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Plasma concentration/time curve of erythromycin after a 12-hour intravenous infusion of erythromycin lactobionate in man

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Summary

As the pharmacokinetics after a slow infusion had not previously been evaluated in the doses used in this study, it was decided to measure the plasma concentration/time curve after a twelve-hour intravenous infusion of 2·0 g of erythromycin lactobionate in 2 litres of 0·9% normal saline. Six healthy medical students with no past history of cardiovascular, renal, hepatic, metabolic or gastrointestinal disease and no past drug allergy participated. The concentration of erythromycin base in venous blood was measured by small plate microbiological assay. Venous blood was taken at zero, 15, 30, 45, 60 min and at 2, 3, 4, 6, 8, 12, 16, 20 and 24 hr after starting the infusions. Duplicate assays were performed on all plasma samples at Guy's and at the manufacturer's laboratories. A full haematological and biochemical screening profile was performed before and after the study.

The mean ± s.e. plasma erythromycin base concentration rose from 0·7 ± 0·2 μg/ml at 15 min to 6·06 ± 1·6 μg/ml at 1 hr. The peak plasma concentration was between 1·48 ± 0·25 μg/ml at 30 min and 7·21 ± 0·93 μg/ml at 4 hr. The plasma concentration at 12 hr was 6·17 ± 0·33 μg/ml, and fell to 0·37 ± 0·05 μg/ml at 24 hr.

These findings suggest that therapeutically effective plasma concentrations follow a slow intravenous infusion of erythromycin lactobionate. There was no evidence of adverse haematological or biochemical function in the tests of blood, hepatic or renal function, apart from two volunteers who vomited after the infusions were discontinued.

Introduction

In view of the claim (Neaverson, 1976) that intermittent intravenous chemotherapy is preferable to continuous infusion, it was decided to examine the pharmacokinetics after a 12-hr intravenous infusion of 2·0 g of erythromycin lactobionate.

The authors' previous interest in the assay (Paddock, Parsons and Vickers, 1975) and pharmacokinetics of erythromycin in healthy volunteers (Parsons and Paddock, 1976) and patients with different types of malabsorption (Parsons, Hossack and Paddock, 1975; Parsons, Jusko and Lewis, 1976b; Parsons, Paddock, Hossack and Hailey, 1976c) led the manufacturers of erythromycin lactobionate (Erythrocin i.v.) to ask the authors to evaluate the safety, pharmacokinetics and tolerability of this mode of administration in healthy volunteers.

Subjects and methods

Conduct of the study

Approval for this study was first obtained from the Ethical Committee of Guy's Hospital Medical School. Written informed consent was then given by six healthy male medical students, whose mean ± s.e. mean age, height and weight were 21·2 ± 0·4 (range 20–22) years, 66·6 ± 2·7 (range 61·5–79·5) kg and 175·8 ± 1·9 (range 168–180·5) cm respectively. The participants had no past history of cardiovascular, hepatic, renal, metabolic or gastrointestinal disease and no previous drug allergy. The results of physical examination and the following biochemical and haematological investigations: haemoglobin, packed cell volume, mean corpuscular volume, mean corpuscular haemoglobin concentration, total and differential white blood count, platelet count, ESR, blood urea and urate, serum electrolytes, bilirubin, calcium, creatinine, phosphate, alkaline phosphatase, transaminases, total proteins and electrophoretic strip, performed before administration of erythromycin were normal by the standard methods used in the routine haematology and chemical pathology laboratories.

Each participant was requested to abstain from alcohol during the study and to take no other drugs

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for seven days before the study day. All studies were commenced on the same day at 7.00 a.m. after a complete fast (fluids and food) that lasted for twelve hours before the infusions were started. Breakfast was taken at 9.00 a.m., two hours after the infusions began. Lunch and supper were served at 1.00 p.m. (six hours after starting the infusions) and 6.00 p.m. (11 hours after starting the infusions) respectively.

Mode of administration of intravenous infusions

1·0 g of erythromycin lactobionate powder was dissolved in each litre of 0·9% normal saline. The total dose (2·0 g) of erythromycin lactobionate was given to each participant in 2 litres of normal saline at a constant infusion rate of 2·78 mg/min over 12 hr. Each one-litre infusion was prepared immediately before administration and was given over 6 hr. All the infusions were stopped at 7.00 p.m. on the evening of the study day.

Blood sampling

Venous blood samples were taken from an indwelling butterfly infusion set that was fitted with a heparin lock. The needles were put into the opposite arm to that used for the infusion. The first blood sample was taken immediately before starting the infusion at 7.00 a.m. Further blood samples were taken at 15, 30, 45, 60, 90 min. and 2, 3, 4, 6, 8, 12, 20 and 24 hr after starting the infusions.

An additional 20 ml of blood was taken with the first and last samples for haematological and biochemical investigations as outlined previously.

Microbiological assay

The plasma concentration of free erythromycin base was measured by a small plate microbiological method based on that of Grove and Randall (1955). The assay organism (*Sarcina lutea*) was inoculated into reconstituted molten Penassay seed agar which was poured into disposable plastic Petri dishes. A suitable set of standards of erythromycin base of known potency was prepared in 90% pooled human plasma, initially by dissolving 54·05 mg of erythromycin base in 2·0 ml of methanol. This was then further diluted with pH 7·9 phosphate buffer. The final concentration range of the diluted standard solutions was 3·2, 1·6, 0·8, 0·4, 0·2 and 0·1 μg/ml. These standards and eight duplicates of each test plasma sample were placed into wells bored into the hardened agar. After overnight incubation at 35°C, the diameters of the inhibition zones of the test and standard wells were measured with the Fisher–Lilly zone reader. A standard curve of the concentration of the standards against their zone diameters was drawn on semilog paper from which the concentration of erythromycin base in the plasma samples was ascertained.

Results

Table 1 shows the individual and group mean ± s.e.mean plasma erythromycin concentrations estimated in the laboratory at Guy's. The assay results of the duplicate coded samples that were sent to the manufacturer's laboratory are given in Table 2. There was a highly significant correlation ($r = 0·89$, $P < 0·01$) between the results of the plasma concentrations obtained in the two laboratories.

The peak plasma concentration of erythromycin base in every subject occurred between 45 min and 1 hr. The mean ± s.e. mean plasma concentration of erythromycin values showed that the initial mean ± s.e. mean peak of 6·06 μg/ml at one hour was

TABLE 1. Individual and group mean ± s.e. mean plasma concentrations of erythromycin base after a 12-hr intravenous infusion of 2 g of erythromycin lactobionate (Erythrocin i.v.). Samples analysed by laboratories at Guy's

	Plasma concentration of erythromycin base (μg/ml)						
Subject	1	2	3	4	5	6	Group mean (± s.e. mean)
Time (hr)							
0·25	1·6	0·94	0·27	0·47	1·04	0	0·72 (0·23)
0·5	2·56	1·38	1·04	0·73	1·58	1·6	1·48 (0·25)
0·75	4·2	3·65	9·0	0·64	2·95	2·1	3·75 (1·16)
1	9·75	10·75	2·13	0·73	7·25	5·75	6·06 (1·64)
1·5	2·3	2·35	2·7	6·4	4·8	1·05	3·26 (0·79)
2	1·9	2·15	2·45	2·65	3·35	3·85	2·72 (0·29)
3	5·2	4·1	5·6	6·3	5·9	5·15	5·37 (0·30)
4	4·9	5·0	9·7	8·7	9·4	5·6	7·21 (0·93)
6	7·1	6·8	9·0	3·35	5·9	6·0	6·35 (0·75)
8	5·15	4·1	4·1	2·3	2·15	2·9	3·45 (0·48)
12	7·7	6·3	5·9	5·9	5·95	5·3	6·17 (0·33)
16	2·23	2·3	1·9	1·35	1·65	1·55	1·83 (0·15)
20	0·82	1·0	0·9	0·6	0·58	0·61	0·75 (0·06)
24	0·35	0·54	0·56	0·3	0·19	0·31	0·37 (0·05)

TABLE 2. Individual and group mean ± s.e. mean plasma concentrations of erythromycin base after a 12-hr i.v. infusion of 2 g of erythromycin lactobionate (Erythrocin i.v.). Duplicate samples analysed by manufacturer's laboratories

	Plasma concentration of erythromycin base (μg/ml)						
Subject	1	2	3	4	5	6	Group mean (± s.e. mean)
Time (hr)							
0·25	1·75	0·92	0·07	0·62	1·07	<0·025	0·74 (0·26)
0·5	2·17	2·50	1·26	0·73	1·77	2·85	1·88 (0·31)
0·75	2·65	3·05	>4·0	0·66	2·08	1·56	>2·33 (0·47)
1	>4·0	>4·0	1·19	0·45	>4·0	3·57	>2·86 (0·65)
1·5	1·88	1·20	1·55	3·15	3·05	1·01	1·97 (0·37)
2	1·25	1·15	1·86	1·75	2·77	2·72	1·91 (0·28)
3	3·94	3·05	2·51	2·85	3·58	>4·0	3·32 (0·24)
4	>4·0	>4·0	3·97	>4·0	>4·0	3·45	>3·90 (0·09)
6	>4·0	>4·0	>4·0	2·36	3·70	3·25	>3·55 (0·26)
8	>4·0	>4·0	2·90	1·54	1·30	2·08	>2·63 (0·48)
12	>4·0	>4·0	>4·0	>4·0	>4·0	2·40	>3·73 (0·26)
16	1·62	2·35	1·55	1·07	1·72	1·38	1·61 (0·16)
20	0·88	1·09	0·92	0·63	0·69	0·58	0·79 (0·06)
24	0·63	0·53	0·61	0·36	0·30	0·45	0·48 (0·04)

followed at 4 hr by a secondary peak, the mean ± s.e. mean value for which was 7·21 ± 0·93 μg/ml. This pattern was repeated in most of the individual plasma concentration/time curves.

Discussion

Parenteral chemotherapy – route and mode of administration

Intravenous antibiotics are increasingly being used both for the treatment of septicaemia (Parsons *et al.*, 1976a) and for the prophylaxis of infection during elective surgery, for example total hip replacement for osteoarthrosis of the hip (Willis, 1974; Parsons *et al.*, 1978; 1977). This mode of antibiotic administration has made it necessary to evaluate the pharmacokinetics and therapeutic efficacy after intravenous antibiotics, which may be given either as a bolus injection in the sidearm of the infusion tube or as a slow infusion over several hours.

Most manufacturers' literature recommends that stock solutions of parenterally administered antibiotic should initially be prepared in small volumes of sterile water. This should then be well diluted in the appropriate infusion fluid and administered slowly over several hours. This recommendation is designed to reduce the risk of thrombophlebitis and other toxic effects (e.g. haemolysis) that might follow the sudden injection of a highly concentrated antibiotic solution at low pH directly into the systemic circulation. A further hazard of intravenous antibiotics is the risk of drug inactivation by unwanted pharmaceutical interactions with the infusion fluid. Most antibiotics are given in isotonic saline to reduce this hazard.

The current recommendation of the manufacturers of erythromycin lactobionate is that a dose of 300–600 mg of this drug should be given as a 1% solution over 6–8 hr. This dose should be doubled in severe infections. Thus an objective pharmacokinetic evaluation of the therapeutic efficacy of this mode of administration is now required.

Microbiological assay

In view of the authors' previous experience with duplicate assay of coded samples of erythromycin and rifampicin at their own and the manufacturer's laboratories (Paddock *et al.*, 1976), they decided to cross-check the results of small plate microbiological assay of the plasma samples obtained by their own laboratory with those obtained by the manufacturer's laboratory. Duplicate coded plasma samples that were taken from each subject during the study were given to the technician performing the assay at the manufacturer's laboratory who did not know the therapeutic regime, the time at which the sample was taken or the likely concentration that might be found in each plasma sample. The close correlation between the results obtained in the two laboratories confirms the accuracy of microbiological assay as a method of drug analysis. In experienced hands it is a consistently reproducible and reliable and accurate technique.

Results of the haematological and biochemical tests of bone marrow, hepatic and renal function

The blood taken 24 hours after starting the infusions, which was sent to the routine laboratories for standard tests of haematological and biochemical evidence of bone marrow, hepatic and renal disease, showed no evidence of any change in the function of

these organs. All the subjects complained of a salty taste in their mouth after the infusions had been given. This led to vomiting in two subjects after the end of the study. This might have been due to a relative salt overload from sudden infusion of 2 litres of saline into the systemic circulation of healthy subjects who had fasted completely from both fluids and food for 12 hr before the study began. It may be wise to restrict the total fluid intake in well hydrated subjects to one litre of intravenous normal saline when giving a slow intravenous infusion of erythromycin.

Therapeutic efficacy of a twelve-hr intravenous infusion of erythromycin lactobionate

The peak and mean ± s.e. mean plasma concentration of erythromycin base were above the minimal inhibitory concentrations (MIC) of most of the organisms in Table 3 from 30 min until 16 hr after starting the infusions.

TABLE 3. Minimal inhibitory concentrations (MIC) of erythromycin against pathogens

Organism	m.i.c. (μg/ml)
Staphylococcus aureus, penicillin-sensitive	0·12
Staph. aureus, penicillin-resistant	0·12
Streptococcus pyogenes	0·03
Strep. faecalis	0·5
Strep. pneumoniae	0·03
Clostridium welchii	2
Bacillus anthracis	0·25
Listeria monocytogenes	0·25
Neisseria gonorrhoeae	0·06
N. meningitidis	0·5
Haemophilus influenzae	3·2
Bordetella pertussis	0·06
Salmonella sp.	64 – R
Shigella sp.	8 – R
Brucella abortus	32
Pasteurella septica	1
Bacteroides fragilis	1–4

R = resistant

Conclusion

A 12-hr intravenous infusion of erythromycin lactobionate 2·0 g in normal saline produces therapeutic plasma levels which are maintained for at least 8 hr after stopping the infusion. This empirical regime would provide therapeutically effective plasma concentrations of erythromycin base for all infections that are caused by sensitive organisms, whilst the infusion was running. Satisfactory plasma levels are maintained for up to 12 hr. This suggests that this mode of administration is satisfactory.

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