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Concentration of Norfloxacin in Human Gallbladder Tissue and Bile after Single-Dose Oral Administration

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Concomitant concentrations of norfloxacin in serum and in gallbladder tissue and bile were determined in 10 patients after a single oral dose of 400 mg given before cholecystectomy. Concentrations in gallbladder bile ranged from 0.6 to 15.6 μg/ml, with a mean bile/serum ratio of 7.0. The mean concentration in gallbladder tissue was 1.8 ± 0.8 (standard error) μg/g.

The fluoroquinolones are a new group of antimicrobial agents which are active against most common species of gram-negative and gram-positive bacteria, as well as mycobacteria, chlamydiae, mycoplasmas, and rickettsiae (1, 3, 4). These compounds are well absorbed after oral administration and achieve high concentrations in a variety of tissues, with few adverse reactions (3, 4). Review of the English literature has revealed a paucity of data concerning the excretion of these agents into the human biliary system.

Ten adult patients (seven females and three males) scheduled for elective cholecystectomy were studied. The mean patient age was 61.7 years (range, 40 to 79 years), and mean body mass was 71.7 kg (range, 46 to 110 kg). Serum creatinine concentrations were <12 mg/liter in all instances. None of the patients had received antacids or antimicrobial agents in the preceding 72 h. None of the patients had clinical or operative evidence of biliary tract obstruction. Informed consent was obtained according to the guidelines of the Committee on Research Involving Human Subjects of The Edith Wolfson Hospital. Each patient received norfloxacin as a single oral dose of 400 mg before surgery.

To assess biliary concentration in terms of peak level in serum, blood specimens were obtained 1, 2, and 4 h after drug administration. At the time of surgery, an additional blood specimen was taken, and a single bile sample was obtained from the gallbladder. A gallbladder tissue sample was obtained concomitantly and washed in nonbacteriostatic saline. Serum was separated from blood by centrifugation. All the specimens were immediately frozen and stored at −70°C until the time of assay.

Tissue samples were homogenized in a microhomogenizer with antibiotic-free pooled human serum. All the specimens were assayed for norfloxacin activity by a standard bioassay with 6-mm paper disks (Difco Laboratories, Detroit, Mich.) and Iso-Sensitest agar (pH 7.1 to 7.2; Oxoid, Ltd., London, England) seeded with a clinical isolate of *Enterobacter cloacae*. The latter had previously been found to be susceptible to norfloxacin (MIC, 0.015 to 0.030 μg/ml). The assay was sensitive to a minimal concentration of 0.1 μg/ml. Standards for serum and tissue assay were prepared in pooled human serum. Bile specimens and standards for assay of bile were diluted in phosphate-buffered saline (pH 6.2). All the plates were examined after overnight incubation at 36°C.

Standard curves for serum, bile, and tissue assays were prepared in quadruplicate, each with five antibiotic concentrations. In each instance, control curves were identical and exhibited coefficients of variation of ≤5.0% at minimal and maximal concentrations.

Peak concentrations of norfloxacin in serum ranged from 0.6 to 4.7 μg/ml (mean, 2.1 ± 0.37 [standard error] μg/ml) and were generally observed 2 h after administration (Table 1). Concentrations in gallbladder bile ranged from 0.6 to 15.6 μg/ml (mean, 8.1 ± 1.6 μg/ml). The mean ratio of bile/concurrent serum concentrations was 7.0 to 1.

Concentrations in gallbladder tissue ranged from <0.1 to 7.5 μg/g (mean, 1.8 ± 0.8 μg/g). Therapeutic levels in bile and tissue were demonstrable in samples obtained as long as 6 h after drug administration. Concentrations in tissue and bile could not be correlated with one another or with peak level in serum and timing of sample acquisition.

To date, information concerning biliary concentrations of norfloxacin has been limited to anecdotal data from isolated patients after administration of 100 to 200 mg (2).

Norfloxacin is active against most bacterial species associated with biliary infection, with reported MICs for mem-

TABLE 1. Concentrations of norfloxacin in serum and gallbladder tissue and bile

Patient no.	Peak serum concn (μg/ml)	Time of sample (min)	Concurrent concn in:			Bile/serum ratio
			Gallbladder tissue (μg/g)	Gallbladder bile (μg/ml)	Serum (μg/ml)	
1	1.4	225	0.4	3.3	1.4	2.4
2	3.0	240	NA[a]	9.0	1.3	6.9
3	1.8	240	1.1	14.6	1.0	14.6
4	1.4	240	1.7	9.2	NA	
5	0.6	255	0.3	0.6	0.4	1.5
6	1.3	270	1.8	5.8	1.3	4.5
7	2.6	315	3.2	8.2	1.2	6.8
8	2.5	330	<0.1	15.6	1.0	15.6
9	4.7	360	7.5	12.4	1.8	6.9
10	1.8	375	<0.1	2.0	0.5	4.0

[a] NA, Sample not available.

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bers of the family *Enterobacteriaceae* in the range of 0.06 to 0.25 μg/ml (1). Biliary concentrations observed in the present study were relatively low but well in excess of those necessary for inhibition of such pathogens. Because a bioassay was used, the concentrations of norfloxacin metabolites could not be assessed. It should be stressed that none of our patients had evidence of biliary obstruction, a factor known to prevent the entry of antibiotics into bile (L. Schonfeld, Editorial, N. Engl. J. Med. **284**:1213–1214, 1971).

The broad range of antibacterial activity and ability of norfloxacin to achieve therapeutic levels in gallbladder tissue and bile suggest that this drug may be valuable in the prevention and treatment of biliary infections.

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