VASOPRESSIN RESPONSES DURING TRANSURETHRAL RESECTION OF THE PROSTATE

R. G. HAHN AND M. RUNDGREN

Transurethral resection of the prostate (TURP) may be accompanied by several changes in haemodynamic state and fluid balance [1,2]. Irrigating fluid may be absorbed into the circulation either directly or via the perivesical space to cause the "TURP syndrome" which is characterized by signs of water intoxication [3-5]. There is little information on the hormonal changes following various complications during TURP. In a patient who developed the TURP syndrome, the hormonal response to massive irrigant absorption was observed to counteract compensatory mechanisms [6]. At the end of an otherwise uneventful resection under extradural anaesthesia, the patient developed hypertension and complained of blurred vision. The serum concentration of sodium was found to be 115 mmol litre\(^{-1}\) and the serum concentration of arginine vasopressin (S-AVP) was 84.5 pg ml\(^{-1}\) (normal range 2.5—4 pg ml\(^{-1}\)) at an early stage of development of the syndrome. The absence of any obvious physiological stimulus for the AVP secretion in this situation [7] and the possibility that AVP may have been a causative factor in the hypertension [8] led us to study factors influencing S-AVP concentrations during TURP.

PATIENTS AND METHODS

Patients and surgical procedure

Following local Ethics Committee approval and informed patient consent, we studied 32 patients (mean age 71 yr, range 56–82 yr) undergoing TURP for benign prostatic enlargement. They were premedicated with oxazepam 25–50 mg orally. A central venous catheter (Drum-Cartridge) was inserted with the tip in the superior vena cava (confirmed by x-ray) and central venous pressure (CVP) was recorded continuously. Extradural analgesia was induced with 2% mepivacaine 9–13 ml with adrenaline (Carbocain—adrenalin, Astra) to an upper sensory level of T4—T9. Ringer's solution (sodium content 130 mmol litre\(^{-1}\)) 10 ml kg\(^{-1}\) was administered i.v. during preparation of the patient for surgery in the lithotomy position. During TURP, the same solution was given at a rate of 50–150 ml/10 min i.v., depending on the estimated blood loss.

Volumetric fluid balance

During surgery the bladder was filled intermittently with 2.2% glycine in water (Travenol, Bromma; osmolality 290 mosmol kg\(^{-1}\)). After operation, 0.9% saline was used. The irrigating fluid bags were weighed before and after use. A sterile plastic drape was arranged to prevent spillover from the irrigating fluid returns. A
volumetric irrigating fluid balance was obtained at 10-min intervals throughout surgery (collection period) by closing the irrigating fluid inlet, emptying the bladder and replacing the irrigating fluid bag and the collecting bucket. Blood loss was calculated at the time of each volumetric fluid measurement, using the blood concentration of haemoglobin at the end of the collection period for reference [9]. The volume of irrigant absorbed was estimated as the difference between the volumetric fluid balance and the blood loss [10].

Analyses

Serial determinations of the serum osmolality and of the concentrations of blood haemoglobin (B-Hb), serum sodium (S-Na) and serum vasopressin (S-AVP) were made on venous blood samples obtained before and after extradural analgesia was induced, at the end of each collection period, and for 1 and 2 h after surgery. Serum osmolality was measured using a Roebling Microosmometer (Herman Roebling, Berlin) with a coefficient of variation of 0.5%. B-Hb was measured with a Coulter Counter S plus (Counter Electronics) and S-Na measured by flame photometry (AutoCal 543, Instrumentation Laboratory). Fifty duplicate samples from patients showed coefficients of variation of 1.2% for B-Hb and 0.6% for S-Na. The accuracy of the blood loss measurements was 100 ± 5% as checked by dispersion of known amounts of bank blood in irrigating fluid. Samples taken for measurement of S-AVP concentration were placed immediately on ice, centrifuged, and the serum stored at −70 °C until analysis by radioimmunoassay [11]. The sensitivity of the assay, as used in the present study, was 2.5 pg ml⁻¹. Samples with undetectable hormone were assumed to have this value for statistical calculations.

Patient groups

Based on the data obtained related to changes in fluid balance, each patient was classified to one of the following groups [10]:

Group I. No events (n = 13); blood loss < 800 ml and absorption of irrigant < 300 ml.

Group II. Extravascular absorption (n = 5); total irrigating fluid absorption > 300 ml and no significant decrease in S-Na ( < 2 mmol litre⁻¹; P > 0.05) within 20 min of absorption.

Group III. Intravascular absorption (n = 9); irrigant absorption > 300 ml during the same collection period(s) as a decrease in S-Na > 2 mmol litre⁻¹ (P < 0.01) was recorded.

Group IV. Increased blood loss (n = 5); blood loss > 800 ml and absorption of irrigant < 300 ml.

No patient received hypertonic saline solution or diuretics during the study. Erythrocyte concentrates were given after operation to the patients in group IV. Data were expressed as mean values (SD) when the data were distributed normally. When a skewed distribution occurred, median and range were used. Mann–Whitney’s test, Wilcoxon’s rank sum test and stepwise multiple regression were used for statistical analysis, as appropriate; the same tests were undertaken when performing statistical evaluation of the data on S-

**Table 1. Data (mean (SD or range)) in 32 patients undergoing transurethral resection of the prostate**

<table>
<thead>
<tr>
<th></th>
<th>Group I (n = 13)</th>
<th>Group II (n = 5)</th>
<th>Group III (n = 9)</th>
<th>Group IV (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(No events)</td>
<td>(extravascular absorption)</td>
<td>(intravascular absorption)</td>
<td>(increased blood loss)</td>
</tr>
<tr>
<td>Patient age (yr)</td>
<td>72 (5)</td>
<td>67 (9)</td>
<td>68 (8)</td>
<td>72 (7)</td>
</tr>
<tr>
<td>Serum creatinine concn before TURP (μmol litre⁻¹)</td>
<td>130 (52)</td>
<td>121 (43)</td>
<td>102 (33)</td>
<td>96 (10)</td>
</tr>
<tr>
<td>Resection time (min)</td>
<td>41 (10)</td>
<td>44 (11)</td>
<td>48 (8)</td>
<td>68 (20)</td>
</tr>
<tr>
<td>Weight of resectate (g)</td>
<td>17 (7)</td>
<td>24 (18)</td>
<td>27 (8)</td>
<td>40 (20)</td>
</tr>
<tr>
<td>Blood loss (ml)</td>
<td>192 (66–513)</td>
<td>478 (247–1143)</td>
<td>708 (280–934)</td>
<td>1260 (812–1530)</td>
</tr>
<tr>
<td>Irrigating fluid absorption (ml)</td>
<td>59 (0–281)</td>
<td>636 (310–1683)</td>
<td>994 (616–2811)</td>
<td>201 (143–280)</td>
</tr>
<tr>
<td>Maximum change in serum sodium concn (mmol litre⁻¹)</td>
<td>-0.8 (1.6)</td>
<td>-1.6 (0.8)</td>
<td>-9.3 (3.5)</td>
<td>0.0 (3.1)</td>
</tr>
<tr>
<td>Maximum change in CVP (mm Hg)</td>
<td>+1 (-1 to +4)</td>
<td>0 (-2 to +1)</td>
<td>+4 (0 to +7)</td>
<td>-2 (-3 to 0)</td>
</tr>
</tbody>
</table>
AVP concentrations set to the lower limit of detection in the assay used.

RESULTS

Details of the patients studied are shown in Table I.

Changes in S-AVP during TURP

Sudden episodes of hypotension to 80 mm Hg or less were associated with marked increases in S-AVP concentrations (figs 1, 2). Two patients in group I had increased S-AVP concentrations (70.0 and 79.1 pg ml⁻¹, respectively) when the arterial pressure decreased to 75 mm Hg. One of these incidents was interpreted as a vasovagal syndrome (bradycardia and no preceding change in CVP), whereas the second occurred in association with increased administration of fluid (CVP increased by 3 mm Hg). One patient in group III had a reaction interpreted as a vagal reflex accompanied by increased S-AVP concentration (maximum 283.3 pg ml⁻¹) before absorption of irrigating fluid was noted (fig. 2). Three patients in group IV had S-AVP concentrations increased to 348.4, 591.1 (fig. 1) and 20.6 pg ml⁻¹, respectively, in association with sudden hypotension; hypovolaemia obviously contributed to the hypotension, as it was preceded by increased blood loss and changes in the CVP (−3, −3 and −2 mm Hg, respectively).

In patients without hypotension, observations in the different groups were as follows:

Group I (11/13). Only small, non-significant changes in S-AVP concentration were observed. The median S-AVP concentration after induction of anaesthesia was 2.7 pg ml⁻¹ (range 2.5–4.1 pg ml⁻¹) and during TURP 2.6 pg ml⁻¹ (range 2.5–5.7 pg ml⁻¹) (Wilcoxon's test, ns). Changes in the serum osmolality during each TURP were smaller than, or close to, the limit of analysis.

Group II (5/5). Extravascular absorption of irrigating fluid was accompanied by increased S-AVP concentrations. The maximum S-AVP concentrations during absorption were 5.0, 11.8, 13.8, 19.1 and 38.9 pg ml⁻¹ (Wilcoxon's test, ns). Changes in the serum osmolality during each TURP were smaller than, or close to, the limit of analysis.

Group III (8/9). The S-AVP concentration was greater during collection periods with intra-vascular absorption (median 6.1 pg ml⁻¹; range...
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2.5–6.9 pg ml⁻¹) compared with periods when there was no absorption (median 2.8 pg ml⁻¹; range 2.5–4.5 pg ml⁻¹) (Wilcoxon’s test, \( P < 0.01 \)). There was an increase in S-AVP during absorption in all but one patient. Changes in serum osmolality during TURP exceeded the precision of serial determinations in four patients, in whom osmolality decreased by 2–3%.

**Group IV (2/5).** Two patients in this group had a stable arterial pressure in spite of a large blood loss (1260 and 1425 ml) and they had normal S-AVP concentrations (2.9 (0.6) pg ml⁻¹) during the surgical procedure. Also, CVP was largely unaffected (±1 mm Hg) by blood loss in these patients.

**S-AVP and absorption hypertension**

In group III, systolic arterial pressure increased in four of the nine patients by 25 mm Hg or more after 15–25 min of absorption. In contrast, the S-AVP response to absorption was immediate. Furthermore, one patient had a large absorption (1900 ml) following a vasovagal reaction, but did not develop hypertension earlier than the other patients with absorption hypertension, in spite of a substantial increase in the S-AVP concentration (fig. 2). With the exception of the patient presented in figure 2, AVP seemed not to cause hypertension in any patient in group III, as the S-AVP concentrations during absorption in patients with hypertension (6.4, 4.9 and 6.1 pg ml⁻¹) were similar to those in patients without hypertension (6.1, 6.1, 2.5, 5.1 and 6.9 pg ml⁻¹).

**Variables related to S-AVP changes during absorption**

Although increased S-AVP concentrations were observed during intravascular absorption (group III), no significant correlation was found between this variable and the amount of absorbed irrigating fluid. Furthermore, no correlation was found between S-AVP concentration and the CVP, blood loss, arterial pressure, serum osmolality or changes in the serum sodium concentration for all collection periods during irrigant absorption (stepwise multiple regression). However, collection periods with both irrigating fluid absorption and increased CVP were always associated with in-

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**Fig. 2.** Systolic arterial pressure, serum AVP and sodium concentrations, and volume of irrigant absorbed (bars) in one patient with sudden hypotension, interpreted as a vasovagal reaction, after 30 min of TURP surgery. Later, there was irrigant absorption amounting to 1900 ml. Note the late absorption hypertension. n.d. = Not detectable.
creased S-AVP concentration \((n = 8)\), whereas unchanged or decreased CVP was accompanied usually by reduced concentrations of AVP. As expected, fluid retention (fluid absorption minus blood loss) was larger during collection periods with increased S-AVP concentrations (median 284 ml, range 50–616 ml; \(n = 10\)) than during collection periods with decreased values (median –10 ml, range –128 to 372 ml; \(n = 7\)) (Mann-Whitney test, \(P < 0.05\)).

**S-AVP and i.v. fluid overload**

An increase in CVP of 2–4 mm Hg was not associated with irrigant absorption in two patients during TURP and in four patients during follow-up. These events were interpreted as i.v. fluid overload [2] and were not associated with increased S-AVP concentrations.

**Postoperative changes in S-AVP**

Sudden increases in S-AVP concentrations after operation were common in patients with intravascular irrigant absorption (group III). These increases correlated with nausea or unstable arterial pressure, or both; the median S-AVP concentration in group III patients at 1 or 2 h after completion of resection was 7.9 pg ml\(^{-1}\) (range 2.5–24.3 pg ml\(^{-1}\)). In the other groups only occasional postoperative increases in AVP concentration were found.

**DISCUSSION**

The aim of the present study was to investigate the effects of complications during TURP on release of AVP and therefore we avoided those conditions known to affect secretion of AVP. The potential stimulant effect of morphine [12] was avoided by the use of oxazepam as premedication. Changes in serum osmolality by fluid absorption were minimized by use of an isotonic irrigating fluid. Extradural analgesia was used because it has been reported to reduce the effect of surgery on release of AVP [13].

We have demonstrated that uncomplicated TURP surgery under extradural anaesthesia did not stimulate secretion of AVP. However, several changes did cause release of AVP. Sudden hypotension was found to be the most potent stimulus for release of AVP. On the other hand, excessive blood loss, accompanied by a decrease in CVP, did not stimulate AVP secretion, provided that normotension was maintained. This is in agreement with observations in animals [14]. Recent studies in man also support the concept that high-pressure rather than low-pressure baro-receptors are important in control of AVP secretion [15].

It is concluded that extravascular absorption of irrigating fluid stimulated release of AVP, although in two of the patients in group II other causes may have been responsible for the changes observed. Postoperative decrease in urinary excretion has been reported in association with extravascular fluid absorption [16,17]. The direct measurement of AVP in our study suggests that this water retention may be mediated via antidiuretic hormone. The mechanism of release of AVP is obscure, but it is possible that a stimulatory effect similar to that of visceral traction [18] may have contributed.

Intravascular absorption of irrigating fluid was followed immediately by increase in secretion of S-AVP (fig. 3). Doubling of S-AVP concentration results in water retention [7], which may aggravate the dilution hyponatraemia caused by absorption of irrigant (table I). As the hypervolaemia and hypo-osmolality induced by fluid absorption should inhibit release of AVP, it is possible that increased serum concentrations of glycine may, directly or indirectly, stimulate secretion of AVP. There is no experimental evidence for this hypothesis; on the contrary, application of strychnine, an antagonist of glycine, to the ventral surface of the brainstem in animals has been shown to induce release of AVP [19].

CVP is thought to be an excellent guide for assessing absorption of irrigating fluid [2,20]. This was confirmed by our observations in most patients of this study (table I). However, this may be masked by concomitant blood loss [21], and as increases in CVP may occur without simultaneous absorption, it is sometimes unreliable.

Absorption of irrigating fluid may be associated with hypertension [1,4]. The patient described in the introduction, who developed hypertension in association with irrigating fluid absorption, had an increased concentration of S-AVP (84.5 pg ml\(^{-1}\)) which may have contributed to the hypertension. However, it is unlikely that AVP was a main factor in the development of hypertension occurring in association with irrigating fluid absorption in the present study. There were only minor differences in S-AVP concentration during absorption between patients with and without hypertension (although the numbers are small).
The S-AVP concentrations achieved during absorption were smaller than those considered generally to affect arterial pressure in subjects with intact baroreflexes [22]. Furthermore, the increase in S-AVP concentration and hypertension were not time-related.

Postoperative increases in S-AVP concentration were common in patients with absorption of intravascular fluid during TURP surgery (group III). In contrast to that seen during the surgical procedure, these events correlated with factors known to stimulate secretion of AVP, such as nausea and unstable arterial pressure [7,23]. Nausea may occur after absorption of large amounts of irrigating fluid, possibly because of glycine toxicity [24].

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REFERENCES


