THE ANTIDIURETIC ACTION OF CARBAMAZEPINE IN MAN

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SUMMARY

1. Carbamazepine had an antidiuretic effect in six patients with neurohypophyseal diabetes insipidus due to various causes. The effect was qualitatively similar to that of antidiuretic hormone.

2. At the time of maximal antidiuresis plasma arginine vasopressin levels, measured by radioimmunoassay, were below the limit of detectability in all patients.

3. In one of two control subjects a temporary decrease in water excretion was observed during administration of carbamazepine.

4. In the two control subjects plasma arginine vasopressin levels dropped from normal to below the level of detectability during administration of the drug.

5. It is concluded that the antidiuretic effect of carbamazepine is not the result of releasing endogenous antidiuretic hormone or of prolonging its half-life.

6. The most likely explanation for the observed results is either a direct effect of carbamazepine on the distal renal tubular cell or an increase of renal responsiveness to endogenous antidiuretic hormone.

Key words: neurohypophyseal diabetes insipidus, carbamazepine, antidiuretic action, plasma arginine vasopressin.

Substitution therapy with antidiuretic hormone (ADH) in neurohypophyseal diabetes insipidus (DI) can usually be replaced by treatment with certain drugs which do not bear an obvious structural relation to ADH. One of these drugs, which has been studied extensively, is an oral antidiabetic agent of the sulphonylurea group, chlorpropamide (Arduino, Ferraz & Rodriguez, 1966; Meinders, Touber & De Vries, 1967; Miller & Moses, 1970), which exerts a striking antidiuretic action in neurohypophyseal DI, but has the drawback of inducing hyperinsulinaemia (Meinders, Cejka, Bleyenberg & Belt van den Bosch, 1973; Meinders, Cejka & Bleyenberg, 1974) and hypoglycaemia, especially in children. Recently two other
drugs with an antidiuretic effect in neurohypophyseal DI have been described: clofibrate (De Gennes, Bertrand, Bigorie & Truffert, 1970) and carbamazepine [dibenz-(b,f)-azepine-5-carboxamide] (Braunhofer & Zicha, 1966). Frahm & Smejkal (1969) suggested that carbamazepine produced its antidiuretic effect by releasing ADH from the diseased hypothalamic-hypophysal system. In their work plasma ADH was measured by bioassay. In the present study the effect of carbamazepine has been studied in detail in six patients with neurohypophyseal DI and in two control subjects by using a radioimmunoassay for the measurement of plasma ADH. Conclusions as to the mode of action of carbamazepine in DI have been drawn which differ from those of Frahm & Smejkal (1969).

**TABLE 1. Patients with neurohypophyseal diabetes insipidus**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age</th>
<th>Sex</th>
<th>Duration of illness (years)</th>
<th>Aetiology</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14</td>
<td>M</td>
<td>6</td>
<td>Unknown</td>
<td>—</td>
</tr>
<tr>
<td>2(1)</td>
<td>54</td>
<td>F</td>
<td>54</td>
<td>Familial</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>3(1)</td>
<td>29</td>
<td>F</td>
<td>29</td>
<td>Familial</td>
<td>Autosomal dominant</td>
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<tr>
<td>4(1)</td>
<td>28</td>
<td>F</td>
<td>28</td>
<td>Familial</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>5</td>
<td>63</td>
<td>M</td>
<td>7</td>
<td>Unknown</td>
<td>Hypogonadotrophic hypogonadism</td>
</tr>
<tr>
<td>6</td>
<td>31</td>
<td>M</td>
<td>10</td>
<td>Post-traumatic</td>
<td>Pituitary hypothyroidism</td>
</tr>
</tbody>
</table>

(1) Patients nos. 2, 3 and 4 are members of the same family.

**SUBJECTS AND METHODS**

Consent for the performed studies was obtained from all patients with DI and from the control subjects after full explanation of the purpose, nature and risks of all procedures used. This study was approved by the Ethical Committee of the institution.

Clinical data of the patients with DI are presented in Table 1. None of the patients reacted with a decreased free water clearance after hypertonic saline infusion (Carter & Robbins, 1947) but all reacted with a brisk decrease in water excretion after intravenous administration of lysine vasopressin.

Patient 1 did not receive antidiuretic therapy before being given carbamazepine. The other five patients had been effectively treated with chlorpropamide. During this treatment urine production had fallen to between 10 and 20% of the volume produced in the untreated period. After discontinuing this drug the antidiuretic effect disappeared within 5 days. Thereafter, another 3 days without antidiuretic therapy were allowed to obtain baseline observations for urinary output and osmolality before treatment with carbamazepine was started.

Patients 2–6, who were well trained in collecting their daily urine volume, were studied in the outpatient department without dietary restriction. They received 0·90 mmol (200 mg) of carbamazepine twice daily for 2 weeks. Venous blood samples were obtained and body weight was measured on the last day of chlorpropamide therapy and on the 14th day of carbamazepine therapy. They measured their 24 h urine production the day before starting the carbamazepine medication and the last 3 days of taking the drug, aliquots of these 24 h collections being saved.
Antidiuretic action of carbamazepine

for measurement of osmolality (vapour pressure osmometer, Mechrolab) and creatinine. The daily creatinine output of these patients is known from earlier clinical observations. By measuring the creatinine concentration in the collected samples it was possible to obtain an estimate of the daily urine production and to confirm the measurements made by the patients.

Patient 1 and patient 6 (after the 2 weeks of carbamazepine treatment in the outpatient department) were admitted to the hospital for more detailed studies. Two subjects with a duodenal ulcer in an inactive phase and without endocrine or kidney disease were also admitted to the hospital and functioned as controls. Two patients with DI (1 and 6) and the two control subjects were observed under strictly standardized conditions. Every 3 h they received an equal amount of identical food, minerals and fluid (e.g. biscuits, milk, butter, cheese). The DI patients had free access to water and their water intake was recorded. The control subjects had a fixed water intake. Body weight was recorded twice daily (De Vries, Ten Holt, van Daatselaar, Mulder & Borst, 1960). The control subjects were on complete bed rest: the two DI patients were allowed to walk around from 09.00 to 12.00 hours and from 15.00 to 18.00 hours.

Urine was collected every 3 h and when necessary at shorter intervals. The urine volume and osmolality and the concentrations of sodium, potassium and creatinine were measured. Twice weekly or more frequently if necessary venous blood was drawn at 09.00 hours for haemoglobin, sodium, potassium and creatinine determination.

Plasma arginine vasopressin (AVP) was measured with a radioimmunoassay (Robertson, Mahr, Athar & Sinha, 1973). Venous blood samples were obtained in heparin and immediately spun for 20 min. Within 30 min after the blood was taken, the plasma samples were stored at -20°C. The time-interval between the samples being taken and their assay was 19–90 days. The lowest concentration of plasma AVP detectable in this assay is 0.46 pmol/l (0.5 pg/ml). The likelihood of cross-reactions with peptides other than AVP is very low. Even lysine vasopressin and arginine vasotocin are less than one-third and one-sixth as reactive as AVP in this assay. Recovery of AVP added to AVP-deficient plasma is almost 100%. The interassay coefficient of variation is 17%. The intra-assay coefficient of variation varied from 7% (high AVP concentration) to 25% [low AVP concentration: <0.92 pmol/l (1 pg/ml)]. It is unlikely that carbamazepine inhibits the assay, as the expected plasma AVP concentrations are found after i.m. pitressin tannate in oil and i.v. lysine vasopressin during treatment with carbamazepine.

RESULTS

Neurohypophyseal diabetes insipidus (Table 2 and Figs. 1, 2 and 3)

After oral administration of 0.9–3.6 mmol (200–800 mg) of carbamazepine daily all six patients responded with a decreased urinary water output and an increased urinary osmolality. In the two patients studied in detail the characteristic diurnal excretion pattern (De Vries et al., 1960) of sodium and potassium remained unchanged. Haemoglobin, plasma sodium, potassium and creatinine remained virtually constant in all patients. Body weight remained constant in five of the six patients. In patient 6 a weight loss of 2 kg was observed, due to a diet lower in calories than his usual diet [6700 kJ (1600 kcal)/day]. The decreased water intake in the two patients studied in detail occurred simultaneously with and did not precede the decreased urinary water output.
Table 2. Effect of carbamazepine in patients with neurohypophyseal diabetes insipidus

<table>
<thead>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (a)</td>
<td>0.9 (200)</td>
<td>12.0</td>
<td>5.5</td>
<td>80</td>
<td>180</td>
<td>18.4</td>
<td>38.4</td>
<td>14.7</td>
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<tr>
<td>2</td>
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<td>12.0</td>
<td>6.0</td>
<td>80</td>
<td>200</td>
<td>18.4</td>
<td>38.4</td>
<td>14.7</td>
</tr>
<tr>
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<td>1.8 (400)</td>
<td>10.0</td>
<td>5.3</td>
<td>60</td>
<td>216</td>
<td>10.52</td>
<td>75.6</td>
<td>13.5</td>
</tr>
<tr>
<td>4</td>
<td>1.8 (400)</td>
<td>10.0</td>
<td>5.3</td>
<td>65</td>
<td>193</td>
<td>7.56</td>
<td>14.3</td>
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<tr>
<td>5</td>
<td>1.8 (400)</td>
<td>4.0</td>
<td>1.8</td>
<td>60</td>
<td>216</td>
<td>10.52</td>
<td>75.6</td>
<td>13.5</td>
</tr>
<tr>
<td>6</td>
<td>1.8 (400)</td>
<td>4.0</td>
<td>1.8</td>
<td>60</td>
<td>216</td>
<td>10.52</td>
<td>75.6</td>
<td>13.5</td>
</tr>
</tbody>
</table>

(a) No antidiuretic therapy before the carbamazepine administration.
Antidiuretic action of carbamazepine

Plasma AVP concentrations were below the level of detectability at the time of distinct antidiuresis in all six patients. Three determinations were made in patient 1 and two in patient 6 (Figs. 1 and 2). The plasma AVP concentration in patient 1 was in the expected low range for untreated neurohypophyseal DI patients before carbamazepine treatment started and became
undetectable during treatment. After stopping the drug in patient 1 the antidiuretic effect disappeared within 48 h (Fig. 3).

**Control subjects**

Daily oral administration of 1·8 mmol (400 mg) of carbamazepine to the first control subject (male, 32 years; Fig. 4) was followed neither by a decreased water excretion nor by a change in the excretion of any of the other measured urinary constituents. Haemoglobin and the

![Graph](image)

**Fig. 2.** Effect of 1·8 and 3·6 mmol (400 and 800 mg) of carbamazepine daily on plasma AVP concentrations and on the urinary excretion of water, sodium, potassium, creatinine and the urinary osmolality in patient 6 (male, 31 years; neurohypophyseal diabetes insipidus). Before day 1 he had received 1·8 mmol (400 mg) of carbamazepine daily for 14 days. The patient was ambulatory from 09.00 to 12.00 hours and from 15.00 to 18.00 hours. Urine was collected every 3 h. Water intake was free. For blood chemistry and body weight see Table 2.
Antidiuretic action of carbamazepine

plasma concentrations of sodium, potassium and creatinine remained unchanged. During administration of the carbamazepine 69% of an acute water load was excreted within 3 h as compared with 86% of an identical water load given 63 h after the last dose of the drug. This timing of the second load was chosen since in patient 1 (DI) the antidiuretic action disappeared within 48 h after stopping the carbamazepine.

During treatment no AVP was detected in the plasma, whereas before treatment the AVP concentration was normal in relation to urinary osmolality (Robertson et al., 1973).

![Graph showing the effect of carbamazepine on daily urinary excretion of water, sodium, potassium and creatinine and the urinary osmolality. The first 11 days are shown in more detail in Fig. 1.](image-url)
Control subject 2 (male, 35 years; Fig. 5) received 3.6 mmol (800 mg) of carbamazepine daily. In the first 3 days a decreased water excretion with an increased urinary osmolality was observed. In this period he gained 1.5 kg body weight. On the fourth day, without changing the dose of carbamazepine, water excretion and urinary osmolality returned to control values. Body weight dropped from the fourth day but returned to the pretreatment weight only 48 h after the last dose of the drug was given (on day 12 at 18.00 hours). A transient and minimal increase of sodium excretion was observed during administration of carbamazepine. The excretion of potassium and creatinine was not influenced by the carbamazepine. Haemoglobin and plasma creatinine and potassium remained unchanged. A slight fall of plasma sodium (from 136 mmol/l to 130 mmol/l) was observed, which returned to control values 48 h after the last dose of the drug was given. In the presence of carbamazepine 70% of an acute water

![Graph](image-url)

**Fig. 4.** Effect of 1.8 mmol (400 mg) of carbamazepine daily on body weight, plasma AVP concentrations and on the urinary excretion of water, sodium, potassium, creatinine and the urinary osmolality in control subject 1 (male, 32 years; complete bed rest). Fluid intake was fixed (183 ml/h).
load was excreted in 3 h as compared with 80% of an identical water load administered before carbamazepine was given. A normal plasma AVP concentration before treatment dropped to undetectable levels during administration of carbamazepine.

**Fig. 5.** Effect of 3·6 mmol (800 mg) of carbamazepine daily on body weight, plasma AVP concentrations and the urinary excretion of water, sodium, potassium and the urinary osmolality in control subject 2 (male, 35 years; complete bed rest). Fluid intake was fixed (183 ml/h).

**DISCUSSION**

The antidiuretic effect of carbamazepine in patients with neurohypophyseal DI was confirmed. This effect is qualitatively similar to that of ADH since the increased urinary osmolality was due entirely to decreased water excretion. No change was seen in the characteristic diurnal excretion pattern of sodium and potassium. The creatinine excretion and plasma creatinine concentrations remained constant. There was no evidence that carbamazepine suppresses thirst and fluid intake, leading to a decreased water excretion, as body weight remained constant in five of the six patients (in one patient weight reduction was the result of caloric restriction) and plasma sodium and haemoglobin concentrations remained unchanged. In the patients
studied in detail it became clear that the decrease in water intake occurred simultaneously with the decrease in urinary water output. Frahm & Smejkal (1969), using a bioassay, found that during administration of carbamazepine an increase in plasma antidiuretic activity occurred in patients with DI but not in control subjects.

Uhlich, Loeschke & Eigler (1972) demonstrated that the drug had an antidiuretic effect in control rats but not in the rats with neurohypophyseal DI (Brattleboro strain). In addition they were unable to detect any effect on water movement across the toad bladder wall, which they used as a model for the distal renal tubule. From these studies they concluded that carbamazepine releases ADH from the diseased hypothalamic–posterior pituitary system. It is not apparent why Frahm & Smejkal (1969) did not find an increase in plasma antidiuretic activity in persons with a normally functioning ADH-producing system, despite the observed anti-diuresis during administration of the drug in normal man and animals. It is also questionable whether the bioassay method is an appropriate method of measuring ADH in this context because it is possible that an ADH-like activity of carbamazepine is detected. By radio-immunoassay we were unable to demonstrate a rise in plasma AVP levels in patients with neurohypophyseal DI due to various causes; throughout the study AVP remained undetectable in the plasma. Moreover, AVP disappeared from the plasma in the two control subjects during administration of the drug, though their water excretion remained constant or decreased.

It seems that the carbamazepine took over or potentiated the antidiuretic action of ADH in these two control subjects. In our experience untreated normal subjects and DI patients hardly ever have undetectable plasma AVP levels when the urinary osmolality is as high as that found during treatment with carbamazepine. We conclude that carbamazepine does not release ADH either from an intact or a diseased hypothalamic–posterior pituitary system. It is unlikely that carbamazepine inhibits the breakdown of vasopressin as one would not then expect the plasma AVP concentration to fall to undetectable levels. The possibility remains that carbamazepine sensitizes the distal renal tubular cell to small undetectable amounts of endogenous ADH. The decrease in measurable plasma AVP in the control subjects would be compatible with this hypothesis. Another explanation could be that carbamazepine acts directly on the distal renal tubular cell independently of ADH. Although our results favour the theory that carbamazepine has an action on the distal renal tubular cell, as does chlorpropamide, it is not clear why even in combination with small amounts of vasopressin Uhlich et al. (1972) did not find an antidiuretic action of the drug in the Brattleboro rats or in the toad bladder preparation.

For practical purposes carbamazepine seems to be a valuable antidiuretic agent in the treatment of neurohypophyseal DI. The drug is widely used in patients with neurological abnormalities, in dosage as high as 6.3 mmol (1400 mg) daily. In these patients one might expect the occasional occurrence of water intoxication with hyponatraemia and a high urinary osmolality as in the syndrome of inappropriate ADH secretion (Bartter & Schwartz, 1967); a report of such a case has been recently published (Radø, 1973).

REFERENCES


Antidiuretic action of carbamazepine


