Pharmacokinetics, pharmacodynamics, long-term efficacy and safety of oral 1-deamino-8-D-arginine vasopressin in adult patients with central diabetes insipidus

K. S. L. LAM, M. S. WAT, K. L. CHOI, T. P. IP, R. W. C. PANG¹ & C. R. KUMANA

Department of Medicine and ¹Clinical Biochemistry Unit, The University of Hong Kong, Queen Mary Hospital, Hong Kong

- 1 The pharmacokinetics and pharmacodynamics of intranasal (IN) and oral 1-deamino-8-D-arginine vasopressin (DDAVP) were compared in 10 Chinese adults with central diabetes insipidus previously controlled on IN DDAVP. This was followed by comparison of the acute pharmacodynamics of commonly used oral preparations (containing 100, 200 and 400 µg per tablet) and a 1 year prospective evaluation of the long-term safety and efficacy of oral DDAVP.
- 2 Following 20 µg IN and 200 µg orally, respective plasma DDAVP concentrations peaked after 45.6 ± 7.3 and 93.3 ± 3.3 (mean $\pm$ s.e.mean) min, reaching 24.1 ± 4.7 and 15.1 ± 3.2 pmol l⁻¹ and respective terminal half-lives were 2.2 ± 0.1 and 2.0 ± 0.1 h. Based on the area under the concentration-time-curve, the bioequivalent IN/oral ratio was 1:16.
- 3 As judged by changes in urine flow rate and osmolality after IN or oral (100, 200 or 400 µg) DDAVP, antidiuretic activity increased rapidly during the second hour and peaked at 4 h. The antidiuresis duration and magnitude correlated with the oral dose ($P < 0.001$ and < 0.05 respectively), and was least following 100 µg ($P < 0.01$ vs 200 or 400 µg). Increasing the dose from 200 to 400 µg did not increase maximal antidiuretic activity significantly, but there was a trend towards a longer duration of action ($P = 0.076$).
- 4 During the 1-year prospective study with oral DDAVP 300–600 µg per day in two to three doses, stable and satisfactory antidiuresis (comparable with that on previous IN therapy) was maintained; tablets were well-tolerated and no side-effect warranted drug withdrawal.
- 5 These findings suggest that the 100 and 200 µg preparations of oral DDAVP are adequate for the long-term control of central diabetes insipidus in our population, and that the 400 µg preparation may have a role if the frequency of administration is to be reduced.

Keywords DDAVP pharmacokinetics pharmacodynamics intranasal oral diabetes insipidus

Introduction

The synthetic vasopressin analogue, 1-deamino-8-D-arginine (DDAVP) has been the standard treatment for central diabetes insipidus for over 20 years [1]. Although the commonly used intranasal (IN) preparations, employing the rhinyle or spray method [2] are highly

efficacious in most patients, there are situations when an oral preparation may be preferred, such as in young children and patients with nasal problems. Since 1983 it has been demonstrated that orally administered DDAVP can be absorbed from the gastrointestinal tract and result in a dose-dependent antidiuretic response in dogs and humans [3, 4]. DDAVP tablets have been

Correspondence: Dr Karen S. L. Lam, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Pokfulam Road, Hong Kong.

registered for clinical use in Sweden since 1987, but have only recently become more widely available. In children with central diabetes insipidus [5], the pharmacokinetics and pharmacodynamics of oral DDAVP have been well studied and its long-term efficacy and safety documented [6]. In adults, the pharmacokinetics and pharmacodynamics of oral *vs* IN DDAVP have only been studied in normal subjects [7]. Although in one study [8], similar pharmacokinetics were found in patients with central diabetes insipidus and normal subjects following the 200 µg oral dose, apparently the magnitude and duration of antidiuresis were dissimilar. Furthermore, in normal subjects or patients, there are no published data comparing the pharmacodynamics of all three commonly used oral DDAVP preparations (containing 100, 200 and 400 µg). In adults, moreover, there is very little information on the long-term safety of oral DDAVP; one case report involved only three patients followed for up to 45 months [9] and another described eight patients whose mean follow up was only 5 months [10].

We report here the pharmacokinetics and acute dose-dependent antidiuretic effects of IN and oral DDAVP in patients with central diabetes insipidus as well as a prospective study of the long-term efficacy, dosage requirement and safety of oral DDAVP.

Methods

Ten Chinese adults with central diabetes insipidus, aged 36.4 ± 6.7 years (mean $\pm$ s.d.) and weighing 63.9 ± 11.1 kg, whose clinical data are summarized in Table 1, participated in the study. All had satisfactory control of their disease on IN DDAVP (Ferring Pharmaceuticals, Malmö, Sweden) for at least 1 year prior to the study, eight of them using the rhinyle and two, the nasal spray. All were studied after written informed consent and according to a protocol approved by the Ethics Committee of the University of Hong Kong.

Study protocol

One week prior to hospitalization for this study, patients were asked to record their daily urine output on at least 2 days of maintenance therapy with IN DDAVP and random plasma and urine osmolalities were checked. The subsequent follow up was divided into acute and chronic phases. For the acute phase, all patients were hospitalized in the Metabolic Ward for 1 week (starting on Day 0), during which they were studied according to a fixed schedule as described in Table 2. Maintenance IN DDAVP was stopped 24 h prior to Day 1 and no DDAVP was administered on Day 2. On Days 1 and 3, the pharmacokinetics and antidiuretic activity (as represented by changes in urine flow rate and osmolality) of a single dose of IN and oral (tablet form) DDAVP 20 µg and 200 µg respectively, were studied. From Days 4 to 6, a dose-ranging study was carried out using single oral tablets of DDAVP 100, 200 and 400 µg respectively — in order to determine the minimum dose at which adequate antidiuresis could be achieved for approximately 8 h.

On Days 1 and 3, 5 ml blood samples were collected in vacutainer tubes containing potassium EDTA before and at 20, 40, 60, 90, 120, 180, 240, 360 and 480 min after DDAVP administration. The samples were centrifuged, freshly separated and the plasma stored at -70°C for later analysis of the DDAVP concentration. Hourly urine output, urine and plasma osmolalities were measured before and at 1, 2, 4, 6 and 8 h after DDAVP administration. In addition, on Days 4 to 6, urine osmolality was also measured at 12 h and urine output was recorded 4 hourly up to 24 h. Plasma osmolality was measured before and at 4 h only. Each patient was discharged from hospital on Day 7 taking a dose of oral DDAVP (2–3 times/day) depending on the results of the dose-ranging study.

During the chronic phase (outpatient follow-up), patients were asked to record daily body weight and chart their fluid intake and urine output on at least 2 days per week for the first 4 weeks. Unless otherwise

Table 1 Clinical data and dosages of IN/oral DDAVP (2–3 times daily) of 10 adult patients with central diabetes insipidus (DI)

Patients	Sex/Age (years)	Weight (kg)	IN DDAVP (µg)	Oral DDAVP (µg)	Diagnosis	Other medication
1	M/38	78.7	5/7.5	200/200/200	Idiopathic	
2	M/35	77.4	10/10	200/200/200	Post-traumatic	
3	M/46	55.8	10/10	200/200	Idiopathic	
4	M/34	76.9	10/10/7.5	200/200/200	Idiopathic	
5	F/37	70.9	3.75/3.75	200/200/200	Pituitary tumour	Cortisol
6	F/39	52.2	10/10	200/100/200	Rathke's pouch cyst	Premarin and medroxy-progesterone
7	F/40	60.0	10/10/10	100/200/200	Idiopathic	
8	F/40	56.8	7.5/7.5	200/200/100	Septooptic dysplasia	
9	M/40	60.5	7.5/7.5/10	200/200/200	Idiopathic	
10	M/19	49.7	2.5/2.5	100/100/100	Idiopathic	

Table 2 Acute phase study protocol

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
DDAVP (μg)	0	20 IN	0	200 oral	100 oral	200 oral	400 oral
Pharmacokinetics	—	+	—	+	—	—	—
Pharmacodynamics	—	+	—	+	+	+	+
Fluid intake and output over 24h	+	+	+	+	+	+	+

+, measured; —, not measured.

indicated, complete blood counts, plasma electrolytes, renal and liver function tests, as well as plasma and urine osmolalities were checked and dosage adjustments made as necessary at weekly intervals for 4 weeks and at 3 monthly intervals thereafter. Patients were asked to record their 24-h urine output on one day shortly before each 3 month clinic visit.

Assays

Plasma samples for DDAVP assay were transported in dry ice from Hong Kong to Sweden and the concentrations measured by radioimmunoassay at the laboratory of Ferring Pharmaceuticals, using a modification of the method described by Lundin *et al.* [11]. The samples were extracted with acetone/petroleum ether prior to analyses; the recovery of DDAVP after extraction being 97.7% and 98.9% at 5 and 10 pmol l^{-1} respectively. Monoiodinated DDAVP was prepared by the chloramine-T method and immediately purified by reversed phase chromatography. The antiserum employed was developed according to the method of Sofroniew *et al.* [12] and showed 0.03% cross-reactivity with AVP. The minimum quantifiable concentration of the assay was 2.34 pmol l^{-1} . All samples of each patient were included in the same assay. Mean intra- and inter-assay coefficients of variation were 7.4% and 12.4% respectively.

Plasma and urine osmolalities were determined by freezing point depression using the Advanced Micro-Osmometer (Advanced Instruments, Inc., Massachusetts, USA). Plasma electrolytes, renal and liver function tests (urea, creatinine, liver enzymes, albumin and bilirubin levels) were measured on the Ektachem 500 analyser using the dry-film chemistry technology from Kodak (Eastman Kodak, Rochester, New York, USA).

Pharmacokinetic calculations and statistical analysis

After corresponding treatments in each patient, the maximum DDAVP concentration (C_{max}) encountered and the time at which this occurred (t_{max}) were recorded. The area under the DDAVP time/concentration curve (AUC) between 0 and 8 h was calculated by the linear trapezoidal rule. Respective individual values for the first order elimination rate constant (λ_z) and the elimination half-life ($t_{1/2}$) were computed, assuming first order decay after the highest plasma DDAVP concentration encountered. The latter assumption appeared justified by the extremely high regression values (range

0.85–0.99) for the corresponding log concentration/time plots. An HP calculator and 'curve fitting' standard pack programme SD-O3A were used for the calculation.

Statistical analysis was performed using two-way analysis of variance and Student's two-tailed paired *t*-test after the data were ascertained to be normally distributed using the Lilliefors test. Wilcoxon matched pair signed-rank test was used to compare the duration of antidiuresis, which was not normally distributed. Pearson's correlation analysis was employed for assessing the relationship between DDAVP dose and effects. The level of significance was set at $P < 0.05$.

Results

Pharmacokinetics of DDAVP

The plasma concentrations of DDAVP at various intervals after DDAVP 20 μg IN or 200 μg oral are shown in Figure 1a. Plasma DDAVP concentration was undetectable (< 2.34 pmol l^{-1}) in all patients before DDAVP administration. It became detectable in all patients 20 and 20–60 min respectively following IN and oral administration. The C_{max} and t_{max} for the two DDAVP preparations are summarized in Table 3. The mean elimination half-life ($t_{1/2,z}$) was 2.2 h and 2.0 h after IN and oral administration respectively. Assuming first order absorption and elimination, the mean calculated equidose IN/oral AUC ratio was 1:16.

Patient 8 had plasma DDAVP levels comparable with those of the other patients following IN DDAVP, but following oral DDAVP on Day 3, plasma DDAVP was undetectable except at 3 and 4 h post dosing, when levels of 11.2 pmol l^{-1} and 8.6 pmol l^{-1} were encountered. Her urine osmolality at 2 h was only 93 mosm kg^{-1} but on Day 5, (despite similar baseline values), it was 607 mosm kg^{-1} within 2 h of taking a similar dose. This suggested possible erratic and inconsistent absorption on Day 3 which was probably not representative of her usual response to oral DDAVP—as attested to by her much better antidiuretic responses on days 4–6. Thus, her data were excluded from the pharmacokinetic analysis.

Antidiuretic responses to IN and oral DDAVP

Acute studies On Day 0 and Day 2, when no DDAVP was administered, diuresis of similar magnitude was observed. Mean urine flow rate was 401 ± 46

Figure 1 (a) Plasma DDAVP concentrations ($n=9$), b) urine osmolality and c) urine flow rate at varying intervals after the administration of IN or oral DDAVP in 10 adult patients with central diabetes insipidus. Data are mean $\pm$ s.e.mean. (—●—) 20 μ g IN, (—▲—) 100 μ g oral, (—■—) 200 μ g oral, (—◆—) 400 μ g oral DDAVP.

(mean $\pm$ s.e.mean) and 425 ± 52 ml h⁻¹ for Day 0 and Day 2 respectively ($P=0.73$).

As shown in Figure 1b and 1c, following all doses of DDAVP (IN or oral), urine osmolality increased and flow rate decreased rapidly during the second hour,

with maximal antidiuretic activity being achieved 4 h after administration.

Urine osmolality and urine flow rate (Figure 1b and c) at each time point following IN (Day 1) or oral (Day 4–6) DDAVP administration were compared. No significant difference in urine osmolality (Figure 1b) was found between the four dosage forms until 4 h after administration, when a higher osmolality was achieved with IN 20 μ g ($P<0.05$ vs all oral doses). From 4 to 8 h after drug administration, urine osmolality was lower with the 100 μ g oral dose than with all other doses ($P<0.005$) but the corresponding differences associated with the other three dosage forms were neither clinically nor statistically significant. For the difference in mean urine osmolality between the 200 and 400 μ g doses, 95% confidence intervals were (–32.2, 49.2), (–98.2, 45.0) and (–244.2, 30.2) at 4, 6 and 8 h respectively ($P>0.1$ for the difference at all three time points). Converse changes in urine flow rate (Figure 1c) were also evident. From 4 to 8 h, the effect was smaller with the 100 μ g oral dose than with the other dosage forms ($P<0.005$), but there were no clinically or statistically significant differences between corresponding changes in urine flow following the 20 μ g IN, and 200 and 400 μ g oral doses. For the difference in mean urine flow rate between the 200 and 400 μ g doses, 95% confidence intervals were (–6.72, 9.32), (–7.04, 8.04) and (–9.65, 58.45) at 4, 6 and 8 h respectively ($P>0.1$ at all 3 time points).

Changes in urine osmolality (up to 12 h) and urine flow rate (up to 24 h) indicated a dose-dependent antidiuretic response to oral DDAVP (Table 4). There was a positive correlation between oral DDAVP dose and the duration of antidiuresis, defined as the total duration of having either a urine osmolality ≥ 400 mosm kg⁻¹ or a urine flow rate ≤ 100 ml h⁻¹ ($P<0.001$, $n=30$, $r=0.64$ and $r=0.62$ respectively). There was a weak positive correlation between maximum urine osmolality and DDAVP dose ($r=0.362$, $P<0.05$). However, increasing the dosage from 200 μ g to 400 μ g did not result in any statistically significant increase in maximum urine osmolality ($P=0.37$), although a trend towards an increased duration of action was present ($P=0.076$ for the duration of urine flow rate ≤ 100 ml h⁻¹).

Long-term follow-up study The dosage requirement of oral DDAVP during the 1 year study is shown in Table 1. The mean daily dose was 18.3 ± 8.3 μ g (mean $\pm$ s.d.) and 520 ± 103 μ g for IN and oral DDAVP respectively. No significant correlation ($r=0.339$) was

Table 3 Pharmacokinetics of DDAVP in Chinese adults with central diabetes insipidus

	$t_{1/2,z}$ (h)	AUC (pmol l ⁻¹ h)	C_{max} (pmol l ⁻¹)	t_{max} (min)
IN 20 μ g	2.2 ± 0.1	74.7 ± 15.0	24.1 ± 4.7	40 (20–90)
Oral 200 μ g	2.0 ± 0.1	47.0 ± 11.6^a	15.1 ± 3.2	90 (90–120)

Data are mean $\pm$ s.e.mean except for t_{max} which is median (range); $n=9$; a, 45.6 ± 10.5 if patient 8 included (see Results section).

Table 4 Dose-dependent antidiuretic responses (mean $\pm$ s.e.mean, $n = 10$) to single daily dose of oral DDAVP

DDAVP dose	Maximum urine osmolality (mosm kg ⁻¹)	Duration of antidiuresis (h)	
		Urine osmolality ≥ 400 mosm kg ⁻¹	Urine flow rate ≤ 100 ml h ⁻¹
100 μ g	621 $\pm$ 23	4.8 $\pm$ 0.5	5.0 $\pm$ 0.5
200 μ g	691 $\pm$ 27 ^a	7.8 $\pm$ 0.9 ^c	8.0 $\pm$ 0.7 ^c
400 μ g	703 $\pm$ 34 ^b	9.6 $\pm$ 0.9 ^b	10.6 $\pm$ 1.4 ^c

a, $P < 0.005$, b, $P < 0.01$, c, $P < 0.05$, vs 100 μ g.

Table 5 Plasma and urine osmolalities and urine flow rate (mean $\pm$ s.e.mean, $n = 10$) on long-term IN and oral DDAVP

	Previous IN DDAVP	1 month	Oral DDAVP 6 months	12 months
Plasma osmolality (mosm kg ⁻¹)	292 $\pm$ 2	290 $\pm$ 2	293 $\pm$ 2	290 $\pm$ 1
Urine osmolality (mosm kg ⁻¹)	548 $\pm$ 9	684 $\pm$ 70	668 $\pm$ 83	720 $\pm$ 85
Urine flow rate (ml h ⁻¹)	128 $\pm$ 26	71 $\pm$ 6 ^a	—	—

a, $P < 0.05$ vs IN DDAVP.

found between the IN and oral doses required. As shown in Table 5, satisfactory plasma and urine osmolalities were maintained throughout the study period, without any need for dosage adjustment after the first month. Compared with findings on IN DDAVP, plasma and urine osmolalities showed no significant difference after the change to oral DDAVP therapy, whereas there was a lower urine flow rate after 1 month ($P < 0.05$).

Side-effects and laboratory safety profile

The tablets were well tolerated and all patients preferred to continue on oral DDAVP after completion of the study. No significant changes in complete blood count, plasma creatinine and electrolytes were observed. A transient asymptomatic increase in plasma aspartate aminotransferase (AST) to $\geq$ two times the upper normal range (33 iu l⁻¹ for men and 28 iu l⁻¹ for women), which reverted to baseline levels despite continuation of oral DDAVP, was noted in patients 1 and 8 (Table 1). Both had pre-existing elevated AST values. In patient 1, plasma AST levels at baseline, 1 week (peak level), 2 weeks and 1 year were 62, 99, 47 and 46 iu l⁻¹ respectively. In patient 8, plasma AST levels at baseline, 4 weeks (peak level), 8 weeks and 1 year were 30, 59, 29 and 23 iu l⁻¹ respectively. No other change in liver function test was observed. Both were non-drinkers and had no serological markers of active or chronic hepatitis A, B or C.

Discussion

Oral DDAVP was well absorbed in our patients resulting in maximum plasma DDAVP levels one and a half hours after drug administration, in agreement with published data in healthy adults [7, 8]. There were considerable individual variations in pharmacokinetics,

and the findings in patient 8 also suggest day to day variations in absorption in the same individual. Large individual variations in the absorption of DDAVP following oral administration have also been observed in children with central diabetes insipidus [5]. The mean plasma half-life of 120 min was similar to the figure of 126 min reported in a British study [8]. The oral/IN AUC ratio was calculated to be 1:16, somewhat less than the ratio of 1:25 reported for normal adults in Sweden [7]. In that study, mean AUCs for IN and more especially for oral DDAVP were smaller than the corresponding values in our patients, even after crude corrections for mean body weights. Furthermore, after taking 200 μ g orally, plasma DDAVP concentration became detectable in all nine of our patients but remained undetectable in two of the eight subjects. As to whether these findings suggest real inter-ethnic difference in pharmacokinetics due to better gastrointestinal absorption of DDAVP in Chinese or other factors remains unclear. Whereas, such differences have been reported with other drugs [13], this study did not involve prospective comparison with Caucasian patients, the sample size was small and there was considerable interindividual variation. Orally, our patients appeared to need smaller multiples of their respective IN DDAVP dosages (17–80; mean 40) than reported for Italian patients (40–60) [9] but larger than those recorded in a British study (7.5–30; mean 15) [10].

This is the first report (a) comparing the pharmacodynamics of 100, 200 and 400 μ g, the three commonly used oral doses in patients with central diabetes insipidus and (b) detailing the pharmacodynamics of 400 μ g oral doses of DDAVP in adults. The doses were chosen according to previous clinical experience which suggested that both in adults [10] and children [14, 15] to obtain adequate therapeutic effects usually requires 100 μ g or more. The duration of antidiuresis and to a lesser extent, the maximum urine osmolality were shown to be dose dependent. The duration of antidiuretic activity following 100 μ g was significantly shorter than

after the two higher doses, although the maximum urine osmolality was only slightly lower. There was no clinically significant improvement in the magnitude of antidiuresis when the dose was increased from 200 to 400 µg. However, the trend towards an increased duration of action with the 400 µg preparation may be of clinical relevance if the patient wishes to decrease the frequency of administration. The rapid rise in urine osmolality in the second hour after the 200 µg dose correlated well with the rise in plasma DDAVP level. Although the DDAVP AUC after 20 µg IN was almost twice that following 200 µg orally, the maximum mean urine osmolality at 4 h was only marginally higher, and there was no statistically significant difference in respective mean urine flow rates for up to 8 h.

Most Chinese patients with central diabetes insipidus can attain adequate antidiuresis with IN DDAVP dosages of not more than 10 µg every 8 h. Considering the 16-fold greater bioavailability (AUC) via the latter route, it may be surmised that substitution with 200 µg oral doses should suffice. Figure 1 actually confirms that a single oral dose of 200 µg produces a sustained discernible effect lasting at least 8 h. It also illustrates that there is a time lag of about 2 h between the measured acute response and the administration of IN or oral DDAVP.

The acute antidiuretic responses to the different doses of oral DDAVP correlated very well with the observation on long-term follow-up. None of the patients required more than 200 µg three times per day while the 100 µg oral dose provided adequate antidiuresis up to 8 h in only four patients. Such dosage requirements appear to be less variable and much lower (especially when corrected for body weight) than those reported from a long-term study in Caucasian children [6]. In the latter, the maximum total daily doses were as high as 1700 µg (900 µg in the evening). This difference in dosage requirement is not readily explained by the pharmacokinetic data [5] and may be related to the necessity in children of increasing the evening dose to ensure a satisfactory antidiuresis during sleep, their higher metabolic rates (surface area/mass ratios), and the severity of their diabetic insipidus. In agreement with a 5 month follow-up study in Caucasian patients [10], there was no significant correlation between the oral and IN dosage requirements of individual patients.

DDAVP tablets were well tolerated and provided satisfactory long-term disease control comparable with that of previous IN therapy. They achieved better patient compliance and were preferred by all patients. This may account for the more satisfactory control of urine output 1 month after changing to oral DDAVP. In the first month after changing to oral therapy increasing plasma AST levels were observed in two patients with pre-existing abnormal values, but there were no associated symptoms. Whether the transient increases in their plasma AST could be related to the higher DDAVP dosage administered and a possible increase in DDAVP concentration reaching the liver following absorption into the portal circulation remains speculative. Whereas such increases in AST have not been described previously in other prospective

studies [6, 10], there have been isolated case reports [16].

In conclusion, for the long-term treatment of adult patients with central diabetes insipidus, we have found oral DDAVP to be a safe and efficacious alternative to IN preparations and is preferred by the end-user. It is clearly advantageous in patients who have difficulty with the inhalation therapy, such as those at the extremes of age, the mentally or physically handicapped, those with chronic allergic rhinitis and patients with nasal packing following transsphenoidal surgery. Furthermore, as the tablets are stable at room temperature while the IN solution requires refrigeration, oral therapy may be preferred in places with hot climate like Hong Kong. Most adult patients with central diabetes insipidus can be satisfactorily controlled on 300 to 600 µg per day (in two to three divided doses). In view of the large individual variations in pharmacokinetics and the lack of correlation between the oral and IN dose requirement, weekly outpatient dosage adjustment according to plasma and urine osmolalities and home monitoring of urine output is recommended during the first month of oral therapy with DDAVP.

We thank the nurses of the Metabolic Ward, Queen Mary Hospital for clinical assistance, Ms Catarina Larsson and Anja Broeders for the measurement of plasma DDAVP concentration, Ferring Pharmaceuticals for providing the oral DDAVP tablets, Ms Maybelle Kou and Mr Stanley Yeung for assistance with data processing, and Ms Venus Yuen for secretarial support.

References

- Andersson KE, Arner B. Effects of DDAVP, a synthetic analogue of vasopressin, in patients with cranial diabetes insipidus. *Acta Med Scand* 1972; **192**: 21–27.
- Grossman A, Fabri A, Goldberg PL, Besser GM. Two new modes of desmopressin (DDAVP) administration. *Br Med J* 1980; **280**: 1215.
- Vilhardt H, Bie P. Antidiuretic response in conscious dogs following peroral administration of arginine vasopressin and its analogues. *Eur J Pharmacol* 1983; **93**: 201–204.
- Vilhardt H, Bie P. Antidiuretic effect of perorally administered DDAVP in hydrated humans. *Acta Endocrinol* 1984; **105**: 474–478.
- Fjellestad-Paulsen A, Tubiana-Rufi N, Harris A, Czernichow P. Central diabetes insipidus in children. Antidiuretic effect and pharmacokinetics of intranasal and peroral 1-deamino-8-D-arginine vasopressin. *Acta Endocrinol* 1987; **115**: 307–312.
- Fjellestad-Paulsen A, Laborde K, Kindermans C, Czernichow P. Water-balance hormones during long-term follow-up of oral DDAVP treatment in diabetes insipidus. *Acta Paediatr* 1993; **82**: 752–757.
- Fjellestad-Paulsen A, Hoglund P, Lundin S, Paulsen O. Pharmacokinetics of 1-deamino-8-D-arginine vasopressin after various routes of administration in healthy volunteers. *Clin Endocrinol* 1993; **38**: 177–182.
- Williams TDM, Dunger DB, Lyon CC, Lewis RJ, Taylor F, Lightman SL. Antidiuretic effect and pharmacokinetics of oral 1-desamino-8-D-arginine vasopressin. 1. Studies in adults and children. *J Clin Endocrinol Metab* 1986; **63**: 129–132.

- 9 Carraro A, Fano M, Cuttica M, Bernareggi V, Giusti M, Giordano G. Long-term treatment of central diabetes insipidus with oral DDAVP. *Minerva Endocrinol* 1992; **17**: 189–193.
- 10 Cunnah D, Ross G, Besser GM. Management of cranial diabetes insipidus with oral desmopressin (DDAVP). *Clin Endocrinol* 1986; **24**: 253–257.
- 11 Lundin S, Melin P, Vilhardt H. Plasma concentrations of 1-deamino-8-D-arginine vasopressin after intragastric administration in the rat. *Acta Endocrinol* 1985; **108**: 179–183.
- 12 Sofroniew MW, Madler M, Muller OH, Scriba PC, Fresenius Z. A method for the consistent production of high quality antisera to small peptide hormones. *Anal Chem* 1978; **290**: 163.
- 13 Kumana CR, Lauder IJ, Chan M, Ko W, Lin HJ. Differences in diazepam pharmacokinetics in Chinese and white Caucasians-relation to body lipid stores. *Eur J Clin Pharmacol* 1987; **32**: 211–215.
- 14 Westgren U, Wittstrom C, Harris AS. Oral desmopressin in central diabetes insipidus. *Arch Dis Child* 1986; **61**: 247–250.
- 15 Fjellestad A, Czernichow P. Central diabetes insipidus in children. V. Oral treatment with a vasopressin hormone analogue (DDAVP). *Acta Paediatr Scand* 1986; **75**: 605–610.
- 16 Gelli D, Riolo A, Carioni E, Albano M. Clinical evaluation of 2 new formulations of desmopressin (DDAVP), spray and tablets in the therapy of diabetes insipidus. *Minerva Endocrinol* 1989; **14**: 227–232.

(Received 17 October 1995,
accepted 13 March 1996)