the combination of CBZ with barbiturates and sodium valproate seemed to enhance hyponatremia, whereas phenytoin and ethosuximide appeared to have an opposite effect. Our patient developed fluid retention with cardiomegaly during treatment with CBZ alone at a normal dose and for a short time.

With this case report, we further emphasize that SIADH due to CBZ therapy is rarely seen in childhood. We recommend plasma sodium concentration and osmolality should be measured although the plasma concentration of CBZ is lower than the normal therapeutic range. If cardiomegaly is observed in patients receiving CBZ, it should be remembered that SIADH is a complication
REFERENCES