Hypotensive Effect of Ethacrynic Acid

By James Conway, M.D., Ph.D., and Gastone Leonetti, M.D.

The benzothiadiazine derivatives were the first diuretic compounds that could safely be administered over considerable periods of time and yet retain their effectiveness. In the course of the investigation of their diuretic properties in man it became apparent that they also possessed weak antihypertensive properties. The mechanism of this action remains uncertain, and there is doubt as to whether these drugs have an independent action on vascular smooth muscle or whether the fall in blood pressure is the result of their saluretic effects.

The objective of this report is first to determine whether a chemically unrelated diuretic, ethacrynic acid, possesses antihypertensive properties similar to those of hydrochlorothiazide and secondly to ascertain whether the fall in arterial blood pressure produced by the thiazide diuretics could be materially increased by increasing the sodium depletion.

Methods

Two groups of patients have been studied in this investigation. Ten out-patients with mild hypertension who constituted the first group were placed alternately on a thiazide diuretic, (hydrochlorothiazide, 100 mg./day or chlorothiazide 1 Gm./day) or ethacrynic acid, 150 mg./day for periods of 21 to 32 days. The drug to be given first was chosen at random, and each drug period was preceded by a similar period on placebo. At the completion of this trial and after a further placebo period six of these patients were placed on both drugs together. In order to achieve this without excessive or sudden weight loss, the patients were instructed to take the thiazide diuretic alone for a period of 1 week and then to add the ethacrynic acid for a period of 3 weeks. All patients received supplementary potassium (40 to 65 mEq./day) throughout the study and at each outpatient visit measurements were made of serum sodium, potassium, carbon dioxide, chloride, uric acid, and blood urea nitrogen. The patients recorded their blood pressure in the recumbent position twice daily at home during the entire study, and also recorded their weight daily, on arising in the morning and after emptying the bladder. For each period of observation an average was taken of the readings over the final 5 days.

The second group consisted of seven patients with severe hypertension already on thiazide diuretics, all of whom were permitted to continue with hydrochlorothiazide during the control period; however, five who had been receiving autonomic blocking agents had these stopped before the period of study. The combined effect of chlorothiazide, ethacrynic acid, and a low-sodium diet (750 to 1,000 mg./day) was then studied. The doses of ethacrynic acid and of potassium were adjusted according to the individual response. This regimen was started during a period of hospitalization in order to insure that serious electrolyte imbalance or azotemia could be prevented.

Toxicity studies consisting of serum glutamic oxaloacetic transaminase, hemoglobin, white blood cell count, and urinalysis were performed on all patients at 3 or 4 weekly intervals.

Results

In the first study the mean of all the placebo periods taken together gave a recumbent pressure of 158/100 mm. Hg, and body weight was 175 lb. On the thiazide diuretic, the mean blood pressure fell to 140/91 mm. Hg, with a mean fall in body weight of 4 lb. On ethacrynic acid, the average blood pressure was 144/92 mm. Hg, with a mean fall in body weight of 5 lb. Although the blood pressure level with each drug differed significantly from control ($p<0.01$) there was no significant difference between the effects of the two drugs (table 1). For the six patients who took the two diuretics together the mean control blood pressure was 16/100 mm. Hg, with body weight of 167 lb. When both diuretics were taken the mean body weight was reduced by 8 lb. and the blood pressure declined to 135/87 mm. Hg, an effect practically
changes showed and uretics were given together there was a rise of serum potassium and chloride.

In the patients with severe hypertension the mean recumbent blood pressure while on thiazide diuretics was 210/122 mm. Hg. After 2 weeks of combined therapy with both diuretics and a low-sodium diet in the hospital the mean recumbent pressure had fallen to 168/112 mm. Hg and the body weight by 12 lb. After discharge from the hospital, and after 6 to 8 weeks on the same program, the blood pressure was of the same order, 163/109 mm. Hg; after 10 to 13 weeks it was unaltered, 162/104 mm. Hg (table 4, fig. 1). The patients on this regimen felt well and were able to continue their normal occupations, although there was an average rise in blood urea nitrogen of 18.6 mg. per cent. The objective of the present report is to demonstrate the magnitude of the change in blood pressure to be expected from this regimen; the data,

<table>
<thead>
<tr>
<th>No.</th>
<th>Placebo</th>
<th>Thiazide</th>
<th>Ethacrynic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BP, mm. Hg</td>
<td>Wt., lb</td>
<td>BP, mm. Hg</td>
</tr>
<tr>
<td>1</td>
<td>161/100</td>
<td>167</td>
<td>148/94</td>
</tr>
<tr>
<td>2</td>
<td>10.3/6.9</td>
<td>25.0</td>
<td>12.3/13.3</td>
</tr>
</tbody>
</table>

*Or chlorothiazide 1,000 mg./day.
†Mean of the placebo periods preceding each drug period.
Table 3
Mean Changes in Serum Electrolytes, Uric Acid, and Blood Urea Nitrogen during Diuretic Therapy

<table>
<thead>
<tr>
<th></th>
<th>Na (mEq./L.)</th>
<th>K (mEq./L.)</th>
<th>CO₂ (mm Hg)</th>
<th>Cl (mEq./L.)</th>
<th>Uric acid (mg.%)</th>
<th>BUN (mg.%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo*</td>
<td>142.0</td>
<td>4.2</td>
<td>29.2</td>
<td>99.7</td>
<td>6.8</td>
<td>18.6</td>
</tr>
<tr>
<td>Thiazide†</td>
<td>140.0</td>
<td>3.8</td>
<td>31.0</td>
<td>96.0</td>
<td>8.0</td>
<td>23.0</td>
</tr>
<tr>
<td>Ethacrynic acid;</td>
<td>143.5</td>
<td>4.1</td>
<td>28.4</td>
<td>96.8</td>
<td>8.3</td>
<td>18.5</td>
</tr>
<tr>
<td>Thiazide + ethacrynic acid</td>
<td>138.0</td>
<td>2.5</td>
<td>32.8</td>
<td>88.2</td>
<td>8.4</td>
<td>20.7</td>
</tr>
</tbody>
</table>

*All patients received potassium supplements, 40 to 60 mEq./day, throughout the study.
†Hydrochlorothiazide 100 mg./day or chlorothiazide 1,000 mg./day.
††Ethacrynic acid 150 mg./day.

Table 4
Combined Antihypertensive Effect on the Blood Pressure of Low-Sodium Diet (750 to 1,000 Mg.) and Ethacrynic Acid (50 to 150 Mg./Day) Added to Hydrochlorothiazide Therapy (100 Mg./Day)

<table>
<thead>
<tr>
<th>No.</th>
<th>Control on thiazide</th>
<th>Combined B with diet, chlorothiazide, and ethacrynic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BP, Wt., mm. Hg, lb.</td>
<td>2 weeks of B, Wt., mm. Hg, lb.</td>
</tr>
<tr>
<td>1</td>
<td>188/130 259</td>
<td>139/107 244</td>
</tr>
<tr>
<td>2</td>
<td>151/97 184</td>
<td>132/91 174</td>
</tr>
<tr>
<td>3</td>
<td>263/134 189</td>
<td>176/121 176</td>
</tr>
<tr>
<td>4</td>
<td>203/122 168</td>
<td>153/105 152</td>
</tr>
<tr>
<td>5</td>
<td>210/140 166</td>
<td>197/129 152</td>
</tr>
<tr>
<td>6</td>
<td>238/118 244</td>
<td>199/119 228</td>
</tr>
<tr>
<td>7</td>
<td>217/112 159</td>
<td>183/115 154</td>
</tr>
</tbody>
</table>

Mean 210/122 195    168/112 183    163/109 183    162/104 187
sd 36.1/14.6 39.6    27.2/12.5 37.9    31.1/15.6 40.1    23.0/13.0 38.7

EFFECT OF SODIUM DEPLETION
THIAZIDE+ETHACRYNIC ACID

Figure 1
The mean effect on the blood pressure in seven patients of adding a low-sodium diet (750 to 1,000 mg.) and ethacrynic acid to thiazide therapy.

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therefore, on sodium balance and hemodynamic changes in this aspect of the study are to be reported later.

Throughout the study few side effects of ethacrynic acid were detected, with the exception of nausea and diarrhea and sometimes vomiting, which developed in five patients. The severity of the symptoms required withdrawal of one patient from the trial. The cause of this symptom has not been elucidated, but it was not associated with hematologic abnormalities or with changes in the serum glutamic oxaloacetic transaminase levels. It is probably dose-dependent, since preliminary studies had shown that doses of 300 mg./day of ethacrynic acid frequently produced gastrointestinal difficulty. But once the symptom had appeared, a second challenge with a single oral dose of 50 mg., which was given
to three patients in the group, resulted in nausea and vomiting.

Discussion

These studies indicate that ethacrynic acid, though chemically unrelated to chlorothiazide, possesses the same antihypertensive action. In this respect our findings are similar to those of Dollery et al. When an additional diuretic response is obtained by the use of both drugs simultaneously a further fall in blood pressure is obtained. It is possible that the entire effect could be obtained by use of ethacrynic acid alone, but in our hands the dose required, approximately 300 mg./day, frequently produced gastrointestinal side effects. Since it has been shown that increasing the dosage of the thiazide derivatives above that generally used produces little additional diuretic or antihypertensive response, resort had to be made to the two drugs taken together.

When dietary restriction of sodium and ethacrynic acid were added to thiazide therapy in patients with severe hypertension the average fall in recumbent blood pressure was 48/18 mm. Hg. This is extremely encouraging, since it demonstrates that diuretic therapy alone is potentially capable of controlling blood pressure even in severe disease and, alone, it may offer a reasonable alternative to the use of autonomic blocking agents. It will be appreciated, of course, that the use of such extensive sodium depletion is not without danger. The patients with severe hypertension were closely followed in the hospital at the initiation of therapy and further investigation of the feasibility of this regimen on larger numbers of patients is being undertaken.

The means by which diuretic agents reduce blood pressure is, of course, unknown; but on evidence presently available, there is little to suggest that they do this by virtue of a vascular action that is independent of their diuretic effect.

Summary

Ethacrynic acid has been found to possess a similar antihypertensive action to the thiazide diuretics. The use of the two drugs together results in a greater fall in pressure than that obtained with either drug alone. When thiazide therapy is supplemented by ethacrynic acid and dietary restriction of sodium a substantial additional reduction in blood pressure averaging 48/18 mm. Hg was obtained.

References

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