placenta praevia subsequently confirmed clinically. In a personal series of 672 patients there were 20 (3%) errors of clinical significance. In the same review the results of 3,972 *x*-ray examinations were analysed, errors of clinical significance being found in 221 (5·6%). Failure to diagnose placenta praevia occurred in 30 out of 639 cases (4·7%).

When comparing these figures it must be remembered that in most of the isotope series very few cases were rejected as unsuitable for investigation, whereas restrictions were commonly imposed on the selection of patients in the *x*-ray series. It should also be recalled that, in the present series, as a matter of deliberate policy the majority of investigations were carried out by the resident obstetric staff, and the results reflect those which could be obtained in any obstetric unit that has the simple isotopic facilities required.

From a detailed study of the results it is evident that the principal source of error is in cases where the placenta is situated on the posterior uterine wall and its upper margin does not reach to the fundus of the uterus. In such cases there is a tendency, probably engendered by caution, to overestimate the degree of placenta praevia. This occurred particularly in patients examined early in the third trimester. In many cases the diagnosis was refuted by a repeat examination later in pregnancy, by a lateral *x*-ray examination of the pelvic brim if the foetal head presented, or solely by the clinical course of events. Though these errors never led to unnecessary major surgical procedures they did sometimes result in the patient being kept in hospital unnecessarily.

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Ampicillin Levels in Human Bile in the Presence of Biliary Tract Disease

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Summary: Ampicillin levels were measured in the serum and in the bile from both the gall bladder and the common bile duct in patients undergoing surgery for biliary tract diseases. In patients with radiologically non-functioning gall bladders ampicillin was either not present or its concentration was lower than normal. Therapeutic levels were present in the common bile duct of all patients except those with obstruction of the common bile duct. Hence ampicillin fails appreciably to penetrate the obstructed viscus in obstructive biliary tract disease, and it is unlikely to be effective in treating infection associated with this.

Introduction

Ampicillin is frequently used in the treatment of acute cholecystitis and ascending cholangitis, as it is well recognized that in experimental animals the drug is actively concentrated in the liver, with resulting high levels in the bile. Stewart and Harrison (1961) showed that in rats the liver was capable of concentrating ampicillin to produce a level in the bile of up to 40 times the peak plasma concentration. Brown and Acred (1961), using dogs, found that the biliary concentration of ampicillin was up to 300 times that found in the blood. However, Ayliffe and Davies (1965), in the only previous study in man, found lower levels of ampicillin in gall bladder bile from patients with diseased biliary tracts than in their normal controls.

The object of the present study was to determine the concentration of ampicillin in the serum and in the bile from both the common bile duct and the gall bladder in patients with biliary tract disease one and a half to two hours after intramuscular injection.

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Methods

Twenty-three patients were studied. They were divided into three groups based on preoperative clinical, laboratory, and radiological findings.

Group 1.—Eleven patients with cholelithiasis and normal liver function tests, but without any evidence of obstruction of the cystic or common bile duct on oral or intravenous cholangiography.

Group 2.—Six patients with a blocked cystic duct, but no evidence of obstruction of the common bile duct or liver damage.

Group 3.—Six patients with obstructive jaundice.

No normal controls were included. It was considered unjustified to take samples of bile from patients who were not to have operations on the biliary tract.

All patients were given 500 mg. of ampicillin one and a half to two hours before the samples of bile and serum were obtained. At operation bile was obtained from the gall bladder through a fine needle, and where possible from the common bile duct through a fine catheter which was inserted via the cystic duct. A sample of systemic venous blood was obtained at the same time.

Ampicillin assays were performed by the diffusion method, described by Bennett *et al.* (1966), using *Sarcina lutea* as the test organism. The samples of bile and their controls were diluted in M/20 phosphate buffer *p*H 7·0. The samples of serum and their controls were diluted in pooled sterile normal human serum.

Results

Group 1.—The concentration of ampicillin found in the samples from patients of group 1, with cholelithiasis alone, are shown in Table I. The concentration of ampicillin in common bile duct samples was at least twice the serum level. The concentration in the gall bladder was in no case higher than in the common bile duct sample, and there was considerable variation in the level obtained. Some samples of gall bladder

bile contained less antibiotic than the serum samples. Two patients (Cases 10 and 11) were found at operation to have stones in their common bile duct, but without obstruction.

TABLE I.—*Patients with Cholelithiasis But No Evidence of Obstruction to Either Cystic or Common Bile Duct*

Case No.	Ampicillin Concentration (μg./ml.)		
	Serum	Common Bile Duct Bile	Gall Bladder Bile
1	2·9	11·0	11·0
2	6·0	No estimation	12·5
3	6·8	No estimation	21·0
4	7·5	36·0	29·0
5	8·5	16·5	10·5
6	7·0	36·0	27·5
7	5·0	10·0	1·3
8	4·8	No estimation	3·3
9	8·0	15·6	5·3
10	6·3	35·0	6·8
11	5·8	18·0	15·6
Mean	6·2	22·3	13·1
S.E.M.	0·4609	3·7763	2·6909

Statistical Analysis.—With Student's *t* test for paired observations the difference between the levels of ampicillin in the serum and common bile duct is statistically significant, $t = 4{\cdot}140$, $n = 7$, $P < 0{\cdot}005$, as is the difference between the levels in the serum and gall bladder bile, $t = 2{\cdot}510$, $n = 7$, $P < 0{\cdot}05$. The increased excretion of ampicillin in the common bile duct bile compared with the levels in the gall bladder bile is statistically significant, $t = 2{\cdot}900$, $n = 7$, $P < 0{\cdot}025$.

Group 2.—The concentrations of ampicillin found in the samples from the patients of group 2 who had obstructed cystic ducts are shown in Table II. In samples from three of the six patients there was no detectable ampicillin in the gall bladder bile, though the concentration of the antibiotic in the common bile duct was again greater than the level in the serum.

TABLE II.—*Patients with Blocked Cystic Ducts But No Evidence of Common Bile Duct Obstruction*

Case No.	Ampicillin Concentration (μg./ml.)		
	Serum	Common Bile Duct Bile	Gall Bladder Bile
12	3·8	7·0	0·3
13	2·6	6·4	4·7
14	8·8	24·0	0·0
15	5·6	No estimation	0·0
16	5·8	15·2	0·0
17	8·0	11·7	3·7
Mean	5·8	12·9	1·45
S.E.M.	0·8838	2·8775	0·8037

Statistical Analysis.—The difference between the serum levels and levels in the common bile duct is statistically significant, $t = 3{\cdot}010$, $n = 4$, $P < 0{\cdot}05$. The difference between the serum levels and levels in the gall bladder is statistically significant, $t = 2{\cdot}900$, $n = 5$, $P < 0{\cdot}05$. The difference between the common bile duct levels and gall bladder levels is statistically significant, $t = 2{\cdot}866$, $n = 4$, $P < 0{\cdot}05$.

Group 3.—Samples were examined from six patients with obstructive jaundice. No ampicillin could be found in the gall bladder bile or in two of the three samples of common bile duct bile. The results are shown in Table III.

TABLE III.—*Patients with Blocked Common Bile Ducts*

Case No.	Ampicillin Concentration (μg./ml.)		
	Serum	Common Bile Duct Bile	Gall Bladder Bile
18*	5·0	0·5	0·0
19	8·3	0·0	0·0
20	6·2	No estimation	0·0
21	12·0	No estimation	0·0
22	4·5	0·0	0·0
23	4·5	No estimation	0·0
Mean	6·8	—	—
S.E.M.	1·0986	—	—

* This patient had previously suffered obstructive jaundice and at operation was found to have a stone impacted in the distal end of a tensely dilated common bile duct.

Statistical Analysis.—The difference between the serum levels and levels in the common bile duct is statistically significant, $t = 4{\cdot}589$, $n = 2$, $P < 0{\cdot}05$. The difference between the serum levels and levels in the gall bladder is statistically significant, $t = 5{\cdot}630$, $n = 5$, $P < 0{\cdot}005$.

Discussion

The levels of ampicillin found in gall bladder samples from group 1 patients are similar to those of Ayliffe and Davies (1965) after oral therapy. Brown and Acred (1961) reported that the concentration of ampicillin in the bile of dogs was 300 times that found in the blood, and Harrison and Stewart (1961) found in rats that the peak concentrations in the bile were about 40 times higher than the corresponding blood levels. These results suggest that the reported animal work is not wholly applicable to man.

It was suggested by Harrison and Stewart (1961) that a higher gall bladder bile level would result from concentration within the gall bladder lumen. Results from the group 1 patients, who concentrated radio-opaque contrast media on oral cholecystogram, do not support this hypothesis. In the eight patients in whom both common bile duct and gall bladder bile was obtained the concentration of ampicillin in the latter was the same as or lower than in the former. In this respect the results are similar to those of Zaslow *et al.* (1947), who, when studying penicillin excretion, found that the concentration in the gall bladder was equal to or slightly lower than in the hepatic bile.

Ayliffe and Davies (1965) found conflicting results when they compared the ampicillin concentration in hepatic bile after oral and intramuscular therapy. In this series the levels of ampicillin in samples from unobstructed common bile ducts were higher than they found in two patients who had been jaundiced but lower than the very high levels they found in two patients after oral therapy.

Ampicillin was not detected in the gall bladder bile of three out of six patients with radiologically non-functioning gall bladders. Lower levels were found in the gall bladder bile than in the common bile duct sample in the remaining three. These findings are in agreement with those of Zaslow *et al.* (1947), who were unable to demonstrate any penicillin in the bile of five out of 10 patients with non-functioning gall bladders. These results suggest that radiological non-function of the gall bladder in the presence of normal liver function tests indicates that there will be either failure of or considerable reduction in the penetration of the penicillins into the lumen of the gall bladder.

Bullock (1963) and Tynes and Utz (1962), when treating salmonella carriers with ampicillin, had a lower cure rate in the patients with gall bladder disease than in those with normal biliary tracts. It is suggested that failure of the antibiotic to penetrate into the lumen of the gall bladder is one explanation for this observation.

It was found that therapeutic concentrations of ampicillin were present in the common bile duct of all patients except the three with obstructed common bile ducts. One of these (Case 18) was thought preoperatively to be unobstructed, but at operation was found to have a stone impacted at the lower end of a tensely dilated common bile duct.

These results suggest that ampicillin is unlikely to be effective in the treatment of infection associated with obstructive biliary tract disease.

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