Bioavailability of Flufenamic Acid in Hard and Soft Gelatin Capsules

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Abstract □ The biological availability of flufenamic acid after oral administration of the drug in both hard and soft gelatin capsules was studied in dogs and humans. The soft gelatin capsules produced consistently higher plasma concentration–time curves.

Keyphrases □ Flufenamic acid—bioavailability, hard and soft gelatin capsules, dogs, humans □ Bioavailability—flufenamic acid, hard and soft gelatin capsules, dogs, humans □ Gelatin capsules—hard and soft, effect on bioavailability of flufenamic acid, dogs, humans □ Anti-inflammatory agents—flufenamic acid, bioavailability in hard and soft gelatin capsules, dogs, humans

Pharmaceutical technology is able to produce a variety of preparations for oral administration to ensure palatable qualities, constancy of dosage, and stability of the active ingredients. However, these preparations may have different degrees of biological availability. It has been demonstrated that depending on the type of capsule—hard (microprecipitated drug) or soft (polysorbate 80, dissolved drug) gelatin—remarkable differences in absorption of a drug may occur (1). These differences, in turn, may be followed by important differences in plasma drug concentrations and, consequently, in therapeutic efficacy. Such factors may play an important role when drugs are administered in one or very few doses, from which amelioration or relief is expected in the shortest time possible, *e.g.*, analgesics, antipyretics, and antiallergics.

This paper reports on a study of plasma concentrations of flufenamic acid, an analgesic–anti-inflammatory agent, after administration to dogs and humans in the form of hard gelatin capsules in comparison with soft gelatin capsules. Some important changes in biological availability were observed.

EXPERIMENTAL

Subjects—*Dogs*—For the study of plasma levels, 10 mongrel dogs, 10–28 kg, were housed in individual kennels and fed on canteen surplus food. Flufenamic acid, 200 mg, in one of the two capsule forms was administered to each animal after fasting for 10 hr.

Table II—Areas (Micrograms per Milliliter times Minutes) under Plasma Concentration–Time Curves of Flufenamic Acid (200 mg) Administered in Hard or Soft Capsule to Dogs

Dog	Hard	Soft	Percent[a]
1	46.62	60.25	29.22
2	99.25	128.50	29.5
3	93.00	118.50	27.4
4	34.00	73.75	116.9
5	92.75	141.75	52.8
6	98.50	133.00	35.0
7	55.00	82.75	50.4
8	96.00	108.00	12.5
9	55.25	64.25	16.3
10	52.50	61.25	16.7
Mean	72.29	97.20	34.5
SE	±8.12	±10.18	
Student's *t* test	5.685 ($p = 0.001$)		
Wilcoxon's signed rank test	T+ = 55.0 ($p = 0.01$) T− = 0		

[a] Soft compared with hard.

This dose was followed using the alternative capsule form 15 days later. The order of drug administration was randomized in the sense that five dogs received one soft capsule each and five were given hard capsules on the same day. Blood samples were drawn at 30, 90, 150, and 210 min after administration.

Humans—Nine healthy male volunteers, 60–78 kg, received flufenamic acid, 200 mg, in the same two capsule forms after fasting for 10 hr. A 15-day interval was allowed between treatments, and the order of drug administration was randomized as in the dog study. Blood samples were drawn at 90, 180, and 360 min after administration.

Treatments—The hard capsule contained 200 mg of flufenamic acid and 20 mg of magnesium stearate. The soft capsule contained 200 mg of flufenamic acid, 100 mg of vegetable oil, 40 mg of hydrogenated vegetable oils, 8 mg of beeswax, and 5 mg of soya lecithin.

Dissolution time of capsules in simulated gastric fluid was studied in accordance with the USP XVIII method (120 rpm, 150 ml, one capsule); the quantity of the drug released in the dissolution medium was determined. The values ($n = 6$) were 65 ± 1.4 (*SEM*) and 60 ± 1.4% at 15 min and 93 ± 1.4 and 98 ± 0.7% at 30 min of the total present in the soft and hard capsules, respectively. The determination of flufenamic acid was carried out spectrophotofluorometrically (2) on plasma from venous blood drawn with a heparinized syringe.

Table I—Flufenamic Acid Plasma Levels (Micrograms per Milliliter) in 10 Dogs at Various Times after the Administration of 200 mg in Hard or Soft Gelatin Capsules

Minutes	Mean ± *SE*		Percent[a]	Student's *t* Test[b]	Wilcoxon's Signed Rank Test[b]
	Hard	Soft			
30	24.05 ± 3.84	30.80 ± 5.03	28.1	2.188 (NS)	T+ = 45.5 (NS) T− = 9.5
90	25.90 ± 3.23	35.70 ± 3.68	37.8	5.580 ($p = 0.001$)	T+ = 55.0 ($p = 0.01$) T− = 0
150	21.75 ± 2.06	28.70 ± 3.89	32.0	2.286 ($p = 0.05$)	T+ = 50.0 ($p = 0.05$) T− = 5.0
210	13.20 ± 1.64	19.40 ± 2.66	47.0	2.577 ($p = 0.05$)	T+ = 51.5 ($p = 0.05$) T− = 3.5

[a] Soft compared with hard. [b] NS = not significant.

Table III—Flufenamic Acid Plasma Levels (Micrograms per Milliliter) in Nine Men at Various Times after the Administration of 200 mg in Hard or Soft Gelatin Capsules

Minutes	Mean ± SE		Percent[a]	Student's t Test[b]	Wilcoxon's Signed Rank Test[b]
	Hard	Soft			
90	6.33 ± 1.08	15.07 ± 0.70	138.1	6.608 ($p = 0.001$)	T+ = 45.0 ($p = 0.01$) T− = 0
180	6.79 ± 0.48	6.60 ± 0.52	−2.8	−0.406 (NS)	T+ = 16.6 (NS) T− = 28.5
360	2.21 ± 0.15	1.42 ± 0.19	−35.8	−3.310 ($p = 0.05$)	T+ = 3.0 ($p = 0.05$) T− = 42.0

[a] Soft compared with hard. [b] NS = not significant.

Mean plasma concentrations at the various time intervals were statistically analyzed for differences depending on the pharmaceutical forms as well as for differences in the mean areas under plasma concentration–time curves, calculated by means of the trapezoidal rule.

Statistical significance was evaluated by the Student parametric *t* test for paired data (3). Wilcoxon's (4) signed rank nonparametric test was also used and is particularly suitable small samples.

RESULTS AND DISCUSSION

In all of the dogs, the soft capsule produced, as compared to the hard type, higher plasma levels of flufenamic acid at each time interval, except for one animal at 30 min and another at 210 min. The average difference was statistically significant for the entire observation period, except at 30 min (Table I), and attained its maximum (47%) at 210 min. The average area described by the plasma concentration–time curve of flufenamic acid was significantly greater following the soft capsule as compared to the hard one (Table II). The average increase was 34% with a range of 12–116%.

In the human subjects, plasma levels of flufenamic acid following soft capsule administration were higher only at 90 min as compared to the hard type (in all subjects), and the average value at this time was more than double (Table III). The crossover comparison between plasma levels following hard and soft capsule administration was also carried out by adjusting concentrations in absolute values (micrograms per milliliter) into relative values (micrograms per milliliter divided by milligrams per kilogram). Statistical analysis of these recalculated data confirmed that the average peak concentration at 90 min was higher with soft capsules, both in dogs and in humans.

In dogs, the average area under the plasma concentration–time curve was greater with soft capsules. Since a crossover design was used and data were analyzed by paired comparisons, no drawback ensued that might have been caused by a difference in the per kilogram dosage of flufenamic acid in dogs. This involved a variation in the absorption rate from animal to animal. However, the conclusion of this study is limited because the time intervals for plasma sample collections in humans were not the best in order to obtain a satisfactory profile of the actual concentration–time curves of flufenamic acid in plasma. The results for humans must be considered preliminary.

Bearing these points in mind, it may be concluded that the soft gelatin capsule enables higher plasma concentrations of the drug to be attained as compared with the hard capsule. The biological availability of the drug was quantitatively increased. When dogs received the soft gelatin capsule, plasma concentrations of flufenamic acid were higher than those following administration of the hard capsule, even during the decreasing phase. An appropriate study in humans might achieve similar results.

The different bioavailability of flufenamic acid due to the pharmaceutical dosage form may be dependent on physicochemical factors, brought into play by adjuvants in the soft gelatin capsule, which effect more rapid and complete drug absorption. With the hard capsule, absorption of the drug probably takes place more slowly and incompletely. The role of these factors is substantiated by the fact that the difference in bioavailability of the two dosage forms could not be correlated with the difference in their dissolution rates *in vitro*. Inasmuch as latency, intensity, and duration of action depend on the magnitude of the plasma levels and on the rate of their reaching critical values and remaining above them, it is to be assumed that the type of dosage form greatly determines the course of effect of single doses of flufenamic acid.

REFERENCES

(1) J. G. Wagner, E. S. Gerard, and D. G. Kaiser, *Clin. Pharmacol. Ther.*, **7**, 610(1966).

(2) R. A. Buchanan, C. J. Eaton, S. T. Koeff, and A. W. Kinkel, *Curr. Ther. Res.*, **11**, 533(1969).

(3) W. C. Guenther, "Analysis of Variance," Prentice Hall, Englewood Cliffs, N.J., 1964.

(4) F. Wilcoxon, *Biometrics*, **1**, 80(1945).

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