In Vitro Activity of Cinoxacin, Ampicillin, and Chloramphenicol Against Shigella and Nontyphoid Salmonella

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The in vitro antibacterial activity of cinoxacin was compared with that of ampicillin and chloramphenicol against 26 strains of nontyphoid Salmonella and 44 strains of Shigella. Cinoxacin was found to have a lower minimal inhibitory concentration than ampicillin and chloramphenicol against all Salmonella and Shigella sonnei strains. Cinoxacin had minimal inhibitory concentrations similar to those of chloramphenicol but lower than those of ampicillin against Shigella flexneri and S. boydii strains.

Cinoxacin, 1-ethyl-4(1H)-oxo-(1,3)diazido(4,5-g)cinnoline-3-carboxylic acid, is a new antibacterial agent (6) with activity similar to that of nalidixic acid and oxolonic acid, which are effective in vitro against Salmonella and Shigella strains (1, 4).

Because of the emergence of chloramphenicol- and ampicillin-resistant Shigella and Salmonella strains, we tested cinoxacin against recent isolates of nontyphoid Salmonella and Shigella strains and compared its activity with that of ampicillin and chloramphenicol.

MATERIALS AND METHODS

Twenty-six strains of nontyphoid Salmonella and 44 strains of Shigella isolated recently in Israel were tested. The strains were typed by the Shigella and Salmonella reference laboratories of the Ministry of Health. Included were nine strains of Salmonella typhimurium, five strains of S. heidelberg, four strains of S. anatum, two strains of S. dublin, and one strain each of S. carmel, S. sophia, S. muenchen, S. newport, S. blackley, and S. ille. The Shigella strains included: 12 S. sonnei, 14 S. flexneri, 18 S. boydii. All strains were kept in lyophilized form. Organisms were incubated overnight at 37°C in Mueller-Hinton broth before testing.

Antibacterial activity was determined by antibiotic dilution methods performed in Mueller-Hinton agar by use of a Steers replicator device (5). The inoculum used was a 10^-3 dilution of an overnight broth culture of each strain tested. The minimal inhibitory concentration (MIC) was defined as the lowest concentration of the drug that inhibited macroscopic colonial growth.

Stock solutions containing 1,000 μg of cinoxacin or 1,000 μg of ampicillin per ml were prepared in phosphate buffer (pH 7). Chloramphenicol was dissolved in dimethyl sulfoxide and water to a concentration of 500 μg/ml. All stock solutions were stored at -20°C and used within 2 weeks.

RESULTS

The mean MIC of cinoxacin for inhibition of Salmonella typhimurium was 2.8 μg/ml (range, 1.5 to 4.5 μg/ml). The mean MIC of ampicillin was 51.2 μg/ml (range, 2.5 to >100 μg/ml). Four of the nine strains tested were resistant to 100 μg of ampicillin per ml. The mean MIC of chloramphenicol was 14.8 μg/ml (range, 3.1 to 50 μg/ml). The mean MIC for S. heidelberg was 2 μg/ml (range, 1 to 3.5 μg/ml). The mean MIC of ampicillin was 22 μg/ml (range, 2.5 to >100 μg/ml). One strain was resistant to 100 μg of ampicillin per ml. The mean MIC of chloramphenicol was 28.5 μg/ml (range, 0.35 to >100 μg/ml). One strain was resistant to 100 μg of chloramphenicol per ml. The mean MIC of cinoxacin against S. anatum was 2.5 μg/ml; that of ampicillin was 38.12 μg/ml and that of chloramphenicol was 33.5 μg/ml. In this group there was one isolate resistant to ampicillin and one resistant to chloramphenicol.

Of the group including S. dublin, S. carmel, S. sophia, S. muenchen, S. newport, S. blackley, and S. ille, the mean MIC of cinoxacin was 3 μg/ml. The mean MIC of ampicillin was 28.75 μg/ml, and that of chloramphenicol was 11.87 μg/ml. The cumulative percentage of all Salmonella isolates inhibited by cinoxacin, ampicillin, and chloramphenicol is shown in Fig. 1.

Whereas nine of our Salmonella strains were resistant to 100 μg of ampicillin or chloramphenicol per ml, all strains were susceptible to 4.5 μg or less of cinoxacin per ml. Except for
one strain each of *S. heidelberg* and *S. sofia*, against which the MIC of chloramphenicol was lower than that of cinoxacin, for all strains tested, the MIC of cinoxacin was lower than that of either ampicillin or chloramphenicol. The mean MIC of cinoxacin against all *Salmonella* strains was 2.8 μg/ml, whereas that of ampicillin was 36.5 μg/ml and that of chloramphenicol was 19.5 μg/ml.

*Shigella* strains. The mean MIC of cinoxacin against *Shigella sonnei* was 1.31 μg/ml (range, 0.7 to 3.1 μg/ml). The mean MIC of ampicillin was 14.7 μg/ml (range, 4.5 to 25 μg/ml). The mean MIC of chloramphenicol was 19 μg/ml (range, 0.7 to >100 μg/ml). Two strains were resistant to at least 100 μg of chloramphenicol per ml.

The mean MIC of cinoxacin against *S. flexneri* was 1.34 (range, 0.7 to 1.5 μg/ml). The mean MIC of ampicillin was 10.7 μg/ml (range, 1.5 to 25 μg/ml). The mean MIC of chloramphenicol was 2.24 μg/ml (range, 0.5 to 4.5 μg/ml). The mean MIC of cinoxacin against *S. boydii* was 2.27 μg/ml (range, 1 to 2.5 μg/ml). The mean MIC of ampicillin was 29.3 μg/ml (range, 7.5 to >100 μg/ml). Three strains were resistant to 100 μg of ampicillin per ml. The mean MIC of chloramphenicol was 2.62 μg/ml (range, 0.7 to 3.1 μg/ml).

The cumulative percentage of all *Shigella* strains inhibited by cinoxacin, ampicillin, and chloramphenicol is shown in Fig. 2. The mean MIC of cinoxacin against all 44 strains of *Shigella* was 1.71 μg/ml, that of ampicillin was

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**Fig. 1.** Cumulative percentage of 26 strains of nontyphoid Salmonella inhibited by various concentrations of cinoxacin, ampicillin, and chloramphenicol.

**Fig. 2.** Cumulative percentage of 44 Shigella strains inhibited by cinoxacin, ampicillin, and chloramphenicol.
12.4 μg/ml, and that of chloramphenicol was 6.9 μg/ml. None of the strains was resistant to cinoxacin, whereas five strains were resistant to 100 μg of either ampicillin or chloramphenicol per ml. For nine strains of *Shigella*, the MIC of cinoxacin was equal to or higher than that of either chloramphenicol or ampicillin.

**DISCUSSION**

Our results demonstrate that cinoxacin is significantly more active in vitro than ampicillin and chloramphenicol against *Salmonella typhimurium*, *S. heidelberg*, and *S. anatum* and against a variety of other *Salmonella* species. Cinoxacin is significantly more active in vitro than either ampicillin or chloramphenicol against *Shigella sonnei*, but cinoxacin and chloramphenicol are equally active against strains of *S. flexneri* and *S. boydii*. Ampicillin was less active than chloramphenicol and cinoxacin against *S. flexneri* and *S. boydii*

The recent increase in *Shigella* and *Salmonella* strains resistant to chloramphenicol and ampicillin requires new agents active against these pathogens.

Moorhead and Parry found an 88.5% cure rate among patients with *S. sonnei* dysentery treated with nalidixic acid (2). Haltalin et al. (1) found nalidixic acid to be inferior to ampicillin in the treatment of severe shigellosis susceptible to ampicillin, but recommended nalidixic acid for treatment of ampicillin-resistant shigella dysentery. We believe that because of the favorable in vitro activity of cinoxacin against *Shigella* and *Salmonella* strains and because of the paucity of its side effects (3), clinical trials with cinoxacin are warranted in cases of shigella gastroenteritis.

**LITERATURE CITED**