Paradoxical diuresis after vasopressin administration to patients with neurohypophyseal diabetes insipidus treated with chlorpropamide, carbamazepine or clofibrate

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Summary

1. Chlorpropamide, carbamazepine and clofibrate have an antidiuretic action in patients with neurohypophyseal diabetes insipidus which is qualitatively similar to that of antidiuretic hormone (ADH).

2. An additive antidiuretic effect is produced by combination of chlorpropamide and carbamazepine with small dosages of ADH.

3. After an immediate and transient antidiuresis, a single intravenous bolus injection of lysine vasopressin given during treatment with chlorpropamide, chlorpropamide with a continuous intravenous infusion of lysine vasopressin, carbamazepine or clofibrate, resulted in increased water diuresis for 12–24 h or longer.

4. This paradoxical diuresis was not observed during treatment with chlorothiazide.

5. It is suggested that the antidiuretic action of chlorpropamide, carbamazepine and clofibrate is localized at the receptor site for ADH in the distal renal tubular cell.

Key words: antidiuretic hormone, carbamazepine, chlorpropamide, clofibrate, neurohypophyseal diabetes insipidus.

Introduction

In recent years, several different drugs have been advocated for the treatment of patients with neurohypophyseal diabetes insipidus. Of these, chlorpropamide, carbamazepine and clofibrate have an action qualitatively identical with that of antidiuretic hormone. They induce a decrease in water excretion without affecting the excretion of other urinary constituents and are ineffective in patients with nephrogenic diabetes insipidus (Arduino, Ferraz & Rodriguks, 1966; Frahm & Smejkal, 1969; de Gennes, Bertrand, Bigorie & Truffert, 1970).

The mode of antidiuretic action of these three drugs has not been established and three possible mechanisms have been considered, namely: (1) increase of available endogenous arginine vasopressin either by augmented neurohypophyseal output or by decreased disposal rate; (2) direct antidiuretic effect on the distal renal tubular cell without the intervention of ADH; (3) potentiation of small amounts of residual endogenous ADH. The choice between these alternatives must take into account our observation that a paradoxical water diuresis follows a bolus injection of vasopressin in patients with neurohypophyseal diabetes insipidus during treatment with any of these three drugs.

Subjects and methods

Consent for the studies was obtained from all patients with diabetes insipidus after full explana

(1) Abbreviation: ADH, antidiuretic hormone.
tion of the purpose, nature and risks of all procedures used. The study was approved by the Ethical Committee of the institution. Clinical data of the patients are presented in Table 1. None of them reacted with a decreased free water clearance after infusion of hypertonic sodium chloride (Carter & Robins, 1947) but all reacted with a brisk decrease in water excretion after intravenous administration of lysine vasopressin. All five patients reacted with a selective decrease of water excretion to any of the three drugs that were studied (Meinders, Touber & de Vries, 1967; Meinders, van Leeuwen & de Vries, 1969; Meinders, Cejka & Robertson, 1974). All patients were admitted to the hospital and 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). Their water intake was free and carefully recorded. Body weight was recorded twice daily. Bed rest was complete except in patient no. 4 and patient no. 5, who were allowed to walk around from 09.00 to 12.00 hours and from 15.00 to 18.00 hours. The urine was collected every 3 h and when necessary at shorter intervals (de Vries, ten Holt, van Daatselaar, Mulder & Borst, 1960). The urine volume and osmolality (vapour pressure osmometer, Mechrolab) and the concentration of sodium, potassium and creatinine were measured. Before the study was started all former antidiuretic treatment was withheld for at least 7 days. During the study the patients were treated with chlorpropamide, or clofibrate or carbamazepine. Twice weekly at 09.00 hours, or more frequently if necessary, 10 ml of venous blood was drawn for haemoglobin, sodium, potassium and creatinine determination. Plasma Arg-vasopressin was kindly measured by Dr G. L. Robertson by radioimmunoassay sensitive to at least 0.18 pmol/l (Robertson, Mahr, Athar & Sinha, 1973; Meinders et al., 1974). Chlorpropamide, carbamazepine and clofibrate do not inhibit this assay; the expected plasma Arg-vasopressin concentrations are found after intramuscular injection of pitressin tannate in oil or Lys-vasopressin administration intravenously during treatment with any of these three drugs.

Results

During chlorpropamide-induced antiuresis in patients no. 1 and no. 2 no Arg-vasopressin was detectable in their plasma (Table 1). No plasma Arg-vasopressin determinations were done during the studies shown in Figs. 1–3. No Arg-vasopressin activity was detectable in plasma during carbamazepine-induced antidiuresis in patient no. 4. At the time of the measurements in patients no. 1, no. 2 and no. 4 the lowest concentration of plasma Arg-vasopressin detectable in this assay was 0.46 pmol/l (0.5 pg/ml). In patient no. 5, plasma Arg-vasopressin varied from 0.18 to 0.62 pmol/l (0.2–0.7 pg/ml) during treatment with clofibrate. Concentrations of haemoglobin in blood and of sodium, potassium and creatinine in plasma remained unchanged during treatment with chlorpropamide, carbamazepine and clofibrate in all five patients, regardless of the administration of ADH. Patient no. 4 lost 2 kg as a result of a low-energy diet but the body weight of the other patients remained constant once treatment was established. An intravenous bolus injection of 1 unit of Lys-vasopressin was given within a few seconds after the antidiuretic effect of chlorpropamide, carbamazepine or clofibrate had stabilized. A total of five Lys-vasopressin bolus injections were given in three different patients during treatment with only chlorpropamide. One Lys-vasopressin bolus injection was given during treatment with chlorpropamide in combination with a continuous low dose (2.37 munits/h) infusion of Lys-vasopressin (patient no. 3). Finally one patient (no. 2) was also given three Lys-vasopressin bolus injections with time-intervals of 48 h or more during treatment with salt restriction and chlorothiazide, a drug with an antidiuretic effect different from the other three drugs and lacking an ADH-like action (Crawford, Kennedy & Hill, 1960; van der Korst, 1963). Examples of the effect of these bolus injections on the urinary excretion pattern are shown in the Figs. 1–5.

After the expected transient strong antidiuretic effect with a rise of the urinary osmolality that was recorded after the intravenous Lys-vasopressin bolus injection, a selective increase of the water excretion with a fall of the urinary osmolality was observed which lasted 12 h to more than 24 h (paradoxic diuresis) in the patients treated with chlorpropamide alone, in the one given chlorpropamide in combination with small amounts of Lys-vasopressin, and in those treated with carbamazepine or clofibrate, but not in the patient treated with chlorothiazide. During this paradoxical water excretion no change was observed in the characteristic diurnal excretion patterns of sodium, potassium.
<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Aetiology</th>
<th>Duration of illness (years)</th>
<th>Treatment [mmol (mg)/day]</th>
<th>Plasma vasopressin during treatment [pmol/l (pg/ml)]</th>
<th>Urine volume (l/24 h)</th>
<th>Urine osmolality (mosmol/kg of water)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(1)</td>
<td>67</td>
<td>M</td>
<td>Autosomal dominant familial</td>
<td>67</td>
<td>Chlorpropamide [1·8 (500)]</td>
<td>&lt;0·46 (0·5)(2)</td>
<td>14·2-16·0</td>
<td>1·2-2·0</td>
</tr>
<tr>
<td>2(1)</td>
<td>22</td>
<td>F</td>
<td>Autosomal dominant familial</td>
<td>22</td>
<td>Chlorpropamide [1·8 (500)]</td>
<td>&lt;0·46 (0·5)(2)</td>
<td>15·2-16·5</td>
<td>1·5-2·0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chlorothiazide [1·7 (500)] and salt restriction</td>
<td>Not performed</td>
<td>15·2-16·5</td>
<td>3·4-3·6</td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>M</td>
<td>Idiopathic</td>
<td>8</td>
<td>Chlorpropamide [1·8 (500)]</td>
<td>Not performed</td>
<td>13·2-13·8</td>
<td>1·3-2·4</td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>M</td>
<td>Post traumatic</td>
<td>10</td>
<td>Carbamazepine [3·4 (800)]</td>
<td>&lt;0·46 (0·5)(2)</td>
<td>14·0-16·2</td>
<td>1·4-1·7</td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>M</td>
<td>Idiopathic</td>
<td>7</td>
<td>Clofibrate [4·2 (1000)]</td>
<td>0·18-0·62 (0·2-0·7)</td>
<td>11·9-12·2</td>
<td>2·3-3·0</td>
</tr>
</tbody>
</table>

(1) Patients no. 1 and no. 2 are members of the same family.

(2) The lowest plasma vasopressin concentration measurable at the time of these determinations was 0·46 pmol/l (0·5 pg/ml).
Fig. 1. Effect of chlorpropamide alone, in combination with an intravenous bolus injection of lysine vasopressin and in combination with pitressin tannate in oil intramuscularly, on the urinary excretion of water, sodium, potassium, creatinine and the urinary osmolality in patient no. 1. Chlorpropamide treatment was started 2 weeks before day 1.

Fig. 2. Effect of an intravenous bolus injection of lysine vasopressin during treatment either with chlorothiazide in combination with complete salt restriction or with chlorpropamide in patient no. 2. Chlorothiazide and salt-restriction treatment was started 5 days before day 1.
Paradoxical water diuresis after ADH

![Graph showing time (days) vs. amounts of chlorpropamide, lys-vasopressin, Na, Water, K, Creatinine, and Osmolality over 5 days.]

**Fig. 3.** Effect of an intravenous bolus injection of lysine vasopressin during treatment with chlorpropamide in combination with a low-dose continuous intravenous administration of lysine vasopressin in patient no. 3. The urine was not collected at shorter intervals after the intravenous bolus injection of lysine vasopressin. Chlorpropamide treatment was started 7 days before day 1.

and creatinine. Also the measured variables in the plasma remained unchanged. The increased water intake followed and did not precede the increased water excretion. Administration of an intramuscular injection of 1 unit of the gradually released antidiuretic substance pitressin tannate in oil during treatment with carbamazepine (not shown) or chlorpropamide (Fig. 1) resulted in a lengthy additive antidiuretic effect of several days. In the same patients intramuscular administration of 1 unit of pitressin tannate in oil alone had an antidiuretic action of only about 12 h. A similar additive antidiuretic effect was observed during treatment with chlorpropamide in combination with a continuous low-dose (2.37 munits/h) infusion of Lys-vasopressin (Fig. 3).

**Discussion**

We have no evidence that the ADH-like effect of chlorpropamide, carbamazepine or clofibrate results from release of endogenous Arg-vasopressin from the diseased hypothalamic posterior pituitary system in patients with neurohypophyseal diabetes insipidus. All the plasma Arg-vasopressin concentrations measured during treatment with these drugs are very low. In our experience, patients with diabetes insipidus hardly ever have such low plasma concentrations when the urinary osmolality is as high as that found during treatment with any of these drugs. On the contrary, in some patients we found a disappearance of Arg-vasopressin activity from the plasma during treatment with these anti-
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![Graph showing the effect of Lys-vasopressin and carbamazepine on various parameters over time.](image)

**Fig. 4.** Effect of an intravenous bolus injection of lysine vasopressin during treatment with carbamazepine in patient no. 4. Carbamazepine treatment was started 2 weeks before day 1.

Diuretic drugs (Frahm & Smejkal, 1969; Ettinger & Forsham, 1970; Moses, Numann & Miller, 1973; Meinders et al., 1974). It seems more likely that all three drugs act at the distal renal tubular cell level by potentiating the antidiuretic effect of small amounts of remaining endogenous Arg-vasopressin (Miller & Moses, 1970; Zweig, Ettinger & Early, 1971; Mendoza & Brown, 1974). The additive effect of chlorpropamide or carbamazepine and small doses of ADH administered either by a continuous infusion of Lys-vasopressin (2.37 munits/h) or by an intramuscular injection of pitressin tannate in oil (1 unit) is compatible with this theory but does not exclude a direct effect of these drugs on the distal renal tubular cell without intervention of ADH (Adreani, Cinotti & Stirati, 1969; Danisi, Genta, Timoner & Marcondes, 1970).

The transient strong antidiuretic effect of an intravenous bolus injection of Lys-vasopressin during treatment with any of the four drugs, including chlorothiazide, is the same as in untreated diabetes insipidus or in normal control subjects (de Vries et al., 1960). After the strong antidiuretic effect has disappeared during chlorothiazide treatment (Fig. 2) the level of water excretion and urinary osmolality of the pre-injection period was regained and no paradoxical diuresis was observed. Chlorothiazide has no ADH-like activity and its antidiuretic effect is mediated by contraction of the extracellular fluid volume as a result of sodium and
water depletion in the first treatment days (van der Korst, 1965). This initial diuretic effect of chlorothiazide is localized at a site different from the site of action of ADH in the distal renal tubule (Early, Kahn & Orloff, 1961).

A different situation exists with regard to chlorpropamide, carbamazepine and clofibrate. These drugs reduce water excretion without influencing other urinary constituents. This makes it likely that they act at the same renal tubular site as ADH. However, after the transient, strong antidiuretic effect of a bolus injection of Lys-vasopressin during treatment with these three drugs the water diuresis was greater than in the pre-injection period for 12–24 h or longer. In other words, during this period none of the three drugs was as active as before the bolus injection of Lys-vasopressin. Lys-vasopressin has a very short biological half-life (less than 30 min; Lauson, 1967), so that this compound itself cannot be present at the time of the paradoxical water diuresis. The concentration of endogenous plasma Arg-vasopressin is extremely low. If one assumes that these three drugs act at the same receptor site as ADH, the observed paradoxical diuresis can be explained in the following way. All three drugs act at the receptor site either directly or by sensitizing it to small amounts of endogenous Arg-vasopressin, which are difficult to detect with present methods. Lys-vasopressin has a much higher affinity for the receptor sites than these three drugs and is a more potent antidiuretic agent. Because of the short half-life of the injected Lys-vasopressin its antidiuretic effect is transient. After a large single intravenous dose of Lys-vasopressin the receptor sites are flooded with ADH and any of the three drugs is replaced by ADH, resulting in a considerable increase in antidiuresis. The paradoxical diuresis which follows can then be explained by assuming that it takes some time before any of the three drugs again occupy a sufficient number of receptor sites and exert their maximal antidiuretic effect. This lag period is in accordance with the observation that the maximal antidiuresis was not obtained until several days after starting these drugs (Meinders et al., 1967).

When the majority of receptor sites have been
blocked by a constant infusion of a high concentration of Lys-vasopressin (125 munits/h) an intravenous bolus of Lys-vasopressin failed to produce a paradoxical diuresis after the transient initial antidiuresis. However, in a similar antidiuresis resulting from treatment with chlorpropamide and a low-dose constant infusion (2.37 munits/h) of Lys-vasopressin (patient no. 3), an intravenous bolus injection is followed by a paradoxical diuresis. Presumably the part of the antidiuresis that is induced by chlorpropamide is temporarily blocked.

References


