'Low sodium' diuresis and ileal loss in patients with ileostomies: effect of desmopressin

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Abstract

Patients with ileostomies show an early diuresis when sodium restricted; this, together with an obligatory ileal sodium loss, predisposes them to severe salt and water depletion. The role of arginine vasopressin in this circumstance and whether it is natriuretic, or antinatriuretic, is unclear. There is also controversy over its likely effect on small bowel fluid reabsorption. We have examined the effect of the non-pressor (V_2) synthetic vasopressin analogue 1-deamino-8-D-arginine (desmopressin) on renal and ileal sodium and water excretion in ileostomy patients during acute adaptation to a low sodium diet. Patients were studied on two separate occasions (non-randomised) with and without the administration of desmopressin (0.75 μ g intramuscular, three times a day). In eight subjects without desmopressin there was pronounced diuresis on the first low sodium day, associated with a fall in renal sodium excretion and no change in ileal output or composition. In five (of the original) subjects with desmopressin there was pronounced antidiuresis, no change in renal sodium excretion, and no change in ileal output or composition. In both studies rises in plasma renin activity and salivary aldosterone concentration lagged behind the early decline in renal sodium excretion. We have confirmed the phenomenon of 'low sodium' diuresis after sodium restriction in ileostomy patients and shown that it can be prevented by desmopressin. Desmopressin has no direct or indirect effect on renal sodium excretion or ileal fluid and electrolyte loss in humans.

Patients with ileostomies are at greater risk of developing salt and water depletion because of a fixed ileal sodium and water loss.¹ If dietary sodium intake falls these patients rapidly become dehydrated and hypovolaemic, despite normal renal function and adaptation.² This can be an important clinical problem, patients commonly presenting with lethargy, postural hypotension, and in severe cases prerenal uraemia.³ Despite substantial sodium losses, normal plasma sodium concentration (and osmolality) is usually maintained because of a simultaneous water diuresis matching sodium and water deficits.⁴ The mechanism of this diuresis is uncertain but is presumed to entail a change in arginine vasopressin secretion, although in previous studies on these patients and in normal subjects no significant change in plasma arginine vasopressin concentration was found.^{2,4-6} Small changes in plasma arginine vasopressin concentration can produce large changes in urine volume, and it is possible

that any decrease in plasma arginine vasopressin concentration may be too small to be detected, or that the kidney's sensitivity to circulating arginine vasopressin might alter under these conditions.

The importance of arginine vasopressin in the regulation of plasma osmolality and volume through its effect on renal water excretion is well established.^{7,8} This hormone may also affect the renal excretion of sodium: in animals and humans infusions of arginine vasopressin have been shown to increase sodium excretion.⁹⁻¹¹ This raises the possibility of a synergistic effect of arginine vasopressin on renal water and sodium excretion. A fall in arginine vasopressin secretion sufficient to cause diuresis may enhance the kidney's ability to conserve sodium; this might account in part for the close temporal relation between the onset of renal sodium retention and the 'low sodium' diuresis seen in ileostomy patients during sodium restriction.^{1,3,4}

We have examined the effect of desmopressin, a selective V_2 (antidiuretic) vasopressin agonist with a long duration of action, on renal water and sodium excretion and ileal effluent during dietary sodium restriction in patients with ileostomies.

Methods

Eight patients with ileostomies (age range 50-70 years; five women, three men) were studied. All were well and taking no medication at the time of study. Each had undergone total colectomy as treatment for ulcerative colitis between 12 and 27 years previously. The study was approved by the Ethical Committee of St Mary's Hospital and the Ileostomy Association of Great Britain, and patients gave informed consent.

PROTOCOL

Patients were admitted to a ward for four days on two occasions (without and with desmopressin, order not randomised) separated by at least two months. During each four day period they received a low sodium (30 mmol/day) diet. Individual requirements of protein, calories, fat, and carbohydrates were assessed by a dietician and held constant throughout the study. Average daily intake was of 2125 kcal, 90 mmol potassium, 80 g protein, 70 g fat, and 240 g carbohydrate. Daily fluid intake and drinking pattern were held constant according to individual preference established on the first day. During the first three days (1-3), extra sodium was given with meals (NaCl, 500 mg capsules) to raise the daily intake to 250 mmol (high sodium). The abrupt transition to a low sodium diet was achieved by omitting these capsules and reducing

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sodium intake to 30 mmol on day 4 (low sodium). We have found in earlier studies that a pronounced fall in renal sodium excretion and an increase in urine flow rate occur within about 24 hours of dietary sodium restriction.^{4,12} The same protocol was followed in the desmopressin part of the study, which was carried out on five of the original eight patients: desmopressin (1-deamino-8-D-arginine vasopressin, Ferring) was given by intramuscular injection (0.75 µg three times daily) on the low sodium day (day 4) at 08 00, 15 00, and 22 00 hours. This dose is comparable with that used to control nocturnal polyuria in patients with autonomic failure and produces a moderate and sustained antidiuresis.¹³

Subjects were weighed at 08 00 each day. Blood pressure was recorded lying at 10 00 and 18 30. After 30 minutes supine venous blood was sampled (via an indwelling Teflon cannula introduced into a forearm vein under lignocaine local anaesthesia) at 10 00, 14 00, and 18 00 on days 3 (high sodium) and 4 (low sodium) for measurement of plasma renin activity, sodium, potassium, creatinine, total protein, and osmolality. Urine and ileal fluid were collected throughout each day; urine samples were stored at -20°C until analysis for sodium, potassium, osmolality, creatinine, and arginine vasopressin concentration. Ileal effluent was homogenised in a Waring blender and ultracentrifuged, decanted, and the supernatant analysed for sodium and potassium concentration.

LABORATORY ANALYSES

Sodium and potassium concentrations in plasma, urine, and ileal fluid were measured by flame photometry (Corning model 430) and osmolality cryoscopically (Gonotec Osmomat 300). Creatinine in urine and plasma was measured colorimetrically, as creatinine alkaline picrate and total plasma protein by the Biuret method (Chemlab auto-analyser). Ileal effluent dry weight was measured from dessicated samples of the homogenised ileal effluent and electrolyte concentrations expressed in terms of ileal water. Plasma renin activity was measured by the radioimmunoassay of angiotensin I generated from endogenous substrate¹⁴; salivary aldosterone concentration was measured by radioimmunoassay.¹⁵ Urinary arginine vasopressin was measured by radioimmunoassay; high performance liquid chromatography data confirmed that the immunoreactive molecule co-eluted with synthetic arginine vasopressin and bioassay studies in the ethanol anaesthetised and water loaded rat confirmed the biological activity of urinary arginine vasopressin.¹⁶ The cross reactivity of the arginine vasopressin assay with desmopressin in urine was 0.014% and the lowest detectable limit was 1.25 pmol/l of urine. In samples from the control study calcium and phosphate were measured colorimetrically.¹⁷

DATA ANALYSIS

Data from the first two days of each study were excluded from the analysis as this was the time necessary to allow equilibration from individual differences in prestudy sodium intake. For each

variable, comparison between observations on days 3 (last high sodium) and 4 (first low sodium) was made by two way analysis of variance and covariance (factors: subject, day; covariate: phase - control *v* desmopressin); results are given as mean (SEM). Plasma renin activity, salivary aldosterone concentration, and renal arginine vasopressin excretion were found to be log normally distributed and their logarithms used in the statistical analysis; therefore, results are given as geometric mean (antilog of mean of logarithms) and 95% confidence intervals.

Results

BLOOD PRESSURE AND BODY WEIGHT

Supine arterial blood pressure did not change during sodium restriction and was unaffected by desmopressin: control 143 (12)/85 (4) to 139 (10)/81 (3) mmHg; desmopressin: 138 (9)/81 (2) to 141 (12)/83 (5) mmHg ($p>0.1$). Body weight fell slightly during the control study (69.3 (7.2) to 68.5 (7.3) kg; $p=0.06$), but there was little change during desmopressin administration (73.3 (11.2) to 72.9 (11.3) kg; $p>0.1$).

URINE

In the control study urine flow rate increased significantly on day 4 (low sodium) and decreased during desmopressin administration; there were corresponding changes in urine osmolality (Fig 1). The falls in renal arginine vasopressin and sodium excretion on day 4 were unaffected by desmopressin administration (Fig 2). There was no change in creatinine clearance (not shown) or renal potassium excretion (control 3.03 (0.27) to 3.14 (0.26) mmol/h; desmopressin 3.14 (0.25) to 2.68 (0.23) mmol/h; $p>0.1$). In the control study renal phosphate excretion (a marker of proximal tubule sodium reabsorption) increased from 1.05 (0.09) to 1.34 (0.10) mmol/h; $p<0.05$.

PLASMA AND SALIVA

Table I summarises the changes in plasma composition and salivary aldosterone concentration. During the control study plasma osmolality fell initially and then recovered, but the plasma sodium concentration continued to fall and the plasma protein concentration increased. The plasma calcium concentration increased with total protein, but the plasma phosphate concen-

Figure 1: Changes in urine flow rate (left panel) and urine osmolality (right panel) after dietary sodium restriction, day 3 (high sodium) to day 4 (low sodium). * $p<0.05$, ** $p<0.01$ compared with the corresponding value on day 3.

Figure 2: Changes in renal arginine vasopressin (left panel) and sodium (right panel) excretion after dietary sodium restriction, day 3 (high sodium) to day 4 (low sodium). * $p < 0.05$, ** $p < 0.01$ compared with the corresponding value on day 3.

tration did not change. Not surprisingly, during desmopressin administration there was a greater fall in plasma osmolality (no recovery) and sodium concentration and no increase in the plasma protein concentration. Plasma renin activity and salivary aldosterone concentration did not increase significantly on day 4 in either study, though there was a rise in the latter on day 4 ($p = 0.09$) of the desmopressin study; plasma renin activity had risen significantly by the morning of day 5 (second low sodium) in both studies. Desmopressin had no effect on plasma renin activity or salivary aldosterone concentration.

ILEAL EFFLUENT

Ileal water and electrolyte losses were unaffected by sodium restriction and desmopressin administration (Table II).

Discussion

The decline in renal sodium excretion after dietary sodium restriction was exponential, with a $t_{1/2}$ of about 50%, the largest absolute fall occurring within the first 24 hours.¹⁸ Because of an obligatory ileal sodium loss of about 100 mmol/day (Table II) patients with ileostomies have an exaggerated renal response to sodium restriction compared with normal subjects and rapidly become sodium depleted. This is illustrated by the early and pronounced fall in plasma sodium concentration and osmolality (Table I). Comparing control with desmopressin administration, the fall in plasma osmolality seems to be corrected by the associated 'low sodium' diuresis (Table I and Fig 1); an appropriate response that

maintains plasma osmolality in the face of solute (mainly sodium) depletion. If ileal diarrhoea becomes a cause of excessive sodium loss ileostomy patients will develop severe sodium and water depletion, in part because of a normal physiological response. A similar diuresis occurs in the sodium depleted rat, where regulation of plasma osmolality may depend on increased renal water excretion and also could entail altered renal sensitivity to arginine vasopressin.¹⁹ In the dog, thirst seems to be a major osmoregulator²⁰; in humans drinking patterns tend to reflect habit and social activity. The mechanism of this early diuresis is not proved but is likely to result from a fall in arginine vasopressin secretion. Repeated studies in normal humans,^{5,6} in whom a 'low sodium' diuresis also occurs,¹² and in ileostomy patients² have failed to detect a change in plasma arginine vasopressin concentration. This is more likely to be due to insensitivity of measurement rather than to an intrinsic change in the kidney's response to arginine vasopressin (compare the rat), since the diuresis is readily reversed by modest doses of desmopressin.

Renal arginine vasopressin excretion was measured because it is believed to be a useful index of arginine vasopressin secretion, particularly when changes in plasma arginine vasopressin concentration are small or undetectable²¹⁻²⁴; however, there is evidence that renal arginine vasopressin excretion may be affected by urine solute concentration or excretion rate.^{25,26} In both the control and desmopressin parts of the study renal arginine vasopressin excretion fell in parallel with renal sodium excretion; it did not correlate with urine flow rate, urine osmolality, or osmolar excretion, but did correlate with sodium excretion (Figs 1 and 2). Clearly, renal arginine vasopressin excretion may not be a reliable index of arginine vasopressin secretion under conditions of altered sodium balance and excretion (compare lithium²⁷).

In the whole animal, including humans, arginine vasopressin can be natriuretic,^{9,10} but at the single nephron level it stimulates sodium reabsorption in some species.²⁸ The former has been attributed to water retention and volume expansion,²⁸ and the latter to cyclic AMP stimulation in the medullary thick ascending limb and collecting duct.²⁹ Natriuresis does occur during arginine vasopressin infusion in sodium and water restricted subjects.¹¹ An explanation for this apparent contradiction may lie in the different receptor types stimulated by arginine vasopressin: the V1 (vascular) receptor is found in

TABLE 1 Changes in plasma composition and salivary aldosterone concentration after dietary sodium restriction in ileostomy patients; day 3 (high sodium, HS) to day 4 (low sodium, LS); control and desmopressin (mean (SEM))

Day	Plasma osmolality (mOsm/kg)	Plasma Na (mmol/l)	Plasma K (mmol/l)	Plasma Ca (mmol/l)	Plasma phosphate (mmol/l)	Total protein (g/l)	Plasma renin activity† (pg/ml/h) (geometric mean + 95% confidence intervals)	Salivary aldosterone† (pmol/l) (geometric mean + 95% confidence intervals)
Control:								
3 (HS)	292.3 (0.8)	138.7 (0.3)	3.97 (0.06)	2.56 (0.02)	1.13 (0.01)	87.0 (0.8)	1560 (1345 to 1808)	93.3 (69.3 to 125.6)
4 (LS)	287.8 (0.9)*	137.1 (0.5)*	3.95 (0.07)	2.64 (0.02)*	1.14 (0.01)	90.2 (0.9)*	1767 (1525 to 2049)	105.0 (76.8 to 143.5)
5 (08 00)	292.4 (1.8)	136.9 (0.7)*	3.93 (0.10)	2.65 (0.02)*	1.14 (0.02)	92.4 (0.7)*	3955 (3062 to 5108)*	—
Desmopressin:								
3 (HS)	289.7 (1.0)	139.7 (0.5)	4.05 (0.09)	—	—	83.7 (1.3)	1823 (1378 to 2410)	63.1 (47.8 to 83.3)
4 (LS)	284.3 (1.2)**	136.4 (0.6)**	3.99 (0.07)	—	—	85.8 (1.3)	2096 (1585 to 2772)	107.0 (80.6 to 142.0)
5 (08 00)	279.2 (3.6)**	133.6 (1.1)**	3.70 (0.06)	—	—	84.6 (2.7)	3407 (1983 to 5855)*	143.3 (77.0 to 266.7)**

* $p < 0.05$ and ** $p < 0.01$ compared with the corresponding value on day 3. †Log-transformed variable.

TABLE II Changes in ileal fluid, sodium, and potassium excretion rates after dietary sodium restriction in ileostomy patients; day 3 (high sodium, HS) to day 4 (low sodium, LS); control and desmopressin (mean (SEM))

	Ileal flow rate (ml/h)	Ileal sodium loss (mmol/h)	Ileal potassium loss (mmol/h)
Control:			
3 (HS)	35.1 (8.1)	5.00 (2.37)	0.41 (0.19)
4 (LS)	31.8 (4.0)	3.12 (0.19)	0.25 (0.07)
Desmopressin:			
3 (HS)	39.8 (3.4)	4.87 (0.95)	0.33 (0.05)
4 (LS)	38.9 (7.6)	5.08 (1.98)	0.32 (0.08)

vascular smooth muscle and mediates the vasoconstrictor effect of arginine vasopressin; the V2 (antidiuretic) receptor is found in the kidney distal tubule and mediates increased water permeability.²⁸⁻³⁰ There is some evidence that V1 receptor stimulation can cause intrarenal release of prostaglandins (PGE₂), which are natriuretic and oppose the antidiuretic effect of arginine vasopressin.²⁹⁻³² This effect of prostaglandins may be directly on the tubule, inhibiting arginine vasopressin induced cAMP stimulation, or secondary to increased medullary blood flow and solute washout.³³ A similar negative feedback mechanism is seen with other pressor agents: angiotensin II and noradrenaline (increased in sodium depletion) also stimulate intrarenal PGE₂ release, which counters their intrinsic effect, although the mechanism of antagonism is unclear (pharmacological or physiological). The net renal effect of prostaglandin release depends on the background concentration of such hormones, only becoming apparent when synthesis is inhibited – for example, by indomethacin.³⁴ Salt depletion per se is associated with increased renal PGE₂ synthesis.³⁵ In our study the V2 receptor agonist desmopressin³¹ did not affect renal sodium excretion; however, there are reports that desmopressin may increase renal PGE₂ production³⁶ (which could obscure any antinatriuretic effect), but not in humans.³⁷ Nevertheless, it is still possible that V1, or a recently postulated V₃,²⁹ receptor stimulation may lead to release of other local mediators, such as neuropeptides,³⁸ resulting in actions distinct from V2 receptor stimulation.

Finally, despite early reports that the stimulatory effect of volume depletion on arginine vasopressin release can overcome the inhibitory effect of reduced plasma osmolality (Table I; weight *v* osmolality), and later reports that hypovolaemia sensitises osmoregulation (reduced threshold), the relation is probably more complex, with one or other dominating under different conditions. In sodium depletion osmolality seems to be dominant.³⁹

The site of renal sodium conservation is probably distal nephron, because phosphate excretion, a marker of proximal tubule reabsorption – for example, by peritubular physical factors such as oncotic pressure – did not fall. The early stimulus to sodium reabsorption is also uncertain: plasma renin activity (and by inference angiotensin II, which has a proximal tubule antinatriuretic effect) and salivary androsterone concentration did not increase appreciably (day 3 *v* day 4) until after the initial decline in renal sodium excretion.¹²

Arginine vasopressin-like immunoreactivity is

present in the rat jejunum⁴⁰ and is thought to regulate the mucosal microcirculation.^{41,42} There are reports of arginine vasopressin either inhibiting sodium and water reabsorption⁴³ or having no effect⁴⁴; increased circulating concentrations have also been implicated as a cause of postoperative paralytic ileus.⁴⁵ In our study desmopressin had no effect on ileal volume or composition, suggesting that any inhibitory effect of native arginine vasopressin may be secondary to its vasoconstrictive action or, like its V1/V3 receptor renal effect, may be due to local release of other mediators such as prostanoids⁴⁶ or neuropeptides.³⁸

The phenomenon of 'low sodium' diuresis may be an important contributing factor to salt and water depletion in patients with ileostomies. While reversing the diuresis of sodium restriction, the V2 agonist desmopressin does not affect renal sodium excretion or ileal loss. It seems likely that the mechanism of the prompt decline in renal sodium excretion involves more than activation of the renin-angiotensin-aldosterone system alone.

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