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Effect of probenecid on the excretion of ampicillin in human bile

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Summary

1. Ampicillin concentrations were determined in serum and bile after intravenous injection into patients with T-tube bile drainage of 1 gram ampicillin before and during probenecid medication. The concentrations were followed up to fifteen hours after injection.

2. Probenecid increased the half-life of ampicillin in serum from 74 minutes to 137 minutes.

3. Ampicillin concentrations in bile were higher following probenecid medication and a concentration over 5 μg/ml was obtained for 3 h longer than before probenecid.

4. The ampicillin concentrations in bile were approximately the same as those in serum both before and during probenecid medication suggesting passive transport of ampicillin from blood to bile.

5. A combined treatment of ampicillin and probenecid might be of clinical value in the therapy of cholangitis and typhoid carriers.

Introduction

Ampicillin has been used in the treatment of cholangitis (Zylka, 1964 ; Ayliffe & Davies, 1965) and in infections caused by *Salmonella typhi* (Phillips, 1971). Klein & Finland (1963) studied serum concentrations and urinary excretion of ampicillin following probenecid medication and demonstrated a decrease in the total amount of ampicillin excreted with sustained elevation of serum ampicillin levels. This elevation of serum ampicillin was explained by a suppression of the renal excretion of ampicillin caused by probenecid but the decrease in the total amount of ampicillin in the urine might be explained by increased excretion of ampicillin in the bile. Few investigators have studied ampicillin levels in human bile (Ayliffe & Davies, 1965 ; Mortimer, Path, Mackie, Chir & Haynes, 1969). These authors demonstrated higher levels of ampicillin in bile than in serum. No studies of the influence of probenecid on ampicillin concentrations in human bile have been reported.

Methods

Nine patients were studied, three women aged 69 to 75 years and 6 men aged 62 to 79 years. Three of the patients had jaundice with serum bilirubin concentra-

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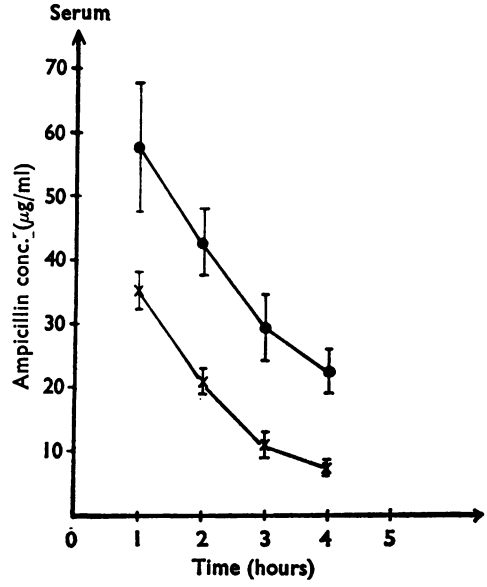
tions of 2·0–5·0 mg per cent during the period of investigation. Renal function was evaluated by endogenous creatinine clearance. In 8 patients with normal serum creatinine values, creatinine clearance varied between 37 and 70 ml/minute. In one patient with elevated serum creatinine (2·2 mg per cent), creatinine clearance was found to be 32 ml/minute. The patients were examined two to ten days after cholecystectomy. The bile was collected from a T-tube in the bile duct. One gramme of ampicillin was given intravenously, and thereafter bile was removed every half hour for the first two hours and thereafter every hour. The bile samples were immediately stored in a deep freeze to await analysis. Blood samples were obtained 4 times at hourly intervals following the ampicillin injection. The experiment was repeated after five days of oral probenecid (2 g per day). In two patients a third examination was performed following another period of five days without probenecid. The ampicillin concentrations in serum and bile were determined by the agar cup method using a strain of *Staphylococcus aureus*. All the bile analyses were carried out within 7 days of collection. The error of the ampicillin determination was evaluated by repeated determinations on the same bile sample and the coefficient of variation was found to be 8·1 per cent. Repeated determination of ampicillin concentration demonstrated its stability in bile during a storage period of at least 10 days. The data were subjected to statistical analysis with Student's *t* test applied to paired data.

Results

The results are shown in the Figure 1. The mean serum levels of ampicillin during a period of 1–4 h following intravenous injection of 1 g ampicillin were significantly higher after probenecid medication than before ($P<0·01$). The mean half-life of ampicillin in serum following the intravenous injection was calculated to be 74 min (range 35–95 minutes). After probenecid the mean value of ampicillin half-life was significantly raised to 137 min ($P<0·01$), (range 75–260 minutes). Renal function as evaluated by serum creatinine was unaltered during the five days of probenecid medication. In all patients, ampicillin concentrations in the bile following probenecid were higher than the concentrations in the bile before probenecid, but this difference was not statistically significant until 2 h after the intravenous injection of ampicillin ($P<0·01$). After probenecid the ampicillin concentrations in the bile also showed a considerably slower decrease in the period 4–15 h after the ampicillin injection and a concentration over 5 μg/ml was maintained for about 7·5 h compared to about 4·5 h in patients before probenecid medication. The mean half-life of ampicillin in the bile was 70 min before probenecid; this was significantly prolonged to 120 min after probenecid ($P<0·01$). Considering the serum concentrations of ampicillin given in Fig. 1, it is evident that from about 1 h after the intravenous injection of ampicillin the serum values of ampicillin are the same as those in bile not only before probenecid but also after 5 days' medication with probenecid. The total volume of the bile recovered from the T-tube was 11 ml/h before probenecid and 13 ml/h afterwards. The total amount of ampicillin in the bile was on average 1·3 mg before probenecid and increased to 2·8 mg after probenecid medication ($P<0·01$).

In the three patients with jaundice, ampicillin concentrations in the bile following intravenous injection of the drug were somewhat lower than those in patients without jaundice. However, an increase in ampicillin concentrations after pro-



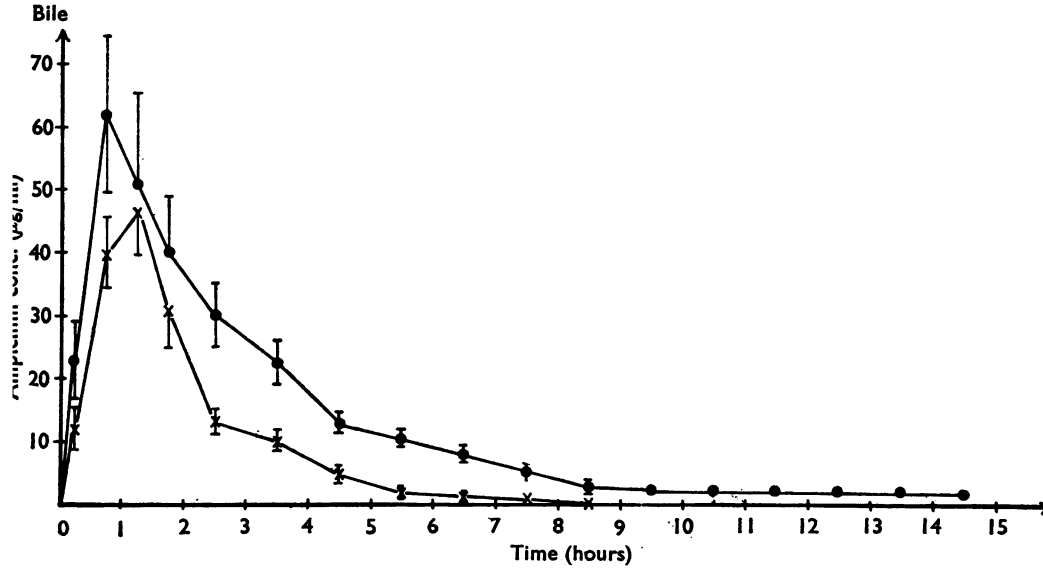


FIG. 1. Ampicillin concentrations in serum and bile before (×——×) and after probenecid (●——●) in 9 patients. The values are given as mean ± S.E.M.

benecid medication for 5 days was also noted in the patients with jaundice, and the increase, when compared to the values before probenecid, was of the same order as in the patients without jaundice. In the two patients examined following withdrawal of probenecid the ampicillin concentrations in the bile were not significantly different from those found in the first examination before probenecid medication.

Discussion

Our finding of a twofold increase in ampicillin half-life in blood following probenecid medication is in agreement with studies by Klein & Finland (1963) and Quinn, Cox, Jones & Zarins (1964).

Comparison with previous studies of ampicillin levels in human bile is made difficult by different methods of collection of the bile and various routes of ampicillin administration. Ayliffe & Davies (1965) collected the bile from a T-tube in the bile duct and Mortimer *et al.* (1969) through a fine catheter which was inserted via the cystic duct during operation on the biliary tract. These authors administered 250 and 500 mg ampicillin respectively by intramuscular injection from half an hour to two hours before the collection of the bile and found higher values of ampicillin in bile than in serum collected simultaneously. In the present study ampicillin levels in bile were estimated following an intravenous injection of 1 g of ampicillin and our values in bile seem to be in fairly good agreement with those of Mortimer *et al.* (1969) 2 h after the ampicillin injection, considering the different doses of ampicillin given. In the study of Mortimer *et al.* (1969), however, serum levels were lower than our values, even allowing for the fact that a lower dose of ampicillin was given than in the present study. We have no explanation of this discrepancy, but it might be explained by different renal function, different technique in bile collection and delayed absorption after intramuscular application. Ayliffe & Davies (1965) found very low bile values in two patients with biliary tract disease after administration of 250 mg ampicillin, using the same technique as in the present study. We have demonstrated that ampicillin is stable for at least 10 days in bile when specimens are stored immediately in a deep freeze (−20° C).

Ampicillin concentrations in blood and bile have not previously been estimated simultaneously over a longer period of time and our finding of approximately equal levels of ampicillin in serum and bile seems to suggest a mainly passive transport of the drug from blood to bile.

However, alterations in liver function affecting ampicillin excretion during the postoperative period cannot be completely ruled out. Two patients were therefore re-examined five days after withdrawal of probenecid at a time when the liver function was probably improved. The ampicillin concentrations in the bile were, however, approximately the same as in the first examination immediately after the operation and before probenecid was given. This suggests that the increased levels of ampicillin in the bile after probenecid were not caused by a coincident improvement in the liver function. Our finding of raised levels of ampicillin in bile following probenecid is presumably due to the increase in serum levels of the drug.

The total amount of ampicillin excreted in the bile was increased by probenecid but only from an average of 1·3 mg to 2·8 mg. This corresponds to less than 1% of the total dose given. Thus the decrease in total amount of ampicillin excreted in the urine following probenecid described by Klein & Finland (1963), does not seem to be explained by increased biliary excretion.

Our results may be of practical clinical importance in the treatment of cholangitis and typhoid carriers with ampicillin.

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