Fludrocortisone suppression test in normal subjects, in patients with essential hypertension and in patients with various forms of aldosteronism

Jens Otto Lund and Meta Damkjær Nielsen

Department of Clinical Physiology, Glostrup Hospital, DK-2600 Glostrup, Copenhagen.

Abstract. The response of urinary diurnal tetrahydroaldosterone (TH-aldo) excretion to fludrocortisone administration (0.3 mg q.i.d. for 3 days) was studied. In normal subjects (n = 13) and in patients with essential hypertension (n = 8), urinary TH-aldo decreased to 36 per cent (range 19–48) and to 51 per cent (range 33–61) of the control value, respectively.

Twenty-four patients with primary aldosteronism were studied. Twenty-two of these showed no significant suppression of urinary TH-aldo in that the excretion of TH-aldo was 79 per cent of the control value or more. Nineteen of these patients were submitted to operation, and an adrenal aldosterone-producing adenoma was disclosed in every single case. Two patients with primary aldosteronism demonstrated a significant suppression of aldosterone production to 62 and 68 per cent, respectively. Adrenal micronodular hyperplasia was verified in one case and suspected in the other.

A significant suppression of aldosterone production was observed in 4 of 5 patients with aldosteronism and normal or high plasma renin levels.

The combination of low plasma renin and autonomy of aldosterone production offers a high degree of certainty for the presence of an aldosterone-producing adenoma.

The classical findings in primary aldosteronism are hypertension, hypokalaemia, increased aldosterone production, low plasma renin activity or renin concentration and the presence of an adrenal cortical adenoma (Conn 1966–67). However, the aldosterone production may be within normal limits (Biglieri et al. 1967), and the plasma renin concentration may be variable and only intermittently low (Brown et al. 1968). Furthermore, identical biochemical abnormalities have been observed in hypertensive patients in whom no adrenal adenoma could be found (Davis et al. 1967; Katz 1967; Laragh et al. 1967), and recent reports state that this occurs in 20–50 per cent of patients with high aldosterone/low renin hypertension (Biglieri et al. 1970; Baer et al. 1970; George et al. 1970; Ferriss et al. 1975). In these cases, the adrenal glands showed bilateral cortical hyperplasia in most cases, but even normal adrenal glands have been described (Baer et al. 1970; Ferriss et al. 1975). Adrenalectomy, total or subtotal, normalized the blood pressure in a few patients only (0–20 per cent) in spite of normal or absent aldosterone production post-operatively (Biglieri et al. 1970; Baer et al. 1970; George et al. 1970; Ferriss et al. 1975).

On the other hand, removal of an aldosterone-producing adenoma is followed by improvement or disappearance of the hypertension in 60–90 per cent of cases (Conn 1966–67; Biglieri et al. 1970; Baer et al. 1970; George et al. 1970; Ferriss et al. 1975).

Evaluation of aldosterone production during a mineralocorticoid load has been proposed as a useful tool in the discrimination between various forms of aldosteronism (Biglieri et al. 1967; Horton 1969).

In this paper we present our experience with a suppression test in normal subjects, in patients with essential hypertension and in various forms of aldosteronism.
Normal subjects and patients

In the first part of the study two control groups were investigated.

1. Normal subjects (Nos. 1–13). Thirteen normal subjects (six females, seven males) aged 19–59 years were investigated. Blood pressure, renal function, cardiovascular status, sodium and potassium concentration in plasma were normal in all. The diurnal excretion of adrenocortical steroid metabolites including tetrahydroaldosterone (TH-ald) were normal.

2. Normokalaemic essential hypertension (Nos. 14–21). Eight hypertensive patients (two females, six males) aged 29–64 years had benign, essential hypertension. Diastolic blood pressure was above 100 mmHg on the third day of admission. Plasma potassium had been below 3.4 mmol/l in 5 of the patients during treatment with thiazides. At the time of the study, without treatment or potassium supplements, plasma potassium was within normal limits in all. The diurnal excretion of TH-ald was normal. Cushing’s syndrome, phaeochromocytoma, coarctation of aorta and renal or renovascular disease were ruled out by appropriate tests. Heart failure or signs of malignant hypertension were absent.

During a 9 year period (1969–1978), 29 patients with hypertension, intermittent or persistent hypokalaemia and high-normal or increased diurnal excretion of TH-ald were referred to our department for evaluation of possible primary aldosteronism. In all patients other known causes of hypertension were ruled out as described for group 2. None had malignant hypertension, renal failure or congestive heart failure. Based upon plasma renin concentration (PRC) two groups were defined:

3. Hypokalaemic, low-renin, high-aldosterone hypertension (Nos. 22–45). Twenty-four patients (twenty females, four

Table 1.

Clinical signs, pre- and post-operative laboratory findings in patients with primary aldosteronism (group 3).

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Blood pressure mmHg</th>
<th>Plasma-K mmol/l</th>
<th>Plasma-Na mmol/l</th>
<th>Blood pressure mmHg</th>
<th>Plasma-K mmol/l</th>
<th>Plasma-Na mmol/l</th>
<th>PRC mIU/1**</th>
<th>TH-ald nmol/24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>40 F</td>
<td></td>
<td>192/127</td>
<td>2.0–2.5</td>
<td>143–155</td>
<td>120/90</td>
<td>4.3</td>
<td>–</td>
<td>17</td>
<td>47</td>
</tr>
<tr>
<td>23</td>
<td>47 F</td>
<td></td>
<td>202/120</td>
<td>1.8–2.7</td>
<td>141–147</td>
<td>148/93</td>
<td>4.0</td>
<td>143</td>
<td>39</td>
<td>66</td>
</tr>
<tr>
<td>24</td>
<td>52 F</td>
<td></td>
<td>188/112</td>
<td>3.0–4.3</td>
<td>139–142</td>
<td>153/98</td>
<td>4.1</td>
<td>142</td>
<td>18</td>
<td>33</td>
</tr>
<tr>
<td>25</td>
<td>56 F</td>
<td></td>
<td>177/111</td>
<td>2.1–2.6</td>
<td>146–150</td>
<td>167/98</td>
<td>4.6</td>
<td>140</td>
<td>61</td>
<td>71</td>
</tr>
<tr>
<td>26</td>
<td>55 F</td>
<td></td>
<td>200/115</td>
<td>2.2–2.8</td>
<td>141–148</td>
<td>140/90</td>
<td>4.4</td>
<td>139</td>
<td>43</td>
<td>55</td>
</tr>
<tr>
<td>27</td>
<td>33 F</td>
<td></td>
<td>190/120</td>
<td>2.1–3.0</td>
<td>138–141</td>
<td>144/107</td>
<td>4.5</td>
<td>139</td>
<td>58</td>
<td>145</td>
</tr>
<tr>
<td>28</td>
<td>11 M</td>
<td></td>
<td>168/122</td>
<td>2.8–2.9</td>
<td>143–145</td>
<td>118/82</td>
<td>4.4</td>
<td>132</td>
<td>45</td>
<td>47</td>
</tr>
<tr>
<td>29</td>
<td>51 F</td>
<td></td>
<td>165/115</td>
<td>2.1–2.8</td>
<td>143–149</td>
<td>125/85</td>
<td>4.5</td>
<td>142</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>30</td>
<td>39 F</td>
<td></td>
<td>160/110</td>
<td>2.7–3.3</td>
<td>139–141</td>
<td>125/92</td>
<td>4.2</td>
<td>134</td>
<td>55</td>
<td>93</td>
</tr>
<tr>
<td>31</td>
<td>52 F</td>
<td></td>
<td>210/117</td>
<td>2.5–2.9</td>
<td>143–145</td>
<td>155/105</td>
<td>4.1</td>
<td>142</td>
<td>42</td>
<td>47</td>
</tr>
<tr>
<td>32</td>
<td>57 M</td>
<td></td>
<td>180/110</td>
<td>3.0–3.7</td>
<td>145–149</td>
<td>155/100</td>
<td>4.3</td>
<td>145</td>
<td>28</td>
<td>55</td>
</tr>
<tr>
<td>33</td>
<td>47 F</td>
<td></td>
<td>165/110</td>
<td>2.1–2.7</td>
<td>140–144</td>
<td>125/95</td>
<td>3.8</td>
<td>140</td>
<td>36</td>
<td>63</td>
</tr>
<tr>
<td>34</td>
<td>23 M</td>
<td></td>
<td>175/120</td>
<td>3.1–3.4</td>
<td>140–145</td>
<td>118/82</td>
<td>4.1</td>
<td>138</td>
<td>32</td>
<td>27</td>
</tr>
<tr>
<td>35</td>
<td>51 F</td>
<td></td>
<td>180/112</td>
<td>1.3–3.3</td>
<td>143–149</td>
<td>150/100</td>
<td>4.4</td>
<td>141</td>
<td>60</td>
<td>41</td>
</tr>
<tr>
<td>36</td>
<td>56 F</td>
<td></td>
<td>200/120</td>
<td>2.3–2.9</td>
<td>144–150</td>
<td>140/90</td>
<td>4.6</td>
<td>138</td>
<td>55</td>
<td>88</td>
</tr>
<tr>
<td>37</td>
<td>34 F</td>
<td></td>
<td>150/110</td>
<td>2.6–3.1</td>
<td>142–143</td>
<td>130/90</td>
<td>4.0</td>
<td>141</td>
<td>20</td>
<td>66</td>
</tr>
<tr>
<td>38</td>
<td>55 F</td>
<td></td>
<td>270/150</td>
<td>2.3–3.7</td>
<td>143–148</td>
<td>180/110</td>
<td>4.7</td>
<td>141</td>
<td>35</td>
<td>41</td>
</tr>
<tr>
<td>39</td>
<td>24 F</td>
<td></td>
<td>190/115</td>
<td>2.8–3.0</td>
<td>139–141</td>
<td>120/70</td>
<td>3.9</td>
<td>142</td>
<td>42</td>
<td>145**</td>
</tr>
<tr>
<td>40</td>
<td>47 F</td>
<td></td>
<td>200/120</td>
<td>1.8–3.4</td>
<td>143–147</td>
<td>140/80</td>
<td>4.3</td>
<td>144</td>
<td>8</td>
<td>14*</td>
</tr>
<tr>
<td>41</td>
<td>65 F</td>
<td></td>
<td>205/130</td>
<td>2.1–2.6</td>
<td>147–150</td>
<td>not operated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>60 F</td>
<td></td>
<td>220/135</td>
<td>2.6–3.5</td>
<td>138–146</td>
<td>not operated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>43</td>
<td>58 F</td>
<td></td>
<td>175/100</td>
<td>2.7–3.1</td>
<td>139–144</td>
<td>not operated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>67 F</td>
<td></td>
<td>213/110</td>
<td>3.3–3.8</td>
<td>143–147</td>
<td>195/125</td>
<td>4.2</td>
<td>142</td>
<td>41</td>
<td>82</td>
</tr>
<tr>
<td>45</td>
<td>49 M</td>
<td></td>
<td>168/113</td>
<td>3.5–4.0</td>
<td>140–143</td>
<td>not operated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Time of observation after operation less than 3 months.

** mIU/l = milli International Units per litre (Bangham et al. 1975).
males) aged 11–67 years were investigated. Data on the patients are given in Table 1. Supine PRC was low (<15 mIU/l) and the diurnal excretion of TH-aldo was increased in all except patient No. 30. These patients are highly suspected of having primary aldosteronism. The degree of hypokalaemia varied, and in some patients (Nos. 24, 32, 38, 44, 45) the hypokalaemia was intermittent.

4. Hypokalaemic, normal/high-renin, high-aldosterone hypertension (Nos. 46–50). Five patients (two females, three males) aged 23–55 years were examined. All patients had plasma potassium below 3.3 mmol/l, supine PRC > 15 mIU/l and a increased diurnal excretion of TH-aldo. The diastolic blood pressure was above 110 mmHg.

Methods
All the patients and the normal subjects were studied during hospitalization. Diuretic and antihypertensive therapy was withdrawn at least 3 weeks before the admission except for 2 patients (Nos. 23 and 38) who were treated with methyldopa 500 mg per day and methyldopa 1500 mg + hydralazine 40 mg per day, respectively, throughout the study.

A regular regime consisting of 12 h bed rest and 12 h normal ambulatory in-patient activity was prescribed. Only minor, non-invasive, diagnostic procedures such as eye-ground investigation, electrocardiography, X-ray of thorax were performed during the suppression test. X-ray examination, requiring an enema, were carried out after completion of the suppression test. For 7 days a constant diet containing 10 mEq sodium and approximately 50 mEq potassium, with a supplement of 100 mEq sodium divided in three daily doses, was given. Three patients with severe hypokalaemia were given additional potassium chloride 45 mEq per day. Twenty-four-hour urine collections were obtained throughout the study.

The suppression test was performed in the following way. After 3 days the patients were in steady state on the diet with respect to intake and urinary excretion of sodium and accustomed to the hospital regime. The urine collected during the fourth day was used for determination of TH-aldo. During days Nos. 5, 6 and 7 the patients were given 9a-fludrocortisone (Florinef®, Squibb) 1.2 mg per 24 h (0.3 mg q.i.d.). The urine collected during the seventh day was used for a second determination of TH-aldo. The degree of suppression was expressed as a ratio: excreted TH-aldo on day No. 7 divided by the control value obtained on day No. 4.

Tetrahydroaldosterone in urine (TH-aldo) was determined in duplicate as previously described (Nielsen et al. 1972). The normal range on a diet with 110 mEq sodium is 30–162 nmol/24 h, and the coefficient of variation (CV) is 12 per cent as determined from 90 duplicate determinations (Nielsen et al. 1972). For a ratio between two measurements a and b, each done in duplicate, CV is given by (Colquhoun 1971):

$$CV^2(a/b) = \frac{CV^2(a)}{2} + \frac{CV^2(b)}{2}$$

Accordingly, the coefficient of variation for a ratio between two measurements of TH-aldo, each done in duplicate, is seen to be 12 per cent. From this follows that the 95 per cent confidence interval for a ratio of 1.00 (unchanged TH-aldo excretion) ranges from 0.76 to 1.24.

Creatinine excretion was measured in all 24 h urines collected. Urine collection during days No. 4 and No. 7 was assumed to be complete if the diurnal creatinine excretion did not differ by more than 10 per cent from the average diurnal creatinine excretion across 7 days for the patient in question.

Plasma renin concentration (PRC) was measured by the method of Giese et al. (1970) on the morning of day No. 4 in the supine patient. Normal range is 6–59 mIU/l, mean 24 mIU/l. The international renin standard, code 68/356, was used as an internal reference in the assay (Bangham et al. 1975).

Blood pressure was measured on 3 consecutive mornings in the supine patient. At the follow-up study the operated patients (group 3) were examined after one hour of quite supine rest.

Results
The results are given in Tables 2 and 3. In normal subjects (group 1) the diurnal excretion of TH-aldo decreased to less than half of the control value. Also in patients with essential hypertension (group 2) a definite suppression was found, but the response was less pronounced than that observed in normal subjects (Mann-Whitney test, $P < 0.05$). However, in all patients with essential hypertension the suppression was significant: none of the patients showed values within the 95 per cent confidence interval defining non-suppression.

Among the patients with primary aldosteronism (group 3) unchanged or increased diurnal excretion of TH-aldo during a fludrocortisone load was found in 22 patients (Nos. 22–43), as the diurnal excretion of TH-aldo was 79 per cent or more of the control value. One patient (No. 30) had normal excretion of TH-aldo on the control day and on the two preceding days (91, 154 and 143 nmol/24 h).
During fludrocortisone the excretion of TH-aldo was 332 nmol/24 h (day 6) and 277 nmol/24 h (day 7).

Unilateral adrenalectomy or resection of one adrenal gland was performed in patients Nos. 22—40 and a solitary adenoma measuring from 8 to 35 mm was removed in all. Micronodules were not found in the surrounding adrenal tissue. Postoperative follow-up performed from ½ to 4 years after the operation (Table 1) revealed normal plasma potassium, normal or subnormal excretion of TH-aldo, normal PRC and a definite fall in blood pressure in all patients. The post-operative blood pressure became normal in 14 patients (diastolic blood pressure less than 100 mmHg) and was only moderately elevated in 5 patients.

In the patients Nos. 41 and 42 a major operation was contraindicated because of arteriosclerotic heart disease with recent myocardial infarction and recent fracture of the femoral neck in a patient with dementia, respectively. Patient No. 43 refused operation. Therefore, a final diagnosis has not been obtained in patients Nos. 41—43.

The patients Nos. 44 and 45 had only slightly elevated diurnal excretion of TH-aldo on the control day. The excretion of TH-aldo decreased significantly during fludrocortisone loading, though not to the values seen in patients with

\[
\begin{array}{|c|c|c|c|c|}
\hline
\text{No.} & \text{PRC mIU/l}^* & \text{TH-aldo nmol/24 h} & \text{TH-aldo}_7 & \text{TH-aldo}_4 \\
\hline
1 & 13 & 93 & 19 & 0.20 \\
2 & 28 & 79 & 22 & 0.28 \\
3 & 18 & 25 & 5 & 0.20 \\
4 & 40 & 79 & 33 & 0.42 \\
5 & 68 & 115 & 22 & 0.19 \\
6 & 30 & 121 & 44 & 0.36 \\
7 & 29 & 71 & 27 & 0.58 \\
8 & 6 & 41 & 16 & 0.39 \\
9 & 14 & 30 & 11 & 0.37 \\
10 & 24 & 82 & 25 & 0.30 \\
11 & 17 & 93 & 38 & 0.41 \\
12 & 25 & 33 & 11 & 0.33 \\
13 & 23 & 79 & 38 & 0.48 \\
\hline
\text{Group 1} & \text{Range} & 6–68 & 25–121 & 5–44 & 0.19–0.48 \\
\text{Median} & 24 & 79 & 22 & 0.36 \\
\hline
14 & 11 & 58 & 33 & 0.57 \\
15 & 5 & 112 & 63 & 0.56 \\
16 & 26 & 145 & 58 & 0.40 \\
17 & 4 & 118 & 58 & 0.49 \\
18 & 29 & 156 & 52 & 0.33 \\
19 & 17 & 129 & 69 & 0.53 \\
20 & 14 & 110 & 44 & 0.40 \\
21 & 25 & 77 & 47 & 0.61 \\
\hline
\text{Group 2} & \text{Range} & 4–29 & 58–156 & 33–69 & 0.33–0.61 \\
\text{Median} & 16 & 115 & 55 & 0.51 \\
\hline
\end{array}
\]

* mIU/l: milli International Units per litre.

** TH-aldo_7 and TH-aldo_4: Tetrahydroaldosterone excretion on day 7 and day 4.
Table 3.
Supine plasma renin concentration (PRC), and excretion of tetrahydroaldosterone (TH-ald) before and during administration of fludrocortisone in patients with hypertension, hypokalaemia and/or aldosteronism.

<table>
<thead>
<tr>
<th>No.</th>
<th>PRC mIU/l</th>
<th>TH-ald nmol/24 h day 4</th>
<th>TH-ald nmol/24 h day 7</th>
<th>TH-ald nmol/24 h day 7/TH-ald nmol/24 h day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>5</td>
<td>600</td>
<td>830</td>
<td>1.38</td>
</tr>
<tr>
<td>23</td>
<td>4</td>
<td>617</td>
<td>527</td>
<td>0.85</td>
</tr>
<tr>
<td>24</td>
<td>5</td>
<td>198</td>
<td>156</td>
<td>0.79</td>
</tr>
<tr>
<td>25</td>
<td>9</td>
<td>724</td>
<td>952</td>
<td>1.31</td>
</tr>
<tr>
<td>26</td>
<td>10</td>
<td>535</td>
<td>486</td>
<td>0.91</td>
</tr>
<tr>
<td>27</td>
<td>3</td>
<td>252</td>
<td>324</td>
<td>1.29</td>
</tr>
<tr>
<td>28</td>
<td>1</td>
<td>283</td>
<td>285</td>
<td>1.01</td>
</tr>
<tr>
<td>29</td>
<td>5</td>
<td>642</td>
<td>642</td>
<td>1.00</td>
</tr>
<tr>
<td>30</td>
<td>7</td>
<td>91</td>
<td>277</td>
<td>3.04</td>
</tr>
<tr>
<td>31</td>
<td>10</td>
<td>187</td>
<td>156</td>
<td>0.83</td>
</tr>
<tr>
<td>32</td>
<td>3</td>
<td>272</td>
<td>258</td>
<td>0.95</td>
</tr>
<tr>
<td>33</td>
<td>4</td>
<td>787</td>
<td>1012</td>
<td>1.29</td>
</tr>
</tbody>
</table>

Goup 3

<table>
<thead>
<tr>
<th>No.</th>
<th>PRC mIU/l</th>
<th>TH-ald nmol/24 h day 4</th>
<th>TH-ald nmol/24 h day 7</th>
<th>TH-ald nmol/24 h day 7/TH-ald nmol/24 h day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>11</td>
<td>170</td>
<td>195</td>
<td>1.15</td>
</tr>
<tr>
<td>35</td>
<td>12</td>
<td>170</td>
<td>187</td>
<td>1.10</td>
</tr>
<tr>
<td>36</td>
<td>8</td>
<td>247</td>
<td>324</td>
<td>1.31</td>
</tr>
<tr>
<td>37</td>
<td>6</td>
<td>477</td>
<td>502</td>
<td>1.05</td>
</tr>
<tr>
<td>38</td>
<td>7</td>
<td>230</td>
<td>225</td>
<td>0.98</td>
</tr>
<tr>
<td>39</td>
<td>5</td>
<td>329</td>
<td>359</td>
<td>1.09</td>
</tr>
<tr>
<td>40</td>
<td>7</td>
<td>395</td>
<td>444</td>
<td>1.12</td>
</tr>
<tr>
<td>41</td>
<td>11</td>
<td>546</td>
<td>647</td>
<td>1.18</td>
</tr>
<tr>
<td>42</td>
<td>6</td>
<td>269</td>
<td>230</td>
<td>0.86</td>
</tr>
<tr>
<td>43</td>
<td>4</td>
<td>211</td>
<td>187</td>
<td>0.88</td>
</tr>
<tr>
<td>44</td>
<td>14</td>
<td>170</td>
<td>115</td>
<td>0.68</td>
</tr>
<tr>
<td>45</td>
<td>6</td>
<td>178</td>
<td>110</td>
<td>0.62</td>
</tr>
<tr>
<td>46</td>
<td>26</td>
<td>200</td>
<td>305</td>
<td>1.53</td>
</tr>
<tr>
<td>47</td>
<td>61</td>
<td>502</td>
<td>247</td>
<td>0.49</td>
</tr>
<tr>
<td>48</td>
<td>38</td>
<td>192</td>
<td>55</td>
<td>0.29</td>
</tr>
<tr>
<td>49</td>
<td>45</td>
<td>219</td>
<td>85</td>
<td>0.39</td>
</tr>
<tr>
<td>50</td>
<td>23</td>
<td>167</td>
<td>71</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Group 4

essential hypertension. Patient No. 44 was studied early in our experience, and an operation was found to be indicated. A small adrenal tumour (6 mm) was found and unilateral adrenalectomy was carried out. In contrast to the findings in patients Nos. 22–40, the surrounding adrenal tissue showed several micronodules and hyperplasia. Post-operatively, the blood pressure remained unaltered (Table 1). Patient No. 45 has not been operated upon (see below).

The patients in group 4 showed significant suppression of TH-ald excretion during fludrocortisone loading except patient No. 46. The degree of suppression for patients Nos. 47–50 was comparable to the findings in group 2.

Discussion

Our results confirm that the aldosterone production is significantly suppressed in normal subjects and in patients with essential hypertension during a high dosage of a synthetic mineralocorticoid (Biglieri et al. 1967).

The patients with primary aldosteronism (group 3) were selected according to accepted definitions of this syndrome (Conn 1966–67; Padfield et al. 1975). In 22 patients the aldosterone production appeared autonomous and in each one of the 19, so far operated upon, a typical adrenal adenoma was disclosed. Post-operatively, the biochemical features of primary aldosteronism disappeared, and
the blood pressure became normal or decreased considerably. These findings imply that the adrenal adenoma had been the sole source of excess aldosterone production. Patient No. 30 was unique in having normal to high-normal diurnal excretion of TH-ald. However, normal excretion of aldosterone-18-glucuronide in primary aldosteronism has been described (Biglieri et al. 1967; Weinberger et al. 1979). Extensive studies by additional measurements of TH-ald before and during the suppression test revealed an exceptional day-to-day variation and a three-fold increase during administration of fludrocortisone. It may be possible that the observed increase in TH-ald excretion is due to an extreme variation in aldosterone production during the whole study.

Two patients (Nos. 44 and 45) of group 3 showed significant suppression of aldosterone production during fludrocortisone loading. Patient No. 44, studied early in our experience, was surgically treated. However, the hypertension was not ameliorated and the pathological findings in the adrenal differed from those in patients Nos. 22–40. Patient No. 45 was studied at a later date when the successful outcome of surgical treatment in a series of patients with autonomous aldosterone secretion had been recorded. Additional studies in this patient, adrenal scintigraphy with $^{[131]}$Icholesterol and venous catheterization with determination of aldosterone in the adrenal efflux, did not reveal any lateralization. Therefore, the presence of bilateral adrenal hyperplasia was considered most likely. Since the outcome of surgical treatment in this condition has been disappointing (Biglieri et al. 1972; Ferriss et al. 1975), a surgical exploration was deemed to be unjustified.

In the patients with high aldosterone production and normal or high plasma renin (group 4) the aldosterone production was significantly suppressed in all patients except No. 46. In this case adrenal scintigraphy as well as venous catheterization was carried out. None of the additional studies revealed any lateralization. This fact, taken together with the higher renin value compared to those found in patients with verified adrenal adenoma, made us consider an aldosterone-producing adenoma less likely in this patient (Baer et al. 1970; George et al. 1970; Ferriss et al. 1970). Final evidence has not been obtained, as a surgical exploration has not been carried out. The patients Nos. 47–50 reacted as patients with essential hypertension.

The diagnostic specificity of the mineralocorticoid suppression test for discrimination between aldosterone-producing adenoma and bilateral adenocortical hyperplasia in primary aldosteronism has been questioned. It is generally accepted that patients with aldosterone-producing adenomas do not lower the aldosterone production or excretion during a mineralocorticoid load (Biglieri et al. 1967, 1972; Cain et al. 1972; Slaton et al. 1969). In their original report Biglieri et al. (1967) demonstrated significant suppression of aldosterone excretion rate in 2 patients without adenoma. In a larger material (Biglieri et al. 1972) non-suppressible aldosterone excretion rate was found in 8 out of 10 patients with surgically proven adrenal hyperplasia without adenoma. A similar experience was reported by Lufkin et al. (1972) in a single case.

The most impressive result of the present study is that all patients fulfilling three criteria: 1) PRC below 15 mIU/l, 2) excretion of TH-ald increased or at the upper limit of normal range and 3) non-suppressible aldosterone production during a high dosage of a synthetic mineralocorticoid, had an aldosterone-producing adenoma. Thus, the integrated predictive value of these criteria was 100 per cent. In our series of patients with primary aldosteronism only one single case of adrenal hyperplasia with micronodules was histologically verified and one additional case was suspected. None of the patients with essential hypertension (group 2) fulfilled the above mentioned three criteria. Besides, the consistently normal plasma potassium levels observed after withdrawal of treatment made the possibility of primary aldosteronism less likely, but it must be admitted that primary aldosteronism cannot be excluded as the adrenal pathology is unknown. Obviously, we are not able to discuss the predictive value of negative suppression test.

Different criteria have been applied for evaluation of suppression tests. Biglieri et al. (1967, 1972) defined an abnormal suppression test as a failure to reduce urinary aldosterone levels into the normal range or to depress normal levels, which may be present in the occasional case of primary aldosteronism (Biglieri et al. 1967). We have evaluated the response during fludrocortisone loading, using our data on the day-to-day variation and the within-analysis variation. In 2 patients (Nos. 24 and 31) the diurnal excretion of TH-ald was suppressed into the normal range, but the change in excretion of TH-ald did not exceed the limits determined by the analytic and biological variation.
Blood sampling and determination of plasma aldosterone have practical and methodological advantages. However, the plasma concentration of aldosterone shows a diurnal variation and several secretory peaks in normal subjects and in patients with aldosterone-producing adenomas or bilateral hyperplasia (Cain et al. 1972; Katz et al. 1972; Kem et al. 1973; Vetter et al. 1974, 1978). The mean value of plasma aldosterone is not suppressed in patients with aldosterone-producing adenomas during fludrocortisone loading (Horton 1969; Padfield et al. 1975; Vetter et al. 1978), but the individual responses are varying. Furthermore, patients with adrenal adenoma and patients with adrenal hyperplasia did not differ with respect to the plasma aldosterone response to fludrocortisone loading (Padfield et al. 1975; Vetter et al. 1978), and the fludrocortisone suppression test – employing plasma aldosterone measurements – was found by these investigators to be of no value.

Methods based on diurnal urinary excretion integrate the aldosterone production over a period of 24 h, thereby minimizing the effect of intermittent secretory bursts. We have found the fludrocortisone suppression test – employing urinary excretion of TH-aldo – to be a valuable diagnostic procedure. In our view the avoidance of unnecessary adrenal surgery is a point of major importance. In our study minor urinary metabolites of aldosterone, such as aldosterone-18-glucuronide and free aldosterone were not measured. The knowledge of small day-to-day variations of urinary TH-aldo during steady state conditions in normals made this parameter most attractive in evaluation of a suppression test (Nielsen et al. 1972).

The discrimination between adrenal adenoma and adrenocortical hyperplasia in primary aldosteronism on the basis of clinical date is impossible (Vetter et al. 1978). The tendency to more pronounced biochemical disturbances in patients with adenoma as compared to those with hyperplasia (Baer et al. 1970; Ferriss et al. 1970; Biglieri et al. 1972; Padfield et al. 1975) have formed basis for a useful statistical analysis for prediction of the lesion (Ferriss et al. 1970; Aitchison et al. 1971). However, this procedure requires a considerable number of patients in each group and may be difficult to transfer to other centres due to methodological differences.

In our series of 24 patients with primary aldosteronism only one case of adrenal hyperplasia was histologically verified and one additional case was suspected. This is a lower frequency than that reported by others (Baer et al. 1970; George et al. 1970; Ferriss et al. 1975; Vetter et al. 1978). A probable explanation of this discrepancy can be the use of more restrictive criteria for inclusion in our study.

Acknowledgments

This study was supported by Statens Almindelige Videnskabsfond, Statens lægevidenskabelige Forskningsråd og Hjerteforeningen.

References


Received on March 26th, 1979.