BIOPHARMACEUTICS & DRUG DISPOSITION, VOL. 10, 505–512 (1989)

ABSORPTION KINETICS OF TOPICAL CLINDAMYCIN PREPARATIONS

MARK G. ELLER,* RANDALL B. SMITH AND J. PAUL PHILLIPS
Clinical Pharmacokinetics Unit, The Upjohn Company, Kalamazoo, MI 49001

ABSTRACT

Systemic clindamycin absorption was examined in 12 male Caucasians without acne who recieved 1 ml of Cleocin-T® and 1 ml of 1 per cent clindamycin HCl in Vehicle-N® (Neutrogena) applied topically the face every 12 h for 4 days according to a crossover design. In a separate phase clindamycin phosphate was administered by an IV infusion of 300 mg over 10 min. Systemic absorption was much higher with clindamycin in Vehicle-N than with Cleocin-T. Absolute bioavailability calculated from cumulative urinary excretion and serum AUCs were in good agreement and averaged 1·7 per cent and 7·5 per cent for Cleocin-T and clindamycin in Vehicle-N, respectively. Peak serum concentrations ranged from less than 0·5 ng ml^{-1} to 6 ng ml^{-1} for Cleocin-T and from 4–20 ng ml^{-1} for clindamycin in Vehicle-N. Absorption profiles indicated zero order absorption with Cleocin-T. No appreciable systemic accumulation from the repeated topical applications was noted. Systemic exposure to clindamycin from these formulations is minimal.

KEY WORDS Clindamycin Cleocin-T Vehicle-N Percutaneous absorption Bioavailability

INTRODUCTION

Topical clindamycin is widely used and is highly effective in the treatment of acne.[1-12] Since September 1981 clindamycin phosphate has been commercially available in a solution formulation, Cleoncin-T® Topical Solution. However topical clindamycin preparations are still occasionally compounded from clindamycin hydrocholoride capsules by pharmacists at the time of dispensing. Vehicle-N® (Neutrogena) is one vehicle commonly used for this purpose.

Although clindamycin has been detected in extracted comedones of acne patients treated with topical clindamycin,[13,14] and has occasionally been found in the urine of these patients,[2,15,16] little quantitative bioavailability data has been reported. The purpose of this study was to examine the percutaneous absorption of clindamycin from Cleocin-T and clindamycin in Vehicle-N.

*Addressee for correspondence. Present address: Merrell Dow Research Institute, 2110 East Galbraith Road, Cincinnati, OH 45215.

0142–2782/89/050505–08$05.00 *Received 24 June 1988*

EXPERIMENTAL

Subject selection and study design

Twelve healthy adult male Caucasian volunteers, without acne, participated in the study. Subjects ranged in age from 20 to 30 years (mean 25·0 years) and were within 15 per cent of their ideal body weight (mean 70·0 Kg). All subjects underwent a comprehensive physical examination, provided a complete medical history and had laboratory parameters within normal ranges. Subjects did not receive any antibacterial or topical medication for a period of 15 days or any long-acting antibacterial medication for a period of 30 days prior to the start of the study. No other medication or alcoholic beverage was permitted for a period of 7 days prior to the study. Written informed consent was obtained for each participant.

In the first phase each subject received Treatment A, 300 mg clindamycin as clindamycin phosphate by intravenous infusion over 10 min. After a 7-day washout each subject received the following treatments according to a two-way Latin square crossover design:

1. 1 ml Cleocin-T Topical Solution (10 mg ml^{-1} clindamycin, as clindamycin phsophate) applied to the face every 12 h for 4 days.
2. 1 ml clindamycin in Vehicle N (10 mg ml^{-1} clindamycin, as clindamycin HCl) applied to the face every 12 h for 4 days.

For the morning dose subjects were required to shave at least 1 h prior to application. One half hour after shaving, subjects washed their face gently with Purpose ® soap. After allowing the skin to dry thoroughly, 1 ml of medication was applied to the cheeks and forehead (approximately 300 cm^2 surface area). In the evening, subjects washed their face again and after the skin was dry received 1 ml of medication applied over the same area as the morning application. Subjects were only allowed to wash their face at these prescribed times during the study. All medication was quantitatively applied by clinic personnel.

The washout period between topical treatments was 10 days. During treatment days, the subjects were confined to the clinic.

For the IV treatment, blood samples were collected at zero hour, 10 min (end of infusion), 0·5 and 1, 2, 4, 6, 8, and 12 h following the dose. Serum was harvested and frozen until assayed. Quantitative urine collections were made over the 0 to 12 and 12 to 24 h post-medication time intervals. Urine volumes were recorded and aliquots were frozen until assayed.

For the topical treatments, quantitative urine collections were made at 12 h intervals from the time of the initial application until 4 days after the last dose of each phase. Serum samples were obtained at 0, 4, 8, 12, 16, and 24 h on the first and last treatment days.

Analysis

Serum and urine samples were assayed for clindamycin by radioimmunoassay based on the method of Gilbertson *et al.*[17] The antibody was purified by

chromatography after synthesis and titred against the label to develop a calibration curve over the range of 0·5 to 128·0 ng ml^{-1}.

Serum clindamycin concentration data following IV administration was fitted to the two-compartment open model using CSTRIP to provide initial parameter estimates. These estimates and NONLIN84 (Statistical Consultants, Lexington, KY) were used to provide the final estimates for the microconstants characterizing the two-compartment model.

A statistical analysis of serum clindamycin concentrations and clindamycin urinary excretion data following the topical treatments was performed with SAS. Analysis of variance for a crossover design was peformed for treatment effects using a mixed effects model with groups, periods, and treatments as fixed effects and subjects within groups as a random effect.

RESULTS AND DISCUSSION

Intravenous clindamycin

An average 13 per cent of the IV dose was ultimately excreted in the urine as clindamycin. As expected, 90 per cent of the total amount excreted was excreted in the first collection interval, indicating that excretion was essentially complete 12 h after drug administration.

The disposition of clindamycin was well characterized by fitting the post-infusion serum data to the two-compartment open model. In every case the coefficient of determination was greater that 0·94. The mean half-life for distribution was 0·7 h and that for elimination was 2·9 h.

The area under the serum concentration curve (AUC) was calculated by the trapezoidal rule (to the last time point). The AUC was extrapolated to infinite time by adding the value of the last concentration divided by the apparent terminal elimination rate constant (ß). Total clearance (Cl) was calculated by dividing dose by AUC; volume of distribution was calculated by dividing Cl by ß. Mean values for these parameters and microconstants for the two compartment model are summarized in Table 1.

Table 1. Mean (SD) IV clindamycin pharmacokinetic parameter estimates

$AUC_{(0-\infty)}$ μg $ml^{-1}h$	39·7 (8·7)
Clearance ($l\,h^{-1}$)	7.9 (2·0)
V_{area} (l)	33·9 (7·2)
α (h^{-1})	5·83 (0.88)
ß (h^{-1})	0·239 (0·056)
k_{12} (h^{-1})	3·51 (0·46)
k_{21} (h^{-1})	0·73 (0·44)
k_{10} (h^{-1})	2·00 (0·66)

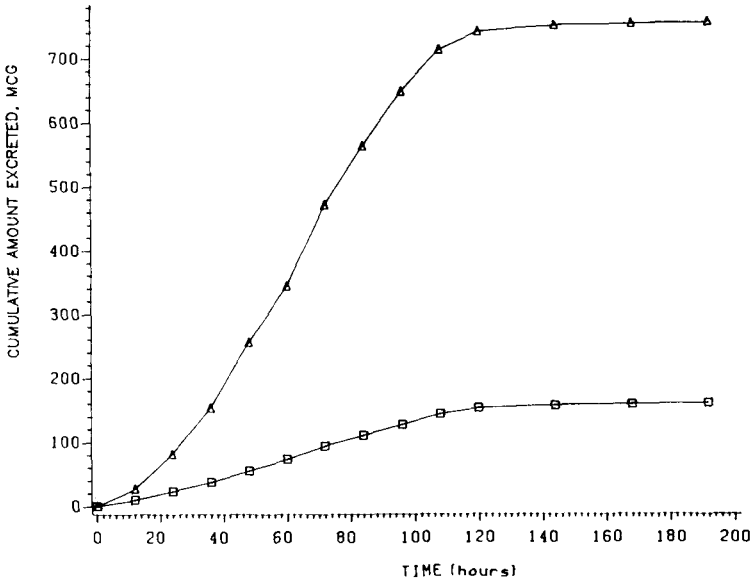

Figure 1. Mean cumulative clindamycin urinary excretion profiles; □—□ treatment B (Cleocin-T), Δ—Δ treatment C (Vehicle-N)

Topical treatments

Detectable levels of clindamycin were found in the urine of all subjects for both treatments. The mean cumulative amount of clindamycin excreted through the end of each collection interval (Xu_T) is compared for the topical treatments in Figure 1. The analysis of variance revealed that the cumulative amount excreted was significantly ($p<0{\cdot}05$) greater for Treatment C at each collection interval.

By comparing the plateau values for cumulative urinary excretion from the topical treatments with those from IV administration, the fraction of dose absorbed from topical application can be calculated:

$$F = \frac{(Xu_\infty / D)\ \text{Topical}}{(Xu_\infty / D)\ \text{IV}} \tag{1}$$

The mean bioavailability of Treatments B and C as calculated from equation (1) were 1·7 per cent and 7·5 per cent, respectively.

Detectable levels of clindamycin were found in the serum of all subjects receiving Treatment C at all (non-zero) sampling times. Clindamycin was not detected at any time point for two of the subjects when Treatment B was administered. For a third subject clindamycin was below detectable levels except at one sampling time.

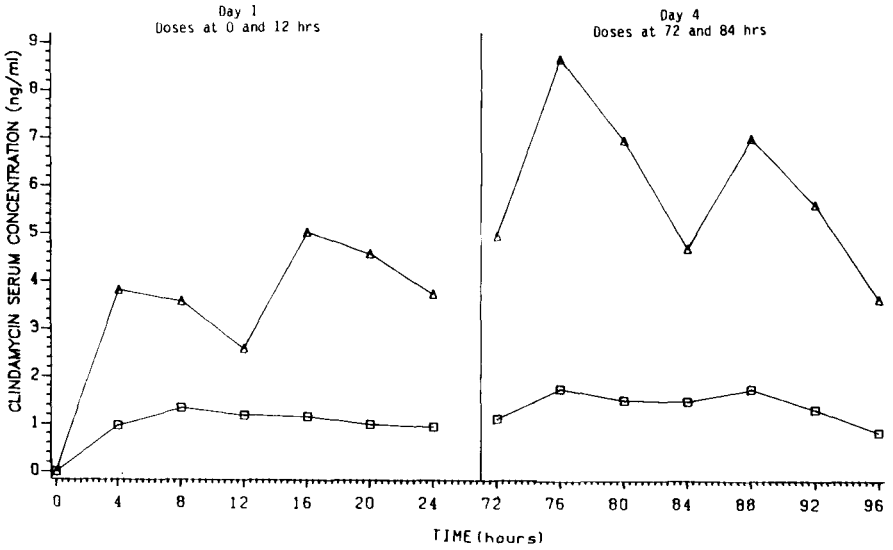

Figure 2. Mean clindamycin serum concentrations; □—□ treatment B (Cleocin-T) Δ—Δ treatment C (Vehicle-N)

Mean serum clindamycin profiles for the topical treatments are given in Figure 2 and mean bioavailability parameters are listed in Table 2. The differences in serum clindamycin levels confirms the differences in bioavailability calculated from urinary excretion data. Analysis of variance showed that serum levels for Treatment C were significantly ($p<0{\cdot}05$) higher than those for Treatment B at all time points. C_{ss} and C_{max} values were also statistically significantly higher with Treatment C. This analysis was repeated assuming that those subjects who had no detectable serum clindamycin on Treatment B actually had levels at the quantitation limit of the assay, 0·5 ng ml^{-1}. The conclusion reached was the same: clindamycin levels are significantly higher with Treatment C.

Bioavailability can be calculated from the AUC during a steady-state dosing interval by equation (2).

$$F = \frac{(AUC_{ss}/D)_{\text{topical}}}{(AUC/D)_{IV}} \tag{2}$$

Bioavailability calculated from equation (2) averaged 6·7 per cent for Treatment C, in good agreement with the value of 7·5 per cent calculated from the urinary excretion data and equation (1).

The fact that some subjects had less than quantifiable serum clindamycin levels on Treatment B precludes an exact statistical comparison of mean

Table 2. Mean (SD) C_{ss} and C_{max} clindamycin serum concentration data on days 1 and 4

	Treatment	
	B*	C
Day 1		
First dose		
C_{ss} (ng ml^{-1})	1·0 (1·2)	2·9 (1·6)
C_{max} (ng ml^{-1})	1·4 (1·6)	4·1 (1·9)
T_{max} (h)	9·0 (1·9)	5·5 (1·9)
Second dose		
C_{ss} (ng ml^{-1})	1·0 (1·3)	4·2 (2·6)
C_{max} (ng ml^{-1})	1·5 (1·7)	5·4 (3·3)
T_{max} (h)	5·8 (4·7)	5·5 (2·6)
Day 4		
First dose		
C_{ss} (ng ml^{-1})	1·5 (1·3)	6·8 (4·1)
C_{max} (ng ml^{-1})	2·1 (1·5)	9·0 (5·3)
T_{max} (h)	7·8 (3·2)	5·0 (2·5)
Second Dose		
C_{ss} (ng ml^{-1})	0·9 (1·0)	4·7 (3·0)
C_{max} (ng ml^{-1})	1·2 (1·3)	6·2 (2·3)
T_{max} (h)	7·4 (2·9)	6·0 (3·3)

*Includes concentration values of 0·0 for three subjects with levels below quantification.

bioavailability. However, much can be learned about the absorption of clindamycin from this treatment by examining the data for those individuals who achieved measurable levels.

The shapes of the individual serum clindamycin profiles are reflected in the mean profile given in Figure 2. Individual profiles for Treatment B were relatively flat, suggesting absorption by a zero order process. No accumulation of drug in the serum was detected over the course of the study. Individual profiles for Treatment C appeared more characteristic of first-order absorption or a burst effect. C_{ss} and C_{max} levels were somewhat higher on day 4 than on day 1. However, terminal blood levels fell rapidly and cumulative urinary excretion was within 90 per cent of its final value 12 h after the last dose. These observations are consistent with the short-half life of clindamycin and indicate that the skin does not provide any substantial reservoir for clindamycin accumulation.

To gain a more thorough understanding of the absorption process, the cumulative amounts of clindamycin absorbed through each sampling time in the first dosing interval were calculated. Consistent with the IV data, a two-compartment open model for the disposition of clindamycin was assumed.

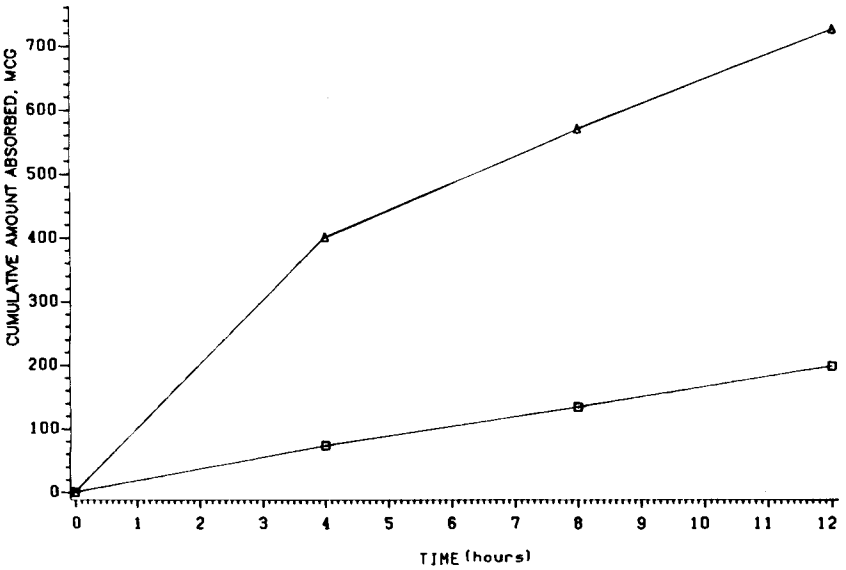

Figure 3. First dose mean cumulative clindamycin absorption profiles; □—□ treatment B (Cleocin-T) Δ—Δ treatment C (Vehicle-N)

Wagner's exact version of the Loo-Riegelman equation[18,19] was used to calculate the cumulative amount of clindamycin absorbed at each sampling time. Mean results for Treatment B do not really reflect the treatment mean since the amount absorbed could not be calculated for three subjects because of low clindamycin serum levels. Mean absorption data for the remaining subjects plotted in Figure 3 indicated zero order absorption of clindamycin with Treatment B. Regression of cumulative amount absorbed against time gave r^2 values greater than 0·94 for each subject. The mean zero order rate constant for these subjects was 16 $\mu g\ h^{-1}$. Absorption could not clearly be characterized as either zero or first order for Treatment C. Instead, there seemed to be a burst followed by near zero order absorption.

These results indicate that systemic absorption from these topical clindamycin preparations is minimal, but is highly dependent on the vehicle used. Cleocin-T is a hydroalcoholic vehicle containing isopropyl alcohol (50 per cent), propylene glycol, and water. Vehicle-N is also a hydroalcoholic vehicle containing propylene glycol. It does, however, contain an unspecified amount of surfactant, Brij 30 (Laureth 4), which may contribute to the enhanced penetration of clindamycin. There is some evidence that similar nonionic surfactants are capable of enhancing percutaneous absorption.[20,21] Alternatively, the differences in absorption could result from differences in the permeability of the two forms of clindamycin used, clindamycin phosphate and clindamycin hydrochloride. This seems unlikely, however, since studies examining clindamycin levels in acne

comedones indicate that clindamycin phosphate is hydrolysed on the skin surface to free clindamycin.[14]

An additional observation which suggests that the differences are due to a vehicle effect rather than differences in the form of clindamycin is that the bioavailability results parallel the *in-vitro* penetration data reported by Franz for clindamycin hydrochloride.[22] He reported 7 per cent net penetration in 24 h with Vehicle-N compared to 1–3 per cent penetration with other simple hydroalcoholic vehicles containing no surfactant.

Since Cleocin-T is effective while limiting systemic bioavailability, it would appear to be superior to extemporaneously compounded topical clindamycin.

REFERENCES

1. W. Resh and R. B. Stoughton, *Arch. Dermatol.*, **112**, 182 (1976)
2. R. B. Stoughton and W. Resh, *Cutis,* **17**, 551 (1976).
3. R. B. Stoughton, *Arch. Dermatol.*, **115**, 486 (1979).
4. J. G. Guin, *Int. J. Dermatol.*, **18**, 164 (1979).
5. R. S. Padilla, J. M. McCabe and L. E. Becker, *Int. J. Dermatol.*, **20**, 445 (1981).
6. L. E. Becker, P. R. Bergstresser, D. A. Whiting *et al.*, *Arch. Dermatol.*, **117**, 482 (1981).
7. M. W. McKenzie, D. C. Beck and N. G. Popovich, *Arch. Dermatol.*, **117**, 630 (1981).
8. D. R. Thomas, S. R. Raimer and E. B. Smith, *Cutis,* **29**, 624 (1982).
9. R. L. Rietschel and S. H. Duncan, *Int. J. Dermatol.*, **22**, 41 (1983).
10. S. B. Tucker, R. Tausend, R. Cochran and S. A. Flannigan, *Brit. J. Dermatol.*, **110**, 487 (1984).
11. A. Katsambas, A. A. Towarky and J. Stratigos, *Brit. J. Dermatol.*, **116**, 387 (1987).
12. J. J. Leyden, A. R. Shalita, G. D. Saatjian and J. Sefton, *J. Am. Acad. Dermatol.*, **16**, 822 (1987).
13. J. D. Guin, R. Reynolds and P. L. Gielerak, *Am. Acad. Dermatol.*, **3**, 153 (1980).
14. J. D. Guin and W. L. Lummis, *J. Am. Acad. Dermatol.*, **7**, 265 (1982).
15. D. A. Varon, *Arch. Dermatol*, **114**, 798 (1978).
16. M. Barza, J. A. Goldstein, A. Kane *et al.*, *J. Am. Acad. Dermatol.* **7**, 208 (1982).
17. T. J. Gilbertson and R. P. Stryd, *Clin. Chem.,* **22**, 828 (1976).
18. J. G. Wagner, *J. Pharm. Sci.*, **72**, 838 (1983).
19. J. H. Proost, *J. Pharm. Sci.*, **74**, 793 (1985).
20. D. L. Sekura and J. Scala, in *Advances in Biology of the Skin*, vol. 12, W. Montaga, E. J. Van Scott and R. B. Stoughton (Eds), Appleton-Century-Crofts, New York, 257 (1972).
21. Z. T. Chowan and R. Pritchard, *J. Pharm. Sci.*, **67**, 1272 (1978).
22. T. J. Franz, *J. Am. Acad. Dermatol.*, **9**, 66 (1983).