Clinical Trial

A COMPARATIVE STUDY OF THE LEVELS OF NALIDIXIC ACID IN PLASMA AND URINE AND ITS ANTIBACTERIAL ACTIVITY IN URINARY INFECTIONS OF PARAPLEGICS

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NALIDIXIC ACID, one of a series of 1, 8-naphthyridine derivatives with antibacterial activity was synthesised by Lesher, Froelich, Gruett, Bailey and Brundage (1962). Chemically it is 1-ethyl-7-methyl-1, 8-naphthyridine-4-one-3-carboxylic acid.

The pharmacology and toxicology have been documented by Ward-McQuaid, Jichlinski and Macis (1963) and Lishman and Swinney (1963), based on unpublished information made available by the Sterling-Winthrop Research Institute. McCchesney, Froelich, Lesher, Crain and Rosi (1964) have carried out studies of urine levels of nalidixic acid in healthy volunteers, in addition to a large series of animal experiments. It was found that nalidixic acid attained higher concentrations in human urine and animal kidney tissue than in any other body fluids or organs respectively.

The effect of nalidixic acid on urinary tract infections has been studied in vitro by Deitz, Froelich and Bailey (1962) and clinically and bacteriologically by Buchbinder, Webb, Anderson and McCabe (1962), Barlow (1963), Carroll (1963), Jameson and Swinney (1963), Lishman and Swinney (1963), McCabe (1963), Slade (1963), Thompson and Rae (1964) and Ward-McQuaid and co-workers (1963).

On the basis of this information we have examined 16 cases in the Liverpool Regional Paraplegic Centre at Southport to estimate the plasma and urine levels of nalidixic acid in patients, and its effect on bacteriological clearance.

Methods and Material

The 17 patients selected for this trial presented no clinical sign or symptom of urinary infection except for turbid or purulent urine. Cases were selected on the basis of urine cultures and sensitivity tests carried out on all paraplegic patients in the unit. Only patients who had organisms in the urine sensitive to nalidixic acid were included in this trial.

Among the 17 cases 2 were female and 15 male, the ages ranging from 19 to 70 years. 15 cases were given nalidixic acid 1 g. 6 hourly, 11 of whom received the drug for 7 days, 3 patients for 12 days and one patient for one day. This last patient had an attack of diarrhoea on the second day, and, for this reason the drug was stopped after one day's therapy. This patient was excluded from the series. 2 cases were given 0.5 g. of nalidixic acid every 6 hours for 7 days and 4 patients had a second course extending from 2-4 weeks. In all cases the drug was administered orally and on the first day only it was given every 4 hours to fit in with the collection of blood and urine samples.

Plasma and Urine Assay

For this purpose five samples of urine and blood were collected on the day of commencement of therapy. One sample of each was taken as a control specimen before the drug was administered. Four samples were collected at intervals of 1, 2, 4 and 8 hours after administration of nalidixic acid. The plasma was separated and both urine and plasma were refrigerated at 4°C until assay was done. On the 2nd and every alternate day a sample of urine only was collected for the drug assay and the collection time varied from 2 to 5 hours after therapy. Collections of both blood and urine were made on the 3rd and every alternate day until completion of therapy.

In the two patients on nalidixic acid 0.5 g. q.i.d., an assay of the drug in the urine and plasma was made after completion of therapy, to check the residual concentration. For this, samples of urine and blood were collected at 15½ hours, 16½ hours, 38½ hours and 39½ hours after therapy.

A physicochemical method was adopted for the determination of nalidixic acid. This was based on the principle that it is readily extracted from an aqueous medium at pH 1-6 by toluene and can be transferred from toluene into water at pH 9.0. On acidification of this aqueous phase to pH 0-1, the compound becomes fluorescent. The activating wavelength is 320 nm (uncorrected) and the fluorescent wave-length is 350 nm (uncorrected), as determined on an Amino Bowman spectrophotofluorimeter.

A calibration graph was prepared by adding known amounts of nalidixic acid to blank biological fluids and subjecting these standards to the analytical procedures. Recoveries were greater than 90% for the range 10-100 μg.

Bacteriological Studies were made on the urine of the patients by a daily collection starting from the day of therapy. 12 out of the 16 patients had
indwelling catheters, and urine in these cases was taken by allowing the first few ml. to escape from the end of the catheter, after which a specimen of 15-20 ml. was collected. Collection of urine in the other four was midstream. All specimens were refrigerated after collection and examined within three hours.

The following investigations were made on all urine specimens:

1. **Culture:** This was carried out by plating a standard 2 mm. loopful of uncentrifuged urine into a blood agar and a MacConkey agar plate. These plates were incubated at 37°C overnight and examined the following day. The organisms commonly isolated were *E. coli*, *A. aerogenes*, atypical coliforms (those coliforms not falling into the two above groups), *Proteus Spp.*, *Ps. pyocyanea* and *Strep. faecalis*.

2. **Sensitivity of Gram-negative Bacilli:** A disc sensitivity technique was employed making use of commercially available paper sensitivity discs containing the various antibacterial agents (Tables 3 & 4). In the case of nalidixic acid 5, 30 and 60 μg. discs were used initially, but later on only 30 μg. discs were used. A well defined zone of inhibition around the disc was recorded as the sign of sensitivity and growth right up to the disc or near the disc as resistance. No attempt was made to measure the zones of inhibition.

Sensitivity was studied against all Gram-negative bacilli in the urine, but not against Gram-positive organisms such as *Strep. faecalis*, *Strep. pyogenes* and *Staphylococci* following the unpublished experimental data in the files of the Sterling-Winthrop Research Institute. Recent reports by Lishman and Swinney (1963), Barlow (1963), Ward-McQuaid and others (1963) show, however, that a few strains of these Gram-positive organisms may sometimes be sensitive to nalidixic acid and occasionally may be responsive to treatment. In our experience, however, these were never cleared up with nalidixic acid therapy.

3. **Bacterial Counts:** were made by a pour-plate method using serial dilutions of urine in digest broth from 10⁻¹ to 10⁻⁴. One ml. of each dilution of urine was mixed with 10 ml. of melted nutrient agar at 50°C in a Petri-dish. The agar was allowed to solidify and this was incubated overnight. Counts were made on the plates showing 30-300 colonies. Any count of less than 10,000 organisms per ml. was considered as showing that infection was absent. (Kass, 1955).

4. **Minimum Inhibitory Concentration:** Tests were carried out with nalidixic acid on all Gram-negative bacilli isolated during the trial. 91 different strains of organisms were tested in this way and those strains that were present on more than one occasion were tested each time they were isolated. Serial doubling dilutions of nalidixic acid solution were made in 1.0 ml. of digest broth giving concentrations from 1 μg./ml. to 256 μg./ml. The tubes were inoculated with 1 drop (0.02 ml.) of a 1/1000 dilution of an overnight broth culture of the test organisms and incubated for 18 hours at 37°C. The minimum inhibitory concentration was recorded as the minimum concentration of nalidixic acid which prevented visible growth.

5. **Pus Cell Count:** The method adopted by McGeachie and Kennedy (1963) was used. 10 ml. of well mixed urine were centrifuged in a graduated tube at 3,000 r.p.m. for 3 minutes. The supernatant liquid was removed leaving 0.5 ml. of urine and sediment. This was mixed using a Pasteur pipette and a Neubauer counting chamber was filled with the suspension. The white blood cells in the area indicated were counted and if the counts were low, several similar areas were counted and the mean taken. The numbers counted were taken as cells per measured area. In the case of urine with a very high cell count uncentrifuged urine was used, and the result multiplied by 20. As found by McGeachie and Kennedy (1963), a count of 10 or more leucocytes per measured area was taken as significant.

### Table 1

<table>
<thead>
<tr>
<th>Name</th>
<th>Daily dose of nalidixic acid</th>
<th>Level of the drug in Plasma</th>
<th>Level of the drug in Urine</th>
<th>Level of the drug in Plasma</th>
<th>Level of the drug in Urine</th>
<th>Level of the drug in Plasma</th>
<th>Level of the drug in Urine</th>
<th>Level of the drug in Plasma</th>
<th>Level of the drug in Urine</th>
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</thead>
<tbody>
<tr>
<td>Mr. W. R.</td>
<td>1 g. q.i.d.</td>
<td>21</td>
<td>240</td>
<td>12.8</td>
<td>248</td>
<td>5</td>
<td>252</td>
<td>10</td>
<td>28</td>
</tr>
<tr>
<td>Mrs. C. V.</td>
<td>1.5 g.</td>
<td>1.5</td>
<td>16.5</td>
<td>13</td>
<td>160</td>
<td>18.5</td>
<td>184</td>
<td>15.5</td>
<td>63</td>
</tr>
<tr>
<td>Mr. J. B.</td>
<td>1.5 g.</td>
<td>1.5</td>
<td>4.4</td>
<td>2</td>
<td>7</td>
<td>4</td>
<td>42</td>
<td>9</td>
<td>83</td>
</tr>
<tr>
<td>Mr. W. D.</td>
<td>$&lt;0.1$ g.</td>
<td>$&lt;0.1$</td>
<td>15.5</td>
<td>7.5</td>
<td>7.5</td>
<td>22.5</td>
<td>14.5</td>
<td>161</td>
<td></td>
</tr>
<tr>
<td>Mr. A. G.</td>
<td>7.6 g.</td>
<td>7.6</td>
<td>11.5</td>
<td>16.8</td>
<td>45</td>
<td>3.3</td>
<td>25</td>
<td>3.3</td>
<td>55</td>
</tr>
<tr>
<td>Mr. K. M.</td>
<td>1.0 g.</td>
<td>1.0</td>
<td>2.75</td>
<td>0.75</td>
<td>8.5</td>
<td>13</td>
<td>51.2</td>
<td>3.75</td>
<td>54</td>
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<tr>
<td>Mr. N. H.</td>
<td>6.3 g.</td>
<td>6.3</td>
<td>18</td>
<td>14</td>
<td>139</td>
<td>7.5</td>
<td>80.5</td>
<td>8.8</td>
<td>48</td>
</tr>
<tr>
<td>Mr. J. S.</td>
<td>14.5 g.</td>
<td>14.5</td>
<td>87</td>
<td>16.7</td>
<td>155</td>
<td>6</td>
<td>202</td>
<td>6.5</td>
<td>163</td>
</tr>
<tr>
<td>Mr. J. P.</td>
<td>14 g.</td>
<td>14</td>
<td>56</td>
<td>18</td>
<td>117</td>
<td>8.5</td>
<td>210</td>
<td>9</td>
<td>160</td>
</tr>
<tr>
<td>Mr. S. J. B.</td>
<td>16.4 g.</td>
<td>16.4</td>
<td>39.6</td>
<td>13</td>
<td>71.5</td>
<td>18</td>
<td>63.5</td>
<td>9.2</td>
<td>55.25</td>
</tr>
<tr>
<td>Mr. J. H.</td>
<td>14.75 g.</td>
<td>14.75</td>
<td>18.5</td>
<td>7.25</td>
<td>43.25</td>
<td>5.25</td>
<td>23.25</td>
<td>12</td>
<td>23.5</td>
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<tr>
<td>Mr. J. S.</td>
<td>49.5 g.</td>
<td>49.5</td>
<td>77</td>
<td>44</td>
<td>185</td>
<td>23.5</td>
<td>170</td>
<td>18</td>
<td>46.2</td>
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<tr>
<td>Mr. W. J.</td>
<td>6 g.</td>
<td>6</td>
<td>41</td>
<td>17</td>
<td>51</td>
<td>14.5</td>
<td>36</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>Mrs. E. B.</td>
<td>9.5 g.</td>
<td>9.5</td>
<td>12.3</td>
<td>0.25</td>
<td>4.8</td>
<td>3.55</td>
<td>29.5</td>
<td>9.1</td>
<td>80.25</td>
</tr>
<tr>
<td>Mr. J. H.</td>
<td>19.5 g.</td>
<td>19.5</td>
<td>95</td>
<td>22.8</td>
<td>177</td>
<td>10</td>
<td>125</td>
<td>2.1</td>
<td>127</td>
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<tr>
<td>Mr. A. C.</td>
<td>0.5 g.</td>
<td>0.5</td>
<td>14.25</td>
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<td>6.75</td>
<td>16</td>
<td>5</td>
<td>96</td>
<td>6.5</td>
</tr>
<tr>
<td>Mr. E. W.</td>
<td>1 g. q.i.d.</td>
<td>1</td>
<td>—</td>
<td>4</td>
<td>105</td>
<td>6</td>
<td>210</td>
<td>10</td>
<td>186</td>
</tr>
</tbody>
</table>

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*Assay of Nalidixic Acid in Plasma and Urine on the 1st Day of Treatment, in μg./ml.*
### Table 2

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>14th Day</td>
<td>17th Day</td>
<td>20th Day</td>
</tr>
<tr>
<td>7th Day</td>
<td>4th Day</td>
<td>1st Day</td>
</tr>
<tr>
<td>6th Day</td>
<td>5th Day</td>
<td>3rd Day</td>
</tr>
<tr>
<td>1st Day</td>
<td>2nd Day</td>
<td>1st Day</td>
</tr>
</tbody>
</table>

**Assay of Nalidixic Acid in Plasma and Urine on the 2nd and Subsequent Days (in mg/ml)**

**GIBBON, BENSTEAD AND MISRA:** Nalidixic Acid
Results

**Plasma and Urine Assay:** A wide range of variation was noted in the results of the assay of nalidixic acid in the plasma and urine of different patients and even in that of the same patient at any particular hour after therapy (Tables 1, 2). On the first day of therapy when 4 samples were taken, the concentration of the drug in the urine after 1 hour of therapy ranged from 2.75 μg./ml to 240 μg./ml. After the second hour it extended from 5.8 μg./ml to 248 μg./ml and after the 4th hour the range was from 22.5 μg./ml to 252 μg./ml. The sample of urine which was collected 8 hours after the commencement of therapy showed a range from 20 μg./ml to 186 μg./ml. All patients, of course, had their 2nd daily dose of nalidixic acid by then. The two patients who had nalidixic acid 0.5 g. q.i.d. did not in fact show any lower concentration of the drug either in the plasma or in the urine, compared to those who had 1 g. q.i.d. On the contrary, there was a very high concentration of the drug in the urine of one of these two patients, but he was without a catheter. The results of the assay on the 2nd and subsequent days show a similar variation in the concentration of the drug both in the plasma and urine, but not to such a great extent (Table 2).

The lowest concentration of the drug in a sample of urine taken after the 1st day of therapy was found to be 17.25 μg./ml, and in more than 90% of the samples the concentration of the drug was above 30 μg./ml. (Table 2) irrespective of the time of collection of the sample; this was usually done from 2 to 5 hours after therapy. The highest level of the drug was found during the 3rd and 4th hour after therapy in the majority of cases.

In one of the two patients who had 0.5 g. nalidixic acid q.i.d., the assay of urine at 15½ hours after completion of therapy, showed 4 μg. of nalidixic acid per ml, and at 38½ hours 2 μg./ml. Even though the other patient did not show an equivalent level of the drug in his urine.
it is interesting to note that up to 38 hours after therapy there could be some nalidixic acid still present in the urine of a proportion of cases. From this it is reasonable to assume that up to 24 hours after therapy there could be an appreciable level of the drug present in the urine.

**Bacteriological Studies**

102 different strains of Gram-negative bacteria were isolated, and studied for relative sensitivity to different chemotherapeutic agents *in vitro* by the disc technique (Table 4). These included the 25 different strains of organisms which were isolated from the pretherapy samples of urine of the 17 patients selected for trial (Table 3).

E. coli: 44 out of 49 strains were sensitive to nalidixic acid, whereas only 34 were sensitive to chloramphenicol and 37 to nitrofurantoin. In the case of kanamycin the sensitivity was identical, i.e. 44 out of 49 (Table 4).

Proteus spp.: 27 out of 31 strains were sensitive to nalidixic acid as compared with 16 to chloramphenicol. 28 out of 31 were sensitive to kanamycin.

Ps. pyocyanea: Out of 12 strains only 1 was sensitive to nalidixic acid whereas 7 were sensitive to chloramphenicol.

A. aerogenes and atypical coliforms: There were 6 strains of the former and 4 of the latter. The sensitivity of these to nalidixic acid was similar to other agents such as chloramphenicol, kanamycin and nitrofurantoin. The sulphonamides and tetracycline were comparatively ineffective.

Following Waterworth's report (1962), mandelamidine was not used for testing against *Proteus spp.*, and only a few strains of other organisms were tested against it (Table 4).

**Bacterial Count:** In most cases it was found difficult to obtain a satisfactory result by the pour-plate method, especially in urine with a high bacterial count. (Often the count obtained from a particular dilution did not show tenfold increase or decrease on the corresponding, preceding or following dilution.) This was almost certainly due to the difficulty in obtaining a homogeneous suspension of organisms, as a result of the bacteria being present in small clumps. On the whole the results were irregular and nothing much was gained from doing this procedure except to gauge the lower limit of infection. This is because a bacterial count of less than 10,000 was regarded as no infection.

**Pus Cell Count:** In the 16 patients where a daily pus cell count was done, 9 showed a progressive but irregular fall and 5 of these showed complete clearance. Out of these 5, 4 were associated with a bacteriological clearance. In the other 7, the count was extremely irregular and two of these in fact showed a considerable increase over the initial count.

**Minimum Inhibitory Concentration:** 91 strains of organisms which were isolated during therapy or at subsequent check-ups were tested for M.I.C. of nalidixic acid, out of which, excluding all the strains of *Ps. pyocyanea*, 80% were found to be in the range of 32 μg./ml, or less (Table 5). In our experience organisms in this range have been found to be responsive to treatment. In the range of 64 μg./ml there were 5 organisms, only one of which appeared during the period of therapy and subsequently disappeared after treatment. 14 out of 21 *Ps. pyocyanea* were in the range > 256 μg./ml and these were considered to be highly resistant. Even those 2 strains of *Ps. pyocyanea* which were found to be in the 32 to 64 μg./ml range soon acquired resistance to nalidixic acid.

**Bacteriological Clearance:** We define bacteriological clearance as the state where there is no growth on plate culture of urine specimens for two consecutive days. On the first day of therapy 10 out of 16 patients had exclusively sensitive organisms in their urine, either one or two in number; the other 6 patients had multiple organisms which were a mixture of sensitive and resistant strains. The sensitive organisms were E. coli and Proteus, 90% of which were cleared up by the 4th day (i.e. 72 hours after therapy). One was cleared up on the 5th day and another on the 7th day after therapy. None of the initially sensitive organisms acquired resistance but in one patient the clearance was associated with replacement by emergent strains. It should be mentioned that some discrepancy will be found between the initial sensitivity chart, presented in Table 3, and the clearance presented here. This could be explained by the fact that paraplegic bladders are often severely diseased and the bacterial flora, cultured from the urine vary from day to day.

### TABLE 5
**Minimum Inhibitory Concentration of Nalidixic Acid on 91 Different Strains of Organisms in Vitro**

<table>
<thead>
<tr>
<th>Organisms</th>
<th>No. of strains</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>16</th>
<th>32</th>
<th>64</th>
<th>128</th>
<th>256</th>
<th>&gt;256</th>
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<tbody>
<tr>
<td>E. coli</td>
<td>46</td>
<td>7</td>
<td>14</td>
<td>10</td>
<td>7</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteus spp.</td>
<td>12</td>
<td>6</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ps. pyocyanea</td>
<td>21</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>16</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical coliforms</td>
<td>9</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. aerogenes</td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>91</strong></td>
<td></td>
<td></td>
<td></td>
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</table>
day. Culture and subsequent sensitivity tests done on a specimen of urine take two days before the results can be studied and thus the organisms noted on a pretherapy culture may be slightly different to those noted on the first day of therapy.

Complete bacteriological clearance was achieved in 9 out of 16 patients and the other 7 did not clear up. A relationship has been shown between the duration of the disease and clearance rate (Table 6). There is a better chance of clearing the infection in those patients with a recently diseased bladder than in those who have had the disease for 1-5 years or longer. Presence of catheter has not been found to delay clearance of sensitive organisms, though emergence of infection or re-infection is quick in those cases. This opinion is based on the fact that 12 out of 16 of the patients had catheters.

Re-infection: This was noted in all the 9 cases after complete bacteriological clearance. 3 were re-infected within the 1st and 3 in the 2nd week after completion of therapy. The infecting organisms were sensitive to nalidixic acid in many cases.

Emergent Organisms: During therapy with nalidixic acid 21 different strains of organisms emerged in the urine of 7 patients (Table 7), these organisms appearing during therapy but before clearance of the initial organisms. Only one of these, an atypical coliform, was sensitive to nalidixic acid. The rest were all resistant. Six patients out of these seven had mixed infections of sensitive and resistant strains and only one had purely sensitive strains initially.

**Automatic Clearance:** Automatic clearance of resistant organisms present initially or emerging afterwards, during or after therapy was found in 7 patients. 25 such organisms were isolated: 20 cleared up within the first four weeks after appearance and the other five cleared up after 6-8 weeks. This was noted when a follow up culture of urine was done on each patient at 1-4 weeks interval. It should be mentioned that the clearance of resistant organisms was often associated with replacement by a fresh organism, either sensitive or resistant to nalidixic acid. The automatic clearance may be attributed to the excess secretion of urine in paraplegics who are always advised to drink more to avoid stone formation.

**Clinical Assessment:** Out of the 16 patients, 14 had marked improvement in the macroscopic picture of their urine, and 9 of these 14 patients had a complete clearance maintained for 1-5 weeks or longer after completion of therapy.

Side effects were few and mild. Nausea, skin rash, weakness, dizziness for one day, and diarrhoea were noted in 4 patients. The condition subsided quickly, and only in one case who had diarrhoea, was the drug discontinued, and this patient has been excluded from this series.

**Discussion**

Assays of nalidixic acid in the serum and urine of healthy volunteers have been undertaken by Deitz and others (1962). Their findings show that the major portion of the drug is excreted through the kidneys and is present for 8 hours
after administration. Buchbinder and others (1962) administered nalidixic acid, 1 g. q.i.d. for 3 days to 6 cases of pyelonephritis, and found serum levels ranging from 3.9 to 31.2 μg./ml. (mean value 6.8 μg./ml.), and urine levels from 62.5 to 500 μg./ml. (mean value 125 μg./ml.). Against these values we found mean concentrations 10.7 and 92.6 μg./ml. in plasma and urine respectively.

The significance of the mean plasma concentration of nalidixic acid as found in this trial, and its relevance to parenchymatous lesions of the kidney and other tissues has yet to be elucidated.

In this trial we found that the drug level attained its height between the 2nd and 4th hour after therapy in the majority of cases and diminished after that, although a fairly high concentration was still present at the end of the 8th hour. Moreover, when continuous therapy was maintained about 90% of urine samples taken after the first day showed a concentration higher than 32 μg./ml. irrespective of the time of collection which varied from 2 to 5 hours after administration. Comparison with the minimum inhibitory concentration shows that 80% of sensitive Gram-negative bacteria in the urine had M.I.C.'s of 32 μg./ml. or lower. These bacteria were thus susceptible to nalidixic acid. Marked individual variation in the concentration of the drug both in the urine and plasma was noted in different patients and in the same patient at different times; this has also been found by Deitz and others (1962) and Buchbinder and others (1962).

Our results regarding minimum inhibitory concentration are comparable with those of Barlow (1963) except that most of his sensitive strains were limited to a M.I.C. of 16 μg./ml. whereas in our experience they extended to 32 μg./ml. A great significance cannot be attached to this variation since the two dilutions are so close to each other. Ps. pyocyanea, as usual, was found to be resistant to nalidixic acid in most cases, only two out of 21 strains being found in the 32 μg./ml. range. These two acquired resistance quickly.

We have noted slightly different results in the disc sensitivity test in vitro, compared to that of Thompson and Rae (1964) who found chloramphenicol to be more effective against E. coli than nalidixic acid. In our experience about 90% of E. coli and Proteus spp., were sensitive to nalidixic acid whereas only about 66% of E. coli and 55% of Proteus spp. were sensitive to chloramphenicol. The probable explanation is that most of these paraplegic patients had chloramphenicol at intervals before this trial and this has caused a number of organisms to build resistance against it. Our results agree with the findings of Slade (1963), Buchbinder (1963), Barlow (1963), Thompson and Rae (1964) and Lishman and Swinney (1963) who showed that nitrofurantoin, sulphonamides and tetracyclines were less effective against E. coli than nalidixic acid. Ward-McQuaid and others (1963) found nalidixic acid to be as effective against Proteus spp. as chloramphenicol and nitrofurantoin, but less effective than kanamycin. We, however, found nalidixic acid to be more effective against Proteus than chloramphenicol and nitrofurantoin. Our findings agreed with these authors regarding the greater effectiveness of kanamycin. Lishman and Swinney (1963) have stated that nalidixic acid is more effective against A. aerogenes, but in our experience A. aerogenes was equally sensitive to nalidixic acid, chloramphenicol and tetracycline, and slightly more sensitive to kanamycin.

From the bacteriological study we found 9 out of 16 patients were completely cleared of their organisms. Re-infection in all these cases was rapid and this is understandable considering the effect of indwelling catheters on the bladders of paraplegics. Automatic clearance of resistant strains was noted in 7 patients though often new organisms emerged in their place. Free and excess urine secretion due to ample fluid intake will explain this phenomenon. Patients who had no catheters were found to maintain clearance for a slightly longer period.

The cure rate in this trial (9 out of 16) i.e. 56% was better than those published by other authors on chronic urinary infections, Rhoads, Billings and O'Conor (1952); Garrod, Shooter and Curwen (1954); Kass (1955); and Turck, Browder, Lindemeyer, Brown, Anderson and Petersdorf (1962). Our results were as good as those reported by Ward-McQuaid and others (1963) but the cure rate in Barlow's series (1963) was better than ours.

Eighty-eight per cent of sensitive E. coli and Proteus were found to be cleared within 72 hours of therapy, the remainder taking 5-7 days to clear up.

From this we were able to suggest that a 5 day course of nalidixic acid, 1 g. q.i.d. should be sufficient to clear up sensitive coliforms and Proteus in about 90% of cases. A urine culture on the 5th day will show the bacteriological state of the disease and if clearance has still not been achieved the drug should be continued.

Summary
A study of the plasma and urine concentrations of nalidixic acid was carried out in 16 paraplegic patients with urinary tract infections who were treated with the drug.

Of the urine samples, 90% had a concentration of nalidixic acid greater than 32 μg./ml. This was correlated with the minimum inhibitory concentrations of all Gram-negative bacteria isolated in the trial. 80% of these bacteria had M.I.C.'s of 32 μg./ml. or less, and were thus susceptible to nalidixic acid.

A comparative study of the activity of other chemotherapeutic drugs commonly used in urinary infections was carried out. Against E. coli and Proteus spp. nalidixic acid was found to be more effective than all other drugs tested
except for kanamycin, but relatively ineffective against Pseudomonas.

Nine of the 14 patients who had improvement in the macroscopic picture of their urine had complete clearance which was maintained for 1-5 weeks after cessation of therapy.

Side-effects were few and mild.

Our opinion of nalidixic acid is that it is a safe antibacterial agent, clears the organisms sensitive to it quickly, and can be administered repeatedly without serious toxic effect.

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REFERENCES


A CLINICAL TRIAL WITHNALIDIXIC ACID ON 22 ACUTE AND CHRONIC URINARY TRACT INFECTIONS WITH FOLLOW-UP FOR 1-5 MONTHS

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Nalidixic acid is one of a series of 1, 8-naphthyridine derivatives. The chemistry, pharmacology and toxicology have been detailed elsewhere, Lishman and Swinney (1963) and Ward-McQuaid, Jichlinski and Macis (1963). In a number of clinical trials published recently this chemotherapeutic agent was shown to be very effective against Gram-negative organisms in urinary tract infections, Lishman and Swinney (1963), Jameson and Swinney (1963), Slade (1963), Barlow (1963), Ward-McQuaid and colleagues (1963), Thompson and Rae (1964), McCabe (1963), Carroll (1963) and Gibson, Benstead and Misra (1965).

On the basis of this information we investigated 22 acute and chronic cases of urinary tract infection with follow-up for 1-5 months.