Antidiuretic effect of perorally administered DDAVP in hydrated humans

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Abstract. Urine volume and osmolality were measured in volunteers hydrated with drinking water (2% of body weight). During maintained water diuresis DDAVP (1-deamino-8-D-arginine vasopressin) dissolved in water was administered per os. Within 15-30 min a dose-dependent antidiuretic response occurred with a concomitant increase in urine osmolality. Administration of DDAVP through a duodenal tube caused similar antidiuretic effects indicating that the intact peptide can be absorbed from the intestinal mucosa.

Small peptide hormones and hormone analogues can be absorbed after buccal, sublingual or intranasal administration. Buccal application of oxytocin to pregnant women at term leads to initiation of uterine contractions concomitant with increased concentrations of oxytocin in plasma (Dawood et al. 1980). The long-acting analogue of vasopressin, 1-deamino-8-D-arginine vasopressin (DDAVP, desmopressin) is administered as an intranasal spray to patients with diabetes insipidus (Aronson et al. 1973; Seif et al. 1978), but is also active after sublingual application (Grossman et al. 1980; Laczi et al. 1980). Although these routes of administration are preferable to injections they are not without disadvantages. The prospect of delivering the peptides in a peroral form seems attractive, but has received little attention, probably because it is generally believed that peptides are completely degraded by the intestinal peptidases.

DDAVP dissolved in the drinking water leads to a reduction in urine production in diabetes insipidus rats (Dunn et al. 1978), however, this effect could be due to absorption of the peptide from the oral mucosa.

It has recently been demonstrated that vasopres-

sin and DDAVP given by gastric tube to anaesthe-
tized rats (Saffran et al. 1979) and to conscious dogs (Vilhardt & Bie 1983) cause an antidiuretic response. The doses of peptide used in these experiments were small (3–4 µg/kg body weight) which encouraged us to investigate the antidiuretic effect of perorally administered DDAVP in normal subjects.

Materials and Methods

Ten normal subjects of both sexes, aged 18–43 years, participated in the study. The purpose of the experiments was explained and written consent was obtained from each volunteer. The study was approved by the Ethical Committee of the Copenhagen Hospital District.

One to 2 h after a normal breakfast the volunteers were hydrated by drinking a volume of tap water corresponding to 2% of their body weight. From then on urine was sampled every 15 min for measurement of volume and osmolality (Advanced Osmometer Model 3DII). To ensure constant overhydration the volunteers currently replaced their fluid loss by drinking a volume of tap water corresponding to the amount of urine voided. After 30–45 min diuresis invariably increased to approximately 200 ml/15 min period at which time DDAVP was administered perorally in 50 ml of distilled water. DDAVP was provided by Ferring Pharmaceuticals (Malmö, Sweden) as a lyophilized powder readily soluble in water. Water diuresis was followed for up to 6 h.

In 2 volunteers a duodenal tube was introduced through the nose and under X-ray guidance the tip was placed in the distal part of the duodenum. Overhydration and urine sampling were then performed as described above.
Urine volumes of more than 200 ml/15 min were taken as an indication that endogenous secretion of vasopressin was suppressed and DDAVP (dissolved in 10 ml of water) was then injected through the tube.

Results

Fig. 1. shows the effect of 3 doses of DDAVP (20, 40 and 200 µg) on water diuresis and urine osmolality in human volunteers. Also shown is free water clearance. There is a dose-dependent effect both on the magnitude of the responses and on their duration.

DDAVP (200 µg) was administered in 2 volunteers through a tube directly into the lumen of the smaller intestine. In both cases a prompt antidiuretic response with a concomitant increase in urine concentration was observed (Fig. 2).

Apart from a slight feeling of abdominal distention in association with the initial overhydration no side effects were experienced.

Discussion

Intestinal absorption of di- and tripeptides has been demonstrated in man (Adibi & Morse 1971) indicating the existence of transport systems for peptides in the intestinal mucosa. Larger peptides like insulin are not absorbed in an intact form after
peroral administration. Absorption of insulin encapsulated into liposomes has been shown (Dapergolas & Gregoriadis 1976), but the bioavailability was very low.

We believe the present data constitute the first report of peroral administration of a peptide hormone leading to a distinct biological effect in man. The antidiuretic effect of DDAVP must be due to absorption of the intact molecule since any enzymatic cleavage of peptide bonds or the disulphide bridge in DDAVP invariably leads to biological inactivation.

Some DDAVP may have been absorbed from the mucosa of the mouth, the oesophagus or the stomach. However, the antidiuretic effect observed after injection of DDAVP through a duodenal tube shows that DDAVP can be absorbed from the small intestine.

The peroral doses of DDAVP used in the present study to provoke antidiuresis are larger than the amounts of DDAVP used intranasally in patients with diabetes insipidus to control their polyuria. The present data, however, indicate the possibility of treating patients with diabetes insipidus with special tablets containing potent analogues of vasopressin.

References


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