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

Department of Medicine and Clinical 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 ± 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 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 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 used in Europe since 1983 and in the USA since 1990. However, the results of this study suggest 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 used in Europe since 1983 and in the USA since 1990. However, the results of this study suggest that the 400 µg preparation may have a role if the frequency of administration is to be reduced.

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

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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 ± 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, as described in Table 1. 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, 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 described in Table 1, each patient was followed up to 45 months [10].

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

<table>
<thead>
<tr>
<th>Patients</th>
<th>Sex/Age (years)</th>
<th>Weight (kg)</th>
<th>IN DDAVP (μg)</th>
<th>Oral DDAVP (μg)</th>
<th>Diagnosis</th>
<th>Other medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 M/38</td>
<td>78.7</td>
<td>5/7.5</td>
<td>200/200/200</td>
<td>Idiopathic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 M/35</td>
<td>77.4</td>
<td>10/10</td>
<td>200/200/200</td>
<td>Post-traumatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 M/46</td>
<td>55.8</td>
<td>30/10</td>
<td>200/200/200</td>
<td>Idiopathic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 M/34</td>
<td>76.9</td>
<td>30/10/7.5</td>
<td>200/200/200</td>
<td>Idiopathic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 F/37</td>
<td>70.9</td>
<td>3.75/3.75</td>
<td>200/200/200</td>
<td>Pituitary tumour</td>
<td>Cortisol</td>
<td></td>
</tr>
<tr>
<td>6 F/39</td>
<td>52.2</td>
<td>30/10</td>
<td>200/100/200</td>
<td>Rathke's pouch cyst</td>
<td>Premarin and medroxy-progesterone</td>
<td></td>
</tr>
<tr>
<td>7 F/40</td>
<td>60.0</td>
<td>10/10/10</td>
<td>100/200/200</td>
<td>Idiopathic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 F/40</td>
<td>56.8</td>
<td>7.5/7.5</td>
<td>200/200/100</td>
<td>Septooptic dysplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 M/40</td>
<td>60.5</td>
<td>7.5/7.5/10</td>
<td>200/200/200</td>
<td>Idiopathic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 M/19</td>
<td>49.7</td>
<td>2.5/2.5</td>
<td>100/100/100</td>
<td>Idiopathic</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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 shown in Figure 1a. Plasma DDAVP concentration was determined equidose IN/oral AUC ratio was 1.6.

**Pharmacokinetic calculations and statistical analysis**

After corresponding treatments in each patient, the maximum DDAVP concentration ($C_{\text{max}}$) encountered and the time at which this occurred ($t_{\text{max}}$) 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 ($k_z$) and the elimination half-life ($t_{1/2,z}$) 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.

**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 $C_{\text{max}}$ and $t_{\text{max}}$ 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.

**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
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 μg (P < 0.05 vs all oral doses). From 4 to 8 h after drug administration, urine osmolality was lower with the 100 μg 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 μg 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 times points).

Converse changes in urine flow rate (Figure 1c) were also evident. From 4 to 8 h, the effect was smaller with the 100 μg 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 μg IN, and 200 and 400 μg oral doses. For the difference in mean urine flow rate between the 200 and 400 μg 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 μg to 400 μg 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 ± 2.2 μg oral, (–0.1 47.0 ± 0.1 74.7 (20–90)

<table>
<thead>
<tr>
<th></th>
<th>tmax (h)</th>
<th>AUC (pmol l⁻¹ h)</th>
<th>Cmax (pmol l⁻¹)</th>
<th>t½ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IN 20 μg</td>
<td>2.7 ± 0.1</td>
<td>47.0 ± 15.0</td>
<td>24.1 ± 4.7</td>
<td>40 (20–90)</td>
</tr>
<tr>
<td>Oral 200 μg</td>
<td>2.0 ± 0.1</td>
<td>47.0 ± 11.6</td>
<td>15.1 ± 3.2</td>
<td>90 (90–120)</td>
</tr>
</tbody>
</table>

Data are mean ± s.e.mean except for t½ which is median (range). n = 9, a, 45.6 ± 10.5 if patient 8 included (see Results section).
found between the IN and oral doses required. As shown in Table 5, satisfactory plasma and urine osmolal-
ities 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 >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 oral DDAVP

<p>| Table 4 Dose-dependent antidiuretic responses (mean±s.e.mean, n=10) to single daily dose of oral DDAVP |</p>
<table>
<thead>
<tr>
<th>DDAVP dose</th>
<th>Maximum urine osmolality (mosm kg⁻¹)</th>
<th>Duration of antidiuresis (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urine osmolality</td>
<td>Urine flow rate</td>
</tr>
<tr>
<td></td>
<td>≥400 mosm kg⁻¹</td>
<td>≤100 ml h⁻¹</td>
</tr>
<tr>
<td>100 µg</td>
<td>621±23</td>
<td>4.8±0.5</td>
</tr>
<tr>
<td>200 µg</td>
<td>691±27*</td>
<td>7.8±0.6*</td>
</tr>
<tr>
<td>400 µg</td>
<td>703±34*</td>
<td>9.6±0.8*</td>
</tr>
</tbody>
</table>

* a, P<0.005; b, P<0.01; c, P<0.05, vs 100 µg.

<table>
<thead>
<tr>
<th>Table 5 Plasma and urine osmolalities and urine flow rate (mean±s.e.mean, n=10) on long-term IN and oral DDAVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous IN DDAVP</td>
</tr>
<tr>
<td>Plasma osmolality (mosm kg⁻¹)</td>
</tr>
<tr>
<td>Urine osmolality (mosm kg⁻¹)</td>
</tr>
<tr>
<td>Urine flow rate (ml h⁻¹)</td>
</tr>
</tbody>
</table>

a, P<0.05 vs IN DDAVP.

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 according to plasma and urine osmolalities and home monitoring of urine output 1 month after changing to oral DDAVP. 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
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