Propoxyphene and Norpropoxyphene: Influence of Type of Controlled-Release Formulation on Intra- and Intersubject Variations

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Abstract □ Two types of controlled-release formulations of propoxyphene hydrochloride, one with a buffer system in the pellet core, were studied with regard to intra- and intersubject variations of C_{max} and T_{max} of propoxyphene as well as propoxyphene plus norpropoxyphene in 35 volunteers after administration of a single 150-mg dose. Statistically significant differences between the formulations in intrasubject variance were revealed, and the availability rate of the buffered product showed significantly better reproducibility, presumably due to the established low sensitivity of its release rate to the *in vitro* environment, *i.e.*, pH.

Keyphrases □ Propoxyphene—influence of type of controlled-release formulation on drug release, pH dependency □ Dosage forms, controlled release—propoxyphene, influence of type of formulation on drug release, pH dependency □ Release rates—propoxyphene, influence of type of controlled-release formulation, pH dependency

The analgesic α-*d*-propoxyphene currently is available in two types of multiple-unit controlled-release formulations. One formulation is supported with a buffer system in the pellet core (1) to secure a pH-independent drug release. The other formulation does not have such a system. *In vitro* studies have shown a pronounced difference in the sensitivity of these two formulations to the nature of the dissolution medium, particularly its pH (Fig. 1).

The present study concerns the significance *in vivo*, in terms of intra- and intersubject variations, of these formulation-related differences in *in vitro* drug release with respect to selected pharmacokinetic parameters.

EXPERIMENTAL

Subjects—Thirty-five volunteers [15 females and 20 males, 18–60 years old (median 24 years old) and 47.4–83.5 kg (median 65 kg)] served as test subjects. Prior to the study, the subjects were found to be healthy by clinical examination and various laboratory tests, including serum creatinine, serum bilirubin, liver enzymes, and hemoglobin. Twenty-four subjects were nonsmokers, and 11 were smokers. Four females were taking oral contraceptives. Informed consent was obtained from all of the subjects.

Blood Sampling—Venous heparinized blood samples (~20 ml) were drawn before (0 hr) and 2, 3, 4, 6, 8, and 12 hr after drug administration. Immediately after sampling, the plasma was separated by centrifugation and frozen at −20° until it was assayed. No deterioration was found with storage.

Assay of Plasma Samples—The plasma concentrations of propoxyphene and norpropoxyphene were measured by a mass fragmentographic method (2). The lower detection limit of the method was 4 ng/ml for propoxyphene and 3 ng/ml for norpropoxyphene. The coefficient of variation was <6%.

Propoxyphene Products—Seven batches of Formulation A[1] and two batches of Formulation B[2] were used. Formulation A (without a buffer system) consisted of a sugar core coated with the drug and a lacquer. Formulation B consisted of the drug and a buffer system in a homogeneous core coated with a lacquer (1). The release rate patterns of both formulations (containing 150 mg of α-*d*-propoxyphene hydrochloride) were designed to yield a controlled, sustained release (Table I). Both formulations were supplied in identical red, hard gelatin capsules.

Dosage Schedule—Except for the contraceptive pill, no drugs were allowed for 7 days before the study. During the study, alcoholic beverages and smoking were not permitted.

Subjects fasted overnight before each treatment and were not permitted to eat until 2 hr after dosing, at which time a standardized breakfast with 300 ml of fluid was given. During the remaining observation period, the ambulatory subjects had free access to fluid and food intake and in this respect imitated the clinical situation. Single 150-mg doses of controlled-release propoxyphene hydrochloride were administered at 9 am with 300 ml of tap water.

Experimental Designs—The study involving Formulation A was performed as an unbalanced, incomplete block design with at least 7 days between dosage days. Each subject received one to three different batches. The study involving Formulation B was performed as a nonrandomized crossover trial with at least 7 days between the two dosage days.

Calculations and Statistical Analyses—The peak plasma concentration (C_{max}) and the time to the peak concentration (T_{max}) of propoxyphene and propoxyphene plus its major metabolite, norpropoxyphene, were used as dependent variables in the statistical analyses.

The intra- and intersubject variations, expressed as the variances in the variance components model (Eq. 1), were estimated using the standard computer program GLIM (3). To estimate intersubject variance corrected for interbatch variation and the standard errors of these parameters, the method described by Searle (4) was applied to the data obtained for Formulation A. The estimation was straightforward in the balanced design for the study involving Formulation B.

A comparison between formulations was made by standard variance ratio F tests for intrasubject variance and by an approximate variance ratio test (5) for intersubject variance. For each formulation, the variation of each dependent pharmacokinetic characteristic (y_{ij}) is expressed by:

$$y_{ij} = \mu + \pi_i + \beta_j + \epsilon_{ij} \qquad \text{(Eq. 1)}$$

for subject i receiving a dose from batch j, where π_i, β_j, and ϵ_{ij} are the values of the independent, normally distributed, random variables with

Table I—Dissolution Test (pH 1.2 USP Buffer excluding Enzymes) of Controlled-Release Propoxyphene of Different Batches of Formulations A [a] and B [b] (n = 4)

Batch	Mean (±*SD*) Amount of Propoxyphene Released, mg: Within 1 hr	Within 2 hr	Within 6 hr
83602[a]	47 (3.0)	79 (2.7)	140 (6.3)
83606[a]	56 (4.2)	89 (4.9)	142 (4.2)
83612[a]	49 (1.5)	89 (5.0)	153 (7.5)
84150[a]	49 (3.6)	86 (1.6)	155 (6.3)
84154[a]	52 (3.5)	87 (5.7)	132 (9.9)
84403[a]	60 (5.2)	91 (5.2)	136 (3.6)
83610[a]	50 (5.0)	77 (3.9)	134 (3.5)
Average	51.9	85.4	141.7
(Pooled estimate)	(3.5)	(4.4)	(6.3)
87055[b]	57 (3.2)	91 (1.7)	132 (1.2)
87056[b]	60 (2.0)	91 (1.7)	132 (1.2)
Average	58.5	91.0	132.0
(Pooled estimate)	(2.7)	(1.7)	(1.2)

[a] Diffucap. [b] Repro-Dose.

[1] Diffucap controlled-release propoxyphene (Batches 83602, 83606, 83612, 84150, 84154, 84403, and 83610), Eurand, Milan, Italy.

[2] Repro-Dose controlled-release propoxyphene (Batches 87055 and 87056), A/S Alfred Benzon, Copenhagen, Denmark.

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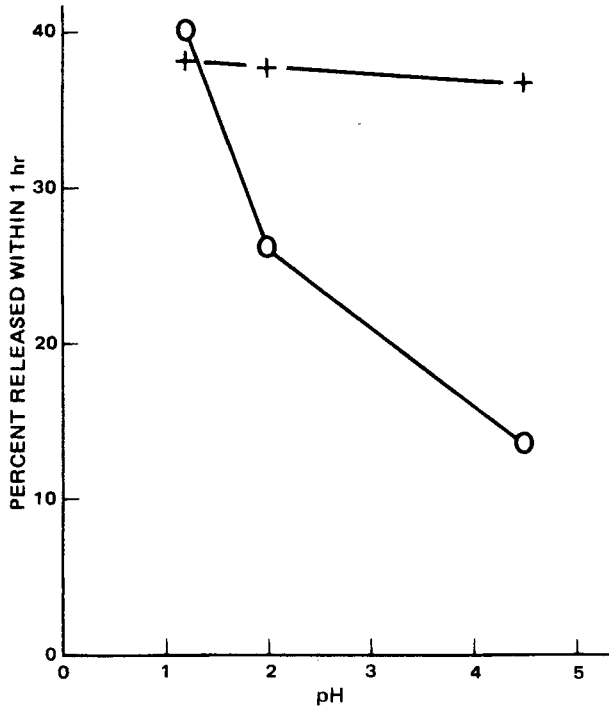

Figure 1—*The pH dependency of drug release from Formulation A (Batch 84403) (○) and from Formulation B (Batch 87055) (+).*

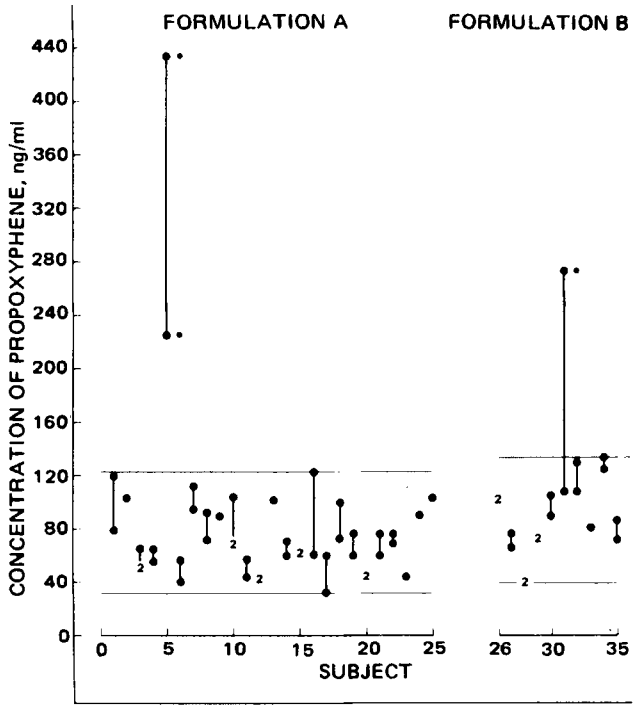

Figure 2—*Individual peak concentrations of propoxyphene after administration of 150 mg of propoxyphene hydrochloride from a batch of Formulation A or B. The symbol 2 indicates equal C_{max} values obtained with different batches; * represents an outlier.*

zero means and variances and are the intersubject, interbatch, and intrasubject variance components, respectively.

The intrasubject variance results from differences in the response from the same subject at different times, but it also is due to subject–batch interactions, to intrabatch variation, and to errors of measurement. The different kinds of variation cannot be separated further on the basis of the existing data.

The fit of the model was assessed with a normal probability plot of residuals in the case where C_{max} was the dependent variable.

Since T_{max} is a discrete variable and thus is in disagreement with the normality assumption of the model, it is irrelevant to test the fit of the model in this case. For the same reason, the variance ratio F test used for comparison of the intersubject variance must be considered as an approximate test with T_{max}.

Dissolution Procedure—The cumulative release of propoxyphene was determined at 1, 2, and 6 hr by means of the NF XIV rotating-bottle procedure (6), which was modified to maintain a constant pH during the dissolution test and to include only one measurement per dosage unit. The rotation speed was 30 ± 1 rpm, and the dissolution medium was 25 ml of sulfate buffer at pH 1.2 or 2.0 or citrate buffer at pH 4.5, thermostated at 37 ± 0.1°. The amount of propoxyphene released was determined by measuring the absorbance at 257 nm (Table I).

RESULTS

Batch Testing *In Vitro*—The release rate pattern of each batch was analyzed (Table I) and found to be in compliance with the specifications for the products, *i.e.*, at least 90% of the capsules released an amount of propoxyphene within 60 ± 15 mg at 1 hr, 93 ± 20 mg at 2 hr, and 132 ± 20 mg at 6 hr. The release data were normally distributed. Both products released 100% of the propoxyphene within 10 hr.

The observed intrabatch standard deviation for Formulation B was statistically significantly lower at 2 ($p < 0.05$) and 6 ($p < 0.001$) hr than the standard deviation for Formulation A (Table I).

pH Dependency *In Vitro*—The amount of propoxyphene released after 1 hr was tested at pH 1.2, 2.0, and 4.5 (Fig. 1). The sensitivity to the pH of the dissolution medium was pronounced for Formulation A, ranging from 40 to 10% of drug released at pH 1.2 and 4.5, respectively. In contrast, virtually no pH-dependent change in released propoxyphene was observed with Formulation B.

Outliers—Three subjects (A5, A17, and B31) were outliers with respect to specific values of C_{max} and T_{max} since the normality assumption of the variance components model (Eq. 1) for these values was not met (Table II). In the statistical tests involving these parameters, as well as for consideration of the ranges (Figs. 1–4), outliers were excluded. No clinical reasons or connection to the smoking or taking of contraceptive pills by the subjects could be applied to the outliers.

Plasma Propoxyphene—The peak concentration of propoxyphene displayed a considerable within-subject variation, with the widest range being 61–123 ng/ml after administration of Formulation A compared to a variation of 107–130 ng/ml after administration of Formulation B (Fig. 2). Total variation, including intra- and intersubject variations, ranged from 32 to 123 ng/ml after administration of Formulation A and from 40 to 134 ng/ml after administration of Formulation B (Fig. 2).

Table II—Comparison of Formulations A [a] and B [b] with Respect to Residual Variance (Intrasubject Variance)

		Formulation A		Formulation B			
	Parameter	Residual Variance, ng^2/ml^2	*DF*	Residual Variance, ng^2/ml^2	*DF* [c]	Variance Ratio, A/B	Outliers: Formulation, Subject, Value
Propoxyphene	C_{max}	226.0	14	76.9	7	2.9 NS [d]	A, 5, 433 A, 5, 224 B, 31, 274
	T_{max}	2.9	14	0.4	8	6.8 ($p < 0.01$)	A, 17, 12 [e]
Propoxyphene plus norpropoxyphene	C_{max}	1242.1	14	185.7	7	6.7 ($p < 0.01$)	A, 5, 588
	T_{max}	4.5	14	0.4	8	11.9 ($p < 0.001$)	B, 31, 432

[a] Diffucap. [b] Repro-Dose. [c] Subject 33 was excluded due to a missing blood sample 4 hr after ingestion of Batch 87056. [d] Not significant. [e] Or later.

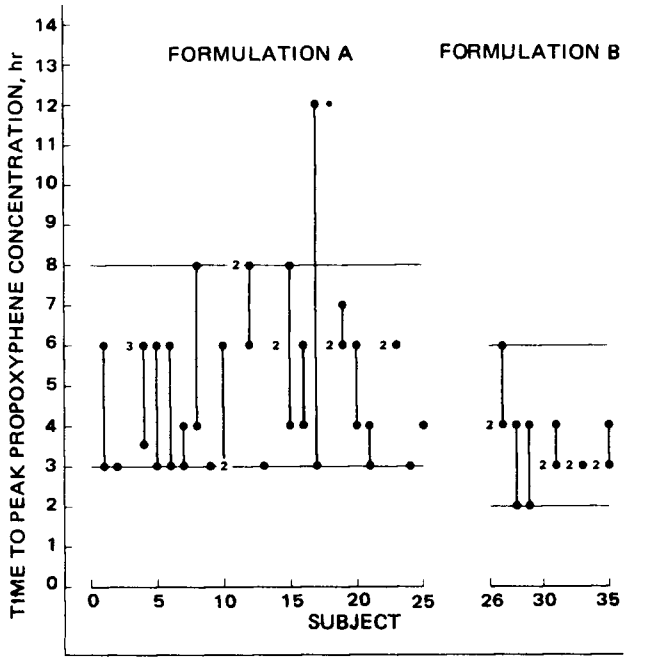

Figure 3—*Individual time to peak concentrations of propoxyphene after administration of 150 mg of propoxyphene hydrochloride from a batch of Formulation A or B. The symbol 2 indicates equal T_{max} values obtained with different batches; * represents an outlier.*

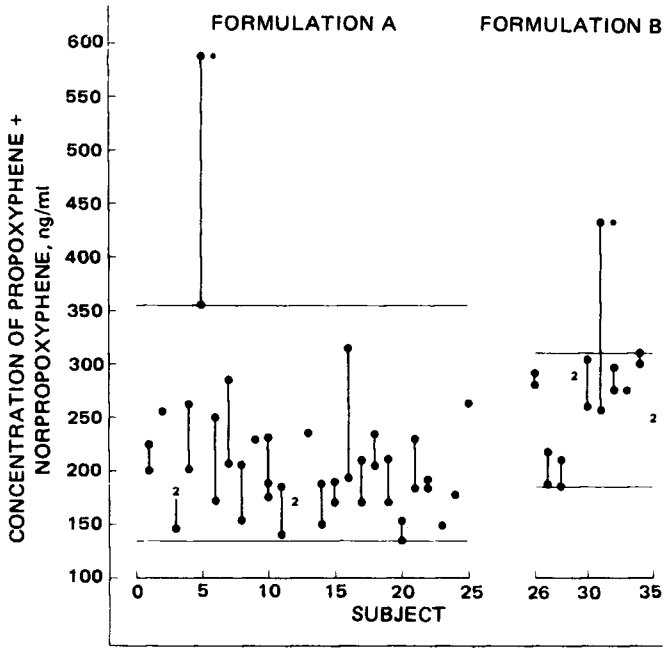

Figure 4—*Individual peak concentrations of propoxyphene plus norpropoxyphene after administration of 150 mg of propoxyphene hydrochloride from a batch of Formulation A or B. The symbol 2 indicates equal C_{max} values obtained with different batches; * represents an outlier.*

The maximum range of T_{max} within a subject was 4 hr or more after ingestion of Formulation A and only 2 hr after ingestion of Formulation B (Fig. 3).

In total, the time to the peak concentration ranged from 3 to 8 hr and from 2 to 6 hr after ingestion of Formulations A and B, respectively (Fig. 3).

Comparison of the two types of controlled-release products with respect to intrasubject variation showed a statistically significantly ($p < 0.01$) lower variance of T_{max}, with a variance 6.8 times greater after administration of Formulation A than after Formulation B (Table II). With respect to C_{max}, the difference in the intrasubject variation between the two formulations was less pronounced; the variance ratio between Formulations A and B was 2.9 but was not statistically significant (Table II). The difference between the two formulations with respect to intersubject variations in C_{max} and T_{max} also was not statistically significant.

Propoxyphene plus Norpropoxyphene—As with propoxyphene, the amount of propoxyphene and its major metabolite, norpropoxyphene, displayed a pronounced intrasubject variation in C_{max}, reaching a maximum of 193–313 ng/ml and of 259–305 ng/ml after administration of Formulations A and B, respectively (Fig. 4). Overall, the peak concentrations ranged from 134 to 355 ng/ml after ingestion of Formulation A and from 184 to 311 ng/ml after administration of Formulation B (Fig. 4).

The maximum range of T_{max} within a subject was >8 hr after administration of Formulation A and only 2 hr after administration of Formulation B (Fig. 5). The total ranges of T_{max} were from 3 to 12 hr or more and from 3 to 6 hr after ingestion of Formulations A and B, respectively (Fig. 5).

Compared to Formulation B, the intrasubject variances of C_{max} and T_{max} were statistically significantly ($p < 0.01$) larger after administration of Formulation A by factors of 6.7 and 11.9, respectively (Table II).

As in the case of propoxyphene alone, no statistically significant difference in the intersubject variance components for C_{max} and T_{max} of propoxyphene plus norpropoxyphene was found.

DISCUSSION

No statistically significant difference was found in either the intra- or intersubject variation of C_{max} of propoxyphene after administration of the two formulations, although the intrasubject variance ratio between Formulations A and B was 2.9 (Table II).

The total range, including the intra- and intersubject variations, of C_{max} of propoxyphene showed a threefold variation (Fig. 2), which was a narrower range compared to the one observed after ingestion of plain propoxyphene products, where C_{max} values showed five- to 10-fold ranges (2, 7–9). Hence, the C_{max} value of propoxyphene for the two controlled-release formulations seems to be subject to a significantly smaller intersubject variation compared to plain products, contrary to what usually is assumed (10). This finding indicates that with controlled-release products, an optimal effect might be obtained by a standard dose regimen with a minimized risk of toxic peak concentrations of propoxyphene. Because single-dose studies are not always applicable to multiple-dose conditions, *i.e.*, the clinical situation, this assumption has to be confirmed.

Among the physiological factors that may influence the bioavailability of a drug from an oral, controlled-release dosage form are the gastric

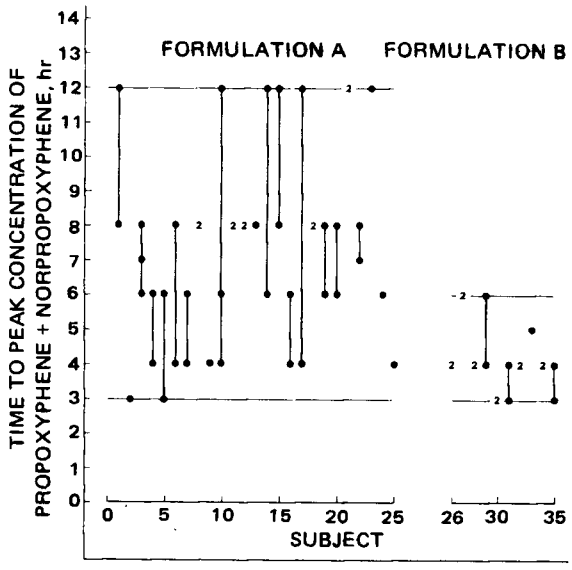

Figure 5—*Individual time to peak concentrations of propoxyphene plus norpropoxyphene after administration of 150 mg of propoxyphene hydrochloride from a batch of Formulation A or B. The symbol 2 indicates equal T_{max} values obtained with different batches; * represents an outlier.*

emptying time, intestinal motility, surface area, specific absorption site, blood flow, and first-pass metabolism (11, 12). The influence of the gastric emptying time and intestinal motility on intra- and intersubject variations in the rate and extent of availability largely can be avoided by the use of multiple-unit, controlled-release dosage forms (11, 13). These dosage forms are comprised of subunits, *e.g.*, pellets or microencapsulated crystals, that are dispersed and distributed throughout the GI tract when the capsule or tablet disintegrates (14).

In the present single-dose study dealing with intra- and intersubject variations in the rate of availability, both formulations were multiple-unit dosage forms, but they showed a highly significant difference in release properties with respect to pH dependency (Fig. 1). When a multiple-unit dosage form is under consideration, the importance of pH dependency is expected to be closely related to the pharmacokinetic characteristics of the drug (*i.e.*, saturable or with an absorption rate-dependent first-pass metabolism) since the influence of gastric emptying on intra- and intersubject variations can be eliminated. However, corroboration of such suggestions is not obtained easily from the literature.

The intrasubject variance of C_{max} of propoxyphene plus norpropoxyphene was significantly lower ($p < 0.01$), by factor of 6.7, after administration of Formulation B (Table II). The rate of appearance of norpropoxyphene in the circulation is a function both of the absorption rate of propoxyphene and of its *N*-demethylation. Because the highest intrasubject variance was observed after ingestion of the formulation whose drug release was most sensitive to the pH of the environment, *i.e.*, Formulation A (Fig. 1), the possibility of an absorption rate-dependent first-pass metabolism cannot be excluded.

With respect to T_{max} of both propoxyphene and propoxyphene plus norpropoxyphene, a significantly ($p < 0.01$) lower intrasubject variance, by factors of 6.7 and 11.9, respectively, was observed after ingestion of Formulation B (Table II). Expressed in terms of intrasubject ranges, identical ranges, *i.e.*, 2 hr for both parameters, were observed after administration of Formulation B. In contrast, the ranges observed for Formulation A were larger and not the same; the ranges were 4 and 8 hr or more, respectively (Figs. 3 and 5). The greater reproducibility of the rate of availability after administration of Formulation B can be ascribed directly to its lower sensitivity to the surrounding pH with respect to drug release. Thus, the significance of the type of controlled-release formulation with regard to minimizing the intrasubject variance in C_{max} and T_{max} has been demonstrated.

Clinically, increased predictability of the time of onset of action presumably is the primary advantage of the improved reproducibility of the plasma concentration pattern with Formulation B compared to Formulation A.

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