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A DOUBLE-BLIND, CONTROLLED, CLINICAL TRIAL OF SPIRONOLACTONE FOR BENIGN PROSTATIC HYPERTROPHY*

BY J. E. CASTRO,

UROLOGICAL UNIT, DEPARTMENT OF SURGERY, ROYAL POSTGRADUATE MEDICAL SCHOOL, AND HAMMERSMITH HOSPITAL, LONDON

H. J. L. GRIFFITHS,

DEPARTMENT OF RADIODIAGNOSIS, HAMMERSMITH HOSPITAL, LONDON

AND D. E. EDWARDS

G. D. SEARLE & CO. LTD., HIGH WYCOMBE, BUCKINGHAMSHIRE

SUMMARY

A double-blind, controlled, clinical trial of spironolactone (Aldactone-A), 50 mg. b.d., showed this to be better than a placebo for the short-term treatment of benign prostatic hypertrophy, although the advantage was not maintained over a longer period of time. There was considerable response to the placebo and the importance of comparative trials with objective measurements is discussed.

BENIGN prostatic hypertrophy is common. Flocks (1964) reported that 65 per cent of American men over the age of 60 years suffer with it, and in a selected group of Danish men 43 per cent had symptoms of the disease (Lund, 1959). There are inherent inaccuracies in such incidence figures but they show the magnitude of the problem. At present, patients with benign hypertrophy who need treatment undergo prostatectomy. The mortality of this depends upon the criteria used to select patients for operation (Barrett, 1962), but most surgeons report a mortality of around 3 per cent (Wells, 1952; Watts, 1968). There is also considerable morbidity, such as infection, incontinence, infertility, and urethral stricture (Caine, 1954; Jeejeebhoy, 1961; Holtgrewe and Valk, 1964). Refinements of surgical technique cannot be expected to reduce these complications significantly, and an alternative treatment for this essentially benign condition is desirable.

Spironolactone may be useful in the treatment of benign prostatic hypertrophy (Fingerhut and Veenema, 1967), and uncontrolled clinical studies suggest that it is useful in 60–65 per cent of patients (Fingerhut and Veenema, 1968).

In this paper we report a double-blind, controlled, clinical trial comparing spironolactone and a placebo in the treatment of benign prostatic hypertrophy.

* Based on a paper presented to the Surgical Research Society in July, 1968.

MATERIALS AND METHODS

Forty-five patients with symptoms of bladder-neck obstruction and benign enlargement of the prostate on digital rectal examinations were studied. Prostatic cancer was excluded by clinical examination, measurements of serum acid phosphatase (Kind and King, 1954), and a radiological skeletal survey.

Patients who had had recent urethral instrumentation, those with coexistent renal disease, those taking drugs known to affect the urinary tract (Feaver, Usher, and MacEwen, 1967), and those with a blood-urea above 80 mg. per 100 ml. were not included in the trial.

Each patient was investigated before treatment was started when his urine was sterile. A total symptom score was obtained compounded from the symptoms of urgency, hesitancy, dysuria, and dribbling, graded from 0 to 3 (0—absent, 1—slight, 2—moderate, 3—severe), and the patient's assessment of his urinary stream graded from 3 to 0. Frequency, the total number of times a patient had to void during 24 hours, and nocturia, the total number of times a patient had to rise from bed to void, were recorded for a week and mean values were deduced.

The transverse diameter of the prostate was estimated by digital rectal examination and the blood-urea estimated by a Technicon AutoAnalyser.

Excretion urograms and retrograde cystograms were done on each patient, and bladder trabeculation, reflux of contrast into the prostatic ducts during micturition, and the length of the prostatic urethra from the bladder base to the external urethral sphincter were measured (Vermooten and Schweinsberg, 1964). The residual urine and any prostatic impression at the bladder base were measured by radiographic planimetry (Griffiths and Castro, 1970). All radiographic measurements were corrected for magnification by fixing a radio-opaque marker of known size to the patient.

Micturating cystography was combined with simultaneous measurements of intravesical pressure, rectal

pressure, and urinary flow rate (von Garrelts, 1956; Castro and Griffiths, 1971a), and direct measurements of residual urine were made by urethral catheterization immediately after micturition. From the intravesical and rectal pressure recordings, measurements were made of the resting pressures, defined as the lowest values before or after micturition, the pressures were repeated after 3 months' and 6 months' treatment.

Statistical Analysis.—Thirty-two measured values and two calculated ones (the calculated effective cross-sectional area of the urethra for both saline and urografin) were made at each assessment and the technique of principal component analysis was used

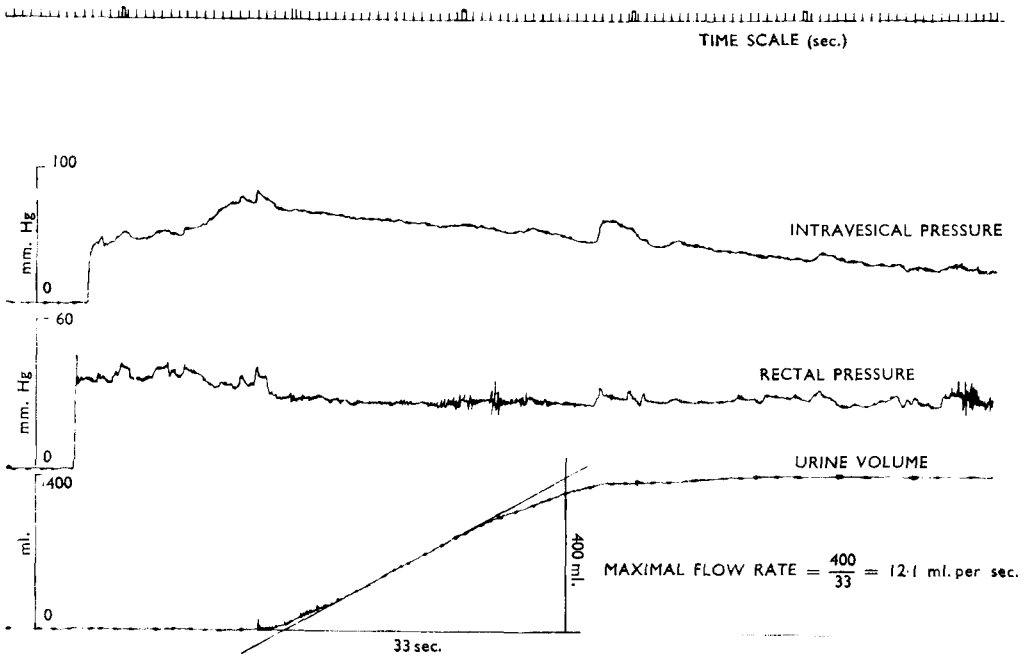

FIG. 1.—Simultaneous recordings of intravesical pressure, rectal pressure, and urinary volume passed. Maximal urinary flow rate is derived from the volume passed by drawing a tangent to the steepest part of the tracing.

at the beginning of micturition, and the average pressures during micturition. The maximal intravesical pressure was also measured. From the tracings of the volume of urine voided the maximal rate of urinary flow was derived (*Fig.* 1), and a 'lag period', which is the time between the beginning of a sustained rise of intravesical pressure and the beginning of urinary flow, was measured when possible. Two measurements of pressure and flow were made, one using saline and the other using 30 per cent urografin in saline; these were considered separately in the subsequent analysis. The measurements of intravesical pressure and urinary flow rate were used to calculate the effective cross-sectional area of the urethra by substitution in the formula $A = 1{\cdot}14F/\sqrt{P}$ (where A is the effective cross-sectional area in $cm.^2$, P the pressure, and F the flow). This has been shown to represent the degree of urethral obstruction (Rankin, 1967).

Patients were allocated to one of two treatment groups by the use of sealed envelopes containing the randomly arranged instructions for treatment. One group received spironolactone, as Aldactone-A, 50 mg. b.d., and the other a placebo (an identical tablet with the active principal omitted). Treatments were dispensed so that the investigators were unaware of the treatment received. The patients were seen at 6-weekly intervals and the base-line measurements (Lawley and Maxwell, 1963) to simplify the interrelated variables. With this method nine components were obtained accounting for approximately 80 per cent of the variability, all with the property of being statistically independent of each other (i.e., $r = 0$). These components were transformed by the Varimax method (Kaiser, 1958) and the factors obtained are summarized in *Table I.* Seven of the nine factors contain data which were clinically interrelated, but factor 7 consisted of a set of components that has no obvious clinical meaning. Factor 8 may also be difficult to interpret. Using these factors Student's

Table I.—FACTORS USED IN THE ANALYSIS OF RESPONSE TO TREATMENT*

Factor	*Measurement*
1	Flow, flow², volume passed, −lag period, calculated effective urethral cross-sectional area
2	All rectal pressures
3	Commencing, average, and maximal bladder pressures
4	All residual urines
5	Frequency, nocturia, digital prostate size
6	Length of the prostatic urethra, radiological prostate size
7	Flow (saline) − flow (urografin), volume (saline) + volume (urografin), catheter residual urine, urine frequency, symptom score, urethral area (saline) − urethral area (urografin)
8	Resting bladder pressures, lag period
9	Frequency, blood-urea, symptom score

* The measurements giving the largest contributions to each factor are listed.

t-tests were done between the treatments on the differences between the base-line measurements and the 3-month assessment and the differences between the base-line measurements and the 6-month assessment.

RESULTS

Forty-five patients were accepted for the trial, of whom 41 completed 3 months and 38 6 months of treatment. Patients were included in the analysis only when their follow-up examinations were complete so that 38 patients, comprised of 17 on spironolactone and 21 on a placebo, were compared after 3 and 6 months of treatment. Seven patients were not included in the analysis owing to urine retention (3), impotence (1), and failure to complete the measurements (3). Three of these patients were in the placebo group.

When the effects of spironolactone and a placebo are compared, significance is reached at the 5 per cent level at 3 months by only 2 of the 34 original variables (symptom score and residual urine measured by intravenous pyelography), and at 6 months by none of them. It would, however, be unwise to attach much importance to these isolated results, since the probability of 2 or more out of 68 tests achieving significance at the 5 per cent level when no real difference exists is very high ($P=0{\cdot}85$). The mean values of 10 of the variables are plotted in *Fig.* 2.

Table II.—STUDENT'S *t*-TESTS BETWEEN THE EFFECT OF SPIRONOLACTONE AND A PLACEBO ON BENIGN PROSTATIC HYPERTROPHY

FACTOR	AT 3 MONTHS		AT 6 MONTHS	
	t	*P*	*t*	*P*
1	+0·452	0·67	−1·348	0·19
2	+0·191	0·84	+0·420	0·68
3	+0·814	0·42	−0·409	0·70
4	+0·877	0·40	+0·215	0·83
5	+1·043	0·30	+0·720	0·48
6	+0·602	0·56	+0·335	0·78
7	(2·169)	0·04	(0·042)	0·96
8	+0·158	0·88	−0·393	0·71
9	+1·181	0·24	+0·586	0·57

+, Spironolactone better than a placebo.
−, Placebo better than spironolactone.

The intercorrelation between the variables makes it impossible to deduce any consistent pattern of superiority of one treatment over the other.

The difference between the effect of spironolactone and that of a placebo on each of the nine factors is analysed in *Table II.* The only difference which is statistically significant at the 5 per cent level is factor 7 at 3 months. However, 1 significant result out of 18 is very likely to arise by chance ($P=0{\cdot}60$). Furthermore, the factor that happens to be 'significant' is the least relevant clinically, and the difference between treatments vanishes altogether at 6 months. With the exception of factor 7 it is possible to determine whether a change in any factor is beneficial to the patient, e.g., an increase in factor 7 reflects an improvement in the patient's condition. *Table II* assigns a '+' sign to any factor in which spironolactone was associated with greater improvement (or less deterioration) than a placebo and a '−' sign when the reverse is true. At 3 months, although none of these differences is significant, all favour spironolactone. This is in itself significant ($P=0{\cdot}01$), since if there is no difference between the treatments a placebo can be expected to appear better in 4 out of 8 uncorrelated comparisons. Thus the data suggest that patients on spironolactone, 50 mg. b.d., fare better than patients on a placebo after 3 months of treatment, and that the lack of significance in the individual variables was due more to the small scale of the trial than to a genuine absence of effect. The use of factor analysis has therefore revealed, in this instance, a treatment effect in a trial which was too small for it to be directly apparent.

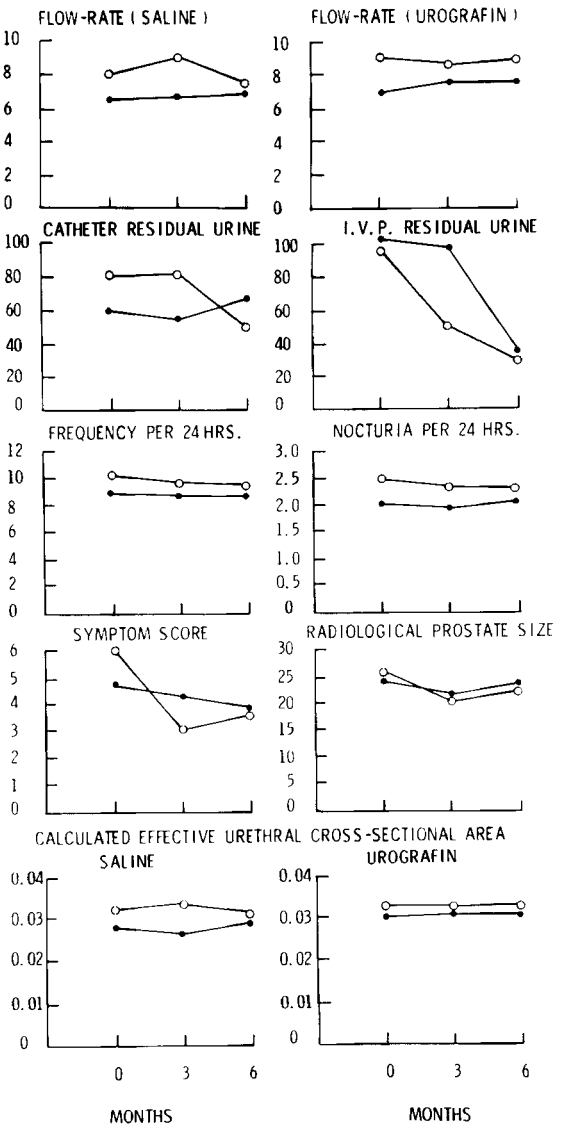

FIG. 2.—Comparison of the effect of spironolactone and a placebo on selected variables: ○—○, spironolactone; ●—●, placebo.

At 6 months, however, factors 1, 3, and 8 favour a placebo, indicating that the difference between treatments at 3 months is not carried forward to 6 months.

The largest *t*-values at 6 months are associated with factors 1, 5, and 6 which are among those of highest clinical importance (*Table I*). The measurements that contribute to these factors are therefore considered in more detail in *Table III*. None of the measurements shown demonstrates a statistically significant difference between the effect of spironolactone and a placebo. However, the differences achieved are clinically important in the cases of flow rate and calculated effective urethral area and also in symptom score.

Table III.—ANALYSIS OF THE VARIABLES IN FACTORS 1, 5, AND 9 AT 6 MONTHS

MEASUREMENT	SPIRONOLACTONE		PLACEBO		*t*-VALUE OF DIFFERENCE IN IMPROVEMENT*
	Pre-treatment	Improvement after Treatment	Pre-treatment	Improvement after Treatment	
Flow rate:—					
Saline (ml. per second)	8·1	+0·5	6·5	+0·6	1·4
Urografin (ml. per second)	9·2	+0·4	7·0	+0·5	1·1
Volume:—					
Saline (c.c.)	302·1	−14·7	297·7	−8·7	0·2
Urografin (c.c.)	334·7	−16·0	313·1	−3·5	0·4
Lag:—					
Saline (seconds)	23·7	−2	23·4	+5·3	0·6
Urografin (seconds)	17·8	−3·8	23·5	−1·5	0·2
Calculated effective area:—					
Saline (sq. cm.)	0·0327	+0·0030	0·0277	+0·0010	1·4
Urografin (sq. cm.)	0·0364	+0·0038	0·0295	+0·0007	1·1
Digital prostate size	5·6	−1·1	5·5	+0·7	0·7
Blood-urea	38·1	−2·6	32·9	−3·2	0·2
Frequency	10·3	+1	9·6	+1·3	0·4
Nocturia	2·6	+0·2	2·5	+0·5	0·6
Symptom score	5·7	+2·1	4·9	+1·2	1·2

* To give a *P*-value of 0·1, *t* must be 1·7; to give a *P*-value of 0·05, *t* must be 2.

DISCUSSION

This study showed a general improvement in patients treated with spironolactone, 50 mg. b.d., as compared with a placebo after 3 months of treatment. In a trial involving only 45 patients it was not possible to quantify this improvement which had largely disappeared after 6 months of treatment.

The dose of spironolactone used has an effect on electrolyte excretion (Winer, 1961) and the occurrence of gynaecomastia in 2 patients suggested that it was sufficient to produce endocrinological effects. Comparison of the 3- and 6-month assessments suggested that a longer period of treatment was unlikely to be more effective. Fingerhut and Veenema (1968) used a similar dose in their studies and found improvement after 6 weeks of treatment.

Many patients taking a placebo improved subjectively during the 6 months of therapy and in 16 out of 21 (76 per cent) of these patients the symptom score was less, in 15 out of 21 (71 per cent) frequency was less, and in 13 out of 21 (62 per cent) nocturia was less. In each of these scores the number of patients who improved was significantly greater than the number who deteriorated. There was, however, no significant difference between patients on active and on placebo treatment.

Objective measurements are important for assessing patients with benign prostatic hypertrophy. Estimation of prostate size by digital rectal examination is inaccurate; anterior enlargement cannot be felt (Randall, 1931) and localized enlargements placed near to the outflow tract may cause disproportionate obstruction (Smith, 1968). In 15 out of 21 patients on a placebo the transverse diameter of the prostate was thought to have decreased by 1 cm. or more, in 1 it was thought to be the same, and in 5 it was thought to have increased, but the average change of 0·9 cm. was not significant.

Radiographic measurements are unsuitable for frequent assessments, their interpretation is partially subjective and retrograde cystography necessitates catheterization. In fact there were significant decreases in the planimetric residual urine in both the intravenous pyelogram (from 121·5 to 35·4; $P=0·0021$) and retrograde cystogram (from 154·5 to 58·6; $P=0·001$) following placebo medication, but the residual urine measured by catheterization remained constant at 67 ml.

Catheterization is necessary to record intravesical pressure and it was interesting that these measurements increased (from 83·3 to 95·9 mm. Hg, using saline; $P=0·11$: from 85·1 to 99·7 mm. Hg, using urografin; $P=0·02$). This may be due to either conscious straining by the patient or actual deterioration. On the other hand, measurement of urinary flow rate by a simple method did not change after placebo treatment (6·5 to 7·1 ml. per second; $P=0·21$). It is an objective measurement reflecting real changes, and was the most useful single measurement in this respect (Castro, Griffiths, and Shackman, 1969; Castro and Griffiths, 1971b).

Several treatments have been tried based on the hormonal control of the prostate, but no objective measurements were made and therapy was given

empirically and not as a controlled trial. The results are therefore conflicting and the value of the treatments is impossible to assess. Day (1939) found improvement following androgens, whilst others (Kahle and Maltry, 1940) found that androgens stimulate prostatic growth. Similarly, Roberts (1966) obtained good results from oestrogens, whereas Cook (1963) concluded that they were of no value. Recent investigations using progestogens have been confusing; Geller, Bora, Roberts, Newman, Lin, and Silva (1965) and Lebech and Nordentoft (1967) found hydroxyprogesterone caproate to be useful, but other uncontrolled studies with the same drug showed it had no effect on the disease (Jacobs, Harper, and Politano, 1967; Weinsberg, 1968). The results of this investigation indicate the importance of properly controlled clinical trials with objective measurements and statistical analyses. It is suggested that valid conclusions regarding the usefulness of drugs for the treatment of benign prostate hypertrophy can only be achieved by such studies.

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THE EFFECT OF SELECTIVE GASTRIC OR EXTRAGASTRIC VAGOTOMY ON GASTRIC SECRETION IN CONSCIOUS CATS

BY JOHN SPENCER* AND MORTON I. GROSSMAN

VETERANS ADMINISTRATION CENTER, AND DEPARTMENTS OF MEDICINE AND PHYSIOLOGY, U.C.L.A. SCHOOL OF MEDICINE, LOS ANGELES, CALIFORNIA

SUMMARY

Earlier studies in dogs showed that in animals with gastric fistulas, selective gastric vagotomy decreased maximal acid secretion in response to gastrin but not to histamine, and that in animals with Heidenhain pouches, selective extragastric vagotomy increased maximal response to gastrin but not to histamine. The present study sought to determine whether similar changes occurred in cats. In cats with gastric fistulas, selective gastric vagotomy reduced maximal response to pentagastrin and to histamine by about the same extent. In cats with Heidenhain pouches, selective extragastric vagotomy had no effect on the response to pentagastrin. It is concluded that there is a species difference between the dog and the cat regarding the effects of selective gastric and selective extragastric vagotomy on gastric acid secretion in response to gastrin. It is not yet known whether man fits the pattern of the dog or the cat.

* Present address: Royal Postgraduate Medical School, London.

IN the dog, selective gastric vagotomy and truncal vagotomy have different effects on gastric acid secretion. In this species, cutting gastric vagal fibres while leaving extragastric vagal fibres intact causes decreased maximal acid secretion in response to gastrin but not to histamine. This has been shown in dogs