Effects of routine heparin therapy on plasma aldosterone concentration

Yo Kageyama¹, Hiromichi Suzuki² and Takao Saruta²

Department of Internal Medicine¹, Tochigi National Hospital, Utsunomiya, and Department of Internal Medicine², Keio University School of Medicine, Tokyo, Japan

Abstract. Changes in plasma aldosterone, plasma renin activity, plasma cortisol, serum sodium and potassium concentrations were studied in 9 patients with thromboembolic diseases treated with heparin. Heparin was administered at doses of 700-1000 units/h for 7-10 days. Plasma aldosterone decreased from 239±33 to 114±25 pmol/l during heparin therapy and returned to basal levels after discontinuation of the therapy. In addition, responses to a low sodium intake (3 g/day) and ACTH were examined in 5 patients during and 2 weeks after heparin therapy. The increase in plasma aldosterone caused by low sodium intake was significantly attenuated during heparin therapy (124±5% increase from baseline) as compared with that 2 weeks after heparin therapy (148±7%, p<0.05). On the other hand, ACTH stimulated plasma aldosterone similarly during and at 2 weeks after heparin therapy (increase from baseline: 190±20% vs 193±9%). These results suggest that heparin decreased plasma aldosterone owing to attenuation of the angiotensin II-induced aldosterone production.

Heparin is commonly used for its anticoagulant properties in the prevention of and therapy for thromboembolism, and to keep blood fluid during extracorporeal circulation (1). Besides its action on blood coagulation, heparin decreases aldosterone production in both humans and experimental animals (2-4). However, the mechanisms responsible for the inhibition of aldosterone production are still controversial (5,6).

The present study was designed to determine the effects of routine heparin therapy on aldosterone production. Furthermore, in order to examine the mechanism, responses to stimulation by a low sodium intake and adrenocorticotropic hormone (ACTH) were compared during and 2 weeks after heparin therapy.

Patients and Methods

Nine hospitalized patients treated with heparin (Mitsui Pharmaceutical Co, Tokyo) for thromboembolic diseases, participated in the study. These comprised 6 men and 3 women, aged 68±4 years. The heparin preparation did not contain any preservative other than calcium hydrochloric acid.

Heparin therapy was initiated with a loading dose of 500 units as a bolus injection, followed by 700-1000 units/h iv for 7-10 days. The activated partial thromboplastin time was examined every day for the first three days and then every other day; the dose of heparin was adjusted to maintain the activated partial thromboplastin time at less than 60 s. Sodium and potassium intake, including that in intravenous fluid, were 150-200 and 60-90 mmol/day, respectively. Plasma aldosterone, plasma renin activity, plasma cortisol, sodium and potassium concentrations were determined before and after heparin therapy.

Responses to synthetic ACTH (tetraacosactide acetate, Organon Inc, USA, 1 mg iv) and a low sodium intake, 3 g/day for 3 days, were examined in 5 patients during treatment with heparin for 10 days, and 2 weeks after discontinuation of the heparin therapy. The studies were approved by the human investigation committee of the Tochigi National Hospital. Details of this protocol were explained and informed consent was obtained from each patient.

Analytical methods

Plasma renin activity was determined by radioimmunoassay of angiotensin I generated during a 60-min incubation at 37°C (7). PMSF (phenyl methyl sulfonyl fluoride) was used to block converting enzyme and angiotensinase activity. The sensitivity of this assay was 80 pmol·1⁻¹·h⁻¹ and the intra-assay coefficient of variation was 5.6%. Plasma aldosterone was measured with an aldosterone-
RIAKIT from Dainabot Co, Tokyo (8). The intra- and inter-assay coefficient of variation were 7.5 and 7.7%, respectively. The sensitivity of this method was 28 pmol/l. Plasma cortisol was determined by radioimmunoassay using a SPAC-CORTISOL KIT II from Daichi Co, Tokyo (9). The intra- and inter-assay coefficients of variation were 4.8 and 5.3%, respectively. The sensitivity of this assay was 15 nmol/l. Blood chemistry was measured using a multichannel autoanalyzer (Hitachi 736-30, Hitachi, Tokyo, 10).

Statistics
All results are expressed as the mean ± SEM. Statistical analysis was performed using non-parametric analysis (Mann-Whitney U-test and Wilcoxon single-rank test, Stat View II, Macintosh, Tokyo, Japan). Changes were considered to be significant at p<0.05.

Results
Table 1 shows the clinical characteristics of the patients. None had diabetes mellitus, renal insufficiency, or severe hypertension. Plasma aldosterone decreased from 239±33 to 114±25 pmol/l during heparin therapy and returned to basal levels 2 weeks after discontinuation of the therapy (Fig. 1). Plasma renin activity, plasma cortisol, sodium and potassium concentrations were not altered during heparin therapy (Table 2).

The decrease in body weight at the end of low sodium intake was 0.7±0.1 kg during heparin therapy, 0.8±0.2 kg 2 weeks after heparin therapy. During heparin therapy, the increases in plasma aldosterone caused by a low sodium intake were minimal (from 119±30 to 144±47 pmol/l), despite the increase in plasma renin activity from 1.2±0.2 to 3.7±0.3 nmol·l⁻¹·h⁻¹. However, 2 weeks after discontinuation of heparin therapy, plasma aldosterone increased from 252±50 to 377±80 pmol/l (p<0.01) during low sodium intake, in accordance with the increase in plasma renin activity, to the same levels as those during heparin therapy (1.1±0.2 to 3.6±0.3 nmol·l⁻¹·h⁻¹, p<0.01). Since basal levels of plasma aldosterone were different before the stimulation, changes were expressed as

![Graph showing changes in plasma aldosterone concentration](https://via.placeholder.com/150)

**Fig. 1.** Changes in plasma aldosterone concentration before and during heparin administration, and 2 weeks after its discontinuation. Values were expressed as mean ± SEM.
Table 2.
Changes in plasma renin activity (PRA), cortisol, serum sodium (Na) and potassium (K) before and during heparin therapy.

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>During</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRA (nmol·L⁻¹·h⁻¹)</td>
<td>1.1±0.2</td>
<td>1.4±0.3</td>
</tr>
<tr>
<td>Cortisol (nmol/l)</td>
<td>386.3±38.6</td>
<td>369.7±44.1</td>
</tr>
<tr>
<td>Na (mmol/l)</td>
<td>138±1</td>
<td>139±1</td>
</tr>
<tr>
<td>K (mmol/l)</td>
<td>4.1±0.3</td>
<td>4.3±0.2</td>
</tr>
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The percent increase from basal levels. The percent increases in plasma aldosterone during heparin therapy were 124±5%, significantly less than those after heparin therapy, 148±7% (p<0.05). On the other hand, ACTH stimulated aldosterone similarly both during and after heparin therapy, the percent increases from basal levels were 190±20, 198±9%, respectively (Fig. 2)

Discussion
The present study demonstrated that 1. routine heparin therapy doses at 700-1000 units/h decreased plasma aldosterone, and 2. the increase in plasma aldosterone owing to stimulation by low sodium intake was attenuated during heparin therapy, whereas the response to ACTH was well preserved.

Heparin and related sulphated mucopolysaccharides are known to produce natriuresis and potassium retention (11). These effects have been shown to be caused by a decrease in aldosterone production, demonstrated in both experimental animals (6,12) and normal subjects (2,3), patients with primary and secondary aldosteronism (13), and patients with chronic glomerulonephritis (4). In the present study, the decrease in plasma aldosterone during heparin therapy was not associated with changes in plasma renin activity, plasma cortisol, and potassium. Plasma cortisol values were considered to reflect the steroidogenic activity of ACTH. Since the renin-angiotensin system, ACTH, and potassium are the major factors regulating aldosterone production (14), the decrease in plasma aldosterone by heparin must be due to a direct effect on the adrenal glomerulosa.

Aldosterone deficiency without alterations in cortisol production is defined as isolated hypoaldosteronism. It is classified as two forms, one with altered functions of the renin-angiotensin system and the other with primary deficiencies in aldosterone biosynthesis. Heparin is one of the causes of isolated hypoaldosteronism, owing to its inhibitory effect on aldosterone production (15). Although decreases in plasma aldosterone with heparin administration are consistent findings, reported changes in electrolyte balances have differed: a decrease in serum sodium (2), natriuresis, an increase in serum potassium (4), and no change in electrolyte balance (3). In the present study, serum sodium and potassium during heparin therapy did not show any change, as was reported by Sherman et al. in healthy volunteers (3). Differences in the doses and duration of heparin, the amount of sodium and potassium intake, and the presence of renal insufficiency and diabetes mellitus might be explanations for the inconsistent results in the electrolyte balances.

Furthermore, although hyperkalemia is the most characteristic laboratory finding of aldosterone deficiency (16), heparin-induced hyperkalemia is rare. The patients reported to have hyperkalemia have factors compromising potassium excretion, such as renal insufficiency or diabetes mellitus (4,15-19). Therefore, aldosterone deficiency alone does not typically result in hyperkalemia, but when combined with other predisposing factors, such as an exogenous or endogenous potassium load, renal insufficiency, diabetes mellitus, or the use of non-steroidal anti-inflammatory agents or potassium-

Fig. 2.
Percent changes of plasma aldosterone from baseline in response to adrenocorticotrophic hormone (ACTH, left) and low sodium intake (right) during and 2 weeks after discontinuation of heparin therapy. Values are expressed as mean ± SEM.

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sparing diuretics (16), the likelihood of heparin-induced hyperkalemia may be increased.

The mechanism(s) by which heparin affects aldosterone secretion are controversial. Impairment of the enzymatic activity that converts corticosterone to 18-hydroxycorticosterone (5), and inhibition of angiotensin II binding owing to a decrease in both the number and affinity of angiotensin II receptors (6) have been proposed. While ACTH stimulated aldosterone both during and after heparin therapy, the increase in plasma aldosterone owing to low sodium intake in the present study was significantly attenuated during heparin therapy, despite a similar increase in plasma renin activity. Sherman et al. (3) reported that the increase in plasma aldosterone stimulated by furosemide and ambulation was attenuated during heparin administration, however, responses to ACTH were not examined in their study. Although we did not measure precursors of aldosterone, the present results suggest that attenuation of angiotensin II-induced aldosterone production rather than inhibition of enzymatic activity might be responsible for the decrease in aldosterone production by heparin.

In conclusion, heparin doses at 700-1000 units/h has a direct effect on the adrenal gland by impairing aldosterone production. This effect of heparin is probably only of clinical significance when patients have factors compromising renal potassium excretion. Thus, when heparin is administered to these patients, the electrolyte balance should be closely followed.

References


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