Effect of Cholera Toxin on Intestinal Elimination of Ciprofloxacin in Rabbits

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The transepithelial intestinal elimination of ciprofloxacin (CPX) was studied in cholera toxin (CT)-challenged and control intestinal loops in the rabbit. CPX concentrations were similar in CT-challenged and control jejunal and ileal loops, while cecal elimination was negligible. The quantities of eliminated CPX per square centimeter of bowel wall were significantly higher in the small intestine CT-challenged loops. The mechanism of elimination of CPX in the small intestine is therefore mainly passive diffusion.

The objective of the present study was to measure the effect of cholera toxin (CT) on the transepithelial elimination of ciprofloxacin (CPX) in the intestinal tract of the rabbit. Twelve New Zealand White albino male rabbits were used for the experiment. The jejunum, ileum, and cecum were identified, and in each section two loops, ca. 5 cm long, were created. In each segment one loop was used for challenge with CT (0.5 ml of lyophilized Vibrio cholerae organisms [Sigma] dissolved in 1 ml of saline), while the other loop was injected with 1 ml of saline. Eighteen hours later, the animals were reanesthetized, a sample of blood was obtained (time zero), and CPX was administered parenterally in a dose of 27 mg/kg of body weight. The abdomen was reopened, and fluid samples were obtained from each intestinal loop along with venous blood samples at 15-min intervals for 2 h. The experiment was terminated by killing the animals with sodium barbital (Sanofi, Utrecht, The Netherlands). The loops were excised, and their mucosal surfaces were measured. The amounts of CPX in blood and intestinal fluid were determined by a bioassay (7). For statistical analysis the Student t test and analysis of variance were used.

The peak concentration of CPX in serum was 24.6 ± 15.1 μg/ml at 15 min; the concentration decreased gradually, reaching 5.9 ± 5.6 μg/ml at 120 min. Intestinal fluid accumulation throughout the 120-min period per loop was as follows (CT-challenged loop versus control loop, respectively): jejunum, 6.6 ± 3.3 versus 5.6 ± 2.0 ml; ileum, 12.4 ± 15.8 versus 8.4 ± 8.0 ml; and cecum, 6.7 ± 3.2 versus 5.3 ± 1.4 ml. During the first 15 min, the fluid volumes for the CT-challenged versus the control loops were, respectively, 1.03 ± 0.67 versus 0.63 ± 0.40 ml in the jejunum, 3.65 ± 3.76 versus 1.99 ± 1.80 ml in the ileum, and 0.99 ± 1.01 versus 0.56 ± 0.68 ml in the cecum. The fluid volumes in the intestinal loops, calculated per square centimeter of bowel mucosa, during the 2 h were 1.12 ± 0.83 versus 0.95 ± 1.13 ml in the jejunum, 1.28 ± 1.14 versus 1.13 ± 0.98 ml in the ileum, and 1.05 ± 1.16 versus 0.93 ± 0.86 ml in the cecum for the CT-challenged versus the control loops, respectively.

Mean concentrations of CPX during the 2-h period for the CT-challenged versus the control loops, respectively, were 11.21 ± 1.25 versus 11.93 ± 2.01 μg/ml in the jejunum, 8.53 ± 2.05 versus 9.42 ± 1.96 μg/ml in the ileum, and 1.12 ± 0.47 versus 4.66 ± 1.32 μg/ml in the cecum (Fig. 1). The total amounts of CPX excreted per loop in the 2-h period for the CT-challenged versus the control loops, respec-

FIG. 1. Concentrations of CPX in CT-challenged (CT) and control (contr) intestinal loops (mean ± 2 standard deviations). mcg, micrograms.

FIG. 2. Quantities of CPX excreted per loop in control (contr) and CT-challenged (CT) loops during 2 h (mean ± 2 standard deviations). mcg, micrograms.
tively, were 35.1 ± 22.7 versus 25.6 ± 17.1 mg in the jejunum, 46.4 ± 24.1 versus 32.1 ± 27.6 mg in the ileum, and 2.6 ± 3.3 versus 4.2 ± 7.3 mg in the cecum (Fig. 2). The amounts per square centimeter of intestinal mucosa were 9.3 ± 5.9 versus 6.1 ± 3.3 mg/cm² in the jejunum, 10.0 ± 6.5 versus 7.8 ± 4.9 mg/cm² in the ileum, and 0.5 ± 0.4 versus 1.2 ± 2.3 mg/cm² in the cecum for the CT-challenged versus the control loops, respectively (Fig. 3).

This animal model was validated by the demonstration of increased secretion of fluid into CT-challenged intestinal loops compared to the secretion into control loops. In the cecum this effect was minimal (6.7 versus 5.3 ml). The strongest effect of CT was observed in the first 15 min of the experiment, suggesting that the removal of CT from the mucosa diminished its effect on intestinal secretion and supporting previous evidence that CT does not bind firmly to intestinal epithelial cells (1–5, 8).

In the present study no significant difference in CPX concentration between CT-challenged and control loops in the small intestine was measurable. The amount of excreted CPX was, however, higher in CT-inoculated small intestine loops (Fig. 2). Excreted amounts of CPX per square centimeter of intestinal mucosa showed an increase in the transepithelial elimination of CPX in the jejunum (by 51%) and in the ileum (by 29%) but not in the cecum.

It has already been clinically established (6) that CPX in a single 1-g daily dose was effective in curing patients with diarrhea caused by V. cholerae O1 or O139. Our data support these clinical results by demonstrating increased amounts of CPX excreted into the intestinal lumen under the influence of CT in concentrations that are bactericidal against V. cholerae.

The facts that CPX concentrations were similar in CT-challenged and control loops but that fluid accumulation and CPX amounts were both higher in jejunal and ileal CT-challenged loops suggest that the elimination of CPX in the small intestine occurs largely through passive diffusion.

FIG. 3. CPX excreted per square centimeter in control (contr) and CT-challenged (CT) intestinal loops (mean ± 2 standard deviations). mcg, micrograms.

REFERENCES