Management of early postoperative diabetes insipidus with parenteral desmopressin

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Abstract. Management of early postneurosurgical diabetes insipidus (DI) requires parenteral vasopressin before intranasal administration of desmopressin-1 desamino-8 D arginine vasopressin (dDAVP) can be initiated. We have evaluated 15 neurosurgical patients the effect and the tolerance of a 3-day regimen of dDAVP administered im every 12 h. Patients were randomly ascribed to one of 3 treatment groups: 1 µg (N = 6), 2 µg (N = 5) or 4 µg (N = 4) were administered twice daily. dDAVP was effective whatever the dose, and DI was corrected by the 6th h of treatment. Effects were maximal on diuresis and urinary osmolality from the 18th h onwards. The effects were sustained throughout the treatment period. Reversal to pretreatment status occurred 24 h after the last injection. Moreover, 72 h after the last injection, natremia and osmolality reached values significantly below pretherapeutic values. The tolerance was excellent: hyponatremia which occurred in 11 patients, either occasionally or throughout the treatment period, remained mild and never had clinical consequences. In conclusion, before initiation of intranasal dDAVP, a 3-day treatment by 1, 2 or 4 µg of dDAVP injected im twice daily in neurosurgical patients corrected DI. Mild overhydration owing to a positive fluid balance was a side-effect which is also encountered in other therapeutic methods necessitating meticulous control of water intake.

Treatent of chronic diabetes insipidus (DI) with desmopressin-1 desamino-8 D arginine vasopressin (dDAVP), the synthetic analogue of natural vasopressin is now routine (Verbalis et al. 1985). Given intranasally the duration of action is from 6 to 24 h (Robinson 1976; Edwards et al. 1973). However, in the treatment of acute DI following transphenoidal surgery, intranasal dDAVP can irritate injured nasal mucosa and its absorption may be impaired by surgical dressing and/or nasogastric or nasotracheal tubes. In this early postoperative period the alternative is parenteral vasopressin administration. Unfortunately sc injections (aqueous vasopressin or tannate-in-oil) have only a brief duration of action (Cobb 1980; Shucart & Jackson 1976) and the subsequent resumption of polyuria can induce dehydration if fluid replacement is delayed (Loirat et al. 1981). Intravenous continuous administration of ultralow doses of vasopressin (pituitrin or vasopressin) by a syringe-pump has recently been proposed to regulate urinary output (Chanson et al. 1987). Intramuscular dDAVP has a sustained action (Edwards et al. 1973) and also produces a regular urinary output.

We have evaluated in 15 postneurosurgical patients the effect and the tolerance of a 3-day treatment with dDAVP administered im every 12 h at a dose of 1, 2 or 4 µg. The treatment was deliberately pursued 3 days for two reasons: firstly, this is the average duration of treatment required in the immediate postoperative period before intranasal administration can be initiated; secondly, it corresponds to the initial phase of triphasic postoperative DI (Verbalis et al. 1985).
Patients and Methods

Fifteen neurosurgical patients (4 men and 11 women, aged 13 to 54 years) presenting with postoperative DI were studied. All had operations on the hypothalamus or on the hypophysis: 2 had prolactinomas, 3 had a non-secreting adenoma, 4 were explored for Cushing's disease, 5 had cranipharyngioma, and one had a chiasma glioma. Diagnosis of postoperative DI was established on three deliberately simplified criteria: urinary output above 100 ml/h, specific gravity below 1.005, and natremia above 142 mmol/l, demonstrating hypotonic polyuria inappropriate to serum osmolality. In one case DI was present preoperatively. In the remaining patients DI occurred 11 to 48 h after operation by transphenoidal (N = 8) or transfrontal (N = 7) approach. Once the diagnosis of DI was established, the patient was randomly ascribed to one of the treatment groups and received an im injection of 1 µg (N = 6), 2 µg (N = 5) or 4 µg (N = 4) of DDAVP every 12 h for 3 days. DDAVP is available in 2-ml vials of 4 µg for parenteral injection (Ferring Pharmaceuticals, Malmö, Sweden). Treatment efficacy was estimated by monitoring water input, urinary volume, specific gravity and osmolality, serum electrolytes and osmolality every 6 h until 36 h after the last injection. Once daily body weight and plasma creatinine were recorded. Blood pressure was measured six-hourly.

Results are expressed as the mean ± SEM. Level of statistical significance as determined by Wilcoxon's non-parametric test was P ≤ 0.05.

Results

The drug corrected DI at the doses of 1, 2 or 4 µg every 12 h. Data obtained from the 2 µg treatment (N = 5) group are shown in Fig. 1. Diuresis dropped to about one tenth of its previous value (1725 ± 491 to 143 ± 87 ml/6 h), specific gravity and urinary osmolality increased from 1.002 to 1.019 and from 126 ± 45 to 589 ± 55 mosmol/kg H2O, respectively. Effects on diuresis (disappearance of polyuria with urine output less than 600 ml/6 h) were obtained by the 6th h of treatment and were maximal (132 ml/6 h ± 85) from the 12th h onwards. The mean specific gravity and urinary osmolality rose by the 6th h to, respectively, 1.008 and 340 ± 96 mosmol/kg H2O. Because the reduction of water intake was delayed, natremia and plasmatic osmolality decreased by the 6th h of treatment from 145.2 ± 1.1 mmol/l and 288.0 ± 3.5 mosmol/kg H2O to 141.7 ± 1.25 mmol/l and 280.4 ± 2.4 mosmol/kg H2O, respectively, but reached the minimal values at the 12th h. The effect was sustained during the 3 days of treatment: diuresis, urinary osmolality and specific gravity did not change significantly from the 18th h onwards. Likewise, natremia and plasmatic osmolality remained stable. Polyuria reappeared 18 h after treatment was stopped; the reversal to pretreatment status (diuresis = 1284 ± 342 ml/6 h, urinary osmolality = 199 ± 94.8 mosmol/kg H2O, specific gravity = 1.004) occurred by the 24th h. Natremia and serum osmolality began to increase between the 18th h and the 24th h, but 72 h after the last injection they reached values which were significantly below pretherapeutic values (respectively 142.5 ± 1.9 mmol/l and 278.2 ± 9.4 mosmol/kg H2O). Results obtained in the 1 µg (N = 6) or in the 4 µg group (N = 4) were not statistically different from those observed after 2 µg injections.

Four patients, after complete improvement, experienced transient resumption of polyuria and urinary hypo-osmolality during the 1 µg (N = 3) or 2 µg (N = 1) treatment period. This never occurred with the 4 µg dosage. Hyponatremia (< 135 mmol/l) occurred in 11 patients, either occasionally (in 1 patient receiving 4 µg/12 h and in 2 patients receiving 1 µg/12 h) or throughout the treatment period (in 3 patients receiving 4 µg/12 h, in 2 patients receiving 2 µg/12 h and in 3 patients receiving 1 µg/12 h). Hyponatremia never caused clinical symptoms. No pressor effects nor renal functional alterations were noted.

Discussion

Two types of hormonal treatment of early DI following hypothalamic or pituitary surgery can be used. Intranasal DDAVP can be administered when nasal passages are free. If parenteral administration is necessary, vasopressin can be injected sc (Cobb 1980; Shucart & Jackson 1976) or iv by a syringe-pump (Chanson et al. 1987). The latter produces a regular urinary output and avoids wide variations of diuresis induced by intermittent sc treatment. However, close monitoring is required in order to prevent extravascular infusion of the agent. DDAVP, a long-acting analogue of vasopressin, can be injected parenterally. To
Evolution of plasmatic and urinary parameters (mean ± SEM) in 5 patients with postoperative DI during a 3-day treatment by parenteral dDAVP administered im at a dose of 2 µg every 12 h. The arrows indicate the time of each injection.
obtain a constant and regular urinary output, we treated 15 patients for 3 days by twice-daily im injections. Whatever the dosage (1, 2 or 4 µg/12 h), the method of treatment was effective in all cases: on the average, diuresis was reduced to a sixth of its previous value and urinary osmolality increased about 6-fold.

The antidiuretic effect was obtained from the 6th h of treatment onwards, but appeared maximal by the 18th h. Throughout the treatment period, the effects were stable and sustained, inducing a regular and constant urinary output. This is particularly useful when patients are insensitive to thirst: this allows accurate fluid replacement. Although the drug was injected regularly every 12 h without taking into account the resumption of polyuria between each injection, the antidiuretic effect remained stable and did not increase after it had been obtained. Moreover, by maintaining stable water intake, hypo-osmolality and hyponatremia did not deteriorate during the course of treatment.

The prolonged action of the drug, by sustaining the antidiuretic effect until the 18th h following the last injection, can be advantageous. Conversely, the slow dissipation of the drug’s effects constitutes an important disadvantage if iatrogenic overhydration by positive fluid balance needs to be rapidly corrected. Although the difference between each group was not statistically significant, it seems that a dose-effect relation could be found: with increasing dose, the antidiuretic effect appeared stronger and lasted longer (data not shown). In order to avoid the consequences of marked antidiuresis and overhydration, we propose a regimen of 2 µg every 12 h, which is sufficient to induce adequate antidiuresis. Hyponatremia, caused by positive fluid balance, occurred in more than two-thirds of the patients. Since the patients had ad libitum access to water, this raises the question of inadequate thirst in some patients presenting postoperative DI and treated with dDAVP. It emphasizes the importance of frequent monitoring of natremia during dDAVP treatment. Alternatively, partial fluid restriction can be proposed. When the dosage was 1 µg, transient resumption of polyuria was noted in a few patients, perhaps owing to incomplete drug administration.

In conclusion, we have evaluated a 3-day treatment by dDAVP injected im twice-daily in patients presenting postoperative DI. The treatment was effective in all patients. Mild overhydration owing to positive fluid balance constitutes a side-effect encountered in other therapeutic methods which necessitates meticulous control of water intake.

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