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Effects of Food on Bioavailability of Two Indomethacin Capsules Containing Different Sizes of Particles

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Two different indomethacin capsules, a commercial one containing fine drug particles and an experimental capsule containing 125—177 μm particles, were employed in this study. The commercial preparation showed faster *in vitro* dissolution than the experimental one. When administered to humans having normal acidity of the gastric juices, the commercial capsule exhibited higher C_{max} and smaller T_{max} and mean residence time (*MRT*) than the experimental one both in fasting and nonfasting states, although the two capsules were equivalent in area under the serum concentration–time curve (*AUC*). The ingestion of a breakfast delayed the gastrointestinal absorption from both preparations, which resulted in larger T_{max}'s and *MRT*'s and smaller C_{max}'s in the nonfasting state. Food, however, did not have any significant effect on the *AUC*'s of the preparations.

Keywords indomethacin; bioavailability; food effect; particle size; dissolution

There have been extensive studies on the effects of food on the bioavailability of drugs.[1–3] Such studies are important to clarify the alteration in the availability caused by food and to find dosage forms whose bioavailabilities and hence therapeutic effects are little influenced by food. However, most of the studies so far have not paid much attention to formulation factors and have been performed with only a single product. The effects of food may vary according to the lots and types of formulations, since food affects not only the gastrointestinal absorption of the drug itself but also the dissolution of drugs and disintegration of formulations. Our previous studies on griseofulvin,[4] nalidixic acid[5] and metronidazole[6] revealed that the effects of food differed in degree among the products. Therefore, formulation factors as well as dietary factors should be taken into consideration when food effects are studied.

In the case of poorly soluble drugs in a physiological fluid the particle size of drugs is often a key factor controlling the dissolution rate and bioavailability, but there have been few studies on food effects with regard to particle size. One study carried out using nitrofurantoin found different effects of food between the macrocrystalline and microcrystalline products,[7,8] which suggests that food effects may differ among drug particles of unequal size.

Indomethacin, having low solubility in acidic fluids, is reported to be effective at the blood level of 3 μg/ml[9] and to cause side effects above 5 μg/ml.[10,11] It is usually administered postprandially in order to avoid gastric irritation. It is clearly of interest to follow the blood level after drug administration with or without food. Previous studies carried out using conventional capsules showed that the gastrointestinal absorption of indomethacin was delayed by food,[10,12–14] especially by a high-carbohydrate meal.[13] However, those studies did not pay any attention to the pharmaceutical characteristics of dosage forms such as the particle size, dissolution, *etc.*

In this study, the effects of food on the bioavailabilities from a commercial capsule and an experimental one which contained fine and large particles of indomethacin, respectively, were investigated.

Experimental

Preparation Inteban® (lot No. L130, Sumitomo Pharmaceutical Co., Ltd.) containing 25 mg of fine particles of indomethacin was selected as a test capsule (A) from among six brands of capsules, because, in the preliminary dissolution test at pH 7.2, it dissolved as rapidly as the other five products (one of the six products dissolved slowly). An experimental capsule (D) containing 25 mg of indomethacin particles in 125—177 μm sieve size mixed with 175 mg of lactose was also used in this study.

Dissolution Rate The dissolution rate of indomethacin from the capsules was determined by the JP XI paddle and rotating basket methods in 900 ml of pH 7.2 buffer for the JP XI dissolution test of indomethacin capsules. The mean dissolution rate was determined after three dissolution runs.

Disintegration Time According to the JP XI disintegration test, the disintegration time of the indomethacin capsules was determined in water, JP XI first fluid (pH 1.2) and pH 7.2 buffer used for the dissolution test.

Bioavailability Test Five healthy male volunteers who were all estimated to have high gastric acidity by Gastro test® (Chugai Pharmaceutical Co., Ltd.)[15] participated in this study. Their ages were 22, 37, 24, 23 and 22 years and their weights were 58, 68, 60, 60 and 78 kg, respectively. Each subject took a test capsule together with 200 ml of water after fasting overnight or 15 min after ingestion of a breakfast which consisted of 100 g of bread, 20 g of butter, 35 g of cucumber, 200 ml of milk and a boiled egg. All subjects then took no food or beverage until 4 h after dosing. Blood samples were taken at intervals up to 24 h after the drug administration and the serum samples were stored frozen until assay. The drug was administered at a two-week interval according to a four-way randomized block design. Serum indomethacin was determined by gas chromatography with an electron capture detector as previously described,[16] using a glass column (2 mm × 90 cm) packed with 10% SP 2250 on 100—120 mesh Supercoport (Gaskuro Kogyo Inc.), with nitrogen gas as a carrier gas. The injection, detector and column temperatures were 275, 275 and 260 °C, respectively. The bioavailability was evaluated using the observed values of maximum serum concentration of the drug (C_{max}), time to C_{max} (T_{max}), mean residence time (*MRT*)[17,18] and the area under the serum concentration–time curves from zero to 24 h (AUC_{24h}) and zero to infinity (AUC_{∞}) calculated by means of a trapezoidal rule and by the method of Wagner,[19] respectively. The cumulative amount of the drug absorbed was calculated by the deconvolution method with nonequal sampling times,[20] using the mean pharmacokinetic parameters reported by Duggan *et al.*,[21] $A=2.95$ mg/ml, $B=0.53$ mg/ml, $\alpha=1.941\ h^{-1}$ and $\beta=0.345\ h^{-1}$ determined on the basis of a two-compartment model with rapid intravenous injection, $C=Ae^{-\alpha t}+Be^{-\beta t}$ (C, blood concentration of the drug; t, time). The cumulative absorbed fractions were normalized on the assumption that the cumulative fractions 24 h after administration of preparation A in fasting subjects were complete.

Results

Dissolution and Disintegration Although most commercial indomethacin capsules are reported to contain less than 10—50 μm of particles,[22] no detailed information is available on the surface areas or particle sizes. Therefore, in order to determine the ratio of surface area of a commercial test product (A) to that of the experimental product (D),

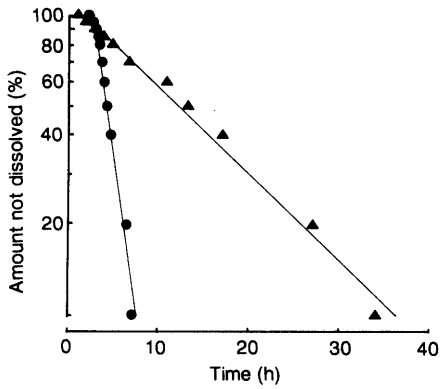

Fig. 1. Dissolution of Indomethacin from Preparations A (●) and D (▲) Plotted in a First-Order Fashion

The values are the means of three determinations by the JP XI paddle method at 120 rpm in 900 ml of pH 7.2 medium.

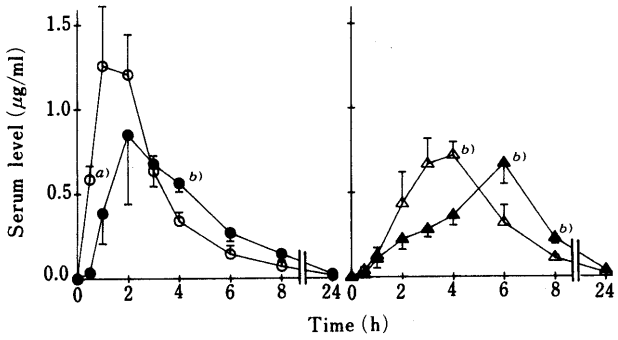

Fig. 2. Mean Serum Levels of Indomethacin after Oral Administration of 25 mg of Preparations A (Left Figure) and D (Right Figure) to Humans ($n=6$) Having Normal Gastric Acidity in Fasting (Open Symbols) and Nonfasting States (Closed Symbols)

The vertical lines show S.E. *a*) $p<0.01$. *b*) $p<0.05$.

the dissolution rates were first determined by the JP XI paddle method at a high stirring rate (120 rpm), where the drug particles were well dispersed in the dissolution medium. Figure 1 shows the mean amount of drug not dissolved *versus* time curves, which declined exponentially.[23] The rate constants determined from the linear portions were 0.452 ± 0.012 min^{-1} (mean $\pm$ S.D., $n=3$) for preparation A and 0.0614 ± 0.0122 min^{-1} for preparation D. Assuming that the surface area is proportional to the rate constant,[23] the ratio of the area of preparation A to that of preparation D is calculated to be 7.4, which means that the diameter of particles in preparation A is about 16—24 μm if the particles are assumed to be spherical.

The dissolution rates of the two preparations were also determined under various conditions which were reported in our previous paper.[24] When determined by the rotating basket method at 100 rpm according to the JP XI specification for indomethacin capsule, more than 95% of the drug was dissolved from capsule A in 20 min while 29.2 ± 1.9% (mean $\pm$ S.D.) was dissolved from capsule D. This means that capsule A met the JP requirement for indomethacin capsules (more than 75% of the drug to be dissolved in 20 min) but capsule D did not.

The disintegration times of preparations A and D determined by the JP XI disintegration test at pH 7.2 were 5.3 ± 0.8 (mean $\pm$ S.D.) and 3.0 ± 1.0 min, respectively, and similar values were obtained in water and pH 1.2 medium.

TABLE I. Mean Pharmacokinetic Parameters after Oral Administration of Two Different Capsules Containing 25 mg of Indomethacin to Humans

Parameter	Capsule	Fasting	Nonfasting	Paired *t*-test
C_{max}	A	$1.638 \pm 0.289^{a,b)}$	1.163 ± 0.322	NS
(μg/ml)	D	$0.883 \pm 0.059^{b)}$	0.677 ± 0.116	NS
T_{max}	A	$1.8 \pm 0.4^{b)}$	2.6 ± 0.5	NS
(h)	D	$3.6 \pm 0.2^{b)}$	5.0 ± 0.6	$p<0.05$
$MRT^{c)}$	A	$3.68 \pm 0.25^{b)}$	$5.52 \pm 0.40^{b)}$	$p<0.05$
(h)	D	$5.70 \pm 0.38^{b)}$	$7.28 \pm 0.24^{b)}$	$p<0.01$
AUC_{24h}	A	4.66 ± 0.65	4.73 ± 0.35	NS
(h·μg/ml)	D	4.11 ± 0.29	4.82 ± 0.67	NS
AUC_{∞}	A	4.89 ± 0.64	5.00 ± 0.40	NS
(h·μg/ml)	D	4.31 ± 0.31	5.12 ± 0.69	NS
$k_{el}{}^{d)}$	A	0.098 ± 0.022	0.115 ± 0.018	NS
(h^{-1})	D	0.112 ± 0.015	0.126 ± 0.011	NS

a) Means $\pm$ S.E. *b*) The difference between capsules A and D was significant at $p<0.05$ by the paired *t*-test. *c*) *MRT* was determined using the serum levels from zero to the final sampling time. *d*) k_{el}: elimination rate constant. NS: not significant at $p<0.05$.

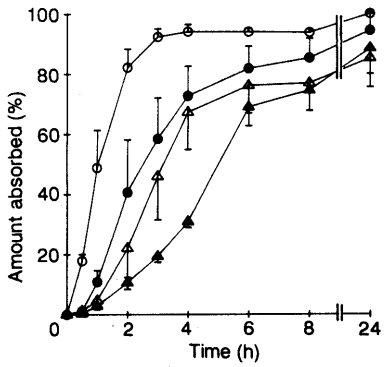

Fig. 3. Mean Cumulative Amounts of Indomethacin Absorbed in Humans ($n=6$) after Oral Administration of Preparations A (○) and D (△) in the Fasting State and Preparations A (●) and D (▲) in the Nonfasting State

The absorption 24 h after administration of preparation A in fasted subjects was assumed to be complete and each value was normalized. The vertical lines show S.E.

Bioavailability The bioavailabilities of the two indomethacin preparations were estimated in human subjects who had normal acidity of the gastric juices in order to avoid the effects of gastric acidity on the bioavailability.[16] Figure 2 shows the mean serum concentration time-curves of the two preparations given under fasting or nonfasting conditions. The serum levels rose more slowly under the nonfasting condition than under fasting. Statistically significant differences between fasting and nonfasting states were found in the serum levels at 0.5 and 4 h for preparation A and at 4, 6 and 8 h for preparation D. Table I lists the *in vivo* parameters. Food had a tendency to delay *MRT*'s and T_{max}'s of both preparations and to reduce the C_{max}'s. The mean C_{max}'s of preparations A and D given with food were about 70 and 80% of those without food, respectively. The findings suggested that food retarded the absorption of the drug in the gastrointestinal tract. This was seen clearly well when the *in vivo* absorption profiles were plotted (Fig. 3). The absorption curves of both preparations shifted to the right due to food, and the average shifts at the 50% absorption level of the two products were similar, namely 1.6 h for preparation A and 1.9 h for preparation D. On the other hand, the *AUC*'s of large and fine particles were

almost equal and food did not significantly affect the *AUC*'s as previously shown,[13,14] which indicates almost complete absorption from the particles.

When the two preparations were compared, preparation D showed slower *in vivo* absorption than preparation A both in the fasting and nonfasting states (Fig. 3). It appears that the *in vivo* as well as *in vitro* dissolution varied depending on the particle sizes, whether food was present or not.

Discussion

There have been a few studies investigating food effects using different sizes of drug particles. In this study food delayed the absorption of indomethacin from both the large and small particles. The delays are probably attributable to retarded dissolution caused by delayed gastric emptying due to food,[25] because indomethacin should dissolve better in the intestine than in the stomach judging from the pH-solubility characteristics, approximately 2 mg/ml at pH 7 and less than 0.025 mg/ml at pH 1—5, respectively.[16] Although food elevates the gastric pH, it would not significantly accelerate the dissolution of indomethacin, since the elevated pH would not much exceed pH 5[26,27] and would not continue long.[28]

In a previous study on nitrofurantoin,[7,8] food also delayed the absorption from the microcrystalline preparation (particle size: $< 10\,\mu m$) but not from the macrocrystalline one (particle size: 74—177 μm) which showed poor availability in the fasting state. Instead, food markedly enhanced the bioavailability. The enhancement was probably attributable to promoted dissolution due to the improved solubility of the drug, because hydrophobic drugs are solubilized by bile,[29] secretion of which is facilitated by food, and also by dietary components. The delayed gastric emptying caused by food might contribute to enhancing the bioavailability, since it makes it possible for a greater amount of drug to be dissolved in the stomach. Such improvements in the drug dissolution and hence in bioavailability seem to more than counterbalance the delayed absorption brought about by food. Accelerated absorption due to food was also observed in microsize and ultramicrosize formulations of griseofulvin.[4]

These findings suggest that, among various factors of food, the solubilization of drugs and the retardation of gastric emptying have great influence on the dissolution and absorption of drug particles, and the observed effects of food vary depending on which effect is larger. The solubilizing effects, especially of biles, are probably more important for such drugs as nitrofurantoin and griseofulvin, which are practically insoluble in physiological fluids, than for indomethacin, which is soluble in the intestinal fluid. When the solubilizing effects are negligible, the absorptions of drug from large and small particles may be only retarded by food, as observed in this study, and the similar delays both in the fine (< 10—50 μm) and large particles (125—177 μm) of indomethacin indicate that food equally delays the gastric emptying of particles smaller than 175 μm while it markedly retards that of particles larger than 0.5—3.0 mm.[30]

In addition to the effects on drug dissolution, food effects on the disintegration and dispersion of dosage forms[6,31] should also be considered. Previous findings of different effects of food on three brands of microcrystalline preparations of nitrofurantoin[8] suggest that food accelerated their disintegration, especially that of poorly available products. However, its effects on the indomethacin preparations employed in this study seemed to be negligible because of their rapid disintegration.

Thus, it is necessary to consider the formulation factors including particle size, dissolution rate, *etc.* in the study of food effects in order to clarify whether the effects are mainly caused by food-drug and/or food-formulation factor interactions, although we found little difference in food effects between large and fine particles of indomethacin in this study.

References

1) P. G. Welling, *J. Pharmacokin. Biopharm.*, **5**, 291 (1977).
2) A. Melander, *Clin. Pharmacokin.*, **3**, 337 (1978).
3) P. G. Welling, *Clin. Pharmacokin.*, **9**, 404 (1984).
4) N. Aoyagi, H. Ogata, N. Kaniwa and A. Ejima, *J. Pharmacobio-Dyn.*, **5**, 120 (1982).
5) H. Ogata, N. Aoyagi, N. Kaniwa and A. Ejima, *J. Pharmacobio-Dyn.*, **7**, 760 (1984).
6) H. Ogata, N. Aoyagi, N. Kaniwa and A. Ejima, *Int. J. Clin. Pharmacol. Ther. Toxicol.*, **24**, 279 (1986).
7) T. R. Bates, J. A. Sequeira and A. V. Tembo, *Clin. Pharmacol. Ther.*, **16**, 63 (1974).
8) H. A. Rosenberg and T. R. Bates, *Clin. Pharmacol. Ther.*, **20**, 227 (1976).
9) F. Gross, "Grundlagenwissenschaften-klinische Pharmakologie," J. F. Lehmann, München, 1971, S. 7—42.
10) N. O. Rothermich, *J. Am. Med. Assoc.*, **195**, 531 (1966).
11) G. Alván, M. Orne, L. Bertilsson, R. Ekstrand and L. Palmér, *Clin. Pharmacol. Ther.*, **18**, 364 (1975).
12) H. W. Emori, H. Paulus, R. Bluestone, G. D. Champion and C. Pearson, *Ann. Rheum. Dis.*, **35**, 333 (1976).
13) W. W. Wallusch, H. Nowak, G. Leopold and K. J. Netter, *Int. J. Clin. Pharmacol.*, **16**, 40 (1978).
14) K. C. Yeh, *Am. J. Med.*, **79**, 3 (1985).
15) N. Aoyagi, H. Ogata, N. Kaniwa, M. Koibuchi, T. Shibazaki, A. Ejima, M. Mizobe, K. Kohno and M. Samejima, *Chem. Pharm. Bull.*, **34**, 281 (1986).
16) N. Aoyagi, H. Ogata, N. Kaniwa and A. Ejima, *Int. J. Clin. Pharmacol. Ther. Toxicol.*, **23**, 469 (1985).
17) K. Yamaoka, T. Nakagawa and T. Uno, *J. Pharmacokin. Biopharm.*, **6**, 547 (1978).
18) D. J. Culter, *J. Pharm. Pharmacol.*, **30**, 476 (1978).
19) J. G. Wagner, "Fundamentals of Clinical Pharmacokinetics," Drug Intelligence Publications, Inc., Hamilton, Illinois, 1975, p. 344.
20) K. Iga, Y. Ogawa, T. Yashiki and T. Shimamoto, *J. Pharmacokin. Biopharm.*, **14**, 213 (1986).
21) D. E. Duggan, A. F. Hogans, K. C. Kwan and F. G. McMahon, *J. Pharmacol. Exp. Ther.*, **181**, 563 (1972).
22) "Nippon Yakkyokuho Kaisetusho," 11th ed., Hirokawa Publishing Co., Ltd., Tokyo, 1986.
23) J. G. Wagner, "Biopharmaceutics and Relevant Pharmacokinetics," Drug Intelligence Publications, Inc., Hamilton, Illinois, 1971, p. 120.
24) N. Aoyagi, H. Ogata, N. Kaniwa and A. Ejima, *Int. J. Clin. Pharmacol. Ther. Toxicol.*, **23**, 529 (1985).
25) H. Maekawa, Y. Takagishi and Y. Doi, *Yakuzaigaku*, **30**, 102 (1970).
26) R. Iinuma and T. Toyama, *Yakuzaigaku*, **21**, 49 (1961).
27) J. R. Malagelada, G. F. Longstreth, W. H. J. Summerskill and V. L. W. Go, *Gastroenterology*, **70**, 203 (1976).
28) M. L. Rocci, P. Mojaverian, R. J. Davis, R. K. Ferguson and P. H. Vlasses, *Clin. Pharmacol. Ther.*, **42**, 45 (1987).
29) T. R. Bates, M. Gibaldi and J. L. Kanig, *J. Pharm. Sci.*, **55**, 901 (1966).
30) J. B. Dressman, *Pharm. Res.*, **3**, 123 (1986).
31) H. Ogata, T. Shibazaki, T. Inoue and A. Ejima, *J. Pharm. Sci.*, **68**, 712 (1979).