

AMPICILLIN LEVELS IN HUMAN BILE

BY

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Ampicillin is a bactericidal drug active against *Salmonella typhi* and most of the organisms infecting the biliary tract. High levels of ampicillin have been found in the bile of rats, but there are few reports of assays on human bile (Stewart & Harrison, 1961; Acred, Brown, Turner & Wilson, 1962; Bullock, 1963).

In the present investigation, ampicillin levels were estimated in serum and bile of patients with normal and diseased biliary tracts.

METHODS

Twenty-seven patients were chosen. They were divided into five groups for study. Patients in groups 1 to 4 were given a single oral dose of 500 mg of ampicillin approximately 4 hr before samples of blood and bile were taken. At operation, bile was aspirated from the gall bladder through a very fine needle and blood was taken simultaneously for serum estimation from a peripheral vein.

Group 1: normal biliary tract. Thirteen patients undergoing abdominal exploration for conditions other than for diseases of the biliary tract were studied.

Group 2: diseased biliary tract without jaundice. Five patients, two with cholelithiasis and three with chronic cholecystitis, were studied.

Group 3: diseased biliary tract without jaundice, but with an obstructed cystic duct. Two patients with cystic duct obstruction due to gall stone impaction were studied. In both these patients there was a mucocoele of the gall bladder without acute inflammation.

Group 4: diseased biliary tract with jaundice. Three patients were studied, two of whom had malignant disease, one having carcinoma of the head of the pancreas, and the other hepatic metastases from carcinoma of the breast. The third patient had a stone impacted in the lower end of the common bile duct. The serum bilirubin levels were 10.7, 16 and 2.5 mg/100 ml. respectively. The patient with hepatic deposits received 250 mg of ampicillin intramuscularly instead of 500 mg orally.

Group 5: postoperative patients with biliary tract disease. Four patients were studied. In two patients a single oral dose of 500 mg of ampicillin, and in the other two patients a single intramuscular dose of 250 mg, was given on each occasion 30 min before the collection of bile from a T-tube in the bile duct.

Ampicillin assays of blood and bile

Ampicillin levels were assayed by the cup-plate method with *Sarcina lutea* or the Oxford staphylococcus as the test organism. Samples of bile, serum, and antibiotic standards were diluted when necessary in

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phosphate buffer, pH 7.0. This was a suitable diluent, since ampicillin is not significantly bound by serum (Bond, Lightbown, Barber & Waterworth, 1963). Several tests were also made with ampicillin-free bile and no antibacterial activity was detected.

RESULTS

Ampicillin levels in the bile of patients with a normal biliary tract are shown in Table 1 and, with one exception, were 3- to 48-times as high as the corresponding serum levels. The levels in the bile of patients with a diseased biliary tract are shown in Table 2. These levels (mean and standard error, 10.0 ± 4.8 $\mu\text{g/ml.}$) were significantly lower ($P < 0.001$) than those obtained from normal patients (mean and standard error, 36.1 ± 9.0 $\mu\text{g/ml.}$). In the patients with obstructive jaundice, the levels in the bile were all lower than the corresponding serum levels, although the serum levels in both groups ranged between

TABLE 1
AMPICILLIN LEVELS IN BILE AND SERUM OF PATIENTS WITH NORMAL BILIARY TRACTS (GROUP 1)

Patient	Diagnosis	Operation	Ampicillin in	
			Serum ($\mu\text{g/ml.}$)	Bile ($\mu\text{g/ml.}$)
1	Gastric ulcer	Gastrectomy	5.0	8.5
2	Carcinoma of colon	Closure of colostomy	3.3	12.5
3	Gastric ulcer	Gastrectomy	12.5	87.5
4	Duodenal ulcer	Gastrectomy	2.5	21.5
5	Gastric ulcer	Gastrectomy	4.8	45.0
6	Gastric ulcer	Gastrectomy	1.3	15.0
7	Abdominal pain	Laparotomy	5.8	65.0
8	Gastric ulcer	Gastrectomy	6.3	78.0
9	Duodenal ulcer	Gastrectomy	2.5	17.5
10	Carcinoma of stomach	Laparotomy	1.7	5.0
11	Duodenal ulcer	Gastrectomy	1.8	87.5
12	Carcinoma of stomach	Gastro-enterostomy	3.5	25.0
13	Carcinoma of stomach	Total gastrectomy	1.7	<1.0

TABLE 2
AMPICILLIN LEVELS IN BILE AND SERUM OF PATIENTS WITH A DISEASED BILIARY TRACT

N.T.=not tested

Patient	Diagnosis	Obstructive jaundice	Ampicillin in	
			Serum ($\mu\text{g/ml.}$)	Bile ($\mu\text{g/ml.}$)
Group 2				
14	Cholelithiasis	Absent	7.7	17.5
15	Cholelithiasis	Absent	6.8	10.0
16	Cholecystitis	Absent	0.8	45.0
17	Cholecystitis	Absent	1.3	11.0
18	Cholecystitis	Absent	1.5	2.5
Group 3				
19	Cholelithiasis (with "white" bile)	Absent	2.5	<1.0
20	Cholelithiasis (with "white" bile)	Absent	4.0	<1.0
Group 4				
21	Carcinoma of pancreas	Present	10.0	<1.0
22	Cholelithiasis	Present	9.5	1.0
23	Secondaries in liver	Present	N.T.	<1.0

TABLE 3

AMPICILLIN LEVELS IN BILE FROM POSTOPERATIVE PATIENTS WITH DRAINAGE OF BILE-DUCT (GROUP 5)

I.m.=intramuscular; N.T.=not tested

Patient	Dose (mg)	Route	Ampicillin ($\mu\text{g/ml.}$) in bile after				
			0.5 hr	1 hr	2 hr	3 hr	5 hr
24	500	Oral	<0.1	316	370	N.T.	91.0 *
25	500	Oral	7.6	229	93	69	70
26	250	I.m.	0.1	8.0	1.7	1.7	<0.1
27	250	I.m.	0.2	1.1	2.5	2.5	N.T.

0.8 and 12.5 $\mu\text{g/ml.}$ The serum ampicillin level (mean and standard error) for the control group was $4.1 \pm 0.9 \mu\text{g/ml.}$ and $4.9 \pm 1.2 \mu\text{g/ml.}$ for those with biliary tract disease. Table 3 shows ampicillin levels in the hepatic bile of four patients with T-tubes in the bile duct. The levels in patients No. 24 and 25 following oral administration were very high, whereas following intramuscular injections the levels were low. Some serum levels were estimated in these four patients and were in the expected normal range.

DISCUSSION

The bile levels of ampicillin in this series, although not as high, confirm the results of the animal experiments (Acrod *et al.*, 1962).

The ampicillin levels reported here in patients without obstructive jaundice are nearly all well above that required for antibacterial activity against most strains of *Salmonella*, *Escherichia coli*, *Streptococcus faecalis*, non-penicillinase forming *Klebsiella* and *Proteus mirabilis* (Rolinson & Stevens, 1961; Barber & Waterworth, 1962). These are organisms commonly found in biliary tract infections, and ampicillin should be effective in the treatment of most cases of cholecystitis or cholangitis. Ampicillin is not, however, effective against penicillin-resistant staphylococci or penicillinase-forming Gram-negative bacilli. Adequate levels were not obtained in any patient with obstructive jaundice; and one unexplained low level occurred in a patient with an apparently normal biliary tract. It is likely that much higher levels would have been obtained in the patients with normal biliary tracts, if samples had been taken 1 to 2 hr after administration of ampicillin.

In the four patients from whom hepatic bile was collected through the T-tube, the results appear to be conflicting. The high levels following oral administration could be explained by reflux from the duodenum. However, the levels obtained after 4 hr are in the same range as the levels obtained in patients with normal biliary tracts (Table 1). The low levels obtained after intramuscular injection are more difficult to explain, for the serum levels were within the normal range. One of the patients was jaundiced and the other had been jaundiced recently, although the serum bilirubin was normal at the time of testing. A possible explanation is that the liver cells were still damaged and, although probably in a stage of recovery, were still not excreting ampicillin normally. Zaslow, Counsellor & Heilman (1947) made a similar observation when studying the excretion of penicillin in bile. They found that in the presence of jaundice penicillin excretion in the bile was low, but increased as serum bilirubin levels fell.

Chloramphenicol is at present the most effective antibiotic in enteric fever, but it is bacteristatic, toxic to the bone marrow and the concentrations of its active form in the bile

are low (Woodward, Smadel & Ley, 1950; Harrison & Stewart, 1961). There are few reports of a comparison between chloramphenicol and ampicillin in the treatment of acute enteric fever. Patel (1964) found that ampicillin was effective in treating early cases of acute typhoid fever, but was less effective in patients who had been ill for more than 7 days; chloramphenicol was usually effective at all stages of the disease. Sleet, Sangster & Murdoch (1964) found chloramphenicol to be more effective than ampicillin in shortening the acute stage of paratyphoid fever. Nevertheless, they suggested that ampicillin was probably more effective than chloramphenicol in the treatment of carriers. In other reports, the results of treatment of salmonellosis and *Salmonella* carriers with ampicillin have been variable (Stewart, Coles, Nixon & Holt, 1961; Trafford, Maclaren, Lillicrap, Barnes, Houston & Knox, 1962; Ross, Lovrien, Zaremba, Bourgeois & Puig, 1962; Pettersson, 1964), and failure was often associated with gall-bladder disease and stones (Tynes & Utz, 1962; Bullock, 1963). The apparent discrepancy between the *in vitro* activity of ampicillin and the results of treatment is often difficult to explain. The present paper suggests that, even in the presence of a diseased biliary tract, as long as jaundice is absent ampicillin levels in the bile are usually in the bactericidal range for sensitive organisms. Therefore failure to respond to treatment must be due to other causes.

SUMMARY

1. Ampicillin levels in the serum and bile of patients with normal and diseased biliary tracts were estimated.
2. In patients with normal biliary tracts, levels up to 48-times those in normal serum were obtained in gall-bladder bile.
3. In patients with diseased biliary tracts (cholecystitis and cholelithiasis), but with patent cystic ducts and without jaundice, adequate therapeutic levels were obtained in the bile.
4. In patients with obstructive jaundice or with an obstructed cystic duct, levels in the bile were lower than corresponding serum levels.

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