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

ETHAN RUBINSTEIN* AND BRACHA SHAINBERG

Sheba Medical Center, Tel-Aviv University, Sackler School of Medicine, Tel-Hashomer, Israel

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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)dioxido(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. sofia*, *S. muenchen*, *S. newport*, *S. blackley*, and *S. lille*. 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^{-2} 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 concen-

tration 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. sofia*, *S. muenchen*, *S. newport*, *S. blackley*, and *S. lille*, 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 $\mu\text{g/ml}$, whereas that of ampicillin was 36.5 $\mu\text{g/ml}$ and that of chloramphenicol was 19.5 $\mu\text{g/ml}$.

Shigella strains. The mean MIC of cinoxacin against *Shigella sonnei* was 1.31 $\mu\text{g/ml}$ (range, 0.7 to 3.1 $\mu\text{g/ml}$). The mean MIC of ampicillin was 14.7 $\mu\text{g/ml}$ (range, 4.5 to 25 $\mu\text{g/ml}$). The mean MIC of chloramphenicol was 19 $\mu\text{g/ml}$ (range, 0.7 to >100 $\mu\text{g/ml}$). 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 $\mu\text{g/ml}$). The mean MIC of ampicillin was 10.7 $\mu\text{g/ml}$ (range, 1.5 to 25 $\mu\text{g/ml}$). The mean MIC of chloramphenicol was 2.24 $\mu\text{g/ml}$ (range, 0.5 to 4.5 $\mu\text{g/ml}$). The mean MIC of cinoxacin against *S. boydii* was 2.27 $\mu\text{g/ml}$ (range, 1 to 2.5 $\mu\text{g/ml}$). The mean MIC of ampicillin was 29.3 $\mu\text{g/ml}$ (range, 7.5 to >100 $\mu\text{g/ml}$). Three strains were resistant to 100 μg of ampicillin per ml. The mean MIC of chloramphenicol was 2.62 $\mu\text{g/ml}$ (range, 0.7 to 3.1 $\mu\text{g/ml}$).

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 $\mu\text{g/ml}$, that of ampicillin was

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 $\mu\text{g/ml}$, and that of chloramphenicol was 6.9 $\mu\text{g/ml}$. 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 ampi-

cillin 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.

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