

A LONG-ACTING DIURETIC SUITABLE FOR OUTPATIENT TREATMENT OF FLUID RETENTION IN OEDEMA OF PREGNANCY AND THE PREMENSTRUAL TENSION SYNDROME

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Before the discovery of salidiuretics the treatment of oedema of pregnancy presented a difficult problem. Owing to the risk of renal damage the physician had to be extremely cautious in prescribing diuretic drugs, especially since the investigations of Fahr¹ and Volhard² suggested that organic lesions of the kidney were responsible for the symptoms of toxæmia of pregnancy. Clearance tests and renal biopsies have in the meanwhile showed that toxæmia of pregnancy is chiefly caused by functional disorders which are reversible after parturition. The earlier passive attitude (usually only rest in bed and dietetic measures in the form of a diet rich in proteins and vitamins and low in salt and sodium, were prescribed) has therefore been largely superceded by active diuretic therapy. The development of oedema is caused by retention of sodium. Sodium is also retained during normal pregnancy. Careful balance tests have shown that the values in the last 2 months of pregnancy attain 70-170 mEq. weekly; this corresponds to a total of 10-15 G. of sodium. In toxæmia of pregnancy the sodium retained amounts to a multiple of this value.

Hormonal factors (heightened secretion of follicular and adrenocortical hormones) play a significant part in producing this increase in sodium retention during normal pregnancy. The excessive retention of sodium in toxæmia, however, is most probably the result of a reduction in the glomerular filtration rate and the simultaneous increase in tubular resorption of sodium and water. This mechanism is also of significance in the development of cardiac oedema. Whereas in normal pregnancy sodium retention causes an increase in extracellular fluid of 4 litres at the most (not taking into account foetal fluid-containing cavities), which results merely in a physiological increase in tissue fluid and possibly in a latent tendency to oedema, an excessive retention of sodium leads to manifest oedema and, under certain conditions, to the well-known clinical signs of toxæmia of pregnancy. It is the duty of the practising obstetrician to recognize its occurrence and to treat it at an early stage.

Only if one bears in mind that even under optimum treatment the foetal mortality in late toxæmia may be as high as 25%, does one realize the magnitude of this task and of the responsibility which the physician has to bear.

THIS STUDY

The following study deals with outpatient, antenatal welfare and treatment of excessive fluid retention in private practice. It is concerned chiefly with the practical problems that determine the therapeutic procedure. Contrary to the old opinion that pregnant women do not require any particular attention until the last trimester of pregnancy, the present belief is that controls should be carried out already in the early months of pregnancy so as to recognize and avoid impending toxæmia. In the first place, the weight gain of the women should be recorded. In addition, the blood pressure is measured and the urine examined. Determination of the protein content of the urine alone is insufficient, since albuminuria only occurs in advanced stages of the disease and is a severe sign of pre-eclampsia.

Theoretically, in normal pregnancy the gain in weight is estimated at 10-12 kg. (20-25 lb.). Half of this pertains to the product of pregnancy and the amniotic fluid; the remaining 50% arises from the increase in size of the uterus, the breasts, and above all, from the extra-cellular fluid. Weight gains exceeding 0.5 kg./week or 1.5-2 kg./month are no longer physiological and suggest the beginning of toxæmia. In these cases it is necessary to search for oedema, which is found not only in the lower limbs, but also in the hands and face and over the sacrum. For the differential diagnosis it is important to know that isolated oedema of the legs is mostly due to static disorders, and disappears during the night. Excessive weight gains without oedema are almost invariably the result of overeating. Here a reduction of calorie intake is indicated, possibly in conjunction with appetite-inhibiting drugs.

Choice of Diuretic

Carrying out this form of antenatal welfare in our private practice, we observed, in the course of 3 months, 30 patients with manifest oedema which did not respond to dietetic therapy alone, and therefore required active diuretic treatment. In our search for a suitable diuretic we excluded from the beginning mercurial preparations, since their parenteral administration produces abrupt shifts in the water and electrolyte balance and the oral administration leads to gastro-intestinal intolerance in a relatively large number of cases. For several reasons the

inhibitors of carbonic anhydrase are also unsuited for our purpose. On the one hand their effect is rapidly exhausted, so that continuous treatment is impossible. On the other hand their diuretic effectiveness is significantly reduced through the acidosis of toxæmia of pregnancy. The pronounced loss of potassium adds to the disadvantages of their use in outpatient practice.

Our choice among the currently available salidiuretics was determined by the aim of establishing a persistent and regular

outflow of water without excessive fluctuations between the diuretic phase and the ensuing phase of oliguria. It fell upon the iso-indoline derivative 'hygroton' which, by virtue of its protracted action, takes a particular position. Reutter and Schaub³ were the first to describe the long-acting effect of hygroton, which has since then been confirmed in numerous publications. The diuretic effect extends over a period of 72 hours, which means that its action is gentle and agreeable for the patient.

TABLE I. CASE HISTORIES

Initials and parity of patient	Age	Week of pregnancy	Clinical findings	Dosage of hygroton	Observation period	Result of treatment with hygroton*
B.B. Primipara	24	37	Severe gain in weight, oedema, B.P. 120/70	1 tablet every 2nd day	3 weeks	+++
G.P. Para 3	33	10	Oedema of hands and legs, B.P. 125/70	1-2 tabs. every 2nd day	5 weeks	+++
B.S. Primipara	23	34	Pre-eclampsia, severe oedema, B.P. 145/105	1-2 tabs. every 2nd day	4 weeks	+
D.K. Primipara	21	15	Oedema of hands and legs	1 tab. every 2nd day	12 weeks	++
E.P. Primipara	23	9	Severe oedema, B.P. 120/80	1-2 tabs. every 2nd day then 1 tab. daily	14 weeks	+++
P.O. Primipara	32	30	Oedema of hands and legs, B.P. 110/70	1 tab. every 2nd day	8 weeks	+++
S.H. Para 2	27	25	Oedema of hands, abdomen, legs	1 tablet every 2nd day	4 weeks	+++
N.R. Para 2	24	37	Oedema of hands and ankles, B.P. 105/60	1-2 tabs. every 2nd day	4 weeks	+++
D.R. Primipara	18	22	Oedema of hands and legs, B.P. 120/65	1 tab. every 2nd day	14 weeks	+++
L.F. Para 4	29	8	Oedema of hands and legs, B.P. 100/45	1 tablet daily	16 weeks	++
P.W. Primipara, twins	23	32	Oedema of hands and legs, B.P. 100/50	1-2 tabs. every 2nd day	5 weeks	+++
R.T. Primipara	23	34	Severe gain in weight, oedema, B.P. 105/55	1 tablet every 2nd day	6 weeks	+++
A.I. Para 4	30	19	Oedema of legs, B.P. 100/55	1 tablet every 2nd day	11 weeks	+++
S.B. Primipara	24	16	Oedema of hands and legs, B.P. 105/65	1 tablet every 2nd day	9 weeks	+++
L.L. Primipara	23	8	Oedema of hands and legs, B.P. 115/65	1 tablet 3-4 times a week	9 weeks	+++
M.V. Para 2	24	16	Slight oedema of legs, B.P. 110/60	1 tablet 4-5 times a week	5 weeks	+++
J.B. Para 2	24	36	Slight oedema of hands and ankles, B.P. 110/60	1 tablet 4 times a week	2 weeks	+++
E.K. Para 2	31	15	Oedema of ankles, B.P. 115/65	1 tab. 5 times a week, then 1 tab. every 2nd day	7 weeks	+++
C.F. Para 3	27	14	Oedema of hands and legs, B.P. 95/50	1-2 tabs. every 2nd day or 1 tab. daily	15 weeks	+++
J. v. d. B. Para 3	35	22	Slight oedema of legs, B.P. 100/55	1 tab. 4 times a week	2 weeks	+++
L.T. Primipara	36	5	No oedema, B.P. 145/85	1 tab. 4 times a week	7 weeks	+++
A.T. Primipara	23	12½	Oedema of hands, B.P. 125/65	1 tab. 4 times a week or 2 tabs. every 2nd day	7½ weeks	+++
D.S. Primipara	26	8	Oedema of ankles, B.P. 135/70	1 tab. every 2nd day or 1 tab. 4 times a week	11 weeks	++
C.S. Primipara	19	9	Slight oedema of ankles, B.P. 125/70	1 tablet 3 times a week	4 weeks	B.P. 95/50 +++
R.C. Primipara	20	8	Slight oedema of legs, B.P. 125/70	1 tablet 4 times a week	10 weeks	+
R.H. Primipara	23	6	Slight oedema of legs, B.P. 100/60	1 tab. every 2nd day	4 weeks	+++
M.V. Para 2	24	8	Oedema of legs, B.P. 135/80	1 tab. every 2nd day	2 weeks	+++
P.S. Primipara	30	33	Severe oedema of legs, B.P. 130/70	1 tablet 3 times a week	3 weeks	+++
P.G. Primipara	24	13	Oedema of hands and ankles, B.P. 130/70	1 tab. every 2nd day	2 weeks	+++
R.B. Primipara	22	14	Oedema of ankles, B.P. 90/45	1 tab. every 2nd day	1 week	+++

* +++ = very good, ++ = good, and + = moderate.

Similar to the other salidiuretics of the sulphonamide series, hygroton promotes natriuresis by inhibiting tubular reabsorption of sodium. Owing to the simultaneous excretion of equivalent quantities of chloride-ions, the acid-base balance is kept more or less constant. In contrast to the inhibitors of carbonic anhydrase, even prolonged administration does not lead to an exhaustion of its effect. In view of these properties we consider hygroton to be especially suited for the long-term treatment aimed at maintaining freedom from oedema during pregnancy. A further advantage is its exceptionally good anti-hypertensive effect and easy gastric tolerability.

RESULTS

Scheef⁴ reports excellent results with hygroton in oedema of pregnancy. Doses of 2-4 tablets weekly led to complete elimination of the retained fluid in all cases. It is particularly noteworthy that the blood pressure did not rise above 140 mm. Hg during treatment with hygroton. Stöckli⁵ treated 40 patients with hygroton. Knowing that pregnant women are hypersensitive to many drugs, he began treatment with a test-dose of $\frac{1}{2}$ tablet (50 mg.), continuing with 1 tablet 2-3 times a week if the former was well tolerated. With this procedure a physiological course of the weight curve was achieved in most cases. Despite pronounced excretion of salt and water, clinical manifestations of hypopotassemia were not observed, though the serum potassium was reduced in occasional instances. Where prolonged treatment with hygroton was necessary, potassium chloride was added.

Our own experiences confirm the excellent effect of hygroton in oedema of pregnancy. Our usual dosage was 1 tablet every second day, which was increased to 2 tablets every second day or 1 tablet daily in occasional instances. The diuretic effect was invariably prompt.

The retained fluid, which in some cases had caused an immense increase in bodyweight, was eliminated within a few days, even in the patients who were beginning to show the classical symptoms of toxæmia of pregnancy. In the follow-up of this series there has been no case of hypertension or proteinuria. We agree, however, with Stöckli⁵ that diuretic therapy can delay the appearance of late symptoms, so that parturition can take place before the full picture of toxæmia of pregnancy has developed.

We also found hygroton to be excellently tolerated. Only one patient complained of nausea, which was, however, more likely due to pregnancy and not to hygroton. Occasional complaints of tiredness, weakness, and cramps in the legs disappeared after reduction of the dosage and addition of KCl tablets. Table I gives a brief survey on the separate results of treatment. It shows that the diuretic effect was good in almost all instances, and that in 2 patients the slightly increased bloodpressure could be reduced to normal values. Symptoms of hypopotassemia were not observed because we prescribed a diet rich in potassium and, where necessary, additional potassium chloride.

Gynaecological Patients

In addition we treated 33 gynaecological patients with hygroton. Of these patients 9 were suffering from oedema of climacteric or static origin, and all responded excellently to hygroton. In 1 patient the weight was reduced by 8½ lb. within 5 days. This patient complained of a general feeling of

weakness and pains in the legs. The dosage of 1 tablet daily was too high. The other 24 patients were suffering from a pronounced premenstrual-tension syndrome, which is frequently encountered in our practice. Oedema of the face and limbs, swelling of the breasts and abdomen, and general tension, spasms of the gastro-intestinal tract, emotional lability, etc., were the chief complaints, and can at least in part be ascribed to premenstrual salt and water retention. As other salidiuretics had already led to good results, we decided to give hygroton a trial. The results were very impressive and in no way inferior to those achieved with other preparations. Diuresis was increased in almost all patients, and they were physically and psychologically relieved. Some of the patients, who had been previously obliged to discontinue work during menstruation, were able to go on working on hygroton therapy.

CONCLUSIONS

In reviewing the effects of hygroton in oedema of pregnancy and other oedematous states encountered in obstetrical and gynaecological practice, the following conclusions can be drawn: Hygroton is an extremely effective diuretic, characterized by its protracted action and excellent tolerability, which affords it considerable advantages for outpatient therapy. If one is familiar with its effects, it can be used in all stages of pregnancy. The dosage and duration of treatment should, however, be individually adapted, taking into account the degree of water retention and the extent of the ensuing diuresis. Careful supervision of the patients is necessary in outpatient treatment, since a decrease in serum potassium is occasionally observed, although large shifts in the electrolyte balance do not occur. This risk can be largely avoided by prescribing a diet rich in potassium or by administering additional potassium.

SUMMARY

30 patients, suffering from oedema of pregnancy, and 33 gynaecological patients, chiefly with premenstrual-tension syndrome, were treated with the long-acting diuretic hygroton. A dosage of 1 tablet of hygroton every 2nd day which, if necessary, was individually adjusted to a higher or lower dosage, produced prompt and reliable diuresis in almost all cases. In patients with oedema of pregnancy, freedom from oedema could be maintained until after the delivery through intermittent treatment. The symptoms of the premenstrual syndrome were distinctly improved through treatment with hygroton.

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