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Ampicillin, Carbenicillin Indanyl Ester, and Nifuratel in the Treatment of Urinary Infection in Domiciliary Practice

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There are a number of reports of the successful use of parenteral carbenicillin in the treatment of urinary infections but controlled trials with this antibiotic are lacking (Davis, Iannetta and Wedgwood, 1971), and it is only minimally absorbed when taken by mouth. The newly introduced indanyl ester of carbenicillin is absorbed when given orally, being rapidly hydrolysed to yield free carbenicillin which is subsequently excreted in the urine in high concentration. For the oral therapy of urinary infection nitrofurantoin is well established, although the recommended dose produces nausea in a substantial number of patients. Another nitrofuran, nifuratel, presented in a 200 mg sugar-coated tablet, has been studied and preliminary reports suggest that it is as effective as nitrofurantoin but causes fewer side-effects. During the planning of the present trial a 400 mg non-sugar-coated nifuratel tablet became available and because of the possibility that the kinetics of absorption might be different (thus influencing the gastrointestinal side-effects as well as altering the therapeutic efficacy of the compound) it was decided to include both nifuratel preparations in the treatment trial.

Since experience with the new preparation of carbenicillin is limited and nifuratel has rarely been used in the treatment of urinary infections (Tynan, Macis and Ward-McQuaid, 1969; Brumfitt, 1972), comparison with a drug of predictable efficacy seemed essential. For this reason, ampicillin, a well established drug in the oral treatment of urinary infection, was selected. Thus it was considered worthwhile to compare ampicillin, carbenicillin indanyl ester and the 2 nifuratel preparations in a double-blind treatment trial in 2 different defined groups of domiciliary patients.

The Patients

Altogether, 120 patients were divided into 2 separate groups, the first being 65 non-pregnant females and 2 males who were referred by their general practitioners to the urinary infection clinic because of dysuria and frequency. These patients had received at least one course of chemotherapy from their own doctors, with unsatisfactory results, and 48 of them (72%) were still symptomatic when first seen at the clinic. The second group consisted of 53 patients referred from the antenatal screening clinic with bacteriuria in pregnancy. Many of them had suffered urinary infections in previous pregnancies and 26 (49%) had urinary symptoms at the first clinic attendance.

The Organisation of the Trial

After each patient was shown to fulfil the criteria for inclusion in the trial (see laboratory methods), a 7-day supply of the allocated drug was given. The dosage employed was 500 mg 6-hourly for ampicillin and carbenicillin indanyl ester, and 400 mg 8-hourly for the 2 nifuratel preparations. The 4 treatments were allocated according to a random number list by a person unconnected with

the trial, and those patients who failed treatment were given 1 of the 3 remaining compounds. Thus 67 non-pregnant patients received 91 courses of treatment, and 53 women with bacteriuria in pregnancy received 72 courses of treatment. At each visit, a proforma was completed and the patients were asked in a general way for their opinions on the treatment just received. After this, they were questioned directly concerning the disappearance of symptoms as well as any side-effects of the drug used. Blood samples were obtained at every visit throughout the study for haematological, biochemical and immunological assessment of the patient's response to infection and to assist in the evaluation of possible side-effects of chemotherapy.

The sole criterion of cure was the eradication of the original infecting organism from the urine at 2 and 6 weeks after the beginning of treatment. The treatment was considered to have failed if the same organism, as judged by its biochemical and serological characteristics, was isolated from either of the follow-up specimens. In some cases this meant that the immediate post-treatment urine was clear, but the specimen taken approximately 6 weeks after the beginning of treatment yielded a significant growth of the original organism. Treatment was considered to be successful even if the urine, either at 2 or 6 weeks, yielded a significant growth of a *different* organism since this must be due to reinfection. Such reinfections were found after 18% of courses in the non-pregnant patients, and after 11% of courses in the pregnant women. When patients had repeated urinary infections despite adequate treatment, intravenous pyelography was carried out to exclude the presence of abnormalities.

The non-pregnant patients who responded to treatment were followed up for at least 6 weeks before being referred back to their general practitioners, and the pregnant women were seen at intervals up to 6 weeks after delivery.

Laboratory Methods

The criterion for inclusion in the treatment trial was that 2 successive mid-stream specimens of urine collected at the clinic were shown to contain more than 10^5 organisms per ml of the same bacteria in pure growth. Mid-stream specimens of urine were collected from the patient after swabbing with sterile water. Antiseptic agents were not used in perineal preparation since it has been shown that they may interfere with bacterial cultures (Roberts, Robinson and Beard, 1967). These mid-stream specimens were tested for protein and glucose, and urinary cell counts were carried out in a modified Fuchs-Rosenthal chamber. Semiquantitative bacterial counts were performed using the blotting paper strip technique (Leigh and Williams, 1964) and those positive by this test were cultured quantitatively by a surface spread plate dilution method. The organisms were identified by standard methods (Cowan and Steel, 1965) and antisera were used to determine the serotype of each *Escherichia coli* isolate. Serum antibody titres against the urinary organisms were estimated by the method of Percival, Brumfitt and de Louvois (1964).

Results

Table I lists the causal organisms in the 2 groups of patients, and analysis of these figures reveals that there is a significant difference in the prevalence of staphylococcal infection in the 2 groups (Fischer exact test, $P = 0{\cdot}03$). There are no significant differences, however, between the figures for *Esch. coli* or *Proteus mirabilis*. The *Esch. coli* serotypes responsible for the infections in both groups of patients were very similar to those described by most other workers (for example, Grüneberg, Leigh and Brumfitt, 1968), with serotypes 06 and 075 predominating in the non-pregnant patients, and 02 and 075 serotypes in the pregnant women with bacteriuria.

Non-Pregnant Patients

The 67 patients in this group received 67 primary, 20 secondary and 4 tertiary courses of treatment. Table II shows that the nifuratel compounds were marginally more effective than ampicillin,

Table I

Infecting Organisms in the 2 Groups of Patients*

Causal Organisms	Non-Pregnant Patients	Pregnant Patients
Escherichia coli	67 (85%)	49 (79%)
Staphylococcus albus	8 (10%)	1
Proteus mirabilis	4 (5%)	6 (10%)
Klebsiella aerogenes	...	4
Streptococcus faecalis	...	2

* *Note:* Some patients had more than one infection whereas others were treated twice or more for the same infection.

Table II

Results of Treatment in Non-Pregnant Patients

Drug	Courses		
	Total	Success (%)	Failure
Ampicillin	22	17 (77%)	5
Carbenicillin ester	25	18 (72%)	7
Nifuratel 200 × 2 coated	19	16 (84%)	3
Nifuratel 400 × 1 uncoated	25	22 (88%)	3
	91	73 (80%)	18
$\chi^2 = 2{\cdot}32$, P = 0·5 = Not significant			

and considerably more effective than the carbenicillin indanyl ester: however, when these figures are examined in more detail the differences are much reduced. There were fewer secondary treatment courses with the sugar-coated nifuratel: if the primary courses only are considered, the success percentages are as follows: ampicillin 88%, carbenicillin ester 76%, coated nifuratel 80%, and uncoated nifuratel 89%. Thus the removal of the secondary courses makes little difference to the results with carbenicillin and the nifuratel compounds, but much improves the results with ampicillin. Analysis of the failures of secondary treatment reveals that they all occurred where the infection was recalcitrant to at least 3 different antimicrobial agents. These patients were referred for full urological investigation.

Patients with Bacteriuria in Pregnancy

A total of 53 patients received 72 courses of treatment, of which 53 (74%) were successful (Table III). The large number of treatment courses is due to the fact that relapse or reinfection occurred in some patients necessitating an additional course of treatment.

Combined Results (All Patients)

The overall results of 163 courses of treatment given to 120 patients are shown in Table IV. It should be noted that combining the results from 2 separate groups of patients disguises the differences found when an individual group, pregnant or non-pregnant, is considered alone. Results of both the primary and total treatment courses showed no statistically significant differences

Table III

Results in Patients With Bacteriuria in Pregnancy

Drug	Courses		
	Total	Success (%)	Failure
Ampicillin	19	13 (68%)	6
Carbenicillin ester	18	14 (77%)	4
Nifuratel 200 × 2 coated	17	11 (65%)	6
Nifuratel 400 × 1 uncoated	18	15 (83%)	3
	72	53 (74%)	19

$\chi^2 = 1{\cdot}99$, P = 0·5 = Not significant

Table IV

Combined Results in the 2 Groups of Patients

Drug	Total Treatment Courses	
	Given	Success (%)
Ampicillin	41	30 (73%)
Carbenicillin ester	43	32 (74%)
Nifuratel—coated	36	27 (75%)
Nifuratel—uncoated	43	37 (86%)
Totals:	163	126 (77%)

between the 4 drug preparations, although the uncoated nifuratel appeared to be marginally superior. A possible explanation for some of the failures with carbenicillin may be the number of unwanted side-effects observed by the patients and the possibility that some treatment courses were not completed.

Unwanted Effects

The frequency of side-effects was significantly greater ($\chi^2 = 6{\cdot}75$, P = 0·01) with the 2 penicillins, considered either separately or together, than with the nifuratel compounds (Table V). There was no significant difference between the penicillins themselves ($\chi^2 = 0{\cdot}43$, P = 0·5) in the number of side-effects encountered.

A number of patients complained of gastrointestinal disturbances (mainly nausea and vomiting) which occurred with all 3 drugs used. They often complained that carbenicillin tablets were difficult to swallow and gave rise to an unpleasant taste sensation, usually described as a "medical" taste. The reason for the side-effects with the carbenicillin ester may be that the tablets consisted of 500 mg of the compressed carbenicillin preparation, and were brick-shaped with sharp edges: no surface coating was provided. Since the present study was concluded, the manufacturers have produced a film-coated 500 mg tablet of smaller size with a smooth surface (Knirsch, Hobbs and Korst, 1973) and a further trial of the new preparation is in progress. Eight of the patients who received ampicillin suffered from diarrhoea of varying degree. Remarkably few side-effects, seldom amounting to more than mild nausea and flatulence, were noted after treatment with either of the nifuratel preparations. Only 1 patient complained of a skin eruption, which was acneiform and apparently related to the administration of carbenicillin. None of the 41 patients who received ampicillin developed a rash. Six patients suffered from oral or vaginal thrush (from which *Candida albicans* was isolated), 3 following ampicillin and 3 after carbenicillin. Mucosal

Table V

Frequency of Unwanted Drug-Effects

Drug	Courses Given	Courses with Side-Effects (%)
Ampicillin	41	13 (32%)
Carbenicillin ester	43	18 (42%)
Nifuratel—coated	36	5 (14%)
Nifuratel—uncoated	43	6 (14%)

Table VI

Side-Effects Noted During Therapy*

Drug Given	Ampicillin	Carbenicillin Ester	Nifuratel Coated	Nifuratel Uncoated
Number of Courses	41	43	36	43
Complaints Noted:				
Unpleasant/ difficult to swallow	...	11	...	...
Vomiting/nausea/ flatulence	...	4	3	3
Diarrhoea	8	2	1	...
Oral/vaginal candidiasis	3	3	...	...
Miscellaneous	4	2	1	4
Totals:	19	22	5	7

* *Note:* Some patients had more than one side-effect during the same course of treatment.

irritation was not found in any patient who received nifuratel. The side-effects noted are recorded in Table VI. The unwanted effects were severe enough to curtail treatment in 3 patients on carbenicillin therapy: all had difficulty in swallowing the tablets and 1 of them also experienced severe diarrhoea. One of the patients given ampicillin reported vaginal and oral thrush as well as severe diarrhoea and discontinued her medication.

Discussion

As can be seen from the results, there was little difference between the effectiveness of the antibacterial compounds used. The carbenicillin ester was satisfactory in treatment but had the disadvantage of being rather poorly tolerated by the patients. The latter finding is in agreement with Bailey and Koutsaimanis (1972) and Turck (1973). With improved formulation now available, this drug should have a place in the treatment of *Pseudomonas aeruginosa* urinary tract infections, particularly in ambulant out-patients (*British Medical Journal*, 1973). However, in the present study no *Ps. aeruginosa* infections were encountered.

When the results of treatment were related to the bacteria isolated, it was found that the majority of the staphylococcal infections (8 out of the 9) were treated with the nifuratel compounds. Our experience in treating such infections is that they almost always respond to chemotherapy within 24 hours; this was also seen in the present study. Thirteen treatment courses were given for *Proteus mirabilis* infection, of which 6 were with the carbenicillin ester and 4 were successful. The nifuratel compounds were used in 4 episodes of infection due to this organism, and were successful in 3 instances. This is surprising since nitrofurantoin, another nitrofuran, generally fails to cure proteus infections. The 3 remaining infections due to the organism were all in pregnant women

and were treated with ampicillin but only 1 was cured. None of the strains of *P. mirabilis* produced penicillinase.

In order to assess the value of the different treatment regimes in the presence of renal tissue involvement, the patients were divided into 2 groups according to the presence, or absence, of a raised titre of bacterial agglutinins in the serum (Percival, Brumfitt and de Louvois, 1964). The results showed that there were no statistically significant differences between the cure rates in the 2 groups of patients. However, it is clear that both nifuratel preparations were effective in patients who had renal tissue infection accompanied by raised serum antibody titres and this has been borne out by the successful use of these drug preparations in patients with acute pyelonephritis. It has been shown that although the nitrofurans reach negligible concentrations in the blood they are capable of diffusing into the medulla of the kidney (Chisholm, Calnan and Waterworth, 1968).

The reversal of the percentage cure rates in pregnant women compared with non-pregnant patients has previously been reported with cephalexin and ampicillin (Brumfitt and Pursell, 1972). In the present study a similar reversal was observed with carbenicillin and ampicillin, suggesting that the lower cure rates with ampicillin in pregnant patients may be evidence of less complete intestinal absorption. As the pregnant women were followed for at least 6 weeks after delivery it was possible to study any teratogenic effects caused by the drugs in the trial. Only in 2 patients (both of whom received carbenicillin and then ampicillin) did foetal morbidity occur. In 1 of them a twin pregnancy aborted at 26 weeks following the development of acute hydramnios and the other, a patient with intractable *Proteus mirabilis* infection and a renal stone, gave birth to an infant with congenital heart disease which proved fatal. The mean birth weights of the infants born to patients in the 4 treatment groups were 7·1, 6·9, 6·8 and 7·1 pounds.

The 2 nifuratel preparations were similar in activity, though there appeared to be a clear advantage in using the uncoated compound, and this drug was particularly effective in bacteriuria in pregnancy. The small number of side-effects was very gratifying, confirming the earlier studies of Brumfitt (1972) in a pilot trial. There were worthwhile additional benefits from its prophylaxis against *Trichomonas vaginalis* and *Candida albicans* (Murphy, 1968; Struthers, 1969; Munro, 1973) although the action against *Trichomonas vaginalis* may be less than that of metronidazole (Fowler and Hussain, 1968; Evans and Catterall, 1970). The cost of these preparations is similar to that of ampicillin.

In view of the findings of minimal antibacterial activity of nifuratel in the urine of volunteers (McGeachie, Robinson and Black, 1972), it is surprising to find such high cure rates following treatment with this drug. Because of this, it is even more surprising that the cure rates were also high in patients with parenchymatous renal infection (judged by raised serum agglutinin titres).

A number of side-effects were seen following the ampicillin courses although the severity was sufficient to stop treatment in only 1 case. By contrast, 3 patients given carbenicillin had to abandon their treatment. The 2 preparations of nifuratel, on the other hand, gave rise to few unwanted effects and also interfered less with the bacterial flora of the bowel, thus reducing the risk of reinfection with resistant organisms (Brumfitt, unpublished data). Further, the lack of toxicity makes these drugs particularly useful for the treatment of bacteriuria in pregnancy. Our results are remarkably similar to those of the preliminary studies reported by Tynan, Macis and Ward-MacQuaid (1969).

Summary

A total of 120 patients, including 53 pregnant women with significant bacteriuria, received 163 7-day courses of oral antimicrobial agents allocated in a randomised manner. The cure rates after 6 weeks' follow-up ranged from 73% to 86%, and there was no statistical difference between preparations of ampicillin, carbenicillin indanyl ester, and 2 different formulations of nifuratel. Side-effects occurred in 30% to 40% of the courses of penicillin drugs, but in under 15% of the course of nifuratel.

It is concluded that the new oral preparation of carbenicillin is a useful addition to the list of antimicrobial agents which are effective in the treatment of urinary infections in domiciliary patients. Furthermore, nifuratel has been confirmed as a highly active non-toxic drug which is valuable in the treatment of urinary infections.

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