BILIARY EXCRETION OF ERYTHROMYCIN AFTER PARENTERAL ADMINISTRATION

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- 1 The biliary excretion of erythromycin has been studied following parenteral administration in 23 patients.
- 2 Mean bile levels of the drug were approximately ten times higher than corresponding serum concentrations 1 h after i.v. (erythromycin lactobionate) and i.m. (erythromycin ethylsuccinate) injection.
- 3 Thus, unlike many antimicrobial agents, these compounds are well concentrated in the bile.

Introduction

There is an increasing awareness of the potential risks consequent to bacteraemias which arise after certain invasive diagnostic procedures, such as endoscopic retrograde cholangiopancreatography (ERCP) and duodenoscopy (Everett & Hirschmann, 1977). A single dose of an appropriate prophylactic antibiotic, given to produce a high blood level at the time when bacteraemia is expected to occur, is a precaution which is now often taken during such procedures. During several months we were troubled by bacteraemias due to Gram-positive cocci. The reason for infections by these organisms over this relatively short period of time was not discovered. However, in view of this experience, erythromycin for prophylaxis was used instead of our usual prophylactic regime (which is chosen for its wide antimicrobial spectrum). We have taken advantage of this to study the excretion into bile of this antibiotic, when given by injection. We are not aware that biliary excretion of parenteral forms of erythromycin has previously been reported.

Methods

Bile specimens were obtained by three different techniques:

Duodenoscopy

Patients undergoing routine duodenoscopy (usually for suspected ulcers) were given 300 mg erythromycin lactobionate i.v. with premedication. When the

examination was completed, the gall bladder was made to contract by an injection of cholecystokinin; the expressed bile was aspirated from the duodenum. A blood sample was taken at the same time.

ERCP

Erythromycin ethyl succinate was given (100 mg i.m.) with the premedication to ten patients being investigated by ERCP. A blood sample was taken at the time when bile was obtained.

Per-operative procedure

Erythromycin lactobionate 300 mg was given i.v. to four patients undergoing biliary surgery. Specimens of blood and gall bladder bile were taken and the time noted.

Assay technique

Bioassay was carried out to determine levels of erythromycin in all specimens. *Staphylococcus aureus* was used as indicator: 1.2 ml of an overnight culture in nutrient broth was mixed with 120 ml molten BHI agar (Oxoid), and poured into 20 × 20 cm bioassay plates (Nunc). Holes (7 mm) were cut; 12 were used for standards (erythromycin base dissolved in pooled normal human plasma or human pooled bile, as appropriate) in triplicate. Plates were incubated overnight at 37°C. This method determines 'total erythromycin' i.e. free base and biologically inactive

ester (Tardrew, Mao & Kenney 1969; Bechtol, Stephens, Pugh, Parker & Coletta, 1976). Any ester present in the specimen is hydrolysed spontaneously during the assay procedure. Volumes of bile obtained were insufficient to allow us to analyse separately for esterified erythromycin alone.

Results

i.v. administration

Erythromycin was usually excreted in high concentrations in the bile following *i.v.* administration. In the specimens taken during duodenoscopy from patients with no biliary abnormalities, the mean value of the ratio bile/serum concentrations was 8.52 (s.d. = 7.6) (Table 1).

Biliary concentrations were much lower in patients with obstruction (Table 2).

i.m. administration

Not surprisingly, serum levels of erythromycin were much lower than after *i.v.* dosage. However, as

Table 3 shows, the mean ratio bile/serum concentration was not significantly different ($P > 0.4$) to that obtained after *i.v.* administration.

Discussion

Although erythromycin is widely believed to be well excreted in the bile, there are few articles in the literature which substantiate this fact in man. Some 20 years ago, Twiss, Berger, Gillette, Aronson & Segal (1956), Pulaski & Fusillo (1955) and Levrat, Brette, Thivolet & Carraz (1957) reported that erythromycin (free base or stearate) when given orally was concentrated to up to 300-fold compared with serum levels in the bile. Hammond & Griffith (1961) found that bile levels were higher following oral administration of the free base than after the propionyl ester (either as such or as its lauryl sulphate salt). For the free base, bile/serum ratios were 30, and 3 for the ester. We have not been able to find any references to biliary excretion following parenteral erythromycin.

Our study shows that both the lactobionate salt and ethylsuccinate ester of erythromycin, given by

Table 1 Erythromycin concentrations in serum and bile following *i.v.* injection of 300 mg erythromycin lactobionate. Bile obtained by duodenoscopy

Patient number	Time of sample (min)	Erythromycin concentration ($\mu\text{g/ml}$)		
		Serum	Bile	Bile/serum ratio
1	60	4.2	17.2	4.1
2	60	10.8	97	9
3	75	6.7	127.2	19.1
4	90	16.8	137.6	8.2
5	55	13	17.6	1.4
6	60	10.3	43.2	4.2
7	85	11.2	40.8	3.6
8	75	10.7	42.2	3.9
9	105	9	208.8	23.2
	Mean (s.d.)	10.3 (3.6)	81.2 (65.7)	8.52 (7.6)

Table 2 Erythromycin levels in serum and bile from 4 patients with partial (nos. 1 and 4) or complete (nos. 2 and 3) obstruction of bile ducts. Erythromycin lactobionate (300 mg) was given *i.v.*

Patient number	Time of sample (min)	Erythromycin concentration ($\mu\text{g/ml}$)		
		Serum	Gall bladder bile	Common duct bile
1	80	3.7	6.4	
	105	2.6		4.9
2	90	6.6	0	0
3	80	7.4	0	0
4	60	3.8	6.1	5.2

Table 3 Erythromycin levels in serum and bile of ten patients following 100 mg erythromycin ethyl succinate i.m. Bile obtained during ERCP.

Patient number	Time of sample (min)	Erythromycin concentration (µg/ml)		
		Serum	Bile	Bile/serum ratio
1	75	0.9	4.6	5.1
2	85	0.9	5.8	6.4
3	65	0.8	11.5	14.4
4	90	0.9	10	11.1
5	70	1.3	8.8	6.8
6	60	1.3	6.4	4.9
7	95	1.1	2.6	2.4
8	100	0.7	3.4	4.9
9	85	0.8	20.4	25.5
10	60	0.8	27.2	34
	Mean (s.d.)	0.95 (0.21)	10.1 (7.9)	11.55 (10.4)

injection, are as well excreted into the unobstructed biliary tract as are the oral forms of this antibiotic. Obstruction, even partial, of the biliary tree largely prevented the excretion of erythromycin into the bile. We were not able to differentiate, for technical reasons, between erythromycin and erythromycin esters in the bile we assayed. However, previous experience (Hammond & Griffith, 1961; Tardrew *et al.*, 1969) has shown that ester hydrolysis is rapid *in vivo*, and after 1 h almost all the esters would have been expected to have been hydrolysed.

For many antibiotics the peak level in the bile occurs at about 1 h after that in the serum; this has not been established for erythromycin, and thus probably merits further investigation. Furthermore, the higher serum levels of erythromycin obtained with a recent new formulation ('Erythrocin 500')

with, presumably, correspondingly higher biliary concentrations might well expand the therapeutic range of this antibiotic in the bile to include Gram-negative aerobic bacteria. The alkaline nature of the bile will also assist to this end (Sabath, Gerstein, Loder & Finland, 1968). Antibiotics, such as gentamicin, which enter the bile only to a limited extent are effective in some patients, by eliminating organisms released from the biliary system during invasive procedures. However, the use of the combined approach of an effective concentration in the bile as well as in the blood has obvious potential advantages.

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