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# Should Erythromycin Dose be Altered in Haemodialysis Patients?

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**Summary.** Erythromycin kinetics were studied in 17 patients with end stage renal failure treated with maintenance haemodialysis and 9 normal volunteers to discover if dialysis patients needed a modified dose. The elimination half life in dialysis patients (on dialysis days) was similar to that reported in normal subjects. Only small amounts of drug appeared in the dialysate, no patient loosing more than 9 mg in one dialysis. Both patients and volunteers had similar plasma concentrations 8 h after the end of a 5-day course. Protein-binding did not change significantly during dialysis and was similar to that reported in normal subjects. We conclude that dialysis patients requiring 1.5 g of erythromycin stearate daily or less can be given normal doses.

**Key words:** erythromycin, haemodialysis; dosage adjustment, pharmacokinetics, protein-binding

The use of erythromycin in renal dialysis patients seems to be increasing but there is little data about the need for dose adjustment. Although erythromycin is eliminated mainly by hepatic metabolism, renal failure is known to alter dose requirements of several other drugs eliminated this way (Reidenberg et al. 1969). Published data on erythromycin is derived from only four patients; three were studied on non-dialysis days (Welling and Craig 1978); another study of one patient who also had hepatic failure (Vaziri et al. 1980) collected limited information during a single dialysis but showed the drug was dialysable. A further study showed that erythromycin kinetics were similar on dialysis and non-dialysis days but gave no data (Davidman et al. 1966). Ototoxicity has been a problem in some patients with renal failure treated with haemodialysis (Kanfer et al. 1980). Because of increasing usage, potential toxicity and relative lack of pharmacokinetic data, we designed this study to discover if dose adjustments were needed for dialysis patients.

## Material and Methods

19 patients and 13 normal volunteers entered the study, two patients were withdrawn because of technical problems with the dialysis. 4 normal volunteers failed to complete the study because of abdominal pain, two also had diarrhoea. No subject had a history of erythromycin allergy or liver disease and none had received any antimicrobial for 2 weeks prior to the study. Informed consent was obtained from each after a full discussion of the experimental procedures and possible adverse drug reactions. The study was conducted with the approval of the appropriate ethics committees. Two of the patients (no. 5 and 10) were receiving erythromycin for therapeutic purposes, the remainder were volunteers.

### *Patients*

The 17 patients (15 males and 2 females) who completed the study were undergoing chronic intermittent haemodialysis for end-stage renal failure (12–18 h weekly), were aged 19 to 53 years and weighed 39 to 84 kg. Four of these patients (Group 1) were given a single 500 mg tablet of erythromycin stearate (Abbott) with their breakfast at least 2.5 h prior to dialysis. Six patients (Group 2) were given 500 mg erythromycin stearate 8 hourly for 5 days, with the last dose taken at least 2.5 h prior to the final dialysis of the course during which blood samples were taken. These 10 patients were dialysed with a single pass dialysate deliv-

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**Table 1.** Individual and mean elimination half-life values (hours) in haemodialysis patients (Groups 1 and 2) on dialysis days derived using one compartment and two compartment model kinetics. The mean elimination $t_{½}$ in normal volunteers from published studies is shown for comparison (Patients 3 and 6 are the same person)

| | One compartment model kinetics | | Two compartment model kinetics | | |
|---|---|---|---|---|---|
| | $t_{½}(\alpha)$ *Single dose* | $t_{½}(\alpha)$ *Multiple dose* | $t_{½}(\beta)$ *Single dose* | $t_{½}(\beta)$ *Multiple dose* | *Treatment* |
| *Dialysis patients* | | | | | |
| Patient No. | | | | | |
| 1 | 6.62 | | – | | Oral stearate 500 mg stat Group 1 |
| 2 | 1.60 | | 2.66 | | |
| 3 | 1.62 | | – | | |
| 4 | 1.57 | | 2.90 | | |
| 5 | | 7.50 | | – | Oral stearate 500 mg/8 h/5 days Group 2 |
| 6 | | 2.25 | | 3.81 | |
| 7 | | 1.80 | | 2.11 | |
| 8 | | 1.62 | | 3.68 | |
| 9 | | 1.56 | | – | |
| 10 | | 4.95 | | 42.27 | |
| | mean (SD) 2.12[a] (1.17) | | 3.03[b] (0.71) | | |

| *Normal volunteers* (published data) Reference | Mean $t_{½}(\alpha)$ (SD) *Single dose* | Mean $t_{½}(\alpha)$ (SD) *Multiple dose* | | |
|---|---|---|---|---|
| (Henry et al. 1980) | 1.18(0.46) | | Oral stearate 500 mg | $n = 6$ |
| (Huin et al. 1980) | 1.88(0.55) | | Oral ethylsuccinate 1 g | $n = 10$ |
| (Welling et al. (1979) | 2.00(0.40) | 2.00(0.40) | Oral stearate 500 mg | $n = 10$, |
| | | | 500 mg/8 h/3 days | $n = 10$ |
| (Knothe et al. 1977) | | 2.10 | Oral stearate 500 mg/8 h/3 days | $n = 12$ |
| (Rutland et al. 1979) | 1.33(0.31) | | Oral stearate 500 mg | $n = 16$ |
| (Austin et al. 1980) | 2.40(0.40) | | i.v. lactobionate 500 mg | $n = 4$ |

[a] Omitting values from patients 1 and 5
[b] Omitting value from patient 10

ery system, using Meltec Kiil (1 $m^2$) with standard cuprofane membrane dialyzer (5 patients), Tri Ex 1 (1 $m^2$) Hollow Fiber dialyzer (3 patients), Nephross Allegro Hollow Fiber Cuprofane (1 patient) and Asahi AM 10 (1 $m^2$) (1 patient). Blood flow was maintained at a constant rate of 200 $ml \cdot min^{-1}$ and dialysate flow at 500 $ml \cdot min^{-1}$. Anticoagulation was accomplished by systemic heparinization. In these 10 patients specimens of arterial blood were obtained from the arterial dialysis line, immediately before dialysis and during dialysis at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7 and 8 h. At the same times dialysate samples were collected from the outflow line. The plasma and dialysate specimens were stored, frozen at −20 °C until assayed.

A further 7 patients (Group 3) were given 500 mg erythromycin stearate 8 hourly for 5 days, but only a single blood sample was collected from each 8 h after the last dose. These patients were dialysed with a single pass dialysate delivery system using a Gambro (1 $m^2$) dialyzer (4 patients) and a Multi-point (1 $m^2$) dialyzer (3 patients), both dialyzers using cuprofane membranes.

### *Normal Volunteers*

The 9 normal volunteers (6 males and 3 females) who completed the study were aged 21 to 38 years and weighed 50 to 75 kg. They were given 500 mg erythromycin stearate 8 hourly for 5 days and single blood samples were collected from each 8 h after the last dose.

### *Analytical Methods*

The erythromycin concentration in the plasma and dialysate samples was determined by a modification of the agar-well diffusion methods [6, 14, 15] using Sarcina lutea NCTC 8340 as test organism and Difco antibiotic medium No. 11. 6 standards and 12 samples were assayed in duplicate on each plate. Stand-

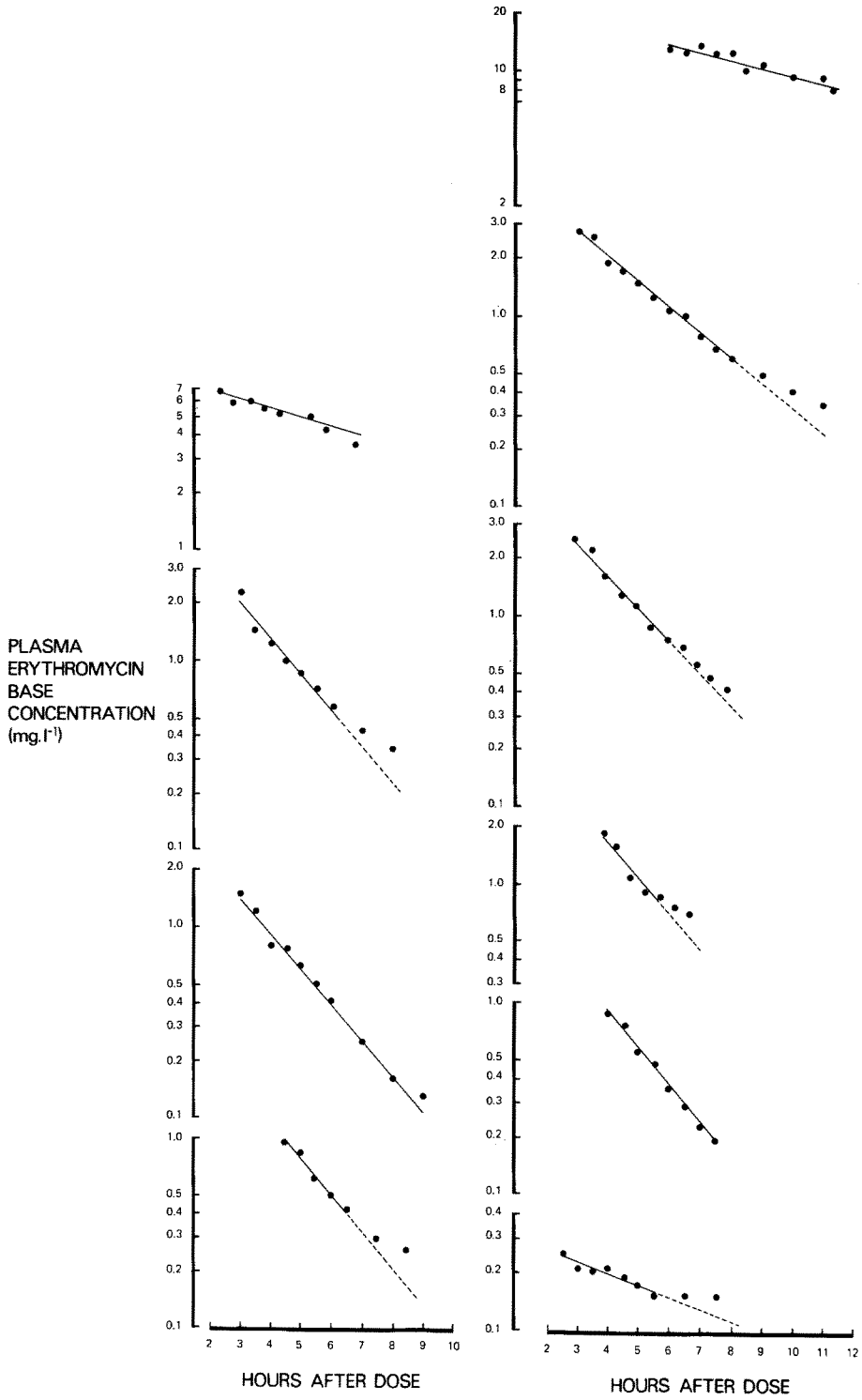


**Fig. 1.** Semilogarithmic plot of plasma erythromycin concentrations against time during haemodialysis for individual patients receiving single oral dose, Group 1 (left column, Patients 1, 2, 3, 4) and 5 day regimen, Group 2 (right column, Patients 5, 6, 7, 8, 9, 10). (Dotted line represents the hypothetical continuation of the solid line. The patients with dotted lines were used to calculate elimination half-life ($\beta$-phase) as well as ($\alpha$-phase)

ards were prepared in pooled human plasma and dialysate fluid. Calibration graphs were linear between 0.05 and 4 μg/ml for plasma and between 0.025 and 1 μg/ml for dialysate. Within assay and between assay coefficients of variation were less than 12% for both specimens.

The protein binding assay was performed by equilibrium dialysis against isotonic phosphate-buffered saline pH 7.3 (Dulbecco 'A' Oxoid Limited, Basingstoke, England) across a 11.5 μm cuprophane membrane in 1 ml acrylic cell. These cells were rotated 45 times $min^{-1}$ at 37 °C for 6 h. Erythromycin concentra-

tions were then measured on both sides of the membrane. The coefficients of variation for percentage within and between assays was less than 3% and less than 13% respectively.

*Pharmacokinetic Analysis*

The elimination half life was calculated from the slope of the log plasma concentration versus time plot using the method of least squares. In those subjects who showed a single exponential decay curve all the declining points were used but in the case of subjects with biexponential decay curves only points before 5.5 h were used.

The amount of drug removed by the dialyzers was calculated as the product of the dialysate concentration, dialysate flow-rate and time. Where no drug was detectable in the dialysate the minimum concentration detectable by our assay (0.02 μg/ml) was used for all time points. This gives a maximum value for the amount removed during one dialysis.

Statistical Analysis was performed using Student's *t*-test for all comparisons. All tests were 2-tailed with a critical value of $\alpha = 0.05$.

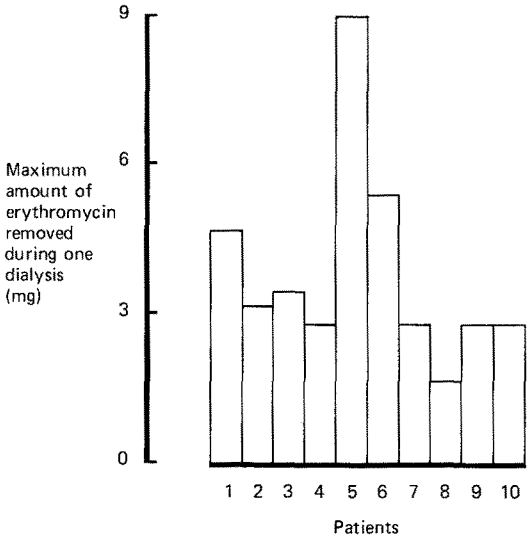


**Fig. 2.** Histogram of the amount of erythromycin recovered in the dialysate during the dialysis calculated from the estimated concentration and the flow rate of each patient

## Results

Individual erythromycin plasma concentration values measured in Groups 1 and 2 of patients during haemodialysis are illustrated in Fig. 1. Elimination half-life values for dialysis patients calculated using one compartment and two compartment model kinetics (Groups 1 and 2) are shown in the upper part of Table 1.

A two compartment analysis was applied to patients 2, 4, 6, 7, 8 and 10 whose plasma profile seemed to differ markedly from the others. The lower part of Table 1 presents the published data on elimination half-life values in normal volunteer studies after single or multiple dose treatments.

The calculated amount of erythromycin lost by each patient during a single dialysis (Groups 1 and 2) is shown in Fig. 2. The greatest amount was 9 mg

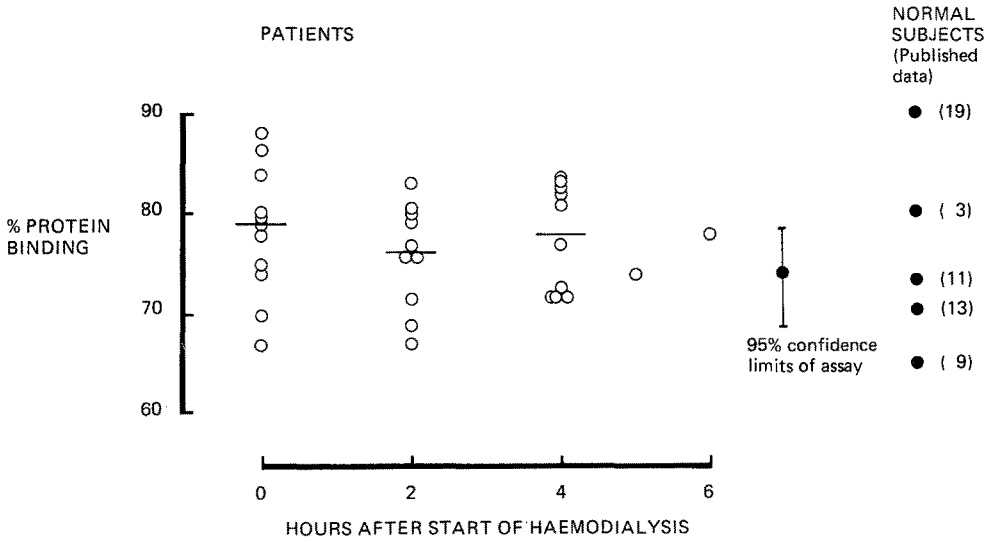


**Fig. 3.** Percentage of protein binding 0, 2, 4 and 6 h after start of haemodialysis in dialysis patients, Groups 1 and 2 (○) and published data in normal subjects (●). No difference was found between 0 time and 2 or 4 h and between 2 and 4 h

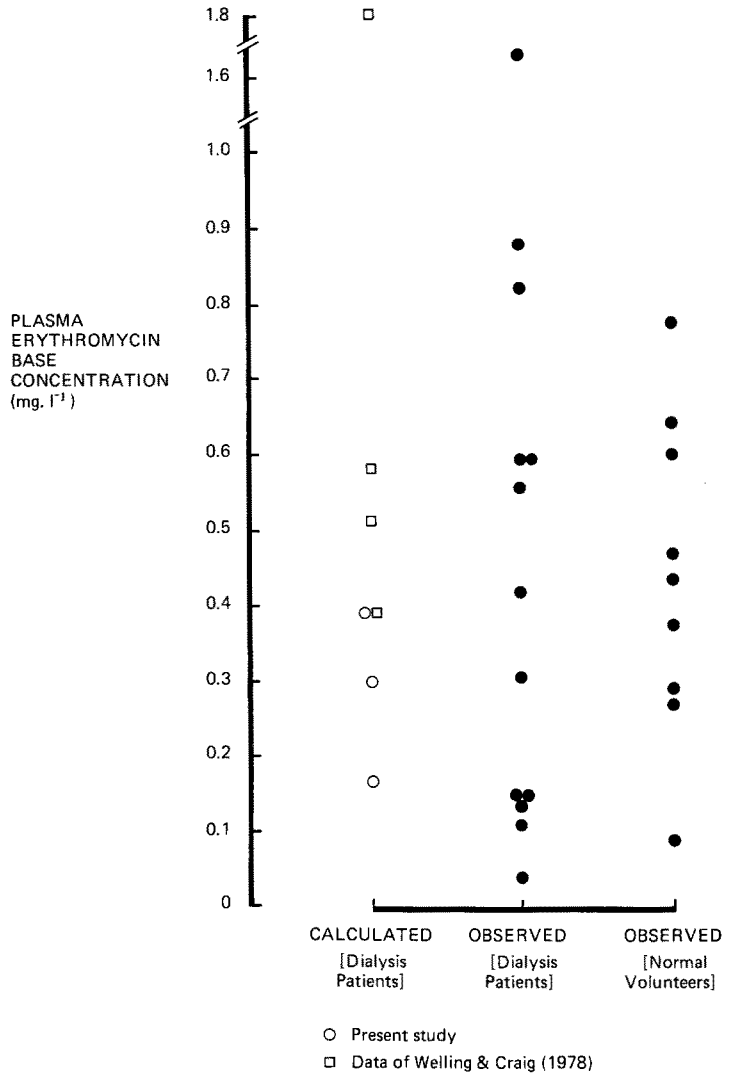


**Fig. 4.** Observed steady state 8 hr level after the final dose of 5 day oral course of erythromycin in dialysis patients Groups 2 and 3 ($n = 13$) and normal volunteers ($n = 9$) (●), in contrast with calculated steady state 8 h level simulating either one compartment model (Patients 3 and 4) or two compartment model (Patient 2) from present study (○) and four dialysis patients (on no dialysis days) from published data (□)

which is only 0.02% of the dose. The individual and median percentage values of protein binding before, 2, 4 and 6 h after start of haemodialysis in Groups 1 and 2 are presented in Fig. 3, and compared with the mean values from published data in normal subjects. None of the differences are significant.

Plasma concentrations 8 h after the 15th dose (minimum steady state concentrations) for dialysis patients Groups 2 and 3 and normal volunteers are shown in Fig. 4.

There were no significant differences between the calculated and the observed levels in dialysis patients or between observed values in the normal subjects and the patients.

## Discussion

The clearance of erythromycin from the plasma of dialysis patients is similar on dialysis and non-dialysis days (Davidman et al. 1966). We have shown that, with a few exceptions, the elimination half-lives in our dialysis patients were similar to those reported for subjects with normal renal function. Although several of the patients' data fitted a one-compartment model there was a strong suggestion that others fitted a two-compartment model better. This supports previous work indicating that the distribution of I.V. erythromycin lactobionate was multicompartment (Welling and Craig 1978; Huin et al. 1980). Although statements that erythromycin is not dialysable (Sande and Mandell 1980) are clearly not correct (Vaziri et al. 1980) the amount removed by the dialysers used in this study was quite unimportant. Because of the suggestion that erythromycin kinetics change during multiple dosing we studied the levels 8 h after the final dose of a 5 day course. Both patients and normal volunteers had similar levels which were within the range that could have been predicted from a single dose

study. Furthermore the free erythromycin concentrations, which presumably mediate the biological effects of the drug, were also similar.

There was wide variation in the observed plasma concentrations for which, as yet, we have no explanation. However, even the lowest concentrations we observed exceed the minimum inhibitory concentrations of most of the sensitive pathogenic microorganisms. These results suggest that, providing the ratio between plasma erythromycin concentration and the tissue concentration is not disturbed in dialysis patients they may be given the same dose as non dialysis patients requiring 1.5 g erythromycin stearate daily or less.

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