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BILIARY EXCRETION OF AMOXYCILLIN AND CEFTRIAXONE AFTER INTRAVENOUS ADMINISTRATION IN MAN

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1 Plasma and biliary concentrations of amoxycillin and ceftriaxone were measured after bolus intravenous administration (500 mg) in four subjects with normal hepato-biliary and renal function.

2 The mean plasma elimination half-life for ceftriaxone ($t_{½}$ = 330 ± 30 min) was considerably longer than that for amoxycillin ($t_{½}$ = 60 ± 9 min).

3 The biliary concentration of ceftriaxone was above plasma concentration of the drug throughout the study period, whereas amoxycillin concentration in the bile was lower than that in plasma.

4 Both plasma and biliary concentrations of ceftriaxone were substantially higher than previously determined minimum inhibitory concentration (MIC) values for *E. coli* (and several other common biliary tract pathogens) for over 6 h following drug administration. Amoxycillin concentration in plasma fell below MIC by 2 h, and did not reach inhibitory concentrations in bile.

Introduction

An ideal antibiotic should combine activity against a wide spectrum of organisms, with high tissue penetration, and a long plasma half-life permitting once or twice daily administration. High drug concentrations in the bile would be useful in eradicating the pathogens responsible for wound sepsis after surgery on the biliary tract.

Ampicillin, a long-established β-lactam antibiotic, has been found to be effective against the pathogens isolated from the bile (Keighley, 1977) and was widely used in the treatment of biliary tract infections. It has been largely replaced by amoxycillin with similar antibacterial activity. In the case of *E. coli*, a most common pathogen responsible for biliary tract infections, amoxycillin probably is a better bactericidal than ampicillin (Rolinson *et al.*, 1977). On oral administration, amoxycillin gives higher serum levels than ampicillin (Kirby *et al.*, 1974; Verbist, 1974, 1976), but the information on biliary drug concentrations is scant.

More recently cephalosporins have been advocated for prophylaxis of post-operative biliary tract infections (Strachan *et al.*, 1977; Pollock & Evans, 1977; Drugs & Therapeutics Bulletin, 1981; Hurlow *et al.*, 1981; Karran *et al.*, 1981). Ceftriaxone is the most potent of the new 'third generation' semi-synthetic cephalosporins. It is not only active against a wide spectrum of gram negative and gram positive organisms (Shelton *et al.*, 1980) but has a longer plasma half-life (Seddon *et al.*, 1980). In animal experiments it has been found to be highly concentrated in the bile. We have, therefore, studied the plasma disappearance and biliary concentration-time curves of ceftriaxone following bolus intravenous administration in man and compared it with that of amoxycillin.

Methods

Four male subjects (age range 34–40 years) who had normal upper gastrointestinal tract (assessed by barium meal and endoscopy of oesophagus, stomach and duodenum), normal hepato-biliary function (normal standard liver function tests and normal ultrasound examination of liver and gallbladder) and normal renal function (assessed from blood urea, electrolytes and serum creatinine) were studied. Written informed consent was obtained from each patient before entering the study, which was approved by the local hospital ethical committee.

On the day of investigation, after an overnight fast, a double-lumen polyvinyl tube was passed via the nose to the duodenojejunal flexure under fluoro-

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scopic control, and then securely fixed to the nose with adhesive tape. The aspiration site was just beyond the ampula of Vater. Baseline blood, urine and duodenal fluid samples were collected. Ceftriaxone (500 mg) dissolved in 5 ml of normal saline was then administered by slow intravenous injection over a period of 5 min. Blood samples were collected at 10, 30, 50, 70, 90, 110, 140, 170, 200, 230, 290 and 350 min after injection, and plasma separated. Bile samples obtained by aspirating bile rich duodenal fluid were collected at 20, 40, 60, 80, 100, 120, 150, 180, 210, 240, 300 and 360 min after drug administration. Urine output was collected for 6 h following injection. All samples were immediately stored at −20°C for subsequent measurement of active ceftriaxone concentration using a sensitive high pressure liquid chromatography (h.p.l.c.) assay. At the end of the study gallbladder bile was collected by aspirating duodenal fluid after giving intravenous cholecystokinin (1 CH unit kg^{-1} min^{-1}) to stimulate gallbladder contraction (Dam *et al.*, 1971). After an interval of at least 4 weeks, three of the four subjects were restudied. On this occasion 500 mg amoxycillin was given by slow intravenous injection. Using the same protocol as described earlier, serum, bile and urine specimens were collected and stored at −70°C for subsequent measurement of amoxycillin using the *Sarcina lutea* cup-plate microbiological assay.

Results

Plasma

The mean (± 1 s.d.) plasma half-life of ceftriaxone was 330 ± 30 min (Figure 1) and that of amoxycillin 60 ± 9 min (Figure 2).

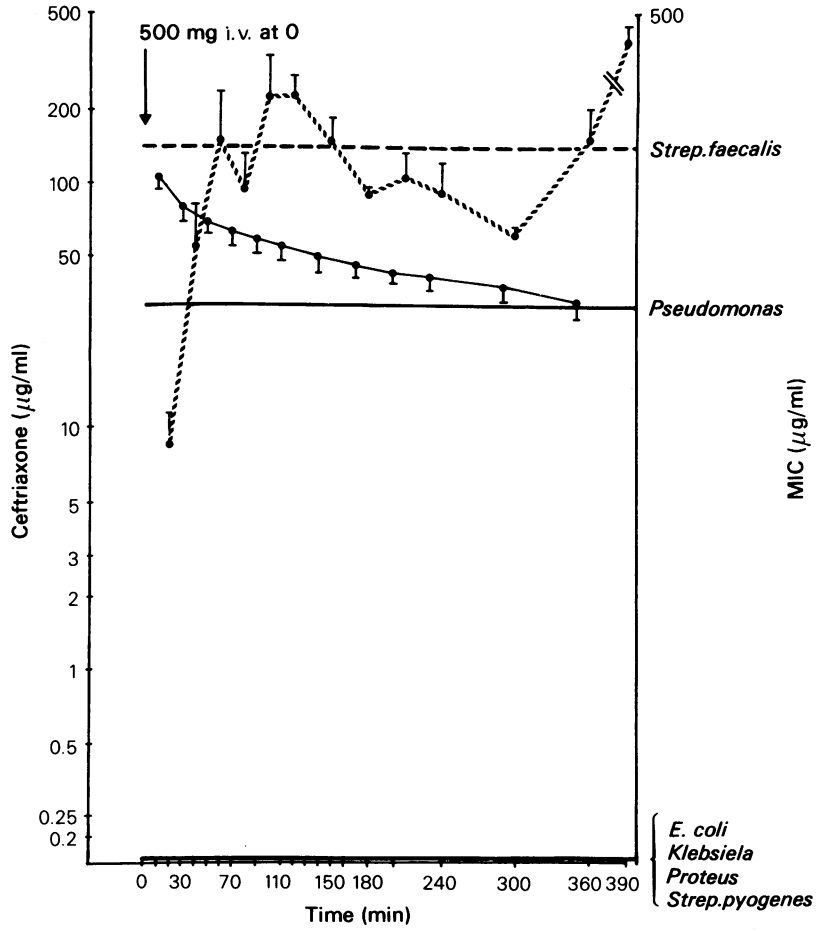

Figure 1 Ceftriaxone concentration in plasma (●——●) and bile (●------●) up to 6 h following i.v. bolus administration, together with the minimum inhibitory drug concentrations for some common biliary tract pathogens.

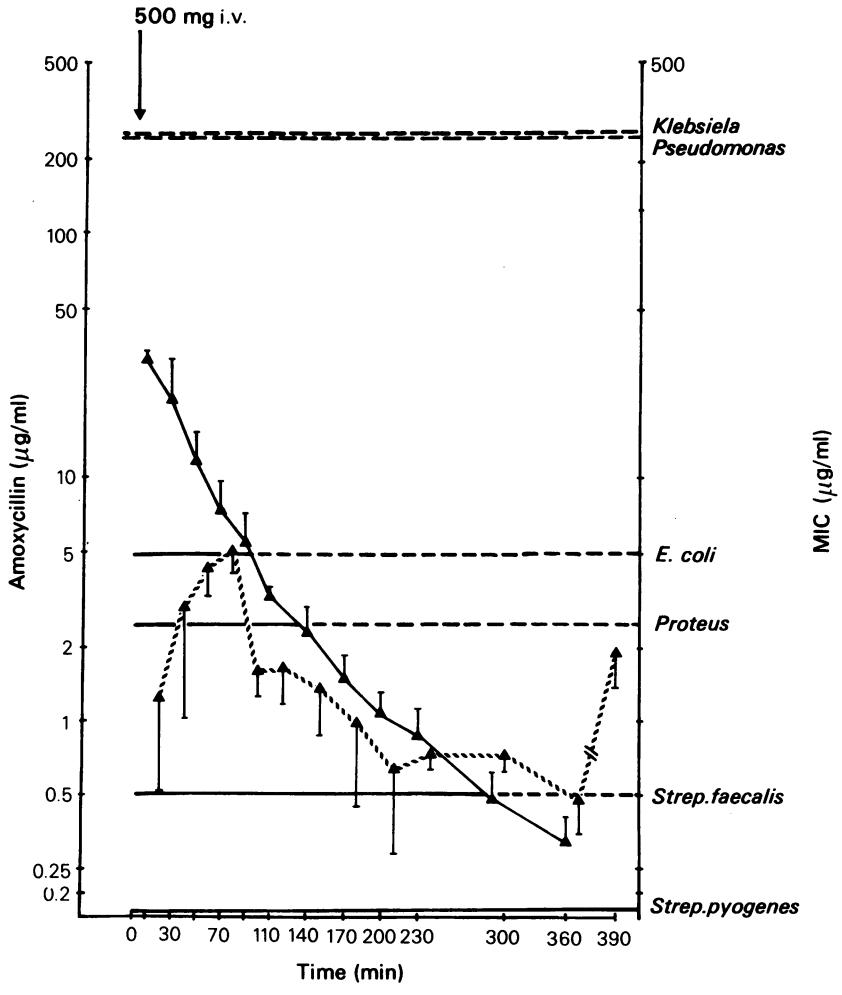

Figure 2 Amoxycillin concentration in plasma (▲——▲) and bile (▲------▲) shown against the minimum inhibitory drug concentration for common biliary tract pathogens.

Bile

Peak concentrations of ceftriaxone in bile were reached 60 to 120 min after intravenous administration. Thereafter the bile concentrations remained consistently higher than plasma levels throughout the study period in all four subjects. Ceftriaxone concentrations in gallbladder bile collected at the end of the study was higher than that from the bile samples collected through the study period (Figure 1).

Peak concentration of amoxycillin in bile was reached 80 min after drug administration. Subsequently biliary concentrations fell rapidly, and remained lower than serum concentrations. Amoxycillin concentration in the gallbladder bile collected at the end of the study was lower than peak concentrations in hepatic bile obtained during the study (Figure 2).

Urine

The cumulative 6 h urinary excretion of ceftriaxone was 22% of the administered dose, while 62% of amoxycillin was excreted in the urine over this time.

Discussion

Our results confirm that ceftriaxone, one of the 'third generation' semi-synthetic parenteral cephalosporins has a substantially longer plasma half-life (4–5 fold)

than other cephalosporins (Wise 1974; Seddon *et al.*, 1980). It also differs from all other cephalosporins in possessing the most potent antibacterial properties (Shelton *et al.*, 1980). We have also demonstrated that the half-life of ceftriaxone is several times longer than that of amoxycillin.

The present study demonstrates that ceftriaxone is highly concentrated in bile, as has been shown in experimental animals. In our subjects biliary concentrations were 2 to 5 times greater than those in plasma which is considerably below the 30 to 100 times increase noted in dogs (unpublished observations, Roche Pharmaceuticals, Ltd). This difference may be explained partly by experimental technique, as animal studies analysed samples of pure bile obtained from dogs with biliary fistulae, while our data was obtained from duodenal aspirates, with inevitably some dilution of bile with gastric, pancreatic and intestinal juice. Collection of bile by direct gallbladder puncture at laparotomy or by t-tube drainage would have yielded higher concentrations for both drugs but these techniques were not suitable for our study carried out in normal subjects. It is unlikely that either of the drugs used in our study would have altered the composition or flow of bile since ampicillin and cephalosporins have been shown to have no effect on bilirubin and cholesterol saturation or on volume of bile collected by t-tube drainage (Acocella *et al.*, 1968). The variable drug concentrations noted in bile probably represent the effect of intermittent gallbladder emptying (Mack & Todd, 1968). We are unable to comment on the exact proportion of ceftriaxone secreted in bile, as in our study intermittent sampling resulted in incomplete collection. Nevertheless the high concentration of ceftriaxone in aspirated bile samples, together with its low urinary secretion, suggests that in man a significant proportion of the drug is removed by hepatobiliary excretion. Several other cephalosporins have been shown to have higher levels in spot samples of bile (Mullinger & House, 1981), but their plasma half-life is much lower than ceftriaxone. In the present study amoxycillin concentrations in aspirated bile were very low, and the drug did not get concentrated in the gallbladder bile obtained at the end of the study. These results confirm the observation of lower amoxycillin concentrations in the bile collected by t-tube or at ERCP (Chevlan *et al.*, 1979), or at laparotomy (Kiss *et al.*, 1981).

It is of interest that there are conflicting reports regarding the biliary excretion of the closely related antibiotic ampicillin. Variable ampicillin excretion in bile has been noted in some reports (Bullock 1961; Ayliffe & Davies, 1965; Acocella *et al.*, 1968), but this was not confirmed in a recent study in which no ampicillin was detected in pure bile aspirated directly from the common bile duct by endoscopic retrograde cholangiography (Roberts & Williams, 1979).

Elective cholecystectomy is complicated by wound infection in up to 30% of cases (Keighley, 1977; Strachan *et al.*, 1977; Hurlow *et al.*, 1981; Karran *et al.*, 1981). Organisms present in the bile at the time of surgery are usually responsible, and those most frequently implicated include *E. coli*, *Strep. pyogenes*, *Klebsiella*, *Strep. faecalis*, *Proteus* and *Pseudomonas* (Keighley 1977; Strachan *et al.*, 1977; Hurlow *et al.*, 1981; Karran *et al.*, 1981). It is of interest to compare the mean drug concentrations of ceftriaxone and amoxycillin in plasma and bile at various time intervals after administration of 500 mg of each drug, with the MIC for common biliary tract organisms. In the case of ceftriaxone, both plasma and bile concentrations were higher than previously determined MIC levels for *E. coli*, *Klebsiella*, *Proteus*, *Strep. pyogenes*, *Pseudomonas*, throughout the 6 h study period but not for *Strep. faecalis* (Figure 1). For amoxycillin on the other hand, the plasma and bile concentrations exceeded the MIC for *Strep. faecalis* and *Strep. pyogenes* but remained substantially lower than MIC for *Klebsiella* and *Pseudomonas* (Figure 2). Plasma amoxycillin concentrations reached MIC levels for *E. coli* and *Proteus* for up to 2 h. Gallbladder bile drug concentration was in excess of the MIC for all common biliary tract pathogens for ceftriaxone but only for *Strep. faecalis* and *Strep. pyogenes* for amoxycillin.

Cephalosporins are currently recommended as the drugs of choice in the prophylaxis of biliary tract infections (Strachan *et al.*, 1977; *Drugs & Therapeutics Bulletin*, 1981; Hurlow *et al.*, 1981; Karran *et al.*, 1981). Combination of long plasma half-life, higher concentration in bile and the activity against a wide spectrum of organisms suggests that ceftriaxone may be the most suitable drug for this purpose. Clinical trials are necessary to study the effectiveness of ceftriaxone in the treatment and/or prophylaxis of biliary tract infections.

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