Amoxycillin: pharmacokinetic studies in normal subjects, patients with pernicious anaemia and those with renal failure

D. H. LAWSON*
M.D., M.R.C.P.

A. K. HENDERSON*
M.B., M.R.C.P.

R. R. McGEACHY
A.I.M.L.T.

Department of Medicine and Bacteriology, Western Infirmary, Glasgow

Summary

This paper presents data on the absorption and disappearance of a new semisynthetic antibiotic—amoxycillin—in patients with pernicious anaemia and those with renal failure. Absorption of this drug is unimpaired in these patients. Adequate serum and urine levels are obtained even in patients with creatinine clearance levels below 10 ml/min. The half-life of this drug is markedly prolonged in patients undergoing regular dialysis therapy, and a single 250 mg dose will provide adequate serum levels for 24 hr, if this is given after dialysis is complete.

Introduction

Amoxycillin is a recently introduced semi-synthetic penicillin. It is reported to be freely absorbed orally, to be uninfluenced by the presence of food in the stomach, to reach higher serum concentrations than ampicillin on a dose-for-dose comparison and to attain therapeutic concentrations in the urine (Sutherland, Croydon and Rolinson, 1972). In addition, this drug has the same wide spectrum of antibacterial activity as ampicillin (Sutherland and Rolinson, 1970).

The present investigation was undertaken to study the handling of this antibiotic in normal subjects, patients with pernicious anaemia and in those with varying degrees of renal impairment.

Methods

Amoxycillin was given in a dose of 250 mg 8-hourly for 7 days. Patients received breakfast as usual on the day of the study and then were given their first dose of amoxycillin at 9 a.m. Serial blood and urine collections were taken for 6-8 hr thereafter. Once

the initial investigations were complete the patients continued to take the amoxycillin regularly until the final dose at 9 a.m. on day 8. Serial blood and urine collections were again taken during the 8 hr following the last dose of antibiotic.

All blood samples were promptly separated and the serum frozen until the assays could be performed—usually within 4 days of collection. The antibacterial activity of each specimen was measured in quadruplicate using the method described by Bennett *et al.* (1966). The test organism used was *Sarcina lutea* NCTC 8340. Similar techniques were used to verify the antibiotic concentration found in a representative group of 250 mg capsules.

Initial studies were performed on four normal patients and the resulting data compared with those found when three patients with treated pernicious anaemia were investigated. The studies were then repeated on nine patients suffering from various degrees of renal impairment. In all cases patients gave their informed consent to the investigation. No patient was included in the study if he had received antibacterial therapy in the preceding 6 weeks.

In addition, three patients with chronic renal failure who required regular dialysis therapy were given single doses of 250 mg amoxycillin immediately after commencing dialysis. In each case, dialysis involved an Ultra-flow twin-coil artificial kidney. The resulting blood levels were then compared with those obtained when the patients received a similar dose of amoxycillin after dialysis was completed.

In all cases blood levels were related to time on a semi-logarithmic scale and regression lines were fitted to the blood levels recorded between 2 and 8 hr after ingestion of the capsule. The resulting equation of the regression line was then used to calculate the half-life of the drug in the serum ($t_{1/2}$), the hypothetical concentration of drug at time zero (C_{s0} , $\mu\text{g/ml}$) and from this the apparent volume of distri-

* Present address: Royal Infirmary, 86 Castle Street, Glasgow G4 0SF.

TABLE 1. Amoxycillin levels attained in patients with normal renal function: a comparison of results obtained after a single dose and after a week's course

Patient	Diagnosis	First study*			Second study*		
		Peak serum level (µg/ml)	Volume of distribution (l)	t _½ (min)	Peak serum level (µg/ml)	Volume of distribution (l)	t _½ (min)
A	Normal	5.0	11.3	52.9	10.4	15.5	61.8
B	Normal	7.2	16.2	109.3	8.0	18.1	138.6
C	Normal	5.6	25.9	82.5	—	27.6	97.6
D	Normal	5.2	15.9	76.1	5.6	33.8	97.6
E	PA	7.2	13.7	93.1	8.8	11.9	103.4
F	PA	4.8	13.8	66.0	5.2	18.5	72.3
G	PA	7.2	9.3	62.4	6.6	14.5	74.0

PA, pernicious anaemia; * First study, data following 250 mg amoxycillin; second study, data following 7-day course of amoxycillin 250 mg 8-hourly.

TABLE 2. Amoxycillin levels attained in patients with renal impairment: a comparison of results obtained after a single dose and after a week's course

Patient	C _{creat}	First study*			Second study*		
		Peak serum level (µg/ml)	Volume of distribution (l)	t _½ (min)	Peak serum level (µg/ml)	Volume of distribution (l)	t _½ (min)
H	42	8.0	16.1	128.3	6.4	18.9	130.7
J	33	7.2	21.7	203.8	7.2	21.7	231.0
K	27	17.6	5.3	169.0	13.2	10.2	277.0
L	19	8.0	10.6	157.0	9.8	15.8	223.5
M	13	6.4	32.7	433.0	17.6	10.0	277.0
N	10	14.4	23.6	911.0	16.0	14.4	761.0
P	5	—	—	—	14.8	12.2	315.0
Q	3	9.2	23.3	648.0	—	—	—

* First study, data following 250 mg amoxycillin; second study, data following 7-day course of amoxycillin 250 mg 8 hourly; C_{creat}, creatinine clearance in ml/min.

bution of the drug (V_d -l). In the case of patients with severe renal impairment the regression lines were fitted to blood levels obtained at least 4 hr after ingestion of the capsule.

Results

In normal subjects peak serum levels were attained at 2 hr after ingestion of the capsule, and ranged from 5 to 7.2 µg/ml. Similar values were obtained in patients with treated pernicious anaemia. There were no significant differences between the peak serum levels observed after a single capsule of amoxycillin and those seen after a 7-day course. Serum levels fell below 1 µg/ml within 6 hr of administering the drug in all patients.

In patients with renal impairment, peak serum levels occurred later than in the controls—between 3 and 4 hr after capsule administration. The mean peak serum level attained on day 1 was 10.1 (s.e. 1.6) µg/ml and on day 8 was 12.1 (s.e. 1.7) µg/ml.

In patients with normal renal function, the half-life of amoxycillin in the serum after a single dose was 77.5 (s.e. 7.3) min, and after the end of a 7-day course it was 92.2 (s.e. 9.7) min ($-t_{\text{paired}} = 4.81$; $P < 0.01$), Table 1. The half-life was prolonged in

all subjects with creatinine clearance levels below 50 ml/min, Table 2, Fig. 1. In addition the half-life calculated on day 8 was significantly longer than that on day 1 in all patients with creatinine clearance levels exceeding 15 ml/min [$t_{\frac{1}{2}}$ (day 1) = 109 (s.e. 15) min; $t_{\frac{1}{2}}$ (day 8) = 137 (s.e. 22) min — $t_{\text{paired}} = 2.90$ $P < 0.05$]. No such relationship was noted in patients with lower glomerular filtration rates.

The calculated volume of distribution of amoxycillin was 17.2 (s.e. 1.3) l. There were no statistically significant differences in this volume of distribution between patients with normal and abnormal renal function or between values estimated at the beginning or end of the study.

The relationship between creatinine clearance and the observed half-life of amoxycillin was an exponential one—the equation most closely expressing the observed results following the initial study was:

$$t_{\frac{1}{2}} = 456.e^{-0.018c} \quad (r = 0.768; P < 0.01).$$

Following the 7-day course of therapy the comparable equation was:

$$t_{\frac{1}{2}} = 391.e^{-0.015c} \quad (r = 0.779; P < 0.01) \text{ (Fig. 1).}$$

FIG. 1. Study 1, ●; study 2, ▲.

The simplest expression most closely describing the findings was therefore:

$$t_{1/2} = 420.e^{-0.015c} \text{ (min)}$$

or

$$= 7.e^{-0.015c} \text{ (hr)},$$

(where c = creatinine clearance in ml/min).

In patients with normal renal function, there were no differences in the concentration of antibiotic in the urine, or in the total amount of drug recovered in the urine when the results of studies taken on day 1 were compared with those on day 8. The mean amount of antibiotic recovered in the urine collected for 6 hr after amoxycillin ingestion was 159 mg. The mean concentration of drug in urine samples taken up to 2 hr after amoxycillin was 344 µg/ml. Comparable concentrations measured at 2–4 hr and at 4–6 hr were 538 µg/ml and 188 µg/ml respectively.

Where patients with chronic renal failure were studied the mean recovery of amoxycillin, and the urine concentrations reached, tended to be lower than normal subjects but even in patients with creatinine clearance levels as low as 5 ml/min, concentrations exceeding 60 µg/ml were recorded.

Data from one patient with severe renal failure were omitted from the above calculations. This patient had a creatinine clearance of 5 ml/min as a result of renal disease attributed to analgesic abuse. She had previously (1970) experienced stomal

ulceration during a course of ampicillin and on this occasion developed severe ulceration on day 3 of amoxycillin therapy. Subsequently, blood levels were found to be grossly elevated, the peak serum level being 31.2 µg/ml at 2 hr. More surprisingly, the observed half-life was low (80 min) and the maximum concentration of amoxycillin in the urine at 2–4 hr was relatively high (220 µg/ml). Some 158 mg of amoxycillin was recovered in the urine during the first 6 hr after a 250 mg dose.

Three patients with severe renal failure requiring regular dialysis therapy were studied during and after haemodialysis. Blood levels attained after a single 250 mg capsule of amoxycillin were higher when the drug was given after dialysis than when it was given at the beginning of the procedure. However, in both situations therapeutic levels were recorded for periods exceeding 6 hr after capsule ingestion.

Finally, the antibacterial activity of 10 capsules of amoxycillin were assayed—all were found to lie between 260 and 280 mg.

Discussion

The results of this investigation confirm that amoxycillin is satisfactorily absorbed orally even in the presence of food in the stomach (Sutherland *et al.*, 1972). Absorption is satisfactory in patients with achlorhydria and remains so even in the presence of severe renal impairment.

Serum levels exceeding 1 µg/ml were present for up to 6 hr after an oral dose of 250 mg in all subjects. Such levels are known to be bactericidal for most strains of *Haemophilus influenzae* and all penicillin-sensitive strains of staphylococci, streptococci and pneumococci (Sutherland *et al.*, 1972). Urine concentrations exceeding 30 µg/ml were present for 6 hr after a 250 mg capsule in all subjects tested, and the mean concentration observed in normal subjects between 2 and 4 hr after treatment was over 500 µg/ml. The mean proportion of the administered dose which was recovered in the urine during the 6 hr after administration was 64% in those with normal renal function and 38% in those with renal impairment. These results indicate that amoxycillin is a suitable drug to use in patients with renal failure who are suffering from a penicillin-sensitive infection. In the case of a urinary tract infection, both serum and urinary concentrations of amoxycillin are well within the therapeutic range even in patients with creatinine clearance levels below 10 ml/min.

The calculated volume of distribution of amoxycillin was relatively constant over a wide range of renal function, and was slightly greater than the expected extracellular fluid volume of these subjects. This finding is compatible with the known protein-binding characteristics of amoxycillin and explains

the apparent increase in the half-life after a 7-day course of treatment.

Amoxycillin levels attained in patients requiring regular dialysis therapy are higher if the drug is given after the end of dialysis. The half-life is markedly prolonged in such patients and a single daily dose of 250 mg should be sufficient to maintain therapeutic concentrations for 24 hr.

Finally, in one subject with severe renal failure, the handling of amoxycillin was unusual, in that much higher than normal concentrations were detected in the patient's serum and the calculated half-life was unusually short for someone with marked renal failure. Such behaviour on the part of a patient with renal failure has previously been reported in the case of cephalexin (Kunin and Finkleberg, 1970), but as yet no satisfactory explanation has been given.

Acknowledgments

We wish to thank Dr J. Price of Beechams for providing the amoxycillin used in this study, Dr J. D. Sleight for his help and advice and Dr J. D. Briggs for permitting free access to patients under his care.

References

- BENNETT, J.V., BRODIE, J.L., BENNER, E.J. & KIRBY, W.M.M. (1966) A simplified, accurate method for antibiotic assay of clinical specimens. *Applied Microbiology*, **14**, 170.
- KUNIN, C.M. & FINKLEBERG, Z. (1970) Oral Cephalexin and Ampicillin: Antimicrobial activity, recovery in urine and persistence in blood of uremic patients. *Annals of Internal Medicine*, **72**, 349.
- SUTHERLAND, R., CROYDON, E.A.P. & ROLINSON, G.N. (1972) Amoxycillin: A new semi-synthetic penicillin. *British Medical Journal*, **3**, 13.
- SUTHERLAND, R. & ROLINSON, G.N. (1970) In: *Antimicrobial Agents and Chemotherapy*, **10**, 411.