diversity of groups is a severe challenge for the connectivity concept, and the good correlation is testimony to the ability of the method to describe structural characteristics important in this case.

SUMMARY

These studies reveal the contribution that molecular connectivity may make in structure–activity studies. Recent advances made in this method, namely the treatment of heteroatoms (1) and the development of extended connectivity terms (7), make possible the consideration of a wide variety of molecules typically found in drug studies. Most importantly, molecular connectivity, as developed to this point, is capable of revealing good relationships with biological activities (9–13). It is expected that this method of structural analysis will find wide application in structure–activity studies.

Furthermore, the method of molecular connectivity relates molecular structure directly to biological activity. No intermediate physical properties are required for satisfactory correlation. The medicinal chemist's intuition concerning structure and activity can be applied directly and quantitatively to drug studies. The demonstrated ability to handle a variety of heteroatoms greatly strengthens the method of molecular connectivity.

REFERENCES

(1) L. B. Kier and L. H. Hall, *J. Pharm. Sci.*, **65**, 1806 (1976).

(2) L. B. Kier and L. H. Hall, "Molecular Connectivity in Chemistry and Drug Research," Academic, New York, N.Y., 1976.

(3) Y. Ichikawa and T. Yamano, *Biochim. Biophys. Acta*, **147**, 518 (1967).

(4) J. Blanksma and D. Hoegen, *Rec. Trav. Chim.*, **65**, 333 (1946).

(5) L. B. Kier, *J. Pharm. Sci.*, **61**, 1394 (1972).

(6) D. V. Carter, P. T. Charlton, A. H. Fenton, J. R. Housey, and B. Lessel, *J. Pharm. Pharmacol., Suppl.*, **10**, 149T (1958).

(7) L. B. Kier, W. J. Murray, M. Randić, and L. H. Hall, *J. Pharm. Sci.*, **65**, 1226 (1976).

(8) R. L. Metcalf and T. R. Fukuto, *J. Econ. Entomol.*, **55**, 340 (1962).

(9) L. B. Kier, L. H. Hall, W. J. Murray, and M. Randić, *J. Pharm. Sci.*, **64**, 1971 (1975).

(10) L. H. Hall, L. B. Kier, and W. J. Murray, *ibid.*, **64**, 1974 (1975).

(11) W. J. Murray, L. H. Hall, and L. B. Kier, *ibid.*, **64**, 1978 (1975).

(12) L. B. Kier, W. J. Murray, and L. H. Hall, *J. Med. Chem.*, **18**, 1272 (1975).

(13) T. DiPaolo, L. B. Kier, and L. H. Hall, *Mol. Pharmacol.*, **13**, 31 (1977).

ACKNOWLEDGMENTS AND ADDRESSES

Received March 10, 1976, from **Eastern Nazarene College, Quincy, MA 02170,* and the *‡Massachusetts College of Pharmacy, Boston, MA 02115.*

Accepted for publication June 23, 1976.

[x] To whom inquiries should be directed.

Bioavailability of Digoxin–Hydroquinone Complex: A New Oral Digoxin Formulation

FELIX BOCHNER *§, DAVID H. HUFFMAN ‡, DANNY D. SHEN *, and DANIEL L. AZARNOFF *x

Abstract □ A new oral digoxin formulation, a digoxin–hydroquinone complex (99% dissolution at 5 min), was evaluated in 12 healthy human volunteers with reference to bioavailability and extent and time of peak serum digoxin levels. This preparation was compared with a commercial digoxin tablet (26% dissolution at 5 min), digoxin elixir, and a parenteral digoxin solution. Bioavailability was assessed by the 24-hr area under the serum digoxin–time curve and 48-hr digoxin excretion in urine. The bioavailability of the complex was similar to that of the elixir but not statistically different from that of the tablet. The tablet was less bioavailable than the elixir. There was less interindividual variation in bioavailability with the complex than with the elixir. Peak serum digoxin levels were higher with the complex than the tablet and were achieved more quickly.

Keyphrases □ Digoxin—bioavailability of complex with hydroquinone compared to other digoxin dosage forms, humans □ Bioavailability—digoxin–hydroquinone complex compared to other digoxin dosage forms, humans □ Complexes—digoxin–hydroquinone, bioavailability compared to other digoxin dosage forms, humans □ Dosage forms, various—digoxin and digoxin–hydroquinone complex, bioavailability compared, humans □ Cardiotonic agents—digoxin–hydroquinone complex, bioavailability compared to other digoxin dosage forms, humans

The bioavailability of oral digoxin preparations has been studied recently (1–11), and several studies (4–10) showed that the bioavailability of solid digoxin dosage forms correlated with the dissolution rate but not the disintegration rate (11). This finding led to the assertion that existing *in vitro* dissolution tests are adequate for predicting commercial digoxin tablet bioavailability. Other investigations (12–16), however, demonstrated that the *in vitro* dissolution rate of commercial digoxin tablets need not correlate with bioavailability, since tablets that did not meet USP XVIII dissolution specifications showed *in vivo* bioavailability characteristics comparable to tablets that did. Thus, the relationship between bioavailability and dissolution rate appears to be unresolved.

The main cause of the unsatisfactory dissolution of digoxin tablets is related primarily to digoxin's low water solubility. Although improved formulation technology has resulted in significant improvement, an intrinsically more soluble form of digoxin should enhance dissolution. Higuchi and Ikeda (17) recently developed such a form by complexing digoxin and hydroquinone. This approach utilizes the concept of free energy of dissolution of molecular complexes (18). The digoxin–hydroquinone[1] complex is more readily soluble than digoxin itself, and total dissolution of digoxin occurs within 5 min (17).

This paper reports a comparison of the bioavailability in humans of the complex with that of a digoxin tablet[2] of

[1] Lot 828-264, supplied by Pennwalt Corp., Pharmaceutical Division, Rochester, N.Y.

[2] Lanoxin, lot 022-1, supplied by the Food and Drug Administration.

Table I—24-hr Area under Concentration–Time Curves (Nanograms × Hours per Milliliter)

Subject	Digoxin–Hydroquinone Complex	Digoxin Tablets	Digoxin Elixir	Digoxin Intravenous Injection
1	19.48	9.63	18.68	31.68
2	15.23	9.49	16.51	31.24
3	10.52	8.24	15.11	23.79
4	13.88	17.48	15.68	31.11
5	17.82	17.12	20.47	15.61
6	14.61	11.82	17.20	20.10
7	10.42	9.66	10.28	26.07
8	15.17	12.05	14.91	28.11
9	14.27	12.96	14.83	28.93
10	14.35	13.32	14.46	17.24
11	21.08	21.26	19.85	28.82
12	11.15	12.48	16.09	18.44
Mean	14.83	12.96	16.17	25.10
CV, %	22.52	29.90	16.90	23.40
Bioavailability, %	59.10	51.60	64.50	—

Analysis of Variance

Source	*df*	Sum of Squares	Mean of Squares	*F* Ratio	*p*
Between subjects	11	306.09	27.83	2.19	<0.05
Between periods	3	61.52	20.51	1.61	>0.1
Between treatments	3	1043.44	347.81	27.38	<0.0005
Error	30	381.16	12.71	—	—
Total	47	1792.21	—	—	—

Multiple Range Analysis

Complex *versus* tablets	$p < 0.08$
Complex *versus* intravenous injection	$p < 0.005$
Complex *versus* elixir	$p > 0.05$
Tablet *versus* intravenous injection	$p < 0.001$
Tablet *versus* elixir	$p < 0.01$
Intravenous injection *versus* elixir	$p < 0.001$

satisfactory dissolution and bioavailability, a digoxin elixir[3], and an intravenous injection[4].

EXPERIMENTAL

Subjects—Twelve healthy volunteers[5], seven female and five male, ages 22–41 years (median 31), were studied. There was no evidence of cardiac, hepatic, renal, GI, or hematopoietic disease from the history, physical examination, ECG, complete blood count, creatinine clearance, urinalysis, and bilirubin, alkaline phosphatase, glutamic-pyruvic transaminase, and thyroxine levels.

Drug Administration—The volunteers abstained from drugs, including alcohol, for at least 48 hr prior to each dosing period. The dosage form was administered between 7 and 8 am after an overnight fast of at least 10 hr. During the first 4 hr after drug administration, the subjects were not allowed to eat or to lie down. They were allowed to drink water at a maximum rate of 100 ml/hr.

In a random sequence with at least 2-week intervals, the individuals received each of the following dosage forms: (*a*) two 0.329-mg tablets of digoxin–hydroquinone complex[1] (equivalent to 0.5 mg of digoxin), (*b*) two 0.25-mg digoxin tablets[2], (*c*) 0.5 mg of digoxin elixir[3], and (*d*) 0.5 mg of digoxin intravenous injection[4]. The oral dosage forms were given with 200 ml of water. The parenteral digoxin was injected intravenously over 2–3 min, followed by 200 ml of water orally.

Specimen Collection and Assay—Blood (10 ml) for digoxin estimation was obtained from an antecubital vein with an indwelling catheter[6] at 0, 0.25, 0.50, 0.75, 1.0, 1.5, 2, 3, 4, 6, 8, 10, and 24 hr following an oral dose. Additional early samples were collected at 0.05, 0.1, 0.17, and 0.33 hr following the intravenous dose. Serum was separated from blood and frozen until assayed for digoxin by radioimmunoassay (19). The coefficients of variation of high and low internal standards analyzed daily were 5.3 and 6.4%, respectively.

Complete daily urine collections were obtained for 48 hr following dosing. Each 24-hr urine collection was thoroughly mixed, the volume was determined, and an aliquot was frozen until assayed by a modification of a reported method (20). Each sample also was assayed for creatinine content to aid in the assessment of the completeness of the urine collections.

Analysis—Bioavailability of the various preparations was determined by comparing the 24-hr area under the serum digoxin–time curve ($AUC_{0\rightarrow24}$) following intravenous administration to that following the oral dosage forms, *i.e.*:

$$\frac{(AUC_{0\rightarrow24})_{oral}}{(AUC_{0\rightarrow24})_{iv}} \times 100\%$$

The *AUC* was computed[7] by the trapezoidal rule. Furthermore, the 48-hr excretion of digoxin in urine following intravenous administration was compared to that following the oral dosage forms (20).

The time taken to achieve peak serum digoxin concentrations and the peak concentrations were obtained from the serum concentration profiles. Statistical significance was determined by a two-way analysis of variance (ANOVA). Differences between the individual groups were determined by Duncan's multiple range test (21, 22).

Table II—Time to Achieve Peak Plasma Digoxin Concentration (Hours)

	Digoxin–Hydroquinone Complex	Digoxin Tablets	Digoxin Elixir
Mean	0.83	1.31	0.68
SD	0.29	0.69	0.22

Analysis of Variance

Source of Variation	*df*	Sum of Squares	Mean of Squares	*F* Ratio	*p*
Between subjects	11	2.22	0.20	1.25	>0.05
Between periods	2	1.36	0.68	4.25	<0.05
Between treatments	2	3.27	1.64	10.25	<0.001
Error	20	3.11	0.16	—	—
Total	35	9.96	—	—	—

Multiple Range Analysis

Complex *versus* tablet	$p < 0.005$
Complex *versus* elixir	$p < 0.2$
Tablet *versus* elixir	$p < 0.005$

RESULTS

Dissolution Rate Tests—The dissolution of the complex was 99% complete within 5 min whereas that of the tablets was 26% at 5 min, 61% at 15 min, 74% at 30 min, and 88% at 60 min. All commercial dosage forms met USP specifications.

Bioavailability—The $AUC_{0\rightarrow24}$, time to achieve peak plasma digoxin levels, and peak digoxin levels are presented in Tables I–III. Based on the *AUC* values, the bioavailabilities of the complex, tablet, and elixir were 59.1 (40–83.2), 51.6 (30.4–77.3), and 64.5% (39.4–87.3%), respectively, compared to the intravenous dosage form. The bioavailability of the complex and the tablets was not significantly different ($p < 0.08$), but all oral preparations differed significantly from intravenous digoxin. The elixir was more available than the tablets ($p < 0.005$), but the tablet and the elixir did not differ significantly ($p < 0.2$).

The 48-hr excretion of digoxin in urine following the various dosage forms is given in Table IV. The intravenous form differed significantly from all oral formulations. The complex did not differ significantly from the tablet ($p > 0.3$) or the elixir ($p > 0.1$), although the elixir was different

[3] Lanoxin, lot 456-N, supplied by Burroughs Wellcome, Research Triangle Park, N.C.

[4] Lanoxin, lot 691-O, supplied by Burroughs Wellcome, Research Triangle Park, N.C.

[5] Written informed consent was obtained after discussing with each subject the inconveniences and hazards to be expected.

[6] Teflon (du Pont).

[7] Olivetti Programma 101.

Table III—Peak Plasma Digoxin Concentration (Nanograms per Milliliter)

	Digoxin—Hydroquinone Complex	Digoxin Tablets	Digoxin Elixir
Mean	2.79	1.73	3.27
SD	1.13	0.73	0.91

Analysis of Variance

Source of Variation	*df*	Sum of Squares	Mean of Squares	*F* Ratio	*p*
Between subjects	11	14.73	1.34	2.35	<0.05
Between periods	2	1.65	0.82	1.44	>0.05
Between treatments	2	15.75	7.88	13.82	<0.005
Error	20	11.48	0.57	—	—
Total	35	43.61	—	—	—

Multiple Range Analysis

Complex *versus* tablet	$p < 0.005$
Complex *versus* elixir	$p > 0.05$
Tablet *versus* elixir	$p < 0.005$

Table IV—Urine Digoxin Excretion (Micrograms per 48 hr)

Subject	Digoxin—Hydroquinone Complex	Digoxin Tablets	Digoxin Elixir	Digoxin Intravenous Injection
1	187.2	49.6	182.0	139.4
2	129.4	96.8	108.6	178.3
3	123.6	113.8	146.3	231.7
4	116.2	114.8	136.3	129.3
5	130.2	115.6	85.7	107.2
6	85.3	111.8	143.6	192.7
7	87.2	141.4	127.6	179.2
8	148.8	81.2	141.4	149.0
9	86.3	97.5	136.3	233.0
10	108.3	111.1	116.0	129.3
11	136.3	196.1	226.7	173.5
12	116.5	106.4	147.2	196.7
Mean	121.3	112.7	137.1	174.4
CV, %	24.1	32.05	19.1	24.92
Bioavailability, %	69.6	64.6	78.6	—

Analysis of Variance

Source	*df*	Sum of Squares	Mean of Squares	*F* Ratio	*p*
Between subjects	11	15,668.50	1424.41	1.27	>0.05
Between periods	3	1,732.56	577.52	0.52	>0.05
Between treatments	3	27,586.75	9195.58	8.22	<0.01
Error	30	33,570.13	1119.00	—	—
Total	47	78,557.94	—	—	—

Multiple Range Analysis

Complex *versus* tablet	$p > 0.3$
Complex *versus* intravenous injection	$p < 0.005$
Complex *versus* elixir	$p > 0.1$
Tablet *versus* intravenous injection	$p < 0.005$
Tablet *versus* elixir	$p < 0.01$
Intravenous injection *versus* elixir	$p < 0.005$

from the tablet ($p < 0.01$). If a 10% difference is assumed to be significant, the complex had greater bioavailability than the tablet in six subjects, the two preparations behaved equally in five subjects, and the tablet was more available than the complex in one individual.

Peak Time and Peak Concentration—The peak concentration and the time required to achieve it are presented in Tables II and III. A mean peak value of 2.79 ± 1.13 ng/ml was achieved in 0.83 ± 0.29 hr with the complex; 1.73 ± 0.73 ng/ml was achieved in 1.31 ± 0.69 hr with the tablet, and 3.27 ± 0.91 ng/ml was achieved in 0.68 ± 0.22 hr with the elixir. Compared to the tablet, both the complex ($p < 0.005$) and the elixir ($p < 0.05$) achieved significantly higher peak digoxin levels and in a shorter time (complex, $p < 0.005$; elixir, $p < 0.005$).

DISCUSSION

The bioavailability of oral liquid dosage forms has, in general, been shown to be greater than that of tablet forms (3, 20, 23). Although the bioavailability (based on comparison of *AUC*'s) of the complex, a digoxin preparation of very rapid dissolution, was not statistically different from that of the elixir, it also was not statistically different from that of a solid dosage form. This discrepancy may be related to the fact that the volunteers showed large intersubject variations in the bioavailability of various preparations (Table I).

A considerable variance from the mean $AUC_{0\rightarrow 24}$ and urine digoxin excretion was observed in subjects receiving the complex, but an even greater variance occurred with the tablet. Thus, the complex appeared to be less erratically absorbed than the tablet, which may be advantageous when administered on a chronic basis. The bioavailability of the oral preparations was lower in this study than in a previous one (20), where the elixir was 84.5% absorbed (*cf.*, 64.5% in this study) and a rapid dissolution tablet was 77.8% absorbed (*cf.*, 59.6% in this study). However, the $AUC_{0\rightarrow 24}$ (25.1) following intravenous digoxin agreed closely with values obtained in two other studies, one following single-dose digoxin (25.9) (20) and the other in a steady-state study (22.9) (23). In three subjects (Subjects 1, 4, and 5), the 48-hr excretion of digoxin in urine following intravenous administration was less than that following one of the oral preparations. There is no ready explanation for this finding, except inadequate urine collections by these volunteers; low creatinine excretion in urine confirmed this suspicion.

The complex produced a higher peak serum digoxin level earlier than the tablet. This characteristic may not be desirable, although there is no evidence (24, 25) to suggest that the peak digoxin concentration during absorption and distribution is related to toxicity. The rapid achievement of the higher peak level is similar to that attained with the elixir, which also has not been reported to be associated with more toxicity than a solid dosage form. On the other hand, steady-state serum digoxin concentrations do correlate with therapeutic and toxic responses in patients (26).

The absorption of incompletely absorbed drugs has more inter- and intraindividual variability than that of completely absorbed drugs (23, 27, 28). This variation may have harmful effects in humans if the drug has a narrow therapeutic index, such as digoxin. Considerable data (4–10) demonstrate a direct correlation between the dissolution rate of digoxin tablets and their bioavailability. This relationship is further supported by the observation that various digoxin solutions are more bioavailable than solid dosage forms (3, 20, 23).

The particle size of digoxin in relation to bioavailability was examined (29), and particles below 3.7 μm in size produced better availability than did particles above 12 μm. However, another study (9) found that the bioavailability of a digoxin elixir was not greater than that of digoxin tablets whose dissolution rate exceeded 85% in 1 hr. A recent study (30) compared the availability of a digoxin solution in capsules with tablets that were 97 and 78% dissolved in 1 hr. However, the tablet dissolution rate was not given. The solution in capsules performed better than the tablets, whose availability did not differ despite different *in vitro* dissolution rates. This latter finding is in accord with information obtained in other studies (13–16) and supports the finding of this study that dissolution rates above a certain point may not be associated with increased digoxin absorption. However, in these and other studies (4–10), oral preparations were compared only to each other, whereas in this study the bioavailability of oral digoxin was compared to other oral forms as well as to the intravenous form. Thus, absolute bioavailability cannot be ascertained in most other studies.

It appears, therefore, that the dissolution rate of digoxin tablets may not be the only limiting factor in their incomplete absorption and that the current method of dissolution testing does not discriminate satisfactorily. Digoxin is prescribed for chronic therapy. Single-dose studies may not assess the bioavailability of the dosage forms accurately during chronic use. The results in this single-dose study warrant the further evaluation of the chronic administration of the complex. Steady-state bioavailability studies of digoxin have been reported (23).

The principle of complexing a drug with substances such as hydroquinone to enhance dissolution might be applied to other medications whose absorption is erratic following poor *in vivo* dissolution.

REFERENCES

(1) J. Lindenbaum, M. H. Mellow, M. O. Blackstone, and V. P. Butler, *N. Engl. J. Med.*, **285**, 1344 (1971).

(2) V. Manninen, J. Melin, and G. Hartel, *Lancet*, **2**, 934 (1971).

(3) D. H. Huffman and D. L. Azarnoff, *J. Am. Med. Assoc.*, **222**, 957 (1972).

(4) B. F. Johnson, H. Greer, J. McCrerie, C. Bye, and A. Fowle, *Lancet*, **1**, 1473 (1973).

(5) J. Lindenbaum, V. P. Butler, J. E. Murphy, and R. M. Cresswell, *ibid.*, **1**, 1215 (1973).

(6) E. J. Fraser, R. H. Leach, J. W. Poston, A. M. Bold, L. S. Culank, and A. B. Lipede, *J. Pharm. Pharmacol.*, **25**, 968 (1973).

(7) B. F. Johnson, *Postgrad. Med. J., Suppl. 6*, **50**, 48 (1974).

(8) J. G. Wagner, M. Christensen, E. Sakmar, D. Blair, J. D. Yates, P. W. Willis, III, A. J. Sedman, and R. G. Stoll, *J. Am. Med. Assoc.*, **224**, 199 (1973).

(9) D. J. Greenblatt, D. W. Duhme, J. Koch-Weser, and T. W. Smith, *ibid.*, **229**, 1774 (1974).

(10) E. Steiness, V. Christensen, and H. Johansen, *Clin. Pharmacol. Ther.*, **14**, 949 (1973).

(11) P. F. Binnion, *ibid.*, **16**, 807 (1974).

(12) P. R. Klink, R. I. Poust, J. L. Colaizzi, and R. H. McDonald, *J. Pharm. Sci.*, **63**, 1231 (1974).

(13) P. Ylitalo, G. Wilen, and S. Lundell, *ibid.*, **64**, 1264 (1975).

(14) P. Ylitalo, G. Wilen, and S. Lundell, *Lancet*, **1**, 343 (1975).

(15) *Ibid.*, **1**, 744 (1975).

(16) P. T. Hairsnape, *Br. Med. J.*, **2**, 55 (1974).

(17) T. Higuchi and M. Ikeda, *J. Pharm. Sci.*, **63**, 809 (1974).

(18) E. Shefter and T. Higuchi, *ibid.*, **52**, 781 (1963).

(19) T. W. Smith, V. P. Butler, and E. Haber, *N. Engl. J. Med.*, **281**, 1212 (1969).

(20) D. H. Huffman, C. V. Manion, and D. L. Azarnoff, *J. Pharm. Sci.*, **64**, 433 (1975).

(21) D. B. Duncan, *Biometrics*, **11**, 1 (1955).

(22) H. L. Harter, *ibid.*, **16**, 671 (1960).

(23) D. H. Huffman, C. V. Manion, and D. L. Azarnoff, *Clin. Pharmacol. Ther.*, **16**, 310 (1974).

(24) D. A. Chamberlain, *Postgrad. Med. J., Suppl. 6*, **50**, 29 (1974).

(25) T. R. D. Shaw, K. Raymond, and H. Greenwood, *ibid.*, **50**, 55 (1974).

(26) D. H. Huffman, J. W. Crow, P. Pentikäinen, and D. L. Azarnoff, *Am. Heart J.*, **91**, 28 (1976).

(27) J. Koch-Weser, *N. Engl. J. Med.*, **291**, 233 (1974).

(28) J. G. Wagner, *Pharmacology*, **8**, 102 (1972).

(29) T. R. D. Shaw, J. E. Carless, M. R. Howard, and K. Raymond, *Lancet*, **2**, 209 (1973).

(30) G. J. Mallis, D. H. Schmidt, and J. Lindenbaum, *Clin. Pharmacol. Ther.*, **18**, 761 (1975).

ACKNOWLEDGMENTS AND ADDRESSES

Received April 26, 1976, from the **Clinical Pharmacology and Toxicology Center, Departments of Medicine and Pharmacology, University of Kansas Medical Center, Kansas City, KS 66103,* and the ‡*Medicine and Research Service (Project No. 3704-02), Veterans Administration Hospital, Kansas City, MO 64128.*

Accepted for publication July 1, 1976.

Supported by the Pharmaceutical Division, Pennwalt Corp., and U.S. Public Health Service Grant GM 15956.

The authors thank Jessie Fink for assistance, Dr. K. Hassanein for statistical analyses, and Billie Jean Milanez for technical help. Dissolution rate studies were performed by Dr. Lewis Amsel and Mr. Thomas Matochik, Pharmaceutical Development, Pharmaceutical Division, Pennwalt Corp.

§ Fellow in Clinical Sciences in Clinical Pharmacology of the National Health and Medical Research Council of Australia.

ˣ To whom inquiries should be directed.

Time-Dependent Kinetics I: Exponential Autoinduction of Carbamazepine in Monkeys

WILLIAM H. PITLICK * and RENÉ H. LEVY ˣ

Abstract □ The pharmacokinetics of carbamazepine were studied during a week-long infusion of the drug in 60% polyethylene glycol 400 solution in three rhesus monkeys. Serum concentrations approached steady state within 8–16 hr and then rapidly declined, within 72 hr, to a new asymptotic level approximately 46% of the maximum steady-state concentration. Serum concentrations remained at that level during the rest of the experimental period. The decline from the maximum value to the asymptotic steady state was exponential. It is postulated that the decline in the steady-state concentration is due to autoinduction by carbamazepine of its own metabolism.

Keyphrases □ Time-dependent pharmacokinetics—carbamazepine, 1-week infusion, monkeys □ Carbamazepine—time-dependent pharmacokinetics, 1-week infusion, monkeys □ Pharmacokinetics, time dependent—carbamazepine, 1-week infusion, monkeys □ Analgesics—carbamazepine, time-dependent pharmacokinetics, 1-week infusion, monkeys

Over the past 15 years, awareness of the various facets of dose dependency in drug disposition has increased. As a result, experimental designs of pharmacokinetic investigations often include studies at several dose levels. Examples of dose dependency in absorption, distribution, and elimination have been reported. However, the concept of *time dependency* in pharmacokinetics is still undefined.

BACKGROUND

Studies in this laboratory involving animals and humans clearly indicated that time dependency is a multifaceted phenomenon, at least as complex as dose dependency. Several types of time dependency exist, and this series of papers will provide examples. Carbamazepine is the drug of choice for the treatment of trigeminal neuralgia (1) and was recently approved for use as an anticonvulsant in adults (2). Single-dose intravenous and oral studies in monkeys indicated that the drug has a short biological half-life (1–2 hr) and that chronic oral administration during its efficacy testing in epileptic monkeys would be impractical (3, 4). Consequently, a continuous mode of administration such as constant-rate intravenous infusion in chronically catherized monkeys was considered.

Short-term infusion studies indicated that carbamazepine exhibits dose-dependent kinetics (5, 6). Infusion rates between 8.5 and 40 mg/hr yielded steady-state concentrations of carbamazepine between 2.0 and 5.8 μg/ml (6). However, the increase in steady-state concentration was more than proportional to the increase in infusion rate, and the time required to reach one-half of the steady-state level was not constant. A model with zero-order input and one capacity-limited elimination pathway was adequate to describe the pharmacokinetic behavior of the drug (6).