

Single-dose Treatment of Acute Urinary Tract Infection: a Controlled Trial

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Patients with acute urinary tract infection are usually seen and treated by their family doctor, and the majority either do not stay away from work or return to work as soon as the symptoms are relieved. Though a seven-day course of treatment with a number of antimicrobial agents will eradicate most infections, the relief of symptoms and return to normal activities results in some patients not completing the full course. This leads to a number of infections persisting in an asymptomatic form.

Sulphormethoxine (Fanasil) is a sulphonamide with a half-life in the body of about 150-200 hours (Haegi, 1966), and if therefore a seven-day course is required a single-dose treatment is feasible.

We have carried out a trial to compare this treatment with a seven-day course of ampicillin, which is established as an effective treatment of primary urinary tract infection.

Materials and Methods

Examination of Urine.—Midstream specimens of urine were collected by the clean-catch technique after cleansing with a swab moistened in sterile water. Quantitative bacterial and white cell counts were carried out. The sole criterion of infection was a count of 100,000 bacteria or more per ml. of urine. Organisms were identified by conventional methods, and the O antigen of *Escherichia coli* strains was identified by means of specific antisera.

Serum Antibodies.—Antibodies in the patient's serum against infecting organisms were estimated as previously described (Percival, Brumfitt, and de Louvois, 1964). A titre of 1:320 or more was taken to indicate renal involvement whether localizing symptoms were present or not.

Antibiotic Sensitivities.—These were carried out on para-aminobenzoic-acid (P.A.B.)-free sensitivity agar (Oxoid) with discs containing either 200 µg. of sulphormethoxine or 25 µg. of ampicillin. The plates were lightly inoculated with a wire loop from a single colony of the organism to be tested, the density of the inoculum and activity of the disc being controlled by inoculating the plate in a similar way with *Staphylococcus aureus* (Oxford strain N.C.T.C. 6571). Subsequently the minimal inhibitory concentration was estimated in tubes by the serial dilution method, using a final bacterial density of about 200 organisms per ml. For sulphonamide P.A.B.-free medium was used.

Patients

One hundred and four patients who visited their family doctor with symptoms of urinary tract infection were referred immediately to us for investigation and treatment. Each patient was seen by the same observer (R. N. G.), a full history was taken according to a standard questionnaire, and the patient was then examined clinically. A specimen of urine was collected

and a blood specimen taken for measurement of the serum antibody level against the O antigen of the infecting organism.

If typical symptoms of urinary tract infection were present and no treatment had already been given the patient was admitted to the trial. Treatment was decided by the selection of a random number and the patient was given either a single dose of 2 g. of sulphormethoxine or 500 mg. of ampicillin eight-hourly for seven days.

Follow-up was carried out two and six weeks after the first visit. Patients were again asked about symptoms, a mid-stream specimen of urine was collected, and blood was taken for antibody determination.

Treatment was judged to have been successful if both follow-up specimens of urine were sterile, and to have failed where the organism originally isolated persisted.

Results

Treatment was given to 104 patients who had typical symptoms, but examination of the urine showed that only 50 of these had significant bacteriuria; therefore assessment of the relative chemotherapeutic value of sulphormethoxine and ampicillin was confined to the latter group of patients.

TABLE I.—Comparison of Clinical and Laboratory Findings in the Two Groups

	Sulphormethoxine	Ampicillin
Patients treated	25	25
Females	24	21
Average age	38.0	45.3
Previous history of urinary infection ..	18	17
Loin pain	5	5
Infections due to <i>E. coli</i>	20	17
Infections due to <i>Proteus mirabilis</i> ..	4	6
Infections with urine W.B.C. > 10/cu. mm.	22	23
Serum antibody titre $\geq 1/320$	5	10
$\geq 1/640$	4	6

Table II shows that cure rates were the same with sulphormethoxine and ampicillin, both substances being successful in 22 (88%) of the 25 patients in each group. The three patients who failed to respond to ampicillin all had very high serum antibody titres against the infecting organism, which suggested extensive renal tissue involvement. In two of the three ampi-

TABLE II.—Results of Treatment

Treatment	No. Treated	Cured (6-week Follow-up)
Ampicillin	25	22 (88%)
Sulphormethoxine	25	22 (88%)

cillin failures the organism responsible for the infection was sensitive to sulphormethoxine, as judged by in-vitro testing. These two patients were treated with sulphormethoxine and one was cured.

The three patients who were not cured by sulphormethoxine were given a seven-day course of ampicillin and one was cured. The other two subsequently failed to respond to several courses of other antimicrobial substances.

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The three patients who failed to respond to both sulphormethoxine and ampicillin were later investigated radiologically and all were found to have urinary tract abnormalities.

The side-effects were assessed on all patients treated, regardless of whether or not they were subsequently found to have bacteriological evidence of urinary tract infection.

The 104 patients received 109 courses of treatment (three sulphormethoxine failures were given ampicillin and two ampicillin failures were given sulphormethoxine). Sulphormethoxine was given to 53 patients and two developed side-effects, whereas nine of the 56 given ampicillin developed side-effects (Table III). The difference is statistically significant ($0.05 > P > 0.02$). Side-effects with sulphormethoxine were minimal: one patient felt nauseated for one hour after taking the tablets, and the other had a rash for a similar period. With ampicillin side-effects were more troublesome. One patient had diarrhoea and pruritus for four weeks, and five others had diarrhoea for two weeks or more.

TABLE III.—Side-effects

Treatment	No. of Courses Given	No. of Patients with Side-effects
Ampicillin	56	9 (16.1%)
Sulphormethoxine	53	2 (3.8%)

Rashes occurred in five patients and were maximal on the arms and trunk and non-pruritic. The rashes did not intensify when treatment was continued, and no urticarial rash characteristic of classical penicillin hypersensitivity was seen. Details of the actual side-effects are given in Table IV. They were equally distributed between patients who had true urinary infection and those who had typical symptoms without infected urine.

TABLE IV.—Details of Side-effects Observed

	Ampicillin*	Sulphormethoxine
Diarrhoea	6	—
Nausea	—	1
Rash	5	1
Pruritus	2	—
Other	2	—

* Four of the 9 patients with side-effects showed more than one feature.

Interestingly, three patients who had typical symptoms but no infection when treatment was started were found to be infected at follow-up. One of these patients was subsequently found to have a urinary tract abnormality, and the other two infections were due to organisms resistant to the antibacterial substance used.

Discussion

In a previous study carried out in general practice we found that a seven-day course of sulphadimidine cured 90% of patients with acute urinary tract infection (Mond, Percival, Williams, and Brumfitt, 1965), and in the present investigation 22 out of 25 patients were cured by the long-acting sulphonamide, sulphormethoxine, given in a single dose of 2 g. Ampicillin in conventional dosage cured the same number of patients with similar infections (Tables I and II).

The side-effects of ampicillin were more frequent than those due to sulphormethoxine, but it should be stressed that many of these would be accepted by patients confined to their home. However, effective treatment of patients with less severe clinical forms of urinary infection enabled them to resume normal activities, and under these circumstances side-effects were sometimes troublesome. For example, one patient who returned to work in a factory was unable to continue because of diarrhoea. Patients with side-effects also tend to discontinue the treatment.

The rashes which occurred after ampicillin have been ascribed to hypersensitivity (*British Medical Journal*, 1964), but the evidence for this is uncertain. The rashes were not urticarial and there were none of the other signs usually associated with penicillin hypersensitivity. Furthermore, in such patients skin tests can subsequently be shown to be negative (Stewart, personal communication).

With sulphormethoxine only a single dose was necessary, and therefore there was no danger of the patient forgetting or deliberately omitting to take the treatment. Side-effects were minimal, and many patients remarked favourably on the simplicity of treatment—particularly those who had previously been treated with other courses.

Previous studies have shown that where minimal inhibitory concentrations of sulphonamide are below 50 µg./ml. eradication of urinary infection can be expected, while minimal inhibitory concentrations in excess of 200 µg./ml. usually mean that the infection will prove to be resistant to sulphonamides. We found that 82% of organisms were sensitive to 50 µg. of sulphormethoxine per ml. or less, and these results agreed exactly with those found with sulphadimidine. It was also found that 87% of the organisms were sensitive to 5 µg. of ampicillin per ml. or less.

In the present study failure to respond to treatment was due to resistance of the infecting organism or to the presence of urinary tract abnormalities, and the three patients with sensitive organisms who failed to respond to both sulphormethoxine and ampicillin were all found to have such abnormalities when investigated radiologically.

There has recently been much discussion about the association of long-acting sulphonamides and the Stevens-Johnson syndrome (Carroll, Bryan, and Robinson, 1966; Harris, Wise, and Beveridge, 1966; Seneca, 1966). The syndrome may have a special association with sulphamethoxypyridazine, and it is said to be especially apt to occur in children (Harris *et al.*, 1966). Sulphonamides in general, together with a variety of other substances, have been associated with the Stevens-Johnson syndrome, but over the past five years we have observed several thousand patients treated with sulphadimidine and the long-acting compound sulphamethoxydiazine but have seen no example of the condition. Clearly a new compound must be used cautiously, and in view of the claim that the Stevens-Johnson syndrome is more likely to occur in children it would be best to avoid sulphormethoxine in paediatric practice until more experience has been gained in its use.

Recent but as yet unpublished experience on a very large scale during an outbreak of meningococcal meningitis, in which sulphormethoxine was used prophylactically in very high and repeated doses, has shown that the drug can occasionally produce skin reactions. These usually occurred in children, were mild, and followed a benign course. In some cases, however, they were generalized, more severe, and showed features of Lyell's syndrome (I. Lennox-Smith, personal communication).

The evidence that long-acting sulphonamides produce a more sustained hypersensitivity reaction than the short-acting compounds is in our view unimpressive, but of course no patient with a history of sulphonamide sensitivity must receive the compound.

Our findings suggest that for treatment of patients with urethrotigonitis, such as we have described here, results will be as good as with the other antimicrobials at present available, while the side-effects and inconvenience to the patient are likely to be minimal.

In our view a long-acting compound of this variety is unsuitable for the treatment of patients with fever and evidence of acute pyelonephritis. Also, asymptomatic urinary infections in diabetic patients and pregnant women are more difficult to eradicate than the acute infections seen in general practice (Williams, Brumfitt, Leigh, and Percival, 1965), and the possible

place of sulphormethoxine in these conditions remains to be defined.

Summary

Sulphormethoxine is a sulphonamide with a prolonged action, which makes possible the treatment of some varieties of acute urinary tract infection with a single dose of 2 g. In a controlled trial on ambulant patients it was as effective as a seven-day course of ampicillin given in a dose of 500 mg. eight-hourly. The cure rate was 88% with both substances. Side-effects occurred in 3.8% of patients treated with sulphormethoxine and in 16.1% of those who received ampicillin.

Sulphormethoxine is not recommended for acute pyelonephritis.

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REFERENCES

- Brit. med. J.*, 1964, **1**, 132.
Carroll, O. M., Bryan, P. A., and Robinson, R. J. (1966). *J. Amer. med. Ass.*, 195, 691.
Haegi, V. (1966). *Schweiz. med. Wschr.*, **96**, 1308.
Harris, M. J., Wise, G., and Beveridge, J. (1966). *Aust. paediat. J.*, **2**, 103.
Mond, N. C., Percival, A., Williams, J. D., and Brumfitt, W. (1965). *Lancet*, **1**, 514.
Percival, A., Brumfitt, W., and de Louvois, J. (1964). *Ibid.*, **2**, 1027.
Seneca, H. (1966). *J. Amer. med. Ass.*, **198**, 975.
Williams, J. D., Brumfitt, W., Leigh, D., and Percival, A. (1965). *Lancet*, **1**, 831.

Controlled Trial of Methandienone in Treatment of Diabetic Retinopathy

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Retinopathy is a common concomitant of diabetes and is related more to the duration of the diabetic state than to any other factor. Present methods of controlling the diabetic state are unable to prevent the onset or progress of retinopathy. Several studies have claimed that diabetic retinopathy is improved by the administration of anabolic steroids (Dardenne, 1961; Houtsmuller, 1961; Fabrykant *et al.*, 1964). Unfortunately the natural history of diabetic retinopathy is a variable one, and assessment of the value of therapy is correspondingly difficult. Leopold (1964) stated: "Further well controlled studies on the influence of anabolic steroids in diabetic retinopathy are mandatory."

In the present study methandienone (Dianabol) was chosen as an anabolic steroid which was effective when given by mouth, and retinal photography was used for the quantitative assessment of retinopathic changes. Forty-nine diabetic patients were observed, the double-blind method of comparing treated patients with controls being used.

Design of the Trial

Selection of Patients.—Diabetics with retinopathy of all grades of severity (except severe retinitis proliferans) were admitted to the trial provided they had clear media. The trial started in May 1965 and ended in March 1967. Patients below 20 or over 70 years of age and those with any major illness were excluded, as were those who were unlikely to co-operate. The patients came from the diabetic clinics of a teaching and a district hospital.

Treatment and Supervision.—The patients were divided by random numbers into a group receiving oral methandienone 5 mg. twice daily and a group receiving a placebo tablet of the same size and colour, also twice a day. Patients were observed for an average of one year (span 6 to 22 months). They were seen monthly, and the following factors were among those recorded: blood pressure, blood sugar (glucose oxidase method),

serum cholesterol (Carr and Dreker, 1956), serum aspartate aminotransferase (Reitmann–Frankel units). Side-effects and regularity of tablet-taking were also noted.

Visual Acuity and Retinal Photography.—Visual acuity was measured before treatment, Snellen type being used. Thereafter it was assessed six-monthly. Refractive errors were corrected when present. Retinal photographs were taken on Kodachrome 2 film with a Kowa or Zeiss retinal camera. Initially multiple fields were recorded, but eventually a series of standardized fields (nasal, inferior temporal, and superior temporal) were taken of each eye. The objective was to produce three comparable fields per eye at six-monthly intervals.

Assessment of Retinal Photographs

Two assessors were present for all assessments. Standard retinal photographs as defined by Oakley *et al.* (1967) were used for grading the retinopathy. This system comprises the following features.

(1) The patient's photographic fields are graded by direct comparison with a set of standard fields. The grading for a whole fundus represents the average for the individual fields comprising the fundus.

(2) Five diabetic retinal abnormalities are featured:

(a) **Microaneurysms and Haemorrhages.**—These include all "dots" and "blots" on the retina, but exclude vitreous haemorrhages. The grading is according to the number of lesions present in the field regardless of their size.

(b) **Exudates.**—Hard exudates only, soft ones being ignored. As confluent exudates are common the area of retina involved, rather than the number of lesions, is used for grading.

(c) **New Vessels.**—All abnormal vascular channels, excepting those forming in relation to previously established fibrous retinitis proliferans. Grading according to the area of field involved.

(d) **Venous Irregularities.**—All venous irregularities, including dilatation, segmental irregularities, and "sausaging." Grading according to length of veins involved.

(e) **Retinitis Proliferans.**—Any fibrotic lesion in front of the retina, regardless of its vascular associations, and including any detectable diffuse veiling over the retinal surface. Grading according to the area of field involved.

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