was ~0.6[14]. The tortuosity term must be high, particularly since additional shellac and filler were added in the final stages of pellet preparation. From the dissolution rate of pellets without added filler, a value of 30 was estimated for τ by Eq. 4. By assuming from the pellet core dimensions a matrix thickness of 150 μm and a boundary layer thickness of 100 μm, the ratio of resistances of matrix to unstirred layer is of the order of ~75, so matrix-controlled release proportional to $t^{1/2}$ would be predicted. The zero-order release rates that were observed, however, imply a constant activity of drug in a reservoir, due possibly to a barrier layer on the surface of the pellet where a constant concentration is maintained. Diffusion at constant concentrations through such a barrier layer may be the rate-determining step which results in release being linear with time. This mechanism was confirmed by dissolution from thick films of I dispersed in a shellac-based matrix in the same proportion as in the pellets but without the final drug-free layer. The release was found to be linear with $t^{1/2}$ and agreed with the heterogeneous matrix model. Moreover, the release from pellets made without the outer layer of shellac and filler also adhered to the $t^{1/2}$ relationship.

The sensitivity of the release rates to pH of the external solvent at pH < pH_{max} confirms that the leaching process takes place within a granular matrix. However, the expected decrease of release rate based on the decreased solubility at higher pH was not observed. These results were explained by the self-buffering action of the drug and the tendency to revert toward the apparent pH_{max} in the media of low buffer capacity.

The results of the present investigation indicate that the variability in the dissolution rate of a drug within the GI pH range due to differences in solubility may be reduced by designing controlled-release dosage forms. The importance of internal pH within the polymer matrices in controlling the solubility of drug and hence the dissolution rate has also been noted by Jambhekar and Cobby (15).

[14] The maximum porosity when all of the active drug is dissolved is given by $\epsilon + A(1 - \epsilon)$, where ϵ is the porosity of the pellet equal to 0.07, and A is the concentration of drug in the matrix.

REFERENCES

(1) R. J. Timko and N. G. Lordi, *J. Pharm. Sci.*, **67,** 496 (1978).
(2) S. F. Kramer and G. L. Flynn, *J. Pharm. Sci.*, **61,** 1896 (1972).
(3) Z. T. Chowhan, *J. Pharm. Sci.*, **67,** 1257 (1978).
(4) M. Robinson, in "The Theory and Practice of Industrial Pharmacy," 2nd ed., L. Lachman, H. A. Lieberman, and J. L. Kanig, Eds., Lea & Febiger, Philadelphia, Pa., 1976, p. 456.
(5) L. W. Dittert, T. Higuchi, and D. R. Reese, *J. Pharm. Sci.*, **53,** 1325 (1964).
(6) I. M. Kolthoff, *Biochem. Z.*, **162,** 289 (1925).
(7) V. H. Veley, *J. Chem. Soc.*, **95,** 758 (1909).
(8) A. I. Biggs, *Trans. Faraday Soc.*, **50,** 800 (1954).
(9) J. H. Wood, J. E. Syarto, and H. Letterman, *J. Pharm. Sci.*, **54,** 1068 (1965).
(10) J. B. Bogardus and R. K. Blackwood, *J. Pharm. Sci.*, **68,** 188 (1979).
(11) A. A. Noyes and W. R. Whitney, *J. Am. Chem. Soc.*, **19,** 930 (1897).
(12) E. Nelson, *J. Am. Pharm. Assoc., Sci. Ed.*, **46,** 607 (1957).
(13) K. G. Mooney, M. A. Mintun, K. J. Himmelstein, and V. J. Stella, *J. Pharm. Sci.*, **70,** 13 (1981).
(14) T. Higuchi, *J. Pharm. Sci.*, **52,** 1145 (1963).
(15) S. Jambhekar and J. Cobby, Abstracts, Academy of Pharmaceutical Sciences 29th National Meeting, **10**(2), 86 (1980).

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Serum and Myocardial Kinetics of Amiodarone and Its Deethyl Metabolite After Intravenous Administration in Rabbits

R. KANNAN *x, N. IKEDA ‡, R. WAGNER ‡, M. DRACHENBERG ‡, and B. N. SINGH *

Received July 5, 1983, from the **Department of Cardiology, Veterans Administration Medical Center, West Los Angeles, CA 90073* and the ‡*Department of Medicine, UCLA School of Medicine, Los Angeles, CA.* Accepted for publication October 6, 1983.

Abstract □ The serum kinetics of amiodarone and its major metabolite the deethyl analogue were studied in rabbits after intravenous administration. The elimination of the drug and the metabolite from serum occurred as a biexponential function. Both compounds exhibited a rapid distribution phase (6.5 and 4.4 min, respectively) and had elimination half-lives of 136 and 235 min, respectively. There was a rapid uptake of both drugs by the myocardium, with maximal concentrations at 5 and 15 min. The myocardial concentrations were higher than the respective serum concentrations and declined with time. There was a wide scatter in myocardium-serum ratios, which ranged from 1 to 11 for amiodarone and 12 to 29 for the metabolite. Neither the drug nor the metabolite produced significant changes in the surface electrocardiogram after intravenous administration. These data suggest that accumulation of the metabolite does not account for the slow onset of action of amiodarone.

Keyphrases □ Kinetics—serum and myocardial, amiodarone and its metabolite, rabbits □ Amiodarone—serum and myocardial kinetics, rabbits □ Deethyl metabolite—amiodarone, serum and myocardial kinetics, rabbits

Plasma drug levels are commonly used to monitor the efficacy and toxicity of antiarrhythmic compounds. Such an approach is based on the assumption that the drug level in the myocardium, the presumed site of action of cardioactive agents, is in equilibrium with that in plasma. However, this assumption may not necessarily be valid under conditions of rapidly changing plasma levels of drugs (1). The significance of the myocardium–plasma drug ratios in the interpretation of the pharmacological responses of antidysrhythmic agents such as lidocaine (2), quinidine (3), verapamil (4), disopyramide (5), and *n*-acetylprocainamide (6) has been emphasized. Such studies are particularly relevant in the case of amiodarone, a potent class III antiarrhythmic drug (7), in light of our recent finding which demonstrates a lack of correlation between serum drug concentrations and suppression of premature ventricular contractions in patients with cardiac arrhythmias (8). Chronic amiodarone therapy results in the accumulation of a metabolite, the deethyl analogue, in serum (9). However, neither the pharmacokinetics nor the pharma-

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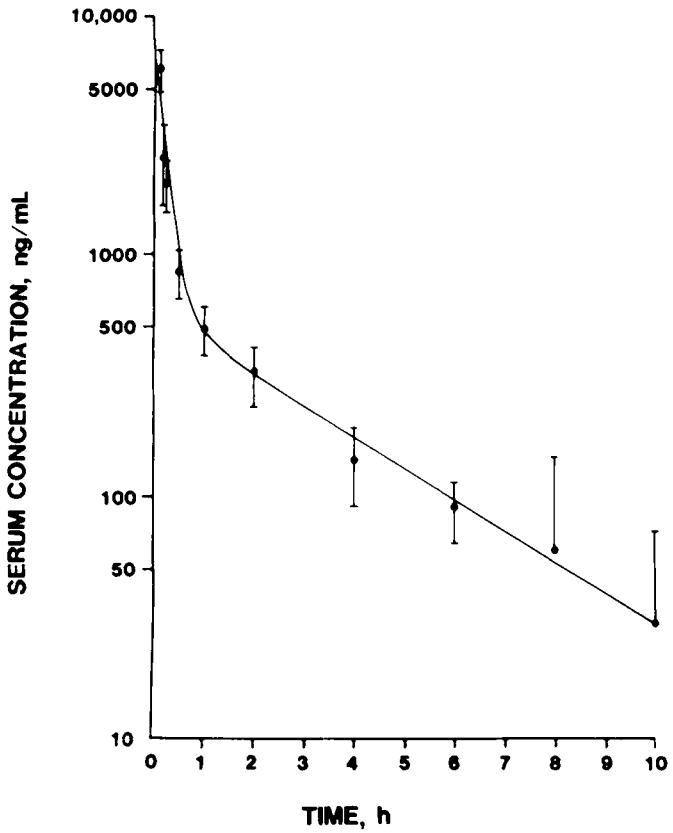

Figure 1—*Semilogarithmic plot of the elimination kinetics of amiodarone after intravenous administration to rabbits. The data represent mean values (±95% confidence limits) from 6 to 14 determinations per time point. The curve drawn is a two-exponential fit to the data.*

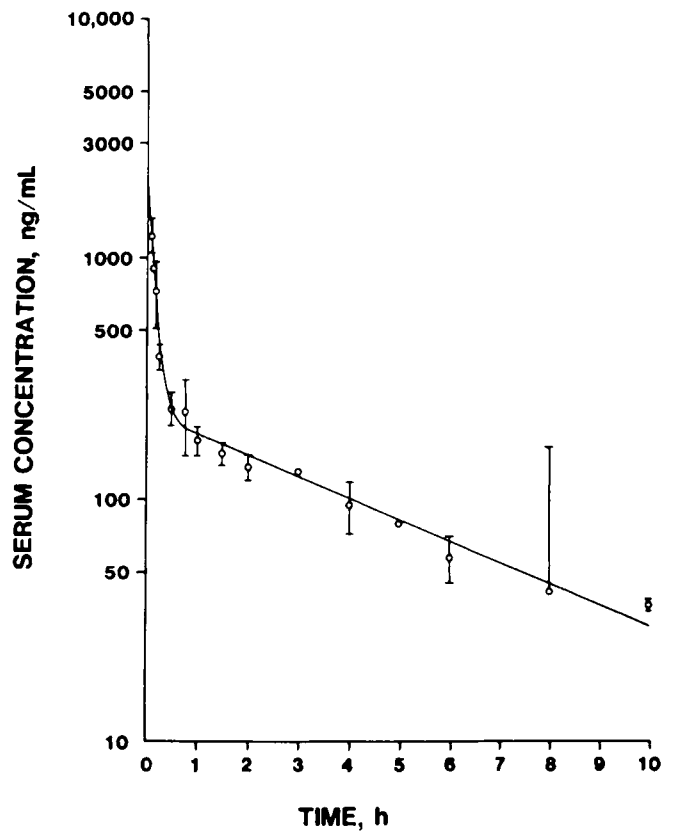

Figure 2—*Semilogarithmic plot of the elimination kinetics of the deethyl analogue after intravenous administration to rabbits. The data represent mean values (±95% confidence limits) from 3 to 9 values per time point. The curve drawn is a two-exponential fit to the data.*

cological properties of the metabolite are known. The purpose of the present study was twofold: first, to make a comparative evaluation of the serum elimination kinetics of amiodarone and its major metabolite after intravenous administration in rabbits and, second, to determine the myocardial concentrations of amiodarone and its deethyl metabolite as a function of time after an intravenous dose and to correlate the tissue levels with the electrocardiographic changes.

EXPERIMENTAL SECTION

Experimental Design—The kinetic and electrophysiological studies were conducted using female New Zealand White rabbits. For the study of amiodarone kinetics, 15 rabbits [body weight, 1.9 ± 0.2 kg (mean ± *SD*)] were used. One rabbit died after the administration of amiodarone, and data from that rabbit were not included in the final analysis. The kinetics of the deethyl analogue were evaluated in 15 rabbits (2.42 ± 0.33 kg). However, three rabbits were excluded since they died from either anesthesia ($n = 1$) or drug ($n = 2$). All animals were anesthetized with pentobarbital[1] (20 mg/kg). Either 5% aqueous amiodarone hydrochloride[2] at a dose of 10 mg/kg or the deethyl analogue as the hydrochloride[2] in 50% ethanol (1.5% solution) at a dose of 10 mg/kg was injected as a single intravenous bolus dose in the marginal vein of the left ear. The total volume of injectant did not exceed 0.30–0.52 mL for amiodarone and 0.7–1.3 mL for the metabolite. Serial blood samples (1–1.7 mL) were drawn from the right ear vein. Up to eight serial blood samples were obtained at the following sampling times: 5, 10, 15, 30, 45, and 60 min and 1.5 h, 2, 4, 6, 8, and 10 h. Blood collected before the drug was injected served as the blank in drug assays. In some rabbits, blood samples were also taken at 2.5, 7.5, and 12.5 min. To obtain myocardial tissue samples, all 15 rabbits used in the amiodarone serum kinetics studies were sacrificed as groups of two to three rabbits each at 5 and 15 min and 1, 2, and 6 h. Similarly, groups of three to four rabbits were sacrificed at 15 min and 2, 4, 6, and 10 h in the metabolite studies. After dissection, the heart tissue was blotted dry, weighed, and kept frozen. Blood samples were spun at 10,000 rpm, after which the serum was separated and stored frozen until analysis. Electrocardiograms (ECGs) were recorded[3] with standard limb leads immediately before injection of the drug and at 15 and 30 min and 1, 3, 4, and 6 h postdose. ECGs of control rabbits that were injected with either equivalent volumes of sterile distilled water or 50% ethanol were recorded for up to 6 h.

Table I—Kinetic Parameters of Amiodarone and its Metabolite, the Deethyl Analogue, After Intravenous Administration in Rabbits [a]

	$t_{1/2,\alpha}$ min	$t_{1/2,\beta}$ min	Vd_{ss}, L/kg	CL, L/min/kg
Amiodarone	6.5 ± 1.2	136 ± 20	6.7	0.055
Deethyl analogue	4.4 ± 0.6	235 ± 7	34.4	0.116

[a] These data are derived from the serum elimination curves for amiodarone and the metabolite shown in Figs. 1 and 2.

Drug Analysis—Analyses were carried out in a liquid chromatograph[4] equipped with a solvent delivery system[5], a valve-type injector[6], a normal-phase silica column[7], and a variable-wavelength UV detector[8] set a 240 nm. Serum concentrations of amiodarone and its metabolite were determined by using a recent modification (10) of the procedure described by Flanagan *et al.* (11). The serum volumes for analysis varied from 0.25 to 0.75 mL, depending on the expected drug concentrations, with corresponding increase in the volume of the extracting solvent, methyl *tert*-butyl ether. The combined ether extract from two extractions was dried under a stream of nitrogen and reconstituted in 25 μL of methanol, of which 20 μL was injected into the liquid chromatograph.

For the measurement of myocardial concentrations of amiodarone and its metabolite, 100–250 mg of ventricular muscle was homogenized with 5 mL of deionized distilled water by sonication, and the homogenate was centrifuged

[1] Nembutal, Abbott.
[2] Labaz Inc., Brussels, Belgium.
[3] Gould Brush 280; Grass Instruments, Quincy, Mass.
[4] Waters Associates, Milford, Mass.
[5] Model 6000A; Waters Associates.
[6] U6K; Waters Associates.
[7] Beckman Instruments, Palo Alto, Calif.
[8] M450; Waters Associates.

Table II—Mean Concentrations of Amiodarone and Its Deethyl Analogue in Serum and Myocardium after Intravenous Administration in Rabbits [a]

Time after Injection	Concentration		Myocardium-Serum Ratio (range) [b]
	Serum, ng/mL	Myocardium, ng/g	
		Amiodarone	
5 min	6050 ± 2200 (14)	8100 ± 4000 (3)	1.2 (0.3–1.7)
15 min	1990 ± 680 (11)	14,400 ± 2800 (3)	5.8 (4.9–7.6)
1 h	490 ± 170 (11)	7000 ± 1900 (3)	11.1 (9.6–12.0)
2 h	320 ± 120 (10)	530 ± 430 (2)	1.3 (0.5–2.1)
6 h	90 ± 30 (6)	362 ± 431 (3)	2.3 (0.7–5.5)
		Deethyl Analogue	
15 min	389 ± 64 (9)	10,800 ± 7850 (3)	28.8 (24.0–33.6)
2 h	136 ± 21 (8)	3444 ± 2910 (3)	26.9 (3.7–47.1)
4 h	95 ± 21 (6)	2590 ± 1150 (2)	25.9 (18.7–33.0)
6 h	58 ± 11 (6)	1006 ± 620 (3)	17.0 (8.6–28.7)
10 h	37 ± 1 (3)	445 ± 358 (4)	11.7 (1.8–24.4)

[a] Data are mean ± *SD*; number of rabbits is given in parentheses. [b] Ratios are presented only for those rabbits for which both serum and myocardial concentrations were available.

at 10,000 rpm for 10 min. Aliquots (2 mL) of the supernatant were extracted twice with 1 mL of methyl *tert*-butyl ether. Further processing of the sample was the same as described above for serum. The extraction efficiency of amiodarone and the metabolite from ventricular muscle of control rabbits was 71.2 ± 2.7% (n = 6), which did not differ from that found in serum (74.0 ± 9.8%; n = 8).

Data Analysis—Mean serum concentrations of amiodarone and the deethyl metabolite were fitted by nonlinear least-squares regression analysis (12). Clearance (CL) and volume of distribution at steady state (Vd_{ss}) were determined by using model-independent calculations (13). The ECG parameters were derived manually from records at 125-mm/s paper speed, and the resulting data were compared at each time point with an ANOVA program.

RESULTS

Serum Kinetics of Amiodarone and the Deethyl Analogue in Rabbits—In Figs. 1 and 2 are shown the serum elimination kinetics of amiodarone and the metabolite, respectively, in rabbits after intravenous administration. The data shown are from 14 rabbits administered amiodarone and 15 rabbits administered the metabolite; in both series of experiments, both serum and myocardial kinetics were studied. A biexponential fall in serum concentrations was observed for the parent drug and the metabolite. The serum concentrations 5 min after administration of the intravenous dose were 6050 and 2660 ng/mL for amiodarone and the metabolite, respectively, and fell to 30 and 38 ng/mL, respectively, in 10 h. The kinetic parameters of serum kinetics of amiodarone and the deethyl analogue are listed in Table I. Both drugs had a rapid distribution phase ($t_{1/2,\alpha}$ 6.5 and 4.4 min for amiodarone and the metabolite, respectively). The elimination half-lives ($t_{1/2,\beta}$) were 136 min for amiodarone and 235 min for the metabolite. The mean volumes of distribution and clearance for amiodarone were 6.7 L/kg and 0.055 L/min/kg, respectively. The corresponding values for the metabolite were 34.4 L/kg and 0.116 L/min/kg, respectively (Table I).

In Table II, the myocardial concentrations of amiodarone and the metabolite in rabbits as a function of time after intravenous administration are summarized. We used ventricular muscle as a representative tissue sample for the determination of the myocardial concentrations. The myocardial concentrations of the parent drug and the metabolite expressed as nanograms per gram of wet tissue were higher than the respective serum concentrations that were obtained throughout the time course of the study. In the postdistributive phase, myocardial concentrations of the metabolite declined approximately parallel to those of serum. Such a similarity was not apparent for amiodarone, partly due to the limited number of data points (2 and 6 h) for myocardial levels of amiodarone in the postdistributive phase. The myocardium-serum ratios (Table II) are derived from only those rabbits for which both serum and myocardial concentrations were available. Although the myocardium-serum ratios of amiodarone and the metabolite overlapped, the ratios for the metabolite (range, 11.7–28.8) were higher than for amiodarone (range 1.3–11.3). The large scatter in the ratios was a result of wide variations in myocardial concentrations.

Electrocardiographic Changes—Electrocardiographic changes accompanying intravenous administration of amiodarone and the metabolite were compared between rabbits injected with drug and a control group (n = 5) injected with the vehicle alone. All rabbits were mildly anesthetized with pentobarbital before administration of the appropriate drug or the vehicle and at other times during the study to obtain ECG recordings that were free of technical artifacts. An analysis of variance among the three groups showed that intravenous administration of either amiodarone or the metabolite did not cause any significant changes in RR, PQ, QRS, and QT_c intervals[9] as compared with the control group, except for an increase in the QRS intervals of the animals treated with the metabolite 15 min after administration of the drug (37.2 ± 4.0 *versus* 29.6 ± 2.8 ms in the controls). However, this increase is only of borderline significance. There were fluctuations in the values of the QRS intervals both in the control and drug-treated groups, although the values of the QRS intervals did not differ significantly from those of the controls at other time points studied.

DISCUSSION

We have determined the serum elimination kinetics and myocardial distribution of amiodarone in rabbits after intravenous administration. The pharmacokinetics of the major metabolite of amiodarone, the deethyl analogue, was compared with those of the parent drug for the first time. The short and long elimination half-lives of amiodarone in patients after acute and chronic oral administrations have been determined by us and others (9, 14, 15). It has been suggested that amiodarone equilibrates rapidly with tissues, such as the myocardium, after acute administration, and the rapid repartitioning between tissue and serum results in a short half-life. On the other hand, the long elimination half-life after chronic administration is attributed to the slowly equilibrating tissues, mainly adipose tissue and muscle. We found that amiodarone was rapidly eliminated from the serum of rabbits after intravenous administration, with an elimination half-life of 136 min, which is similar to that found in dogs (16, 17) but different from that found in rats (18). The disappearance of the intravenously administered metabolite from the serum of rabbits is also rapid ($t_{1/2,el}$ 235 min). There is a rapid uptake of both the drug and its metabolite by the myocardium. Although our limited data did not allow us to determine the precise time of maximal uptake of amiodarone and the metabolite by the myocardium, it can be estimated to be between 5 and 15 min. The myocardial concentrations of amiodarone and the metabolite decreased with time. This decline in myocardial concentrations was approximately parallel to that detected for the metabolite in serum but not for amiodarone. For both the drug and the metabolite, the myocardial concentrations were higher than the respective serum concentrations used throughout the study.

Latini *et al.* (16, 17) have recently reported a detailed investigation on serum kinetics and myocardial disposition of amiodarone in dogs. The mean serum elimination half-life of amiodarone after intravenous administration in dogs (3.01 h) was similar to that in rabbits, as determined in the present study. They observed a large interanimal variability in myocardium-serum ratios in dogs. The average ratio of myocardium-plasma amiodarone concentration was much higher in dogs (range, 34–134) than that in rabbits (range, 1.2–11.3). Whether this represents a species difference or differential binding characteristics of amiodarone is not certain at present. Interestingly, Latini *et al.* (17) have shown by computer simulation, that peak myocardial concentrations were achieved between 15 and 20 min after intravenous administration of amiodarone to dogs. Our limited data on rabbit myocardial levels appear to be in accord with their findings. In spite of high concentrations of amiodarone and the metabolite in the myocardium, no appreciable ECG changes were observed for up to 6 h after intravenous administration, suggesting a complex

[9] Definitions: (RR) duration between two successive heart beats; (PQ) time from the beginning of atrial depolarization to the beginning of ventricular depolarization; (QRS) duration of ventricular depolarization; (QT_c) duration of ventricular repolarization normalized or corrected for heart rate.

pharmacological action of the parent drug and possibly the metabolite. This finding is consistent with our previous observation of no significant alterations in the action potentials of rabbit sinoatrial node, atrioventricular node, and atrial fibers after a 1-h superfusion with therapeutically meaningful concentrations of amiodarone suspended in homologous plasma (19). Although similar studies with microelectrodes will be needed to establish the electrophysiological properties of the metabolite, our preliminary data on ECG changes suggest that the behavior of the metabolite is similar to that of the parent drug under acute conditions. However, this lack of the acute effect does not exclude the possibility that the accumulation of metabolite during chronic therapy may contribute significantly to the pharmacological and electrophysiological action of amiodarone. Thus, more definitive electrophysiological studies in rabbits treated chronically with amiodarone and its metabolite will be required to estimate the contribution of the metabolite to the observed pharmacological action of amiodarone during chronic administration.

In summary, both amiodarone and its major metabolite, the deethyl analogue, have similar serum kinetics after intravenous administration in rabbits and are rapidly taken up by the myocardium. Neither the parent drug nor its metabolite produces significant electrophysiological changes under acute conditions in concentrations that are therapeutically relevant. The data do not exclude the possibility that the metabolite exerts pharmacological effects that are similar to those of the parent compound during chronic dosing.

REFERENCES

(1) R. E. Kates and P. Jaillon, *J. Pharmacol. Exp. Ther.*, **214**, 31 (1980).

(2) N. Benowitz, R. P. Forsyth, K. L. Melmon, and M. Rowland, *Clin. Pharmacol. Ther.*, **16**, 87 (1974).

(3) Y. W. Cho, *Am. Heart J.*, **85**, 648 (1973).

(4) D. L. Keefe and R. E. Kates, *J. Pharmacol. Exp. Ther.*, **220**, 91 (1982).

(5) E. Patterson, P. Stetson, and B. R. Lucchesi, *J. Cardiovasc. Pharmacol.*, **5**, 541 (1979).

(6) A. Yacobi, H. F. Stampfli, C. M. Lai, and B. L. Kamath, *Drug Metab. Dispos.*, **9**, 193 (1981).

(7) K. Nademanee, J. A. Hendrickson, R. Kannan, and B. N. Singh, *Am. Heart J.*, **103**, 950 (1982).

(8) B. N. Singh, K. Nademanee, N. Ikeda, and R. Kannan, in "New Aspects in the Medical Treatment of Tachyarrhythmias," G. Breithardt and F. Loogen, Eds., Urben and Schwarzenberg, Munich, Federal Republic of Germany, 1983, p. 46.

(9) R. Kannan, K. Nademanee, J. A. Hendrickson, H. Rostami, and B. N. Singh, *Clin. Pharmacol. Ther.*, **31**, 438 (1982).

(10) G. C. A. Storey, D. W. Holt, P. Holt, and P. V. L. Curry, *Ther. Drug Monit.*, **4**, 385 (1982).

(11) R. J. Flanagan, G. C. A. Storey, and D. W. Holt, *J. Chromatogr.*, **187**, 391 (1980).

(12) C. M. Metzler, NONLIN, Upjohn Co. Tech. Rep. 7292/69/7291/005, 1974.

(13) M. Gibaldi and D. Perrier, in "Pharmacokinetics," Dekker, New York, N.Y., 1982, p. 412.

(14) L. Harris, W. J. McKenna, E. Rowland, G. C. A. Storey, D. M. Krikler, and D. W. Holt. *Circulation*, **64**, Suppl. IV, 263 (1982).

(15) F. Andreason, H. Agerback, P. Bjergaard, and H. Hotzche, *Eur. J. Clin. Pharmacol.*, **19**, 293 (1981).

(16) R. Latini, S. Conolly, R. Kernoff, and R. E. Kates, *Circulation*, **66**, Suppl. II, 223 (1982).

(17) R. Latini, S. J. Conolly, and R. E. Kates *J. Pharmacol. Exp. Ther.*, **224**, 603 (1982).

(18) E. Riva, M. Gerna, P. Neyroz, R. Urso, I. Bartozek, and A. Guaitani, *J. Cardiovasc. Pharmacol.*, **4**, 270 (1982).

(19) R. Kannan, N. Ikeda, K. Prasad, M. Ookhtens, and B. N. Singh, *Circulation*, **64**, Suppl. IV, 69 (1981).

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Analysis of Carprofen Dosage Forms and Drug Substance by High-Performance Liquid Chromatography

A. J. ROSS, M. D. DEL MAURO, H. K. SOKOLOFF, and D. L. CASEY ˣ

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Abstract □ A high-performance liquid chromatographic method for the analysis of carprofen in solid dosage forms and as the bulk drug substance was developed. The simple, accurate, reproducible, and stability-indicating method was shown to be applicable to drug substance and dosage form stability studies, as well as the quality control of carprofen dosage forms.

Keyphrases □ Carprofen—analysis of dosage forms and drug substances, HPLC □ HPLC—analysis of carprofen dosage forms and drug substance

Carprofen [(±)-6-chloro-α-methylcarbazole-2-acetic acid (I)], under development as a nonsteroidal anti-inflammatory agent (1–9), has been formulated as a solid oral dosage form. Analytical procedures for the analysis of carprofen in biological fluids have appeared in the literature (10–16). However, since carprofen is a relatively new drug entity, analytical procedures suitable for the analysis and control of carprofen drug substance and dosage forms have not appeared in the literature or the USP.

The purpose of this work was to provide specific, accurate, and reproducible liquid chromatographic (HPLC) methods which would be applicable to various quality control functions, *i.e.*, drug substance stability studies, potency and content uniformity assays of dosage forms, and dosage form stability studies. To satisfy these criteria, it was necessary to develop a method which would separate I from all known impurities and potential degradation products and separate the impurities and potential degradation products from each other.

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