Europ. J. clin. Pharmacol. 14, 435–439 (1978)

European Journal of
Clinical Pharmacology
© by Springer-Verlag 1978

Serum and Plasma Concentrations of Clindamycin Following a Single Intramuscular Injection of Clindamycin Phosphate in Maintenance Haemodialysis Patients and Normal Subjects

A. P. Roberts[1], J. B. Eastwood[1], P. E. Gower[1], C. M. Fenton[2], and J. R. Curtis[1]

[1]Department of Medicine, Charing Cross Hospital Medical School, London, U. K. and [2]Upjohn Ltd., U. K.

Summary. Serum levels of clindamycin bioactivity and total clindamycin were studied after single intramuscular injections of 300 mg of clindamycin phosphate in a group of 6 normal subjects and a group of 6 maintenance haemodialysis patients. The patients were studied during a non-dialysis period and then again during haemodialysis. Peak levels tended to be higher and elimination half-lives shorter in the patients than in the normal subjects. Possible reasons for these differences are discussed. There was no evidence that haemodialysis per se influenced the pharmacokinetics of clindamycin phosphate. The proportion of unhydrolysed clindamycin phosphate tended to be higher in the renal failure patients and the reason for this is not apparent. Little, if any, dosage modification is necessary in severe renal failure although there is probably little point in exceeding a dose of 300 mg intramuscularly every 8 h even in severe infections in patients with severe renal failure. The higher peak levels in patients with advanced renal failure indicate the need for further studies with repeated doses.

Key words: Intramuscular Clindamycin Phosphate, serum levels, half-lives, renal Failure, haemodialysis, man.

Clindamycin is a valuable antibacterial drug active against a variety of Gram-positive organisms including certain anaerobes such as Bacteroides. Eastwood and Gower (1974) found that blood levels were not affected by haemodialysis following single doses of oral clindamycin in patients with chronic renal failure and recommended normal adult doses. The introduction of parenteral clindamycin allowed us to study blood levels after single intramuscular injections of clindamycin phosphate in normal subjects and in patients undergoing maintenance haemodialysis.

Material and Methods

A single dose of 300 mg of clindamycin phosphate was given by intramuscular injection to 6 patients with terminal renal failure undergoing maintenance haemodialysis and blood levels were measured at intervals after the dose. The nature of the experiment was fully explained to the patients and their consent obtained. The endogenous creatinine clearances of the 6 patients at the start of maintenance haemodialysis was less than 5 ml per min and they were routinely haemodialysed for 6–10 h twice a week. Each of the 6 patients was studied on two separate occasions, once during a non-dialysis interval and again about one week later during haemodialysis using a 1.05 m^2 Meltec Maxi Multipoint dialyser with cuprophane membrane PT 150 in a single pass system. The intramuscular injections were given into the lateral part of the upper thigh in the patients. Blood was collected just before the drug was given and then at 0.5, 1, 2, 4, 6, 8 and 10 h after administration of the drug during a non-dialysis period. On another occasion, the drug was given 2 h before starting haemodialysis and blood samples were taken just before the administration of the drug and then at 0.5, 1, 2, 4, 6, 8, 10, and 12 h after the administration of the drug and during haemodialysis.

A single dose of 300 mg of clindamycin phosphate was also given by intramuscular injection to 6 normal volunteers and blood samples were taken just before the dose and then at 0.5, 1, 1.5, 2, 4 and 6 h after the administration of the drug. The intramuscular injections in the normal subjects were given into

0031-6970/78/0014/0435/$01.00

Table 1. Details of dialysis patients and normal volunteers

Patient	Age (years)	Weight (kg)	Sex	Diagnosis	Haemoglobin (g per 100 ml)	Alkaline phosphatase (K. A. units per 100 ml)
E. M.	50	55	F	Glomerulonephritis Nephrotic syndrome	6.0	10.0
P. B.	44	64	M	Polycystic kidneys	7.9	3.0
E. C.	35	54.5	M	Glomerulonephritis	10.6	7.0
R. C.	51	61	M	Malignant hypertension	8.8	6.0
C. H.	58	57	F	Chronic pyelonephritis Hypertension	7.8	7.0
W. W.	50	86	M	Hypertension Nephrosclerosis	5.9	7.0
Mean	48	63			7.8	6.6
Range	35–58	54.5–86.0			5.9–10.6	3.0–10.0
Normal subjects						
J. C.	44	81.5	M			
T. R.	39	85.4	M			
J. E.	35	74	M			
M. P.	36	60.5	M			
P. G.	39	67	M			
K. L.	29	75	M			
Mean	34	74				
Range	29–44	60.5–85.4				

the upper outer quadrant of the buttock in 5 subjects and into the deltoid muscle of the remaining normal subject.

All blood samples were collected and centrifuged and the serum (normals and non-dialysis studies) and plasma (dialysis studies) stored at −30 °C until assayed.

Assays for 7(s)chloro-deoxylincomycin (clindamycin) were carried out by a microbiological well-plate agar diffusion method. The assay agar was Pen Assay Seed Agar (Difco) inoculated at 0.2% v/v with Sarcina lutea ATCC9341 (liquid nitrogen frozen suspension). All samples were assayed for 1) clindamycin bioactivity, and 2) total clindamycin; the latter being total bioactivity after hydrolysis of any inactive clindamycin phosphate with an alkaline phosphatase solution. The difference between these two measurements has been termed unhydrolysed clindamycin.

A single compartment pharmacokinetic model was used for the estimation of elimination half-lives. It should be stressed, however, that elimination half life following an intramuscular injection is influenced by continuing release of the drug from the muscle depot. The minimum residual sum of squares estimates were reached using a Simplex optimisation technique carried out on a programmable calculator.

Statistical analysis was undertaken using either Wilcoxon's Sum of Ranks Test for unpaired results or Wilcoxon's Signed Ranks Test for paired results.

Results

Table 1 shows details of the patients undergoing maintenance haemodialysis with age, weight, sex, underlying diagnosis, average haemoglobin concentration and plasma alkaline phosphatase concentration at the time of the investigation. It also shows the age, weight and sex of the normal volunteers. There was no significant difference in weight between the normals and the patients ($P > 0.05$). The normal group were significantly younger than the patient group ($P < 0.05$). All of the patients had a chronic anaemia due to the chronic renal failure with haemoglobin concentrations varying from 5.9–10.6 g per 100 ml. The normals were assumed to have normal haemoglobin concentrations. The plasma alkaline phosphatase concentrations in the patients were all normal at the time of the investigations.

Individual levels of clindamycin bioactivity, total clindamycin and elimination half-lives are shown together with means and standard deviations for the normals (Table 2) and for patients between dialysis (Table 3) and whilst on dialysis (Table 4).

Table 2. Serum clindamycin bioactivity (μg/ml) and total clindamycin (μg/ml) in normal volunteers after a single intramuscular injection of 300 mg clindamycin phosphate. Figures in parentheses are the values for total clindamycin

Clindamycin bioactivity and total clindamycin Normal subjects	Time (hours)						Half-lives (hours)
	0	0.5	1.0	1.5	2.0	4.0	6.0	
J. C.	0(0)	0.9(1.19)	2.14(2.55)	3.09(3.28)	3.20(3.47)	3.28(3.50)	2.78(2.90)	3.05(2.99)
T. R.	0(0)	3.31(3.78)	3.93(4.69)	4.74(5.47)	3.64(4.66)	3.09(3.26)	1.87(1.91)	3.75(3.25)
J. E.	0(0)	2.02(2.50)	3.20(4.07)	3.84(4.88)	4.20(5.10)	4.33(4.69)	3.42(3.56)	5.22(4.26)
M. P.	0(0)	3.97(4.76)	4.45(5.22)	4.79(5.59)	4.84(5.37)	3.59(3.94)	2.59(2.61)	3.92(4.26)
P. G.	0(0)	3.32(3.62)	4.43(4.55)	4.52(4.76)	4.35(4.51)	2.77(2.86)	1.05(1.17)	1.94(2.12)
K. L.	0(0)	6.26(7.46)	7.00(7.72)	6.13(6.75)	5.34(6.46)	3.63(3.86)	2.25(2.38)	3.04(2.93)
Mean:		3.30(3.89)	4.19(4.80)	4.52(5.12)	4.26(4.93)	3.45(3.69)	2.33(2.42)	3.49(3.30)
SD:		1.8(2.1)	1.6(1.7)	1.0(1.1)	0.8(1.0)	0.5(0.63)	0.8(0.82)	

Table 3. Serum clindamycin bioactivity (μg/ml) and total clindamycin (μg/ml) in dialysis patients during a non-dialysis interval and after a single intramuscular injection of 300 mg clindamycin phosphate. Figures in parentheses are the values for total clindamycin

Clindamycin bioactivity and total clindamycin Patients	Time (hours)							Half-live (hours)
	0	0.5	1.0	2.0	4.0	6.0	8.0	10.0	
E. M.	0(0)	2.96(3.52)	3.47(5.60)	4.62(8.33)	4.65(6.78)	3.87(4.96)	1.20(2.39)	–	2.13(1.93)
P. B.	0(0)	5.42(6.56)	6.13(8.35)	7.96(8.71)	6.21(6.59)	4.08(4.56)	2.57(2.96)	1.59(1.80)	3.25(3.69)
E. C.	0(0)	6.31(6.21)	7.37(7.07)	6.48(6.52)	4.66(4.70)	2.50(3.61)	1.45(2.33)	0.77(1.44)	2.89(2.79)
R. C.	0(0)	6.59(6.38)	6.17(8.33)	5.78(7.13)	5.20(4.80)	2.83(2.87)	2.21(1.69)	1.55(0.87)	4.36(4.10)
C. H.	0(0)	4.34(6.42)	7.68(9.43)	8.29(9.27)	5.86(6.54)	3.96(4.37)	2.16(2.29)	1.09(1.28)	2.47(2.83)
W. W.	0(0)	3.94(5.01)	4.78(5.54)	4.02(4.44)	1.95(2.10)	0.95(1.11)	0.58(0.65)	0.57(0.63)	1.89(2.09)
Mean:		4.59(5.68)	5.93(7.39)	6.19(7.40)	4.76(5.25)	3.03(3.58)	1.70(2.05)	1.11(1.20)	2.83(2.90)
SD:		2.1(1.2)	1.6(1.6)	1.7(1.8)	1.5(1.8)	1.2(1.4)	0.8(0.8)	0.5(0.46)	

Table 4. Plasma clindamycin bioactivity (μg/ml) and total clindamycin (μg/ml) in dialysis patients during haemodialysis and after a single intramuscular Injection of 300 mg clindamycin phosphate. Figures in parentheses are the values for total clindamycin. Haemodialysis was started approximately two hours after the injection

Clindamycin bioactivity and total clindamycin	Time (hours)									Half-lives
Patients	0	0.5	1.0	2.0	4.0	6.0	8.0	10.0	12.0	
E. M.	0(0)	4.45(7.46)	8.63(10.06)	9.49(9.77)	5.13(6.96)	3.07(4.39)	2.02(3.15)	–	–	1.80(3.4)
P. B.	0(0)	3.06(4.71)	4.81(5.97)	6.04(6.93)	3.92(4.60)	2.25(2.62)	0.98(1.34)	0.65(0.77)	0.55(0.62)	1.75(2.32)
E. C.	0(0)	9.58(13.61)	11.52(14.26)	11.64(13.26)	7.84(7.78)	5.65(5.37)	3.53(3.86)	1.97(2.48)	–	3.45(3.33)
R. C.	0(0)	3.58(4.81)	4.64(6.07)	5.35(6.77)	4.42(5.45)	1.16(2.76)	1.09(1.36)	0.61(0.84)	0.59(0.62)	1.82(2.31)
C. H.	0(0)	2.58(4.60)	6.71(9.95)	8.16(11.21)	7.42(11.10)	4.80(6.60)	2.81(4.10)	1.51(2.15)	–	2.06(2.01)
W. W.	0(0)	4.68(4.86)	5.72(6.40)	5.77(6.40)	3.20(3.09)	1.37(1.11)	0.60(0.61)	0.59(0.49)	0.51(0.49)	1.97(1.63)
Mean:		4.66(6.68)	7.01(8.79)	7.74(9.06)	5.32(6.50)	3.05(3.81)	1.84(2.40)	1.07(1.35)	0.55(0.58)	2.15(2.50)
SD:		2.5(3.6)	2.6(3.3)	2.5(2.8)	1.9(2.8)	1.8(2.0)	1.2(1.5)	0.6(0.9)	0.04(0.07)	

Table 5. Mean values and ranges for normal subjects, patients during a non-dialysis interval and patients during haemodialysis for the following estimations: peak bioactivity, peak total clindamycin, half-lives of bioactivity and total clindamycin, peak unhydrolysed clindamycin and peak unhydrolysed clindamycin expressed as a percentage of the total clindamycin

	Normal subjects		Patients			
			Non-dialysis interval		During haemodialysis	
	Mean	Range	Mean	Range	Mean	Range
Peak clindamycin bioactivity (μg/ml)	4.78	(3.28–7.00)	6.61	(4.65–8.29)	7.74	(5.35–11.64)
Peak total Clindamycin (μg/ml)	5.36	(3.50–7.72)	7.90	(5.54–9.43)	9.27	(6.4–14.26)
Half-lives Clindamycin bioactivity (hours)	3.49	(1.94–5.22)	2.83	(1.89–4.36)	2.15	(1.79–3.45)
Half-lives Total clindamycin (hours)	3.30	(2.12–4.26)	2.90	(1.93–4.10)	2.50	(1.63–3.40)
Peak unhydrolysed clindamycin (μg/ml)	0.80	(0.30–1.2)	1.82	(0.90–3.71)	2.41	(0.68–4.03)
Peak unhydrolysed clindamycin as a percentage of total clindamycin	16.3	(8.3–21.9)	24.80	(11.5–44.5)	28.7	(10.6–40.4)

Mean values and ranges for peak clindamycin bioactivity, peak total clindamycin, half-lives of clindamycin bioactivity, half-lives of total clindamycin, peak unhydrolysed clindamycin and peak unhydrolysed clindamycin expressed as a percentage of the total clindamycin are shown in Table 5 for normal subjects, patients during a non-dialysis interval and patients during haemodialysis. There is a progressive rise in the mean peak level of clindamycin bioactivity from 4.78 μg/ml in the normals to 6.61 μg/ml in the patients (non-dialysis period) and to 7.74 μg/ml in the patients (during haemodialysis). The difference between the groups only reaches statistical significance when the normals are compared with the patients (during haemodialysis $P < 0.05$). However, the difference between the normals and patients (in a non-dialysis period) only just fails to reach the conventional level of significance.

There is again a progressive rise in the mean peak level of total clindamycin from 5.36 μg/ml in the normals to 7.90 μg/ml in the patients (non-dialysis period) and to 9.27 μg/ml in patients (during haemodialysis). The difference between the normals and patients (non-dialysis period) is significant ($P < 0.05$) and the difference between the normals and patients (during haemodialysis) is also significant ($P < 0.05$).

There is a progressive fall in the mean half life of clindamycin bioactivity from 3.49 h in the normals to 2.83 h in the patients (non-dialysis period) and to 2.15 h in the patients (during haemodialysis). The difference between the groups only reaches significance when the normals are compared with the patients (during haemodialysis; $P \approx 0.05$).

There is also a progressive fall in the mean half-live of total clindamycin from 3.30 h in the normals to 2.90 h in the patients (non-dialysis)period) and to 2.50 h in the patients (during haemodialysis). The differences, however, are not statistically significant.

There is a progressive increase in the mean peak unhydrolysed clindamycin from 0.80 μg/ml in the normals to 1.82 μg/ml in the patients (non-dialysis period) and to 2.41 μg/ml in the patients (during haemodialysis). Only the differences between the normals and the patients (during haemodialysis) achieve statistical significance ($P < 0.05$). The differences in absolute terms might be related to the higher peak levels in the patients. However, as the difference between normals and patients (during haemodialysis) is still significant when expressed as a percentage of the total clindamycin ($P = 0.05$) then that can at best be only a partial explanation.

Discussion and Conclusions

One possible explanation for the differences in peak levels of both clindamycin bioactivity and total clindamycin between normals and patients is the different sites utilised for the intramuscular injections in the two groups. Intramuscular injections into the buttocks are avoided in maintenance haemodialysis patients because of the risk of haematoma formation and sciatic nerve compression as a result of the

heparinisation necessary for haemodialysis. Thus all the patients in this study had their injections into the lateral aspect of the upper thigh whilst all but one of the normals had their injections in the buttock. The remaining normal subject was injected in the deltoid muscle. Wise and Reeves (1975) showed that peak serum levels of cephacetrile were significantly higher after thigh injection than after a buttock injection. There was a similar tendency with gentamicin but in this case the differences were not significant. Serum levels of cephaloridine showed no difference however. It is therefore possible that the higher peak levels in the patients could be accounted for by the more rapid release of the drug from the muscle into the circulation. Although there was no statistically significant difference in body weight between normals and patients the normals were on average 11 kg heavier than the patients who therefore received a bigger dose per kg/body weight. All of the dialysis patients were chronically anaemic and this might be another possible reason for the higher serum levels in the patients. Lummis and Sobota (1970) have reported on the incorporation of clindamycin into red blood cells and found on average 90% of clindamycin in plasma and 10% within the red blood cells. Thus the anaemia in the patients could result theoretically in a slight reduction in the apparent volume of distribution resulting in higher serum and plasma levels.

Clindamycin is normally very strongly protein bound and Gordon et al. (1973) found the serum protein binding of clindamycin to be 94%. It is possible that the protein binding of clindamycin, as with many other drugs, may be reduced in the presence of renal failure and this could be another factor leading to higher levels of clindamycin bioactivity in the patients (Reidenberg, 1977).

The elimination half-lives for both clindamycin bioactivity and total clindamycin were shorter in the patients than in the normals although the differences were only significant when comparing normals with patients during haemodialysis. The shorter half-lives in the patients may reflect a real difference in the elimination rates or alternatively as indicated in the section on Material and Methods may be related to differences in the rate of release of clindamycin from the muscle depot.

When the patients in a non-dialysis period were compared with themselves during haemodialysis, there were no statistically significant differences in any of the parameters calculated including peak levels of bioactivity, peak levels of total clindamycin, elimination half-lives of bioactivity and total clindamycin and peak unhydrolysed clindamycin. Thus haemodialysis per se, at least using the techniques employed during this study, had no obvious effect on the pharmacokinetics of clindamycin phosphate.

The greater proportion of unhydrolysed clindamycin phosphate in the patients is of some interest although differences were only significant when normals were compared with the patients during haemodialysis. The reason for the differences is not known. One could speculate that as ester hydrolysis and other hydrolyses are slowed in renal failure (Reidenberg, 1977) then partial uraemic inhibition of the phosphatase activity, which normally hydrolyses the inactive clindamycin phosphate to bioactive clindamycin, occurs.

In practical terms, the serum levels achieved after a dose of 300 mg clindamycin phosphate intramuscularly in these patients were well above the reported minimum inhibitory concentrations for many aerobic Gram-positive cocci and also the majority of anaerobic bacteria. Indeed there would seem to be no point in exceeding a dose of 300 mg i. m. every 8 h even in severe infections in patients with advanced renal failure. The higher peak levels in the patients indicate the need for further studies using repeated doses to ensure that there is no accumulation of the drug with prolonged treatment. Our data, however, suggests that this is unlikely because the elimination half-lives were shorter in the patients than in the normals.

Acknowledgements. Our thanks are due to Sister Margaret Greatbatch and the Nursing Staff of the Renal Unit, Charing Cross Hospital, who helped with the collection of some of the samples.

References

Eastwood, J. B., Gower, P. E.: A study of the pharmacokinetics of clindamycin in normal subjects and patients with chronic renal failure. Postgrad. Med. J. **50**, 710–712 (1974)

Gordon, R. C., Regamey, C., Kirby, W. M. M.: Serum protein binding of erythromycin, lincomycin and clindamycin. J. Pharm. Sci. **62**, 1074–1077 (1973)

Lummis, W. L., Sobota, J. T.: In vitro human erythrocyte incorporation of an experimental antimalarial compound, U-24, 729A. XIII Int. Cong. of Haematology, Munich, Germany, August 2–8 (1970)

Reidenberg, M. M.: The binding of drugs to plasma proteins and the interpretation of measurements of plasma concentrations of drugs in patients with poor renal function. Am. J. Med. **62**, 466–470 (1977)

Reidenberg, M. M.: The biotransformation of drugs in renal failure. Am. J. Med. **62**, 482–485 (1977)

Wise, R., Reeves, D. S.: Two aspects of the availability of cephalosporins after intramuscular injection. J. Antimicrob. Chemother. **1** (Suppl.), 47–52 (1975)

Received: July 6, 1978
accepted in revised form: October 2, 1978

Dr. J. R. Curtis
Department of Medicine
Charing Cross Hospital Medical School
Fulham Palace Road
London, W6 8RF, UK