The Role of Antibiotics in Infections of the Biliary Tract
Studies in Sensitivity and Biliary Tract Excretion *

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The prevalence and tenacity of cholangitis as a clinical entity has been well established.[6] Patients with this condition are more susceptible to complications, such as stone formation or pancreatitis, than patients with biliary tract disorders of a noninfectious nature.

The purpose of the present investigation was (1) to determine which antibacterial agents are most effective against pathogenic biliary tract organisms, and (2) to ascertain whether bactericidal concentrations of these agents can be obtained in the biliary tract. Various strains of Escherichia coli were selected for this study because this organism is the most prevalent in biliary tract infections and has proven to be the one most resistant to antibiotics.

The study was divided into three parts: (1) Testing the sensitivity of E. coli to various antibacterial substances; (2) determining the bacteriostatic and bactericidal levels of three selected antibiotics; and (3) measuring the concentration of Terramycin® and Achromycin® in the biliary tract, after oral or intramuscular administration.

IN VITRO SENSITIVITY OF ESCHERICHIA COLI TO ANTIBIOTICS

Paper Disc Tests. Strains of E. coli were tested by the standard paper disc method [4] for sensitivity to 14 different antibacterial agents. Standard discs of antibiotics, one-half inch in size, in concentrations of 2, 4, 8, and 16 gamma were used. The results of these tests are listed in Table 1, and show that agents Furadantin®, Achromycin®, Aureomycin®, Terramycin® and Chloromycetin®, listed as Group A, were most effective. Our studies with Furadantin® and erythromycin have been reported previously.[7, 8] E. coli proved to be highly or moderately sensitive to these agents in 90 per cent of the 139 tests performed. Results for the less effective agents are listed in Table 1 under Groups B and C. All the tests were made independently in two different laboratories; identical results were obtained in 95 per cent.

Serial Dilution Tests. Of this group, Achromycin®, Terramycin® and Chloromycetin® were tested further by the test-tube dilution method,[2] to determine what concentration of each was necessary to inhibit growth of E. coli. Clinical observations had suggested that the concomitant use of Tween 80 with some of the antibiotics might render them more effective against E. coli. For this reason, bacteriostatic and bactericidal tests were made by using two sets of serial dilutions of standardized solutions of the antibacterial agents. An equal volume of sterile human bile was added to each test tube, in order to simulate, as far as possible, conditions in the biliary tract. To one set of tubes, there was added one ml. of 4 per cent Tween 80 in sterile solution; an equivalent amount of sterile water was added to the other set, to provide a control. Equal amounts of inoculated broth

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TABLE 1. *Results of Paper Disc Sensitivity Tests* upon Escherichia coli Isolated from a Series of Patients with Chronic Cholangitis*

Antibiotic	No. Tests	Highly Sensitive	Moderately Sensitive	Slightly Sensitive	Resistant
		A. Antibiotics highly effective			
Furadantin®	10	10	0	0	0
Achromycin®	28	24	4	0	0
Aureomycin®	29	24	3	2	0
Terramycin	30	22	6	2	0
Chloromycetin®	42	22	12	6	2
Total	139	102	25	10	2
		B. Antibiotics generally ineffective			
Dihydrostreptomycin	38	7	7	10	14
Penicillin	32	2	0	1	29
Bacitracin	22	1	0	3	18
PolymyxinB®	22	1	0	7	14
Erythromycin	21	0	0	4	17
Magnamycin®	21	0	1	2	18
Total	156	11	8	27	110
		C. Sulfa compounds generally ineffective			
Sulfadiazine	27	1	4	1	21
Gantrisin®	27	1	2	3	21
Triple Sulfas	20	0	0	2	18
Total	74	2	6	6	60

* ½" discs with 2, 4, 8, and 16 gamma of the various antibiotics were used.

TABLE 2. *Effect of Antibacterial Agents upon Escherichia coli*

	Bacteriostatic Level		Bactericidal Level	
	Standard	With Tween 80® Added	Standard	With Tween 80 Added
Terramycin®	7 mcgm./ml.	7 mcgm./ml.	10 mcgm./ml.	7 mcgm./ml.
Achromycin®	14 mcgm./ml.	7 mcgm./ml.	20 mcgm./ml.	10 mcgm./ml.
Chloromycetin®	28 mcgm./ml.	7 mcgm./ml.	28 mcgm./ml.	20 mcgm./ml.

were then added to all tubes, with aseptic precautions.

After 24 hours of incubation at 37° C., the tubes were examined for growth (turbidity). The lowest antibiotic concentration that remained clear was designated as the *bacteriostatic* level. All tubes without turbidity were then subcultured into fresh sterile Pennassay or nutrient broth without bile, and incubated for 24 hours at 37° C. The concentration of antibiotic that gave clear transplants was designated as the *bactericidal* level.

From the results shown in Table 2, it can be seen that the bacteriostatic and bactericidal levels for Achromycin® and Chloromycetin® were lower in the presence of Tween 80®. However, there was little or no difference in the levels for Terramycin®.

Excretion of Antibiotics in the Biliary Tract. Terramycin® (Oxytetracycline) and Achromycin® (Tetracycline) have both

TABLE 3. *Concentration of Terramycin in Bile from T-Tube Drainage Following Intramuscular or Oral Administration*

Patient	No. Days after Operation	Dosage	Concentration in Bile (mcgm./ml.) No. of Hours after Admin. of Drug		
			2	4	6
E. A.	21	100 mg., I.M.	2.7	2.5	—
A. K.	8	100 mg., I.M.	5	8	—
L. S.	63	100 mg., I.M.	15	10	—
E. A.	48	250 mg., P.O.	32	24	—
E. R.	9	250 mg., P.O.	5.6	4.9	7.0
L. S.	79	250 mg., P.O.	23	21	—
E. A.	41	500 mg., P.O.	32	20	—
L. S.	77	500 mg., P.O.	30	48	—
J. B.	Operative	500 mg., P.O.	34.5	—	—
F. B. (portal cirrhosis)	36	500 mg., P.O.	0	0.28	—

been reported by other investigators as being excreted in the bile.[1, 3, 5, 9, 10] We wished to determine whether in the human a sufficient concentration of these antibiotics is excreted in the biliary tract to exert a bacteriostatic or bactericidal effect on Escherichia coli. For this purpose, the concentration of each agent was determined in the gallbladder or common duct bile, following its oral or intramuscular administration.

Terramycin® (Oxytetracycline). The biliary excretion of this agent in humans has been studied by Pulaski and Fusillo,[5] Herrell and Heilman,[3] and Zaslow and Rosenthal.[9] These authors note in their reports that various levels of Terramycin® could be found in bile from the gallbladder and from T-tube drainage, following oral and intravenous administration. They also point out that obstruction of the cystic duct prevented the appearance of the antibiotic in bile from the gallbladder, and that impaired hepatic function interfered with the accumulation of adequate concentrations in bile in the T-tube. However, bactericidal figures for Terramycin® in bile, that could be used for a comparison with the actual levels reported, were not determined.

Terramycin® in Gallbladder Bile. High concentrations of Terramycin® have been reported in gallbladders with a patent cystic duct.[5, 10] These findings have been confirmed by our investigations. Following oral dosage of 500 mg., a level in the gallbladder bile of 76 mcgm./ml. was obtained.

Terramycin® in Bile from the Common Duct. Table 3 shows Terramycin® concentrations obtained in the common duct bile two to six hours after Terramycin® was administered to ten patients, who had T-tube drainage following cholecystectomy. The first three were given a single intramuscular injection of 100 mg., and in two of these patients, a bacteriostatic level of Terramycin® for E. coli was obtained.

In the next series, three patients were given 250 mg. of Terramycin® by mouth, four times on the day preceding the test, and once on the morning of the test. As indicated in Table 3, all three patients attained a bacteriostatic level of Terramycin® and two attained bactericidal levels. The concentration in these two cases was far higher than after a single intramuscular injection.

Four patients were given oral doses of 500 mg. of Terramycin® which resulted in each case in bactericidal levels in the bile, equal to or higher than those produced by a dose of 250 mg. The fourth patient given 500 mg. doses demonstrated practically no

TABLE 4. *Concentrations of Achromycin® in the Common Bile Duct Obtained by T-Tube Drainage in Post-Cholecystectomy Patients Following Oral Administration*

Patient	Days after Cholecystectomy	Dosage	Achromycin® Concentration (Second Day) Mcgm./ml.					
			Bile				Blood Serum	
			Before Morning Dose	Hours after Morning Dose			Hours after Morning Dose	
				2	4	6	2	4
1. M. M.	8	250 mg.	200	226	270	—	8	8.6
2. S. S.	9	250 mg.	72	70	—	—	15.5	13.5
3. M. A.	34	250 mg.	—	48	20	—	—	—
4. E. S.	70	250 mg.	—	20	20	—	—	—
5. M. K.	5	500 mg.	—	—	—	36	9	—
6. M. K.	9	500 mg.	—	48	15	35	1.5	3.5
7. C. B.	7	500 mg.	80	70	90	—	14	12
8. F. B. (portal cirrhosis)	30	500 mg.	5	—	—	—	—	—
9. E. C.	12	500 mg.	1.5	—	—	—	—	—

biliary excretion of terramycin. This patient had been found at operation to have a severe portal cirrhosis.

Achromycin® (Tetracycline). Determinations of this antibiotic in human bile have also been reported. Readings of 50 to 100 mcgm./ml. in bile in the T-tube were found postoperatively in patients without jaundice.[9] Lower figures were obtained when jaundice had been present before operation.

Achromycin® in Gallbladder Bile. Pulaski and Fusillo [5] not only reported good concentrations in bile in the gallbladder in the presence of a patent cystic duct, but were also able to obtain concentrations of 10 to 80 mcgm./ml. in gallbladders with obstructed cystic ducts, after repeated intravenous injections of tetracycline.

In our own experience, oral administration of 500 mg. doses of Achromycin® has given bactericidal levels of 22 mcgm./ml. to 250 mcgm./ml. in the gallbladder bile obtained at operation.

Achromycin® in Bile from the Common Duct. Seven tests were made for the concentration of Achromycin® in bile from the common duct, obtained by T-tube drainage following cholecystectomy (Table 4). In cases 1, 2, 3, and 4, a dose of 250 mg. of Achromycin® was given orally four times on the day preceding the test and once on the morning of the test. In all these patients bactericidal levels were obtained in the bile (Table 2). In cases 5, 6, and 7, the tests were made with a dose of 500 mg. of Achromycin® by the same technic and the antibiotic likewise attained bactericidal levels. These results indicate that a dosage of 250 mg. of Achromycin®, given four times daily, is adequate in attaining bactericidal levels in the bile.

The same procedures, with a dosage of 500 mg., were followed in two patients (8 and 9, on Table 2) with T-tube drainage, each having a known impairment of hepatic function. In one patient (8) with portal cirrhosis the maximum concentration of Achromycin® obtained was 5 mcgm./ml. in bile from the common duct. The other patient (9), recently operated upon for an echinococcus cyst of the liver, had a maximum concentration of 1.5 mcgm./ml.

Achromycin® and terramycin have also been found to give successful results in the

treatment of infections of the biliary tract; this clinical application will be discussed in a later communication.

SUMMARY

1. An investigation has been made of certain factors involved in the treatment of infections of the biliary tract, especially those due to Escherichia coli.

2. Sensitivity tests of the Escherichia coli have shown (a) a high degree susceptibility to Achromycin®, Aureomycin®, Chloromycetin®, Furadantin®, and Terramycin®. When the paper disc method of testing was employed; and (b) bacteriostatic and bactericidal levels for Terramycin® and Achromycin® were obtained in the presence of hepatic bile. These tests were done by the serial dilution method.

3. The effect of a surface wetting agent (Tween 80) on the bactericidal and bacteriostatic levels of antibiotics for Escherichia coli has been examined. The effect of Achromycin® and Chloromycetin® was apparently enhanced by the addition of Tween 80.

4. Following oral administration, inhibitory levels of Achromycin® and Terramycin® were obtained in the gallbladder and bile from the common duct, provided there was no impairment in hepatic function and no extrahepatic obstructive lesions.

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