(2) B. V. Clineschmidt, M. A. McKendry, N. L. Papp, A. B. Pflueger, C. A. Stone, J. A. Totaro, and M. Williams, *J. Pharmacol. Exp. Ther.*, 208, 460 (1979).

(3) H. K. L. Hundt, L. W. Brown, and E. C. Clark, *J. Chromatogr.*, 183, 378 (1980).

ACKNOWLEDGMENTS

The authors thank Dr. D. C. Remy for a sample of the internal standard and Drs. J. D. Arnold and J. D. Irwin for supplying the human plasma samples.

Oral Bioavailability and Intravenous Pharmacokinetics of Amrinone in Humans

GEORGE B. PARK *, RONALD P. KERSHNER *, JON ANGELLOTTI *, ROGER L. WILLIAMS ‡, LESLIE Z. BENET ‡, and JEROME EDELSON *x

Received April 19, 1982, from the **Department of Drug Metabolism, Sterling-Winthrop Research Institute, Rensselaer, NY 12144* and the ‡*Drug Studies Unit, University of California, San Francisco, CA 94143.* Accepted for publication June 24, 1982.

Abstract □ Fourteen healthy males received two 75-mg doses of amrinone as a single capsule and as an intravenous solution in a single-dose crossover study. The mean (±*SD*) bioavailability, based on the area under the plasma concentration *versus* time curves, was 0.93 ± 0.12. The plasma data for these subjects during the intravenous phase was described by an open two-compartment body model with a mean (±*SD*) apparent first-order terminal elimination rate constant, β, of 0.19 ± 0.06 hr^{-1}, which corresponds to a half-life of 3.6 hr.

Keyphrases □ Amrinone—plasma levels in humans after oral and intravenous doses, pharmacokinetics, bioavailability □ Pharmacokinetics—amrinone after an intravenous dose, described by an open two-compartment body model □ Bioavailability—amrinone after oral and intravenous doses, plasma levels, pharmacokinetics

Amrinone[1], 5-amino[3,4′-bipyridin]-6(1*H*)-one, is a novel cardiotonic agent (1–4) which has demonstrated inotropic activity after both oral and parenteral administration to patients suffering from congestive heart failure (5–8). Previous investigations into the relationship between intravenous and peroral amrinone doses have suggested that it required twice as much amrinone by the oral route to achieve the same inotropic response as with an intravenous bolus (9). This report describes the results of our investigations into the bioavailability of amrinone, and includes a nonlinear least-squares estimate of the pharmacokinetic parameters of amrinone following intravenous administration.

EXPERIMENTAL

Study in Human Volunteers—In this single-dose crossover study, 14 healthy male volunteers each received two 75-mg doses of amrinone, as a single oral capsule and as an intravenous solution, with a 1-week washout interval between medications. The sequence of drug administration for each subject was determined by random assignment. Appropriate institutional review and approval were obtained. No subject had a history suggestive of renal, hepatic, or cardiac dysfunction. The mean (±*SEM*) age of these volunteers was 28.9 ± 1.2 years; the mean weight was 77.4 ± 3.4 kg and the mean height was 180 ± 1.7 cm. Blood samples were collected (potassium oxalate) before medication and at 0.17, 0.33, 0.50, 0.75, 1.0, 1.25, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 15.0, and 24.0 hr postdose. The blood was centrifuged; plasma was separated and frozen until it was assayed.

Assay Procedure—The analysis of plasma amrinone followed a published procedure (10) with the following minor changes: a 40° water bath was used to evaporate the residual ethyl acetate and ~2.3% (by volume) of tetrahydrofuran was added to the mobile phase. Plasma standards, which were prepared in normal human plasma, were extracted and analyzed with each set of plasma samples from the subjects in the study. The concentration of amrinone in plasma was determined by comparison with the regression line of the peak height ratios of the standards. The minimum quantifiable level of amrinone was estimated as the concentration whose lower 80% confidence limit just encompassed zero[2] and was ~0.02 μg/ml.

Five separate high-performance liquid chromatographic (HPLC)

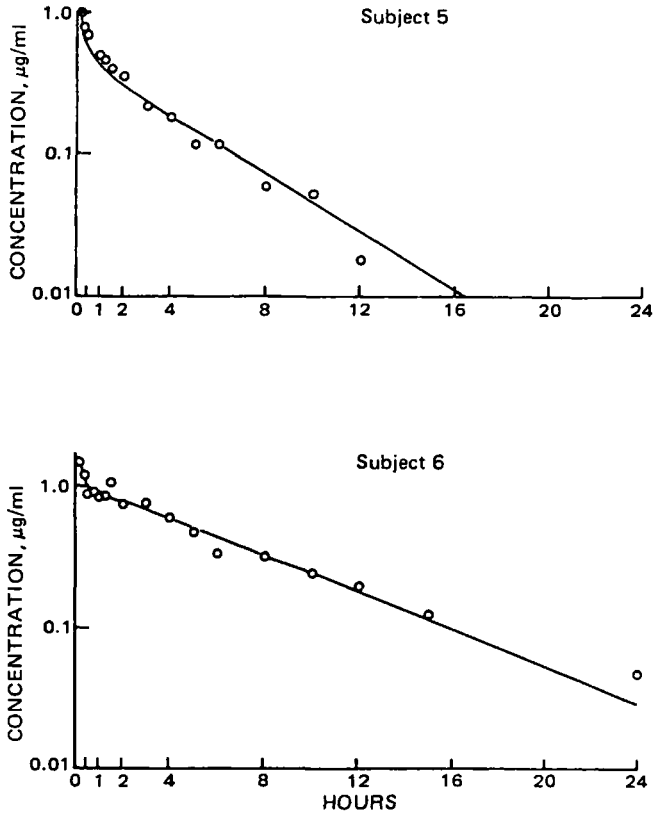

Figure 1—*Plasma concentration of amrinone in human volunteers after intravenous administration of a solution containing 75 mg of amrinone. Plasma concentrations observed (○) in two subjects with widely divergent clearance rates, and concentrations predicted by the open two-compartment body model (—).*

[1] Inocor; Sterling Drug, Inc., New York, N.Y.

[2] R. W. Ross and H. Stander, "Some Statistical Problems in Drug Metabolism," paper presented at the Princeton Conference on Applied Statistics, December 1975.

0022-3549/83/0700-0817$01.00/0

Table I—Pharmacokinetic Parameters in Humans Following a 75-mg iv Dose of Amrinone

Subject	Regression Dependent							Model Independent		
	α, hr^{-1}	β, hr^{-1}	A, $\mu g/ml$	B, $\mu g/ml$	CL, liter/hr	V_β, liter	Vd_{ss}, liter	CL, liter/hr	AUC_0^{24}, $\mu g\ hr/ml$	AUC_0^∞, $\mu g\ hr/ml$
1	9.08	0.14	0.93	0.65	16.1	113	110	16.1	4.78	5.13
2	4.13	0.23	1.30	0.50	30.1	132	116	30.2	2.59	2.59
3	8.06	0.20	2.59	0.64	21.2	106	96.9	20.8	3.86	3.96
4	3.26	0.13	1.32	0.55	16.2	125	114	16.2	4.36	4.36
5	4.29	0.24	1.22	0.50	31.3	132	117	31.4	2.23	2.23
6	7.58	0.15	1.09	1.06	10.1	69.7	68.2	10.1	7.34	7.69
7	4.00	0.17	1.20	0.62	19.4	112	104	19.4	4.28	4.45
8	18.4	0.25	46.4	0.51	16.6	65.4	29.6	16.6	1.89	1.89
9	51.4	0.14	2.20	0.73	14.0	102	101	14.0	5.48	5.85
10	0.33	0.08	0.57	0.35	12.5	151	120	12.4	5.44	6.06
11	4.87	0.29	2.54	0.59	29.1	102	82.4	29.1	2.49	2.49
12	2.04	0.14	0.78	0.73	13.0	96.2	90.3	13.0	5.68	5.98
13	3.19	0.24	0.75	0.74	22.6	94.8	88.7	22.6	3.53	3.62
14	4.45	0.29	1.91	0.74	25.1	86.9	75.2	25.1	2.88	2.88
Mean	8.94	0.19	4.62	0.64	19.8	106	93.9	19.8	4.06	4.23
$\pm SD$	13.0	0.06	12.0	0.17	6.9	23.9	24.6	7.0	1.58	1.74

Table II—Regression-Independent Parameters in Humans Following a Single Oral Capsule Containing 75 mg of Amrinone

Subject	t_{max}, min	C_{max}, g/ml	k_t, hr^{-1}	AUC_0^{24}, $\mu g\ hr/ml$	AUC_0^∞, $\mu g\ hr/ml$	Bioavailability Ratio[a], %
1	30	0.89	0.10	4.61	5.10	99
2	30	1.04	0.20	2.22	2.22	86
3	75	0.84	0.12	3.51	3.76	95
4	60	0.95	0.13	3.91	3.91	90
5	45	0.87	0.25	1.91	1.91	86
6	120	0.81	0.11	6.96	7.48	97
7	45	1.24	0.12	4.13	4.37	98
8	90	0.44	0.24	1.55	1.55	82
9	120	0.78	0.10	6.79	7.50	128
10	90	0.86	0.12	4.63	5.06	83
11	60	0.93	0.26	1.99	1.99	80
12	30	0.92	0.12	4.86	5.20	87
13	30	1.04	0.14	3.57	3.57	99
14	30	1.66	0.27	2.63	2.63	91
Mean	61	0.95	0.16	3.80	4.02	93
$\pm SD$	33	0.27	0.07	1.70	1.92	12

[a] Oral AUC_0^∞ divided by model-independent AUC_0^∞ during the intravenous phase, multiplied by 100.

systems were used. Each contained an automatic injector, a pump, a precolumn[3], a column[4], and an UV detector scanning the effluent from the column at 340 nm.

Pharmacokinetic Calculations—The data obtained from the analysis of the human plasma samples during the intravenous phase of the study was described by an open two-compartment body model by means of an unweighted nonlinear regression (NLIN) procedure (11). An attempt was made to describe the plasma concentration data obtained during the oral phase of the study by either an open one- or two-compartment body model with first-order absorption.

In addition to the regression-dependent parameters, the plasma concentration data also was analyzed with respect to the following model-independent parameters: the maximum observed plasma concentration (C_{max}), the time at which the maximum concentration was observed (t_{max}), and the area under the plasma concentration *versus* time curve (AUC_0^{24}). The latter was calculated by trapezoidal rule, including all of the data for the study period. For those subjects who had detectable concentrations of amrinone in the last sample examined, the AUC was extrapolated to infinite time.

RESULTS AND DISCUSSION

The concentrations of amrinone in the plasma samples from each of the volunteers were determined. After intravenous medication, the plasma concentrations declined biexponentially with time, suggesting that a two-compartment body model would be appropriate. Pharmacokinetic parameters for each subject were estimated after computer-fitting the plasma data by an iterative nonlinear least-squares regression technique (11); results are shown in Table I.

The mean apparent first-order terminal elimination half-life for amrinone was ~3.6 hr. The mean apparent volume of distribution at steady state was 94 liters or, dividing by the mean body weight, 1.2 liters/kg. This value suggests that amrinone may be bound to, or partition favorably into tissues. The mean value for α, 8.94 hr^{-1}, corresponds to a half-life of <5 min. The model-independent clearance (dose/AUC_0^∞) is in reasonable agreement with the clearance calculated from the open two-compartment body model (Table I). Although there is a threefold difference between the highest (subject 5) and lowest (subject 6) clearances, the observed concentration data during the intravenous phase was described adequately by the model for both of these subjects; a comparison of the observed and predicted concentrations is shown in Fig. 1. The agreement between the observed values and those predicted by the open two-compartment body model is apparent. The AUC during the intravenous phase of the study was estimated by the trapezoidal method (Table I). The mean ($\pm SD$) value was 4.23 ± 1.74 μg hr/ml.

The plasma concentration data obtained during the oral phase of the study was not described adequately by either the open one- or two-compartment body model with first-order absorption; several weighting schemes were tried. The AUC was determined by the trapezoidal method and, if necessary, extrapolated to infinite time by use of the plasma concentration in the last observed sample and the apparent first-order terminal elimination rate (Table II).

The mean ($\pm SD$) absolute bioavailability, or oral–parenteral ratio (defined as the ratio of the AUC_0^∞ for the capsule to the regression-independent AUC_0^∞ for the intravenous solution) is 0.93 ± 0.12. Analysis of variance shows that the AUC_0^∞ values for medication by either the intravenous or oral route are not significantly different ($p = 0.24$).

Although no rigorous pharmacokinetic analysis was performed, estimates of the terminal elimination half-life of amrinone from the bloodstream of healthy volunteers have been reported (12). The mean values were 2.6 hr after intravenous medication and 3.7 hr after oral treatment. These previously reported values are less than those obtained in the present study, probably due to the shorter time period during which

[3] Phenyl-Corasil; Waters Associates, Milford, Mass.
[4] μ-Bondapak phenyl; Waters Associates, Milford, Mass.

meaningful observations were made. Converting the mean terminal elimination rate constants generated in this study to half-lives results in values of 3.6 and 4.3 hr for the intravenous and oral treatments, respectively. In contrast, chronic congestive heart failure patients who received oral amrinone had a mean terminal elimination half-life of 8.3 hr (7). Since these patients all had symptoms that were sufficient to place them in class III or IV of the New York Heart Association classification, it is not surprising that their low cardiac output should result in a relatively long half-life for amrinone. Therefore, from the pharmacokinetic considerations discussed above, it would seem that an oral dosage regimen involving medication every 8 hr should be adequate for the treatment of patients with congestive heart failure.

REFERENCES

(1) A. A. Alousi, A. E. Farah, G. Y. Lesher, and C. J. Opalka, Jr., *Fed. Proc. Fed. Am. Soc. Exp. Biol*, **37**, 914 (1978).

(2) A. A. Alousi, A. E. Farah, G. Y. Lesher, and C. J. Opalka, Jr., *Circ. Res.*, **45**, 666 (1979).

(3) A. A. Alousi and J. Edelson, in "Pharmacological and Biochemical Properties of Drug Substances," vol. 3, M. E. Goldberg, Ed., American Pharmaceutical Association, Washington, D.C., 1981, p. 120.

(4) A. E. Farah and A. A. Alousi, *Life Sci.*, **22**, 1139 (1978).

(5) J. R. Benotti, W. Grossman, E. Braunwald, D. D. Davolos, and A. A. Alousi, *N. Engl. J. Med.*, **299**, 1373 (1978).

(6) J. R. Benotti, W. Grossman, E. Braunwald, and B. A. Carabello, *Circulation*, **62**, 28 (1980).

(7) J. Edelson, T. H. LeJemtel, A. A. Alousi, C. E. Biddlecome. C. S. Maskin, and E. H. Sonnenblick, *Clin. Pharmacol. Ther.*, **29**, 723 (1981).

(8) J. Wynne, R. F. Malacoff, J. R. Benotti, G. D. Curfman, W. Grossman, B. L. Holman, T. W. Smith, and E. Braunwald, *Am. J. Cardiol.*, **45**, 1245 (1980).

(9) T. H. LeJemtel, E. C. Keung, W. J. Schwartz, C. S. Maskin, M. A. Greenberg, R. S. Davis, R. Forman, H. S. Ribner, and E. H. Sonnenblick, *Trans. Assoc. Am. Physicians*, **92**, 325 (1979).

(10) M. P. Kullberg, B. Dorrbecker, J. Lennon, R. Rowe, and J. Edelson, *J. Chromatogr.*, **187**, 264 (1980).

(11) J. T. Helwig and K. A. Council, Eds., "SAS User's Guide," SAS Institute, Raleigh, N.C., 1979, p. 317.

(12) M. P. Kullberg, G. B. Freeman, C. Biddlecome, A. A. Alousi, and J. Edelson, *Clin. Pharmacol. Ther.*, **29**, 394 (1981).

Influence of Food on Aspirin Absorption from Tablets and Buffered Solutions

WILLIAM D. MASON[x] and NATHANIEL WINER

Received May 3, 1982, from the *Pharmacokinetics Laboratory, University of Missouri-Kansas City, Schools of Pharmacy and Medicine, Kansas City MO 64108.* Accepted for publication July 14, 1982.

Abstract □ After a standard meal, 12 normal volunteers received three aspirin dosage forms in a single-dose, complete crossover study. The three dosage forms were an unbuffered tablet, an effervescent solution with 16 meq of buffer, and an effervescent solution with 34 meq of buffer. Plasma and urine aspirin, salicylic acid, and salicyluric acid were measured for 10 hr. Significant differences in the absorption kinetics of aspirin were observed, with aspirin from the two solutions being absorbed faster than from the tablet. Urine pH and renal clearance for all three acid compounds were influenced by the buffer during the first 2 hr only. Area under the curve (AUC) and urine accumulation comparisons suggest that 15–20% more aspirin reaches the general circulation after the tablet, but that the total salicylate absorbed is not different. Comparison with an earlier study indicates the solution with 34 meq of buffer is virtually unaffected by the presence of the meal while the solution with 16 meq buffer and the tablet are more slowly absorbed in the nonfasted state.

Keyphrases □ Aspirin absorption—influence of food, comparison of tablets and buffered solutions □ Absorption—aspirin, influence of food

Aspirin is the drug of choice when a mild analgesic–antipyretic is required, and it is also a primary agent used in the chronic management of rheumatoid arthritis and osteoarthritis. After oral administration, rapid absorption is desirable to provide the rapid onset of effects and to reduce contact time with the gastric mucosa. The potential influence of food on the absorption kinetics of aspirin from two different buffered effervescent solutions and an unbuffered tablet dosage form is the subject of this report.

BACKGROUND

A recent report (1) from this laboratory describes the kinetics of aspirin absorption after oral administration of a tablet and two buffered solutions in fasting subjects. It was noted that while the solution with 16 meq of buffer was absorbed more rapidly than the one with 34 meq of buffer, both provided more rapid and less variable absorption than the tablet dosage form. Because the formulation with 34 meq of buffer is frequently used to treat the combined symptoms of headache and upset stomach associated with overindulgence in food and drink, the absorption kinetics of the same three formulations in nonfasted subjects were evaluated.

A recent review (2) describes the effects of food on drug bioavailability in general. Aspirin absorption from two conventional tablet dosage forms is clearly delayed and slowed when administered after a meal (3). Studies of salicylic acid kinetics suggest dispersed dosage forms such as granules (4) and effervescent solutions (5) are less subject to delayed absorption when food is present in the stomach.

Clearly the composition, quantity, and time of aspirin dosing relative to a meal can be significant factors (2, 3) in evaluating the effects of food on drug absorption kinetics. The meal chosen for the present study was previously evaluated (6) to characterize the associated physiological responses of the stomach including emptying rate, pH, and total acid production. Because the titratable acid reaches a maximal plateau between 1 and 2 hr after eating, a dose time 1 hr postcibus should provide a maximal test of the buffered solutions. The study described herein is identical to the one reported previously (1) in all aspects except the subjects in the present study ate a standard meal 1 hr prior to dosing. Two subjects were used in both studies.

EXPERIMENTAL

Dosage Forms—Three commercially available dosage forms were used to provide approximately equal doses of aspirin: two unbuffered tablets[1], each containing 325 mg of aspirin (T); one effervescent tablet[2] containing 640 mg of aspirin, 1.825 g of sodium bicarbonate, and 1.079 g of citric acid (16 meq of buffer) (S-16); and two effervescent tablets[3], each containing 324 mg of aspirin, 1.904 g of sodium bicarbonate, and 1.0 g of citric acid (34 meq of buffer) (S-34).

[1] Bayer Aspirin, Glenbrook Laboratories, Division of Sterling Drug Inc., New York, N.Y.

[2] Aspirvess, Miles Laboratory, Inc., Elkhart, Ind.

[3] Alka-Seltzer, Miles Laboratories, Inc., Elkhart, Ind.

0022-3549/83/0700-0819$01.00/0