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Naproxen Oral Absorption Characteristics

Richard A. Runkel, Karla S. Kraft, Gerhard Boost, Hilli Sevelius, Enrico Forchielli, Robert Hill, Ralph Magoun, J.B. Szakacs, and Eugene Segre

Institute of Pharmaceutical Sciences and the Institute of Clinical Medicine, Syntex Research[1]

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Oral doses of 2.5 mg/kg of naproxen in beagle dogs were found to be rapidly and completely absorbed. In the dog, the sodium and calcium salts of naproxen were absorbed significantly faster than the non-micronized form of naproxen, while the micronized drug could not be distinguished from either the salts or the macro form.

Area responses to intravenous and oral doses of naproxen in two human subjects showed that oral doses of 200 and 250 mg were apparently one hundred percent absorbed. In a comparison of the amount and rate of absorption of naproxen form capsules and tablet formulation variants, no significant difference in either of the parameters could be detected. These results indicated that capsules and tablets were identical in absorption characteristics and furthermore that neither increasing the concentration of magnesium stearate nor changing the tablet lubricant to stearic acid had any effect on availability. Similarly, the tablet formulation with an extraordinarily long disintegration time and the tablet formulated with an alkalinizing agent were not significantly different from the other tablets or the capsules.

A comparison of the results obtained from oral administration of 200 mg of naproxen taken by volunteer subjects in three forms, suspensions, capsules and tablets, revealed an apparent rise in the absorption rate constant with the suspension from but no difference in the amount of drug absorbed. It was suggested that more rapid dissolution of the drug in the wetted and well dispersed form explained the faster appearance of naproxen in the plasma. In a second tablet formulation study where the relative amounts of naproxen and lactose were altered, the drug was absorbed to the same extent, and at the same rate regardless of the fraction of total tablet weight that was naproxen. Finally, although differences in absorption rate constants were not statistically significant, naproxen appeared to be more rapidly absorbed in fasted subjects than in those who took the drug with food. However, there was no diminution in the amount absorbed in the non-fasted subjects.

The chemistry of naproxen [*d*-2-(6-methoxy-2-naphthyl) propionic acid], a potent systemic anti-inflammatory agent, has been reported by Harrison, *et al.*[2] Rooks, *et al.*[3] have described its biological activities. Naproxen was found to be 0.7, 5.5, and 11 times as active as indomethacin, aspirin, and phenylbutazone, respectively, in inhibiting the carrageenan-induced inflammation of the rat paw. Its analgetic activity was found to be approximately 7 times that of aspirin in a phenylquinone induced writhing assay and a dose related antipyretic activity was observed in rats with yeast induced pyresis. No significant cardiovascular or central nervous system activity was noticed. In two recent presentations[4,5] on its human clinical properties, Drs. Katona and Lussier found naproxen to be effective in the relief of the symptoms of active rheumatoid arthritis. An examination of the distribution, metabolism and excretion properties of naproxen in humans and several laboratory animals[6]

1) Location: *Palo Alto, California, 94304.*
2) I.T. Harrison, B. Lewis, P. Nelson, W. Rooks, A. Roskowski, A. Tomolonis, and J.H. Fried, *J. Med. Chem.*, **13**, 203 (1970).
3) W.H. Rooks, II, *Fed. Proc.*, **29**, 420 (1970).
4) G. Katona, Pan American Congr. of Rheumatol., Punta del Este, Uruguay, February 1971.
5) A. Lussier, Seventh Annual Mtg. of the Canad. Soc. of Chemotherapy, Mont Orford, Quebec, May 1971.
6) R. Runkel, M. Chaplin, G. Boost, E. Segre and E. Forchielli, *J. Pharm. Sci.*, **41**, 703 (1972).

revealed that the drug has a volume of distribution in humans similar to that of salicylates and a plasma half-life of approximately 14 hr. This report presents the details of the oral absorption characteristics of naproxen from several dosage forms, including capsules, tablets and suspensions.

Experimental

Dosage Forms——Two fluid dosage forms were employed in the study, a sterile solution for intravenous experiments and an aqueous suspension for certain portions of the human oral experiments. The intravenous solutions were prepared by neutralizing naproxen with equimolar amounts of sodium hydroxide in aqueous solutions and bringing to volume with pH 7.5 phosphate buffer. Sterilization was achieved by filtration. The volume administered to the human subjects was 10 ml while only 5 ml was given to the beagle dogs. The aqueous suspensions were prepared by placing naproxen powder in a ground glass tissue homogenizer with 2 ml of the suspending vehicle[7] and homogenizing for one minute. Following this the slurry was quantitatively transferred with the aid of additional vehicle and brought to a total volume of 10 ml for each individual dose.

Table I. The Formulations and Total Weights of the Solid Dosage Forms[a]

Dosage form	Percent Ingredient Present in Formulation							Total weight	
	Naproxen[b]	Corn starch U.S.P.	Lactose U.S.P. (spray dried)	Polyvinyl-pyrrolidone[c]	Magnesium stearate U.S.P.	Stearic acid U.S.P.	D.A.A.[d]	Human	Dog
All capsules	33.3	6.7	60.0	—	—	—	—	150	75
Tablet formulation B	40	10.0	49.2	0.6	0.2	—	—	125	—
Tablet formulation C	40	10.0	49.2	0.6	—	0.2	—	125	—
Tablet formulation D	40	10.0	48.4	0.6	1.0	—	—	125	—
Tablet formulation E	40	—	59.2	0.6	0.2	—	—	125	—
Tablet formulation F	33.3	10.0	—	1.0	0.2	—	55.5	150	—
Tablet formulation B (concentrated naproxen)	66.7	10.0	21.6	1.5	0.2	—	—	375	—

a) The tablets were compressed to a hardness of 5 to 9 Strong-Cobb units and had a U.S.P. disintegration time of 2—5 minutes, except Formulation E which disintegrated between 15 and 45 minutes.
b) supplied by Syntex Research Corporation, Palo Alto, California.
c) plasdone, Antara Chemicals, New York, New York.
d) dihydroxy aluminum amino acetate N.F., Chattem Chemical, Chattanooga, Tennessee.

The composition of the solid dosage forms used in this study are presented in Table I. The powders filled into the gelatin capsules were dry blended and forced through a number 60 sieve (openings are 250 μ) before encapsulation. The capsule formulation in the oral portion of the dog experiments is also listed in Table I. The drug forms blended with the diluents were naproxen, micronized naproxen, sodium naproxen and calcium naproxen. The 50 mg tablet formulation variants were all compressed to the same size, shape and hardness and the 250 mg tablets had diameter-to-thickness ratio and hardness characteristics identical to the 50 mg tablets. Thus every effort was made to maintain constant tablet characteristics in order to examine the effect of the various ingredients on naproxen bioavailability.

Experiment Design——Six beagle dogs, three male and three female, all approximately 10 kg in weight received 2.5 mg per kg of naproxen or its sodium or calcium salt in equimolar amounts on the same day in five succeeding weeks. The dogs were acclimatized to laboratory conditions for two weeks before the experiment and were fasted overnight, with water allowed ad lib, before each dosing. The drug was adminis-

7) The vehicle consisted of 0.5% sodium carboxymethylcellulose (Hercules type 7 LP, Hercules Powder Co., Wilmington, Delaware) and 0.4% polysorbate 80 (Tween 80, Atlas Powder Co., Wilmington, Delaware) in distilled water.

tered orally or intravenously (by rapid injection into the jugular vein) in a latin square design until all of the five forms had been tested six times. Ten ml blood samples were drawn from the jugular vein into heparinized Vacutainers[8] at fifteen and thirty minutes and at 1,2,3,4,6 and 24 hours after administration of the dose. In addition, a five minute sample was obtained when the animals were dosed intravenously.

The human studies were performed in five phases. Healthy subjects with no previous history of aspirin intolerance or g.i. disorders were selected for these studies. An effort was made to choose subjects within a narrow range of age and weight. The conditions set required that no other drugs or alcohol be ingested 48 hours prior to or during the experiments. In all experiments subjects were fasted overnight with water being allowed ad lib.

The intravenous experiment was performed first; it was initiated by the rapid injection of a sterile aqueous solution of ^{3}H-naproxen. Blood samples were drawn at 1/2, 2, 4, 8 and 24 hours. Details of this experiment have been submitted for publication.[6] Two of the volunteer subjects (J. J.-female, W. K.-male) who took part in the intravenous experiment were later enrolled in some of the oral experiments and a comparison of the data from the two modes of administration will be made here.

The experiment that examined the effect of capsules and tablet formulation variants on plasma profiles was designed so that 14 subjects (12 female, 2 male) received six formulations in three treatment periods. The formulations were administered according to an incomplete, randomized block design. Each tablet formulation was tested six times while the capsule appeared in the schedule twice and consequently was administered twelve times. Since the capsules and tablets in this experiment contained 50 mg of naproxen, four tablets or capsules were administered to achieve the 200 mg dose. Blood samples were drawn at 1,2, 4, 8 and 24 hours following ingestion.

In the second oral experimnet, 200 mg of naproxen were administered in suspension form. The experimental design was simple: three volunteer subjects received a single oral dose on two occasions. The second administration followed the first after a one week interval. Blood samples were drawn at fifteen and thirty minutes and 2, 4, 8 and 24 hours after ingestion of the dose.

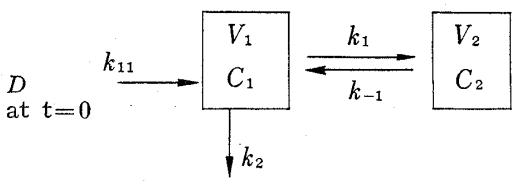
The next oral experiment was designed to compare two formulations, differing in concentration of naproxen within tablets. The first dose consisted of five 50 mg. tablets containing 40 percent naproxen, while the second was a single 250 mg tablet with 66 percent naproxen (see Table I). Eight subjects (four male and four female) received each form twice in a simple cross-over design. Blood samples were drawn at fifteen and thirty minutes and at 1, 2, 4, 8 and 24 hours after ingestion of the dose.

The absorption characteristics of naproxen from suspension under fasted and non-fasted conditions were studied in six subjects three of whom were male and three female. The six subjects received a 250 mg dose first following an overnight fast and then a second time with a standard breakfast consisting of a donut, fruit juice, ham and eggs, and coffee. The non-fasted dose was administered mid-way through the breakfast while the fasted dose was taken with a small glass of water. The drug was presented in suspension in order to eliminate, as much as possible, the effects of disintegration and dissolution which may be complicating factors when solid dosage forms are used. Blood samples were drawn at fifteen and thirty minutes and at 1, 2, 4, 8 and 24 hours after ingestion of the dose.

Analytical Method——The blood specimens, drawn at the times indicated by the experiment protocols, were centrifuged and the resulting plasma samples immediately frozen. Naproxen concentration in the plasma was determined by a gas liquid chromatographic technique which is to be described in detail elsewhere.[9] One ml. of acidified (HCl) plasma sample was extracted with ethyl acetate followed by back extraction of the ethyl acetate layer with aqueous sodium bicarbonate. The naproxen was isolated from the acidified $NaHCO_3$ solution with diethyl ether, and the ethereal solution was treated with diazomethane to form the methyl ester. Quantitation was achieved by gas liquid chromatography using flame ionization detection. The methyl ester of 6-methoxy-2-naphthyl-acetic acid was employed as an internal standard. A 4 ft. long, 3 mm inner diameter glass column packed with 3.8 percent silicone Elastomer[10] on 80 to 100 mesh Diatoport S[11] was used under the following conditions: column temperature was 170°; injection temperature 200°; detector temperature 240° and the carrier gas (helium) flow rate was 70 ml. per minute.

Data Treatment——In this study of the relative bioavailability of naproxen the experimental measurement was plasma concentration of unchanged drug, and the concentration *vs* time curve was analyzed for indications of the relative amount and the rate of drug absorption. In all cases area under the plasma concentation *vs* time curve was taken as a measure of the amount of drug absorption. Areas, in square inches, were obtained from the linear plots of plasma concentration *vs* time by planimetry and subsequently converted to units of μg/ml·hr.

8) Becton-Dickenson Co., Rutherford, New Jersey.
9) L.J. Throop and R.J. Leibrand to be published.
10) SE 30, Applied Science Labs., State College, Pennsylvania.
11) Hewlett-Packard Analytical Instruments, Avondale, Pennsylvania.



In order to define the desired absorption rate constants a mathematical model which yields appropriate equations must be applied. Semilog plots of the plasma concentration data yielded three phase curves, consequently the two compartment open model with first order absorption[12] was assumed to be applicable. Equation 1 which defines the plasma concentration, C_1, as a function of time has the necessary three exponentials; and when it is applied to the individual data sets, k_{11} values can be obtained for each expriement. In this case D is the dose in mg, k_{11} is the absorption rate constant in hours^{-1}, V_1 is the volume in ml. of compartment 1 and A, B, C, α and β are composite constants which contain the individual rate constants shown in the model diagram. Details of this model and Equation 1 may be found in a report by Wagner.[13]

$$C_1 = \frac{k_{11}D}{V_1}[Ae^{-\alpha t}+Be^{-\beta t}+Ce^{-k_{11}t}] \qquad \text{Eq. 1}$$

The absorption rate constants were obtained from the log C_1 *vs* time plots by the graphical technique of feathering.[14] This method of graphical estimation of slopes begins with the terminal phase of the curve and successively isolates the contributions made by each of the three exponentials until the rising portion of the curve may be analyzed separately.

Result and Discussion

Dog Experiments

Figure 1 shows the plasma profiles following intravenous and oral administration of 2.5 mg per kg of naproxen. At all times later than one hour, the oral concentrations are essentially the same as the intravenous concentrations. Consequently, it appears that oral doses in the dog were as effective as intravenous doses in eliciting blood level responses.

Having observed the plasma profiles resulting from the two modes of administration and with the qualitative notion that the two methods of dosing produce similar responses in the blood, it is instructive to look at the areas (Table II) for a more quantitative indication of drug availability. The 2.5 mg/kg dose of naproxen given intravenously and orally caused identical mean area responses 371 (μg/ml·hr) although the standard deviation of the oral form was somewhat larger. Indeed, the data in Table II allow the statement to be even more inclusive because the mean areas are all the same regardless of the mode of administration or the form in which the drug was given. On the basis of these data, one may conclude that naproxen is apparently one hundred percent absorbed when administered orally; moreover the form in which the drug is prepared, micronized or the sodium or calcium salts, has no affect on the amount absorbed.

The plasma profiles in Fig. 2 do, however, suggest some difference in the rates of absorption of oral doses of naproxen. The mean peak concentration following administration of the sodium salt is higher and occurs at an earlier time than that of naproxen suggesting that the former is absorbed faster. That is, even though the drug is apparently one hundred percent absorbed from both forms, the salt allows more rapid absorption. Referring to Table II and the absorption rate constants, k_{11}'s, the mean values for the two salts, 4.6 and 5.0, are significantly different from the naproxen value, 1.4, by the Neuman-Kuhl's[15] range test. This means that in the beagle dog, naproxen is indeed absorbed faster when given as a salt than when administered as unaltered drug. The mean absorption rate constant for micronized naproxen was not found to be significantly different from the non-micronized form. This result implies that little or no advantage, in terms of rate of absorption, could be gained by reducing the particle size of the orally administered drug.

12) J.G. Wagner, *J. Pharm. Sci.*, **58**, 86 (1969).
13) J.G. Wagner, *J. Pharm. Sci.*, **59**, 1049 (1970).
14) J.G. Wagner, *Clin. Pharm. & Therap.*, **8**, 201 (1967).
15) The authors wish to thank Mr. E. Averkin for his statistical treatment of these data.

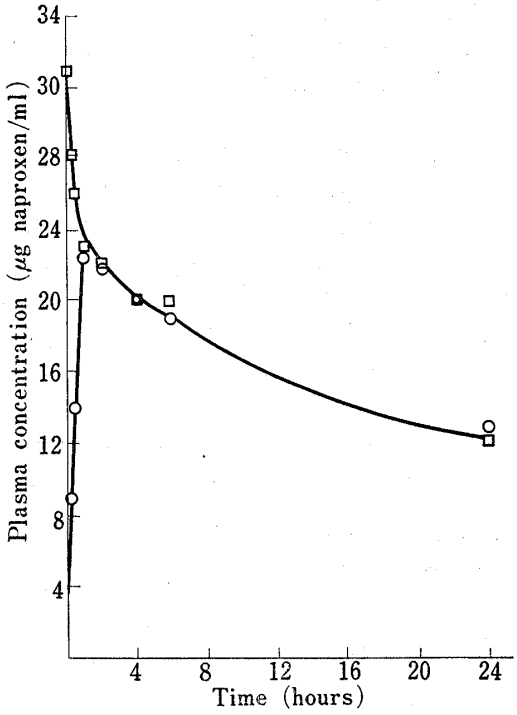


Fig. 1. Plasma Concentrations of Naproxen in Beagle Dogs following Intravenous (□) and Oral (○) Doses of 2.5 mg/kg

The intravenous curve represents the average of six animals and the oral curve the average of 24 animals.

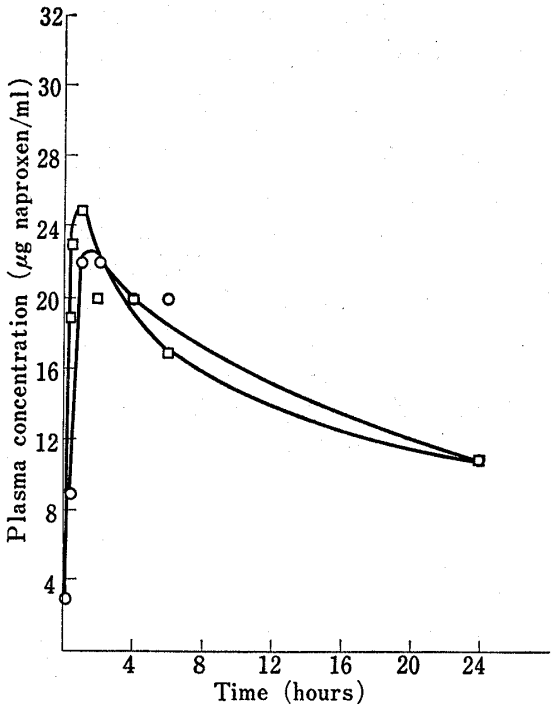


Fig. 2. Plasma Concentrations of Naproxen in Beagle Dogs following Oral Doses of 2.5 mg/kg of Naproxen (○) and Its Sodium Salt (□)

Each point on the two curves represents the average of six experiments.

Table II. The Effect of Intravenous and Various Forms on the Areas under the Curve and the Absorption Rate Constants in Beagle Dogs Following Naproxen Doses of 2.5 mg/kg

Form	Route	Area (O—24 hr) (μg/ml·hr) Mean	±	SD	k_{11} (hr^{-1}) Mean	±	SD	Number of determinations
Solution	*i.v.*	371	±	57		±		6
Naproxen	oral	371	±	101	1.4	±	1.1	6
Naproxen (micronized)	oral	389	±	60	3.0	±	1.5	6
Sodium salt of naproxen	oral	388	±	86	4.6	±	3.3	6
Calcium salt of naproxen	oral	364	±	57	5.0	±	4.6	6

When differences in rate of absorption between solid oral dosage forms of the same drug are observed, those differences generally result from differing drug dissolution rates.[16] Considered in this way, the oral dog results suggest that the dissolution rate of sodium or calcium naproxen is sufficiently faster than naproxen itself to cause significant increases in the rate at which naproxen appears in the blood but does not alter the ultimate amount absorbed.

Human Experiments

Efficiency of Absorption——Figure 3 shows a comparison of the intravenous and oral plasma profiles from one of the two subjects who received naproxen by both routes of administration. Note that the dose subject J.J. received orally was 200 mg while the intravenous

16) G. Levy, "In Prescription Pharmacy," Lippincott, Philadelphia, Pennsylvania 1963, Chapter II.

dose was 93 mg. Justification for plotting one-half of the 200 mg dose concentrations here will be found in the comparative metabolism paper cited earlier in this report[6] where area responses to doses of 100, 200, and 300 mg revealed a linear relationship between the two in the specified dose range.

A quantitative comparison of the area responses to intravenous and oral doses in both volunteer subjects is given in Table III. In female subject J.J. administration of the 200 mg oral dose resulted in a plasma concentration curve with an area of 511 μg/ml·hr, twice the area caused by approximately one-half that dose given intravenously, 263 μg/ml·hr. Similarly in male volunteer W.K. an area of 189 μg/ml·hr was obtained following —100 mg intravenous dose and 2.5 times that value, 466 μg/ml·hr when 250 mg were taken orally. In humans, as in beagles dogs, therefore, it appears that oral doses of naproxen (in the dose range 200 to 250 mg) are completely absorbed.

Formulation Effect on Absorption——The mean area responses to 200 mg oral doses of naproxen in capsules and the various tablet forms are shown in Table IV. Since no signifi-

Table III. The Effect of Route of Administration on the Areas under the Curve in Humans following Doses of Naproxen ranging from 93 to 250 mg

Subject	Route	Dose	Area (0—24 hr) (μg/ml·hr) Mean ± SD	Number of determinations
J.J.	*i.v.*	93 mg	245 ± 26	2
	oral	200 mg	511 ± 33	5
W.K.	*i.v.*	93 mg	189 ± 43	2
	oral	250 mg	466 ± 85	4

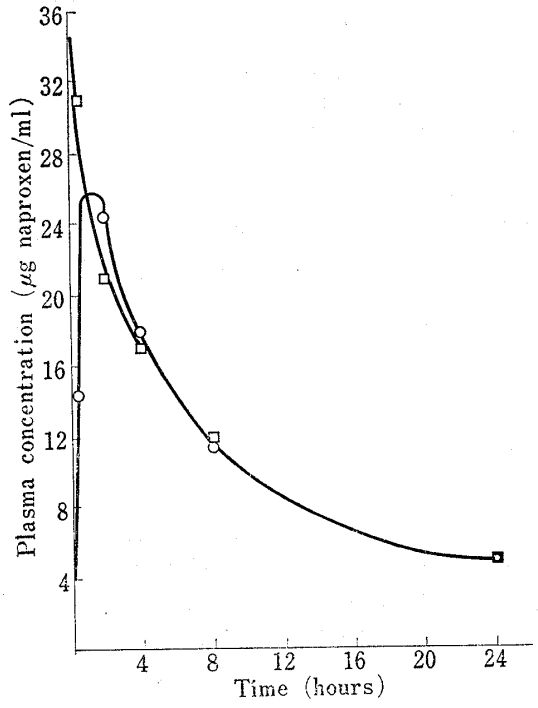


Fig. 3. Plasma Concentrations of Naproxen in Subject J.J. following Intravenous (□) and Oral (○) Doses of Naproxen

One-half the oral plasma concentrations are plotted here because the intravenous dose was approximately 100 mg while the oral dose was 200 mg. The points on the *i.v.* curve represent the average of experiments, and on the oral curve the average of five experiments.

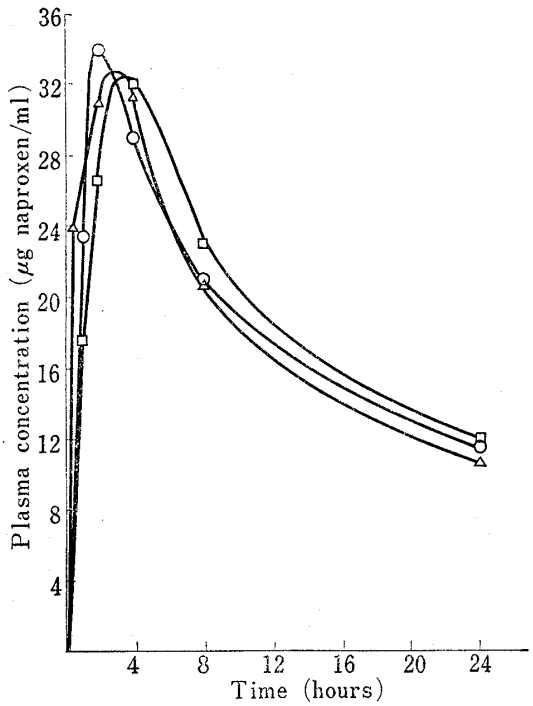


Fig. 4. Plasma Concentrations of Naproxen following Oral Doses of 200 mg of Aqueous Suspension (△), Capsules (○), and Tablets (□)

The curves represent the average of 6, 12 and 24 experiments for the suspension, capsules and tablets respectively.

cant difference among the mean area values could be detected, it appears that naproxen is absorbed equally well in tablet or capsule form. Furthermore, neither replacing magnesium stearate with stearic acid (tablet formulation C) nor increasing the magnesium stearate concentration by a factor of 5 (tablet formulation D) affected the availability of the drug. In this case, considering the relative amounts of drug and lubricant in these tablets, it is not surprising to find absorption unaffected.

Table IV. The Effect of Capsules and Tablet Formulation Variants on the Areas under the Curve and Absorption Rate Constants in Humans following 200 mg Oral Doses of Naproxen

Form	Area (0—24 hr) (μg/ml·hr) Mean ± SD	k_{11} (hr^{-1}) Mean ± SD	Number of determinations
Capsules	464 ± 81	1.3 ± 1.5	12
Tablet B	495 ± 73	0.9 ± 0.6	6
Tablet C	492 ± 64	0.7 ± 0.2	6
Tablet D	453 ± 47	1.6 ± 1.3	6
Tablet E	436 ± 84	0.5 ± 0.3	6
Tablet F	459 ± 79	0.7 ± 0.6	6

The "buffered" tablet (formulation F) also produced the same area response as the capsule; and finally even the tablets prepared without starch (tablet formulation E), which had disintegration times of up (to 45 min, allowed the drug to be equally well absorbed.

The absorption rate constants of the capsules and the tablet formulation variants are presented in Table IV. The presence of dihydroxy aluminum amino acetate in formulation F apparently had no effect on the rate of absorption of naproxen even though Levy, *et al.*[17] were able to detect differences between "plain" aspirin tablets and tablets containing alkaline additives. Statistical analysis of these data revealed no sign ificant differences among any of the dosage forms; however, from a purely pharmaceutical point of view the lower mean value for Formulation E seems reasonable. Because of the unusually long disintegration time *in vitro*, a delayed onset or peak level would be expected. Obviously, more than six experiments or even twelve considering the standard deviation of capsules, 1.3±1.5, would be required to prove significance.

Figure 4 and Table V present the results of the 200 mg oral suspension experiment and make the general comparison of suspension vs capsules and tablets. The capsule data presented here are the results of the twelve experiments in Table IV and the tablet data represent the composite of tablet formulations B, C, D, and F. The area results clearly indicate that

Table V. The Effect of Dosage Forms (Tablet, Capsule and Suspension) on the Areas under the Curve and the Absorption Rate Constants in Humans following Oral Doses of 200 mg of Naproxen

Form	Area (0—24 hr) (μg/ml·hr) Mean ± SD	k_{11}(hr^{-1}) Mean ± SD	Number of determinations
Suspension	462 ± 56	2.2 ± 1.7	6
Capsule	464 ± 81	1.3 ± 1.5	12
Tablets[a]	472 ± 65	1.0 ± 0.8	24

a) The 24 determinations here represent 6 experiments each of tablet formulations B,C,D and F.

17) G. Levy, J.R. Leonards and J.A. Procknal, *J. Pharm. Sci.*, **54**, 1719 (1956).

the 200 mg naproxen dose is equally well absorbed whether given in aqueous suspension, where the drug is wetted with water and well dispersed, or taken in a capsule which must dissolve to release the powder it contains or supplied in tablets which must disintegrate and dissolve before absorption may take place.

The mean absorption rate constant (Table V) of the suspensions is higher than that of capsules or tablets, while the latter two forms apparently produce plasma level responses at the same rate. This result is not surprising in view of the potential for more rapid dissolution with the liquid form.

The final formulation experiment compared naproxen availability from tablet Formulation B (five 50 mg tablets) containing 40 percent naproxen against tablet B "concentrated" (one 250 mg tablet) prepared with 66 percent naproxen. The data in Table VI demonstrate that mean area and absorption constant values remain unchanged as the drug concentration in the tablet varies. This result reiterates the uncomplicated absorption characteristics of naproxen and allows for considerable latitude in formulation alterations which could be made without significantly affecting drug availability.

Table VI. The Effect of Increasing the Concentration of Naproxen in Tablet Formulation B on the Area under the Curve and the Absorption Rate Constants in Humans following Oral Naproxen Doses of 250 mg

Subject	40% Naproxen-five 50 mg tablets		66% Naproxen-one 250 mg tablet	
	(0—24 hr) Area (μg/ml·hr)	k_{11} (hr^{-1})	(0—24 hr) Area (μg/ml·hr)	k_{11} (hr^{-1})
1 a	354	1.5	355	1.2
b	398	1.0	375	1.4
2 a	531	1.7	278	1.0
b	342	1.4	301	1.4
3 a	489	1.4	535	10.0
b	459	1.7	644	1.1
4 a	483	2.1	604	0.6
b	441	1.4	476	1.6
5 a	375	1.4	459	0.7
b	460	2.8	496	1.0
6 a	494	0.8	423	0.4
b	529	2.1	539	0.6
7 a	244	4.1	455	2.3
b	520	1.4	398	2.5
8 a	397	2.8	447	0.6
b	469	2.3	442	3.5
Mean±SD	436±79	1.9±0.8	452±100	1.9±2.3

Effect of Food on Absorption

A number of parameters which may alter drug absorption become operative when a drug is taken on a full stomach compared with delivery to a fasted stomach. Two of these parameters are the following; (1) the pH of the gastric contents increases,[18] and (2) the transit time increases. A rise in the pH results in an increase in the solubility of weak acids such as naproxen thereby speeding up dissolution and possibly absorption; and the time a tablet resides in the stomach may be affected by the transit time of the bulk material in which it is embedded. In the case of naproxen, the average concentration profiles (Fig. 5) suggest that the absorption takes place more rapidly from a fasted stomach and this is indicated also in Table VII where the mean rate constants are 2.8 fasted and 1.4 non-fasted. Although this

18) A.H. James, "The Physiology of Gastric Digestion," Edward Arnold Ltd., London, 1957, p. 42, 43.

Table VII. The Effect of Food on the Areas under the Curve and the Absorption Rate Constants in Humans following Oral Naproxen Doses of 250 mg

Subject No.	Fasted		Non-Fasted	
	Area (0—24 hr) (μg/ml·hr)	k_{11} (hr^{-1})	Area (0—24 hr) (μg/ml·hr)	k_{11} (hr^{-1})
1	405	1.7	644	1.1
2	280	1.2	378	0.9
3	316	2.1	380	3.5
4	482	7.1	500	0.25
5	537	3.5	718	2.3
6	483	1.0	448	0.28
Mean±SD	417±102	2.8±2.3	511±141	1.4±1.3

difference was found to be statistically non-significant it should be noticed that five out of six subjects displayed a lower absorption rate constant when the drug was taken with the standard meal. A number of reasons for the apparent decrease in absorption rate in the non-fasted state may be suggested, but certainly the most likely seems to be delayed stomach emptying time coupled with relatively slow gastric absorption,.

The mean area responses to 250 mg doses of naproxen taken under fasted and non-fasted conditions are 417 and 511, respectively. This apparent increase in the mean of approximately 100 μg/ml·hr was a result of individual increases in five of the six subjects; only subject six failed to show an increase in area over the fasted state. Here again, variance in the areas was large and as a result the significance of the apparent difference is in doubt. Certainly though, the presence of food in the g.i. tract did not adversely affect the extent of naproxen absorption.

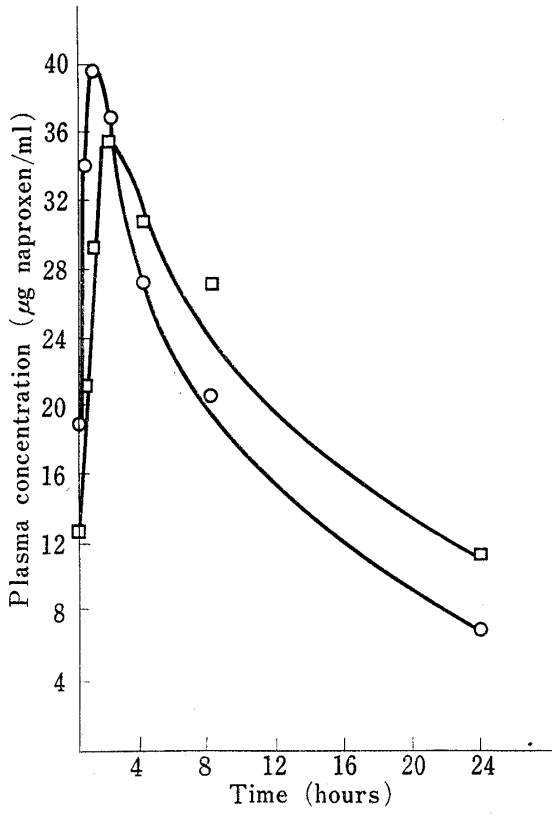


Fig. 5. Plasma Concentrations of Naproxen in Human Subjects following 250 mg Doses under Fasted (○) and Non-Fasted (□) Conditions

Each point represents the average of 6 determinations.

Abstract

The oral absorption characteristics of naproxen in a variety of forms were examined in dogs and humans and these results compared with the responses to intravenous administration. Naproxen was found to be completely absorbed in the dog regardless of the form in which it was delivered. However, the sodium and calcium salts were more rapidly absorbed than the free acid. In humans, also, oral doses were apparently absorbed comoletely whether give as suspensions, capsules or tablets. The drug appeared to be more rapidly absorbed from aqueous suspensions than from capsules or tablets while the blood level response was

the same from the latter two. A tablet lubricant effect on absorption could not be detected nor was there a noticeable change in response when the percent of naproxen in the tablet was altered. Finally, the fasted *vs* non-fasted results suggested that naproxen was absorbed more rapidly in fasted subjects while there was no diminution in the amount absorbed when doses were taken with food.