Clinical Features of Fluid Retention Complicating Treatment with Guanethidine

By A. J. Smith, M.A., B.M., M.R.C.P.

In the course of a clinical trial of the hypotensive drug guanethidine, it was observed that a proportion of treated patients developed edema or an unexplained gain in weight, thought to be a result of fluid retention.\(^1\) This observation was confirmed when Dollery, Emslie-Smith, and Milne\(^2\) reported a further series, noting fluid retention yet being unable to correlate it with any diminution in the urinary excretion of sodium or water in the two patients they studied by balance technics. The association of fluid retention and temporary loss of blood pressure control, both easily reversed by diuretic drugs, was later reported in more detail.\(^3\)

A review of the literature on hypotensive drug treatment reveals many reports of similar fluid retention occurring with a range of different drugs. Perera\(^4\),\(^5\) MacArthur\(^6\), Mellick and McGregor\(^7\), and Winer\(^8\) reported and investigated this side effect during treatment with reserpine while Fraser and Lowe\(^9\) and Rønnov-Jessen\(^10\),\(^11\) recorded its production by ganglion-blocking drugs. More recently, alphamethyl dopa has also been shown to have fluid-retaining properties.\(^12\),\(^13\)

It has been variously assumed that progressive impairment of renal function resulting from postural hypotension, venous pooling in the extremities, or reduction in cardiac output was responsible, either singly or in combination, for this inconvenient and occasionally dangerous side effect. Rønnov-Jessen\(^10\) emphasized the renal factors when he stated: "it is possible that the reduction in the blood pressure prevents an affected kidney from excreting salt and water" although later revising this opinion in 1961 when he wrote: "it is improbable that the changes are primarily dependent on renal factors since they were also seen in some cases where the blood-pressure decrease was negligible."\(^11\)

Some of the authors quoted have divided their treated patients into fluid-retaining and non-fluid-retaining groups and looked for differences between them to explain their different responses. These comparisons have usually been between small groups of patients and, partly for this reason, no convincing or consistent conclusions have emerged.

Material

This report deals with 134 patients treated continuously with guanethidine for at least 1 year in the hypertension clinic of the Royal Infirmary, Sheffield, England. Although most were admitted to the hospital for first assessment and the initiation of treatment, all were seen regularly in the Outpatient Clinic, in the first instance weekly, and, even when stabilized on a constant dose of guanethidine, never at longer than eight weekly intervals. Patients were weighed at each attendance and seen by one of three doctors experienced in the use of guanethidine and particularly interested in side effects induced by it. Thus records were adequate and designed in advance to meet the needs of this survey.

Results

Forty-four (32.8 per cent) of the 134 patients studied had evidence of fluid retention as indicated by edema, raised jugular venous pressure, pulmonary rales, or sudden increase in weight with loss of blood pressure control. Figure 1 shows the number of patients affected at varying stages up to 30 months from the start of treatment. Over half of them had presented before the end of 6 months' treatment and the largest single number in the first month. The following factors were considered.

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Among the 44 patients developing fluid retention, 23 had previously had some form of edema, the proportion for the other group being 28 of 90. The apparent excess of patients with previous edema in the fluid-retaining group achieves statistical significance at the 5-per cent level.

**Previous Renal Disease**

This proved harder to gauge than the other factors considered, for, while patients are likely to have noticed edema, they may have no awareness of previous disturbances of renal function, particularly if these, though relevant, occurred in the distant past. Renal disease for this purpose has included any reference to acute glomerulonephritis, toxemia of pregnancy (although this is noted separately in a subsequent section) and recurrent urinary infections or the nephrotic syndrome. The proportions of patients affected in each group were 17 of 44 and 36 of 90. The ratios were almost identical.

To provide a more objective criterion for the diagnosis of renal impairment, the pretreatment blood urea levels of the 134 patients were examined.

In a routine clinic it was not possible to perform more refined tests of renal function in every patient and those with a pretreatment blood urea exceeding 70 mg./100 ml. were not given as potent a hypotensive agent as guanethidine. The mean value for blood urea in the fluid-retaining group was 34.2 mg./100 ml. (S.D. ± 10.7) and in the other group 37.2 mg./100 ml. (S.D. ± 12.5). No significant difference exists between the two groups on analysis.

**Incidence of Toxemia of Pregnancy**

This was examined in the 73 women of the series. Only three had no previous pregnancies. If these are excluded from the groups,

**Table 1**

<table>
<thead>
<tr>
<th>Age of Patients in the Two Groups</th>
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</thead>
<tbody>
<tr>
<td>Group</td>
</tr>
<tr>
<td>Fluid-retaining</td>
</tr>
<tr>
<td>Nonfluid-retaining</td>
</tr>
</tbody>
</table>

![Graph showing time-incidence of fluid retention in patients treated with guanethidine.](image)

**Figure 1**

Time-incidence of fluid retention in patients treated with guanethidine.

**Sex**

Most of the female patients were postmenopausal, and of the 44 patients with fluid retention 30 were women and only 14 men. Over-all, 30 of 73 women and 14 of 61 men developed the complication. The greater proportion of women with fluid retention just achieves statistical significance at the 5-per cent level (analysis by \( \chi^2 \)).

**Age**

It might be expected that patients developing fluid retention would be on average older than those not affected, particularly so if this is related to impairment of cardiac function. The mean age for each group at the start of treatment was compared, ages being correct to the nearest 3 months. The results are shown in table 1. Analysis of these age distributions demonstrates no significant difference between the groups.

**Previous Edema**

It seemed pertinent to inquire whether patients developing fluid retention were those rendered susceptible by previous illnesses producing edema. For this purpose edema-producing diseases include left ventricular failure, congestive cardiac failure, and renal disease complicated by the occurrence of edema. Liver disease with ascites, allergic edemas, and the local edema associated with vascular inflammation or occlusion had not been experienced by any patient.
five of 28 developing fluid retention and 10 of 42 in the other group had previously experienced toxemia in one or more pregnancies. With these small numbers it was impossible to demonstrate a significant difference.

Changes in the Frequency of Micturition

Vlastaris and Dustan\textsuperscript{14} suggested that the postural hypotension produced by guanethidine was responsible for a reduction in renal sodium filtration and excretion by day, both reverting to normal at night when the patient lies down and the postural effect is lost. To support this they recorded a reduction in urine volumes passed by day and increases in nocturnal frequency of micturition in their patients.

All our patients were questioned on these points and asked to compare their urinary frequency before and after starting treatment with guanethidine. In the fluid-retaining group 14 had noticed a diminution in the amount of urine passed by day and were often rising 3 or 4 times by night to pass moderately large quantities of urine. However, 16 of the 90 unaffected complained of the same symptom. Analysis by $\chi^2$ does not demonstrate any significant difference between the groups in this respect.

Heart Size and Electrocardiographic Changes

The first of these proved impossible to assess as a review of the patients' chest x-rays showed that there had often been difference in the phase of respiration in which these had been taken, and in some cases the films were not true posteroanterior projections.

 Electrocardiographic tracings were available in all cases before treatment started, and the main categories of abnormality and their frequency are shown in table 2.

The only differences between the two groups were the larger proportion of normal electrocardiograms in the group unaffected by fluid retention, and the small proportion of patients in this group with ischemic changes. These differences are small and not significant.

Finally, the incidence of fluid retention was found to bear no relation to the dose of guanethidine used nor was it related to any of the other recognized side effects of this drug.

Discussion

The comparison of clinical data and simple laboratory tests in the two groups of patients can only be as accurate as the information used. However, no outstanding or unique feature distinguishes those patients who developed fluid retention from those who did not. There is evidence that women are more prone to the complication than men and that a previous history of edema may also be a predisposing factor but this is not strong enough to suggest that these two factors explain all the clinical findings.

There exist two alternative explanations. In the first place, the "factor" which favors the development of fluid retention in one group (or prevents its appearance in the other) may not have been recognized. On the other hand, it may be that this factor is nonexistent and the distinction between the two groups an arbitrary one. In this event, fluid retention becomes a graded phenomenon presenting as slight weight gain at one extreme and as overt

| Table 2 |
|---|---|---|---|---|
| Electrocardiographic Findings in the Two Groups |
| Normal | L axis dev. | LV + | LBBB | LV + Isch. |
| Group I | 0 | 11 | 28 | 1 | 4 |
| Group II | 10 | 27 | 47 | 2 | 4 |

Where: L axis dev. = left axis deviation.
LV + = left ventricular preponderance or "strain."
LBBB = left bundle-branch block.
LV + Isch. = left ventricular preponderance with ischemic changes.
edema at the other. Thus the dividing line between the two groups of patients might be drawn at a different point or might even be nonexistent, all patients treated with guanethidine being potentially liable to retain fluid.

The distinction between these two alternatives depends on experimental evidence, but one further clinical observation may be relevant. Full records of change in body weight were available for the 134 patients studied. If those patients who developed fluid retention and were given diuretics and those who were placed on reducing diets are excluded, there remain 57 who were subjected to no deliberate means of altering their body weight. Figure 2 shows the average weight changes for these patients at 3, 6, 9, and 12 months. Though the deviations from constant weight are small, the trend suggests that treatment with guanethidine is associated with weight gain (which could be the result of fluid retention) in most or all patients rather than in a selected group possessing distinguishing features.

**Summary**

Forty-four (32.8 per cent) of 134 patients treated continuously with guanethidine for a period of at least 12 months developed recognizable fluid retention.

Previous edema may be a predisposing factor and fluid retention occurred more commonly in women. Neither of these factors offers a complete explanation of this side effect.

No evidence has been found to suggest that fluid retention occurs preferentially in patients with renal or cardiac insufficiency. The findings are compatible with a universal fluid-retaining influence of guanethidine presenting as a graded phenomenon.

**Acknowledgment**

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**References**


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FLUID RETENTION WITH GUANETHIDINE


Cases and Observations, Illustrative of Renal Disease Accompanied with the Secretion of Albuminous Urine

By Richard Bright—1827

The importance and extensive prevalence of that form of disease, which, after it has continued for some time, is attended by the peculiar changes in the structure of the kidney, now pretty generally known by the names of "mottling," "white degeneration," "contraction," or "granulation," impresses itself every year more and more deeply on my mind; and whether I turn to the wards of the hospital, or reflect on the experience of private practice, I find, on every side, such examples of its fatal progress and unrelenting ravages, as induce me to consider it amongst the most frequent, as well as the most certain causes of death in some classes of the community, while it is of common occurrence in all; and I believe I speak within bounds, when I state, that not less than five hundred die of it annually in London alone. It is, indeed, an humiliating confession, that, although much attention has been directed to this disease for nearly ten years, and during that time there has probably been no period in which at least twenty cases might not have been pointed out in each of the large hospitals of the metropolis—and there is reason to believe that double that number, at this moment, and at all times, be found in the wards of Guy's Hospital—yet little or nothing has been done towards devising a method of permanent relief, when the disease has been confirmed, and no fixed plan has been laid down, as affording a tolerable certainty of cure in the more recent cases.—Original Papers of Richard Bright on Renal Disease. Edited by A. Arnold Osman. London, Oxford University Press, 1937, p. 93.
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