

## Influence of Two Commercial Fibers in the Pharmacokinetics of Ethinylestradiol in Rabbits

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### ABSTRACT

Fiber formulations are used in human nutrition owing to their beneficial properties for health. It is probable that ingestion of fiber coincides with the oral administration of drugs, and a modification of its oral absorption, and therefore of its pharmacokinetics, can appear. In the present study, the compartmental and noncompartmental pharmacokinetic parameters of ethinylestradiol (EE) in rabbits after oral administration were determined. It was also studied whether the presence of two different fiber formulations [A, wheat bran (76.5%), fruit fiber (12%) and guar gum (2%) and B, *Plantago ovata* seeds (65%) and *P. ovata* seed cuticles (2.2%)] in the gastrointestinal tract modified the pharmacokinetics of EE when administered at the same time. Three groups of rabbits were used: control, fiber A

and fiber B. The animals in all three groups received 1 mg/kg b. wt. EE. The estrogen was administered alone in the control group and in the presence of 4 g of fiber A and fiber B, respectively, in the other two groups. After compartmental (two-compartment open model) and noncompartmental analyses of plasma concentrations, statistical analysis revealed that the presence of fiber (both A and B) decreased between 29% and 35% the extent of EE absorbed (represented by the pharmacokinetic parameters area under the curve and the maximum plasma concentration) without affecting the rate of the absorption process (represented by the time to reach maximum concentration and the absorption rate constant).

EE is a synthetic estrogen that is widely used as a component of oral contraceptives. This compound is also used in the treatment of functional uterine bleeding and menopausal symptoms, for the inhibition of lactation and for palliative treatment of breast cancer in postmenopausal women and prostate cancer (Masterson, 1988; Godsland *et al.*, 1992).

In order to avoid its adverse effects, EE is used at low doses; in particular, the dose of EE, when used for oral contraception, has been reduced to 30 to 50  $\mu\text{g}$  per day. When other drugs and/or foods are administered at the same time, interactions may appear and EE blood concentrations may be ineffective (Goldzieher, 1994).

The bioavailability and disposition of oral medications are governed by the processes of absorption and presystemic clearance, and these may be influenced by the presence of certain diet components in the gastrointestinal tract (Melander and McLean, 1983). Dietary fiber is widely accepted as an important part of healthy human nutrition, and fiber

formulations are marketed in the United States and Europe (Silk, 1989; Scheppach *et al.*, 1990) with extensive advertising campaigns directed to the consumer. This information shows these products as highly effective in the treatment of obesity and constipation prevention, for decreasing blood cholesterol and glucose levels and even for preventing the development of gastrointestinal cancer. These aspects induce the public to consume commercial fiber preparations without medical control, in a continued and sometimes abusive way. Under these circumstances, it is highly probable that fiber ingestion coincides with oral administration of any drug, which could modify its oral absorption and therefore its pharmacokinetics. The influence of fiber on the presystemic clearance of drugs is most likely to be clinically relevant with drugs having narrow therapeutic margins (Melander and McLean, 1983), *e.g.*, EE.

Food intake can affect the absorption and bioavailability of several drugs (Welling, 1977; Melander and McLean, 1983), but little information is available regarding contraceptive steroids. Several studies have shown that nutrition and spe-

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**ABBREVIATIONS:** EE, ethinylestradiol SHBG, sex hormone-binding globulin;  $\alpha$  and  $\beta$ , apparent first-order disposition rate constants; A and B,  $\alpha$  and  $\beta$  zero-time intercepts, respectively;  $k_a$ , absorption rate constant;  $k_{10}$ , apparent first-order elimination rate constant from the central compartment;  $k_{12}$ , apparent first-order transfer rate constant from the central compartment to the peripheral compartment;  $k_{21}$ , apparent first-order transfer rate constant from the peripheral compartment to the central compartment; AUC, area under the plasma concentration-time curve;  $C_{\text{max}}$ , maximum plasma concentration;  $t_{\text{max}}$ , time to reach maximum concentration;  $t_{1/2\alpha}$ , half-life associated with  $\alpha$ -phase;  $t_{1/2\beta}$ , half-life associated with  $\beta$ -phase;  $t_{1/2k_a}$ , absorption half-life;  $t_{1/2k_{10}}$ , elimination from the central compartment half-life;  $\lambda$ , noncompartmental apparent first-order disposition rate constant;  $t_{1/2\lambda}$ , half-life associated with  $\lambda$  phase;  $\text{AUC}_{t-\infty}$ , AUC from the last experimental time to infinity.

cific dietary factors influence the metabolism of steroid compounds, which are primarily metabolized in the liver before their excretion in the urine or bile (Anderson and Kappas, 1982). An increase in the protein to carbohydrate ratio in the diet of healthy subjects can increase estrogen 2-hydroxylation (Anderson, *et al.* 1984), decrease androgen 5 $\alpha$ -reduction (Kappas *et al.*, 1983), alter the plasma levels of testosterone and cortisol in a reciprocal fashion and produce parallel changes in the binding globulin for these steroids (Anderson *et al.*, 1987).

The purpose of the present study was to establish the compartmental and noncompartmental pharmacokinetic parameters of EE in rabbits after its oral administration and to determine whether the presence of two different fiber formulations in the gastrointestinal tract modifies the pharmacokinetics of EE when this drug and fiber formulations are administered at the same time.

## Methods

**Animals.** Fifteen healthy, female New Zealand White rabbits weighing 2.9 to 3.5 kg were used. The animals were housed in individual metal cages, which allowed the isolation of feces in a lower container to avoid coprophagia. The environmental conditions were as follows: constant humidity (55  $\pm$  10%), temperature (19  $\pm$  2°C) and a 12-hr light/12-hr dark cycle. The animals were maintained on laboratory chow and water *ad libitum*, and they were fasted for ~24 hr before drug administration, with free access to water.

**Materials.** EE was obtained from Sigma Chemical Co. (St. Louis, MO), sodium pentobarbital from Barcia (Madrid, Spain), heparin from Rovi, S.A. (Madrid, Spain), fiber A from Kneipp-Werke (Würzburg, Germany) and fiber B from Madaus Cerafarm, S.A. (Barcelona, Spain). The fiber composition was as follows: for fiber A, wheat bran (76.5%), fruit fiber (12%) and guar gum (2%) (the rest of the composition appeared as excipients); for fiber B, *Plantago ovata* seeds (65%) and *P. ovata* seed cuticles (2.2%). As well, fiber B contained 18.1% saccharose, and the rest of the composition appeared as excipients.

**Preparation of the experimental animals.** Rabbits were anesthetized with sodium pentobarbital (30 mg/kg b. wt. i.v.), and the left carotid artery was cannulated with a silicone catheter [Silastic medical-grade tubing, 1.02 mm (inner diameter)  $\times$  2.16 mm (outer diameter)]. These cannulas were placed before the trial started. The end of the tubing was passed subcutaneously to emerge at the back of the neck. EE and fiber were administered to the conscious animals ~2 hr after the catheter was inserted.

**Study design.** Animals were randomly divided into three groups of five rabbits each: control, fiber A and fiber B and received the respective following preparations: 1 mg/kg EE p.o., 1 mg/kg EE p.o. and 4 g fiber A p.o. and 1 mg/kg EE p.o. and 4 g fiber B p.o. The five rabbits of the control group received 1 mg/kg EE orally as a solution (1 ml) in a mixture of water and ethanol (4:1, v/v). Likewise, the 10 rabbits of groups A and B were orally treated with EE, but immediately before EE administration, they received 4 g p.o. of fiber A and B, respectively, dispersed in water. Both the EE and fiber solutions were administered by gastric intubation. A total of 50 ml water was used for fiber administration and cannula cleaning.

**Blood sampling.** Blood samples (3 ml) were collected through the carotid artery canula before and at 5, 10, 20, 30, 60, 90, 120, 150, 180 and 240 min after EE administration into heparinized containers. Immediately after collection, plasma was separated by centrifugation and stored at -20°C until analyzed.

**Plasma concentration of EE.** EE plasma concentrations were determined by high-performance liquid chromatography with electrochemical detection according to the method previously described

by Fernandez *et al.* (1993). Intraday and interday accuracy and precision were within 10%.

**Pharmacokinetic analysis.** Pharmacokinetic analysis was performed on the basis of a compartmental as well a noncompartmental description of the observed data. For compartmental analysis, plasma EE concentration-time profiles were individually fitted to the following exponential equation:

$$C_p = \sum_{i=1}^n C_i e^{-\lambda_i t}$$

where  $C_i$  is the y-intercept,  $\lambda_i$  is the slope of each of  $n$  first-order rate processes,  $e$  is the exponential function (base  $e$ ) and  $t$  is time. The estimates of  $C_i$  and  $\lambda_i$  were calculated by using a computer program based on the nonlinear, iterative, least-squares regression analysis PCNONLIN 3.0 (Metzler and Weiner, 1989). The equations were fitted to the data by using a weighting factor  $1/C$ , and the initial estimates of the parameters were determined by JANA (Dunne, 1985). The optimum number of first-order rate processes was determined by application of Akaike's information criterion (Yamaoka *et al.*, 1978a) and graphical analysis of weighted residuals. The other compartmental parameters were calculated by standard methods (Gibaldi and Perrier, 1982).

The model-independent pharmacokinetic parameters were calculated by using expressions based on statistical moments theory (Yamaoka *et al.*, 1978b) and on formulae described by Gibaldi and Perrier (1982). The plasma elimination rate constant ( $\lambda$ ) was calculated by least-squares regression of the logarithm of plasma concentration *versus* time curve over the terminal elimination phase.

The area under the plasma concentration-time curve from time zero to the last determined sample time ( $AUC_{0-t}$ ) was calculated by the trapezoidal rule, and the total area under the plasma AUC was determined by adding  $AUC_{0-t}$  to the residual area  $AUC_{t-\infty}$  (calculated from  $C_t$ , the last experimental plasma concentration divided by the terminal slope  $\lambda$ ).

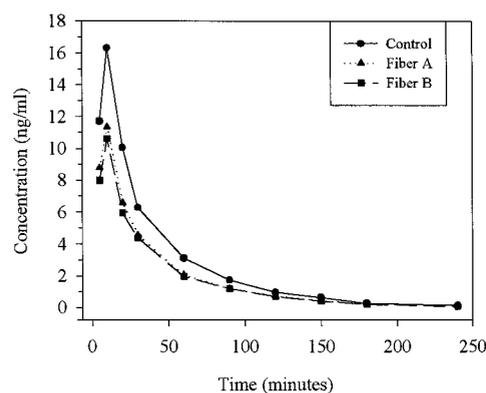
The total body clearance was calculated by dividing the dose by the AUC. The half-life associated with the  $\lambda$  phase ( $t_{1/2\lambda}$ ) was calculated from the quotient  $0.693/\lambda$ . Maximum plasma EE concentration ( $C_{max}$ ) and the time to reach maximum concentration ( $t_{max}$ ) were read directly from the individual plasma concentration-time curves.

**Statistical evaluation.** All pharmacokinetic parameters were calculated for each animal and the data presented as arithmetic means  $\pm$  S.D. The data obtained from the three groups were compared for statistical significance by using the one-way analysis of variance, and Duncan's test was used to evaluate differences between data sets when the results were significant. A  $P \leq .05$  was taken as the level of significance for all analyses.

## Results

Figure 1 shows the plot of the mean plasma concentrations of EE as a function of time after oral administration of 1 mg/kg EE for the three groups studied. This figure shows that the mean plasma concentrations of EE were higher in the control rabbits than in the fiber A and fiber B groups. The values of the pharmacokinetic parameters determined by both compartmental and noncompartmental analyses are given in tables 1 and 2, respectively.

After compartmental analysis, the plasma concentration-time curves were best resolved in all experiments into a two-compartment open model. The EE pharmacokinetic parameters determined by compartmental analysis are given in table 1. The values obtained for  $k_a$  were very similar in the control group (0.151 min<sup>-1</sup>) and in both A (0.156 min<sup>-1</sup>) and B (0.167 min<sup>-1</sup>) groups. The values obtained for AUC were



**Fig. 1.** Mean plasma concentrations of EE in rabbits after oral administration of 1 mg/kg b. wt. EE alone (control) and in the presence of fiber A or fiber B.

1.4 times higher in the control group ( $602.47 \text{ ng}\cdot\text{min}\cdot\text{ml}^{-1}$ ) than in the A group ( $428.44 \text{ ng}\cdot\text{min}\cdot\text{ml}^{-1}$ ) and  $\sim 1.5$  times higher than in the B group ( $398.19 \text{ ng}\cdot\text{min}\cdot\text{ml}^{-1}$ ).  $C_{\text{max}}$  values were also higher in the control group ( $14.487 \text{ ng}\cdot\text{ml}^{-1}$ ) than in A ( $10.368 \text{ ng}\cdot\text{ml}^{-1}$ ) and B ( $9.501 \text{ ng}\cdot\text{ml}^{-1}$ ) groups. With regard to the most representative parameter values of bioavailability, AUC,  $C_{\text{max}}$  and  $t_{\text{max}}$  (Ritchel, 1987; McGilveray *et al.*, 1990), no significant differences were found for  $t_{\text{max}}$  (9.489 min in the control group, 8.570 min in group A and 8.522 in group B), but there were significant differences for  $C_{\text{max}}$  and AUC values between the control group and groups A and B.

$k_a$  values ranged from  $0.1510 \text{ min}^{-1}$  (control group) to  $0.1670 \text{ min}^{-1}$  (B group) and  $\beta$ -values from  $0.0166 \text{ min}^{-1}$  (A and B groups) to  $0.0171 \text{ min}^{-1}$  (control group). There were no significant differences when these parameters, representative of absorption and elimination rates, were compared.

The pharmacokinetic parameters derived from noncompartmental analysis are shown in table 2. In this case, AUC values were also higher in the control group ( $628.67 \text{ ng}\cdot\text{min}\cdot\text{ml}^{-1}$ ) than in A ( $436.60 \text{ ng}\cdot\text{min}\cdot\text{ml}^{-1}$ ) and B ( $418.60 \text{ ng}\cdot\text{min}\cdot\text{ml}^{-1}$ ) groups. Similar results were obtained for  $C_{\text{max}}$ :  $16.33 \text{ ng}\cdot\text{ml}^{-1}$  (control),  $11.35 \text{ ng}\cdot\text{ml}^{-1}$  (A group) and  $10.61 \text{ ng}\cdot\text{ml}^{-1}$  (B group). The  $t_{\text{max}}$  value was 10 min in all three groups. Statistical analysis revealed no significant differ-

ences for  $t_{\text{max}}$  values but significant differences for AUC and  $C_{\text{max}}$  when these parameters were compared between the control group and groups A and B.  $\lambda$ -values were similar to  $\beta$ -values obtained after compartmental analysis.

## Discussion

In a previous study performed in rabbits (Fernández *et al.*, 1996), the pharmacokinetics of EE after intravenous administration was also best described by a two-compartment open model. Hümpel *et al.* (1979) considered EE to behave as a three-compartment open model after an intravenous dose and as a two-compartment model after oral dosing. Furthermore, Goldzieher in 1994, in a revision about this theme, indicated that in most cases the pharmacokinetics of EE after both oral and intravenous administration was best described by a two-compartment open model.

Düsterberg *et al.*, in a study carried out in 1986 in rabbits and with the same dose of EE (1 mg/kg) in a microcrystalline suspension administered by the oral route, found a  $t_{\text{max}}$  value of 15 min, which is similar to our data (10 min). However, these authors reported values for  $C_{\text{max}}$  ( $2.53 \pm 3.8 \text{ ng}\cdot\text{ml}^{-1}$ ) and AUC ( $78 \pm 108 \text{ ng}\cdot\text{min}\cdot\text{ml}^{-1}$ ) that were lower than those shown in this study ( $16.33 \pm 3.62 \text{ ng}\cdot\text{ml}^{-1}$  and  $628.67 \pm 136.77 \text{ ng}\cdot\text{min}\cdot\text{ml}^{-1}$ , respectively). With regard to studies in women, peak concentrations of EE after a variety of doses were reached later, between 120 and 240 min after dosing (Goldzieher, 1994).

Studies of fiber-drug interactions are scarce, as indicated by Kritchevsky (1988) and Eastwood (1992) in two revisions performed on this subject. The results obtained in these studies were variable. Thus, Richter *et al.* (1991) showed that the consumption of a soluble fiber with pectin caused a decrease in the intestinal absorption of the hypolipidemic agent lovastatin. Retuert and Yazdani-Pedram (1992) found that fiber (especially carboxymethylcellulose) induces the decomposition of other drugs like diethylpropion hydrochloride. On the other hand, Astarola *et al.* (1992) found higher levels of L-dopa when administered with an insoluble fiber that contained wheat bran. However, Uusitupa *et al.* (1990) did not find any alteration in the absorption of glibenclamide when this drug was administered with guar gum.

TABLE 1

Pharmacokinetic parameters obtained by compartmental analysis in rabbits after oral administration of 1 mg/kg EE alone (control) and in the presence of fiber A or B

Parameters	Control	Fiber A	Fiber B
A ( $\text{ng} \cdot \text{ml}^{-1}$ )	$102.046 \pm 15.165$	$87.968 \pm 22.671$	$81.905 \pm 40.345$
B ( $\text{ng} \cdot \text{ml}^{-1}$ )	$8.816 \pm 6.455$	$5.293 \pm 1.264$	$5.033 \pm 2.263$
$\alpha$ ( $\text{min}^{-1}$ )	$0.1172 \pm 0.0108$	$0.1214 \pm 0.0115$	$0.1194 \pm 0.0373$
$\beta$ ( $\text{min}^{-1}$ )	$0.0171 \pm 0.0060$	$0.0166 \pm 0.0025$	$0.0166 \pm 0.0028$
$k_a$ ( $\text{min}^{-1}$ )	$0.1510 \pm 0.0080$	$0.1560 \pm 0.0234$	$0.1670 \pm 0.0204$
$k_{12}$ ( $\text{min}^{-1}$ )	$0.0413 \pm 0.0097$	$0.0473 \pm 0.0099$	$0.0457 \pm 0.0190$
$k_{21}$ ( $\text{min}^{-1}$ )	$0.0411 \pm 0.0200$	$0.0388 \pm 0.0060$	$0.0431 \pm 0.0155$
$k_{10}$ ( $\text{min}^{-1}$ )	$0.0519 \pm 0.0087$	$0.0519 \pm 0.0021$	$0.0473 \pm 0.0102$
AUC ( $\text{ng} \cdot \text{min} \cdot \text{ml}^{-1}$ )	$602.466 \pm 143.386$	$428.436 \pm 69.638^a$	$398.186 \pm 110.515^a$
Cl ( $\text{l} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ )	$1.754 \pm 0.501$	$2.378 \pm 0.343$	$2.672 \pm 0.734^a$
$t_{1/2\alpha}$ (min)	$5.956 \pm 0.562$	$5.753 \pm 0.577$	$6.613 \pm 3.280$
$t_{1/2\beta}$ (min)	$39.242 \pm 10.058$	$42.487 \pm 6.540$	$42.525 \pm 6.571$
$t_{1/2k_a}$ (min)	$4.513 \pm 0.261$	$4.524 \pm 0.686$	$4.207 \pm 0.571$
$t_{1/2k_{10}}$ (min)	$13.201 \pm 2.955$	$13.378 \pm 0.546$	$34.602 \pm 48.548$
$t_{\text{max}}$ (min)	$9.489 \pm 1.167$	$8.570 \pm 0.971$	$8.522 \pm 1.331$
$C_{\text{max}}$ ( $\text{ng} \cdot \text{ml}^{-1}$ )	$14.487 \pm 3.186$	$10.368 \pm 2.169^a$	$9.501 \pm 2.871^a$

Values are means  $\pm$  S.D.

Cl, total body clearance.

<sup>a</sup> Significant difference from control at  $P \leq .05$ .

TABLE 2

Pharmacokinetic parameters obtained by noncompartmental analysis in rabbits after oral administration of 1 mg/kg EE alone (control) and in the presence of fiber A or B

Parameters	Control	Fiber A	Fiber B
$\lambda$ (min <sup>-1</sup> )	0.0181 ± 0.0053	0.0177 ± 0.0030	0.0179 ± 0.0029
AUC <sub>t=∞</sub> (ng · min · ml <sup>-1</sup> )	7.094 ± 5.041	11.156 ± 4.920	10.519 ± 7.772
AUC <sub>0-∞</sub> (ng · min · ml <sup>-1</sup> )	628.668 ± 136.765	436.580 ± 67.702 <sup>a</sup>	418.596 ± 110.772 <sup>a</sup>
Cl (l · kg <sup>-1</sup> · min <sup>-1</sup> )	1.660 ± 0.403	2.337 ± 0.334	2.532 ± 0.686 <sup>a</sup>
$t_{1/2\lambda}$ (min)	40.432 ± 9.006	40.004 ± 6.665	39.502 ± 6.469
$C_{\max}$ (ng · ml <sup>-1</sup> )	16.328 ± 3.622	11.348 ± 2.201 <sup>a</sup>	10.608 ± 3.311 <sup>a</sup>
$t_{\max}$ (min)	10.00 —	10.00 —	10.00 —

Values are means ± S.D.

Cl, total body clearance.

<sup>a</sup> Significant difference from control at P ≤ .05.

With regard to interactions between fiber and estrogens, in recent years many studies have suggested that dietary components like fiber and fat may play a role in the regulation of the enterohepatic metabolism of these compounds, in this way influencing the estrogen levels in the body. Nevertheless, we have not found any studies about the modification of the oral absorption of EE in the presence of fiber.

Several studies suggest that fiber-rich food has a reducing effect on estrogen levels in the blood and urine. Vegetarian diets tend to contain less fat and more fiber than nonvegetarian diets, and these differences appear to influence the metabolism of endogenous estrogens (Howie and Shultz, 1985) and/or the reabsorption of biliary estrogens (Goldin *et al.*, 1982; Adlercreutz *et al.*, 1986). A comparison of the plasma steroid levels between omnivorous and vegetarian men has indicated that estradiol concentrations were lower in the vegetarian group (Howie and Shultz, 1985). However, Fotherby (1990) indicates that whether metabolism of contraceptive steroids differs between vegetarians and nonvegetarians is still controversial.

In many of the situations discussed above, changes occur in serum SHBG concentrations, which were increased in vegetarians. Adlercreutz *et al.* (1987) indicated that in the presence of lignan precursors and phytoestrogens in fiber-rich vegetables, legumes and grain, a diet rich in fiber may stimulate SHBG synthesis in the liver and may in this way reduce the levels of free estradiol and testosterone in the plasma. However, these changes will not affect EE, which does not bind to SHBG (Akpoviro *et al.*, 1981).

A type of drug-nutrient interaction involves food as a mechanical barrier that prevents drug access to mucosal surfaces. This interaction results in decreased drug absorption and a shortened duration of action (Kirk, 1995). A meal may also influence the bioavailability by the direct binding of drugs by substances in food or by altering luminal pH, gastric emptying, intestinal transit, mucosal absorption, splanchnic-hepatic blood flow and metabolism of the drug (Anderson, 1988). In the present study we found that the presence of fiber (both *P. ovata* and a mixture of wheat bran, fruit fiber and guar gum) modified the extent of EE absorbed (represented by the pharmacokinetic parameters AUC and  $C_{\max}$ ) without affecting the rate of the absorption process (represented by  $k_a$  and  $t_{\max}$ ). Taking into account that  $C_{\max}$  and AUC are the only parameters that are modified, we think that fiber acts as a mechanical barrier that prevents EE access to mucosal surfaces, resulting in decreased drug absorption and a shortened duration of action.

## References

- Adlercreutz H, Fotsis T, Bannwart C, Hämäläinen E, Bloigu S and Ollus A (1986) Urinary oestrogen profile determination in young Finnish vegetarian and omnivorous women. *J Steroid Biochem* **24**:289–296.
- Adlercreutz H, Höckerstedt K, Bannwart C, Bloigu S, Hamalainen E, Fotsis T and Ollus A. (1987) Effect of dietary components, including lignans and phytoestrogens, on enterohepatic circulation and liver metabolism of oestrogens and on sex hormone binding globulin. *J Steroid Biochem* **27**:1135–1144.
- Akpoviro JO, Mangalam M, Jenkins N and Fotherby K (1981) Binding of the contraceptive steroids medroxyprogesterone acetate and ethinylestradiol in blood of various species. *J Steroid Biochem* **14**:493–498.
- Anderson KE and Kappas A (1982) Hormones and liver function. in *Diseases of the Liver* (Schiff L and Schiff ER eds. pp 167–235, J.B. Lippincott Company, Philadelphia, PA.
- Anderson KE, Kappas A, Conney AH, Bradlow, HL and Fishman J (1984) The influence of dietary protein and carbohydrate on the principal oxidative biotransformations of estradiol in normal subjects. *J Clin Endocrinol Metab* **59**:103–107.
- Anderson KE, Rosner W, Khan MS, New MI, Pang SY, Wissel PS and Kappas A. (1987) Diet-hormone interactions: Protein/carbohydrate ratio alters reciprocally the plasma levels of testosterone and cortisol and their respective binding globulins in man. *Life Sci* **40**:1761–1768.
- Anderson KE (1988) Influences of diet and nutrition on clinical pharmacokinetics. *Clin Pharmacokinet* **14**:325–346.
- Astarola R, Mena MA, Sanchez V, De La Vega L and De Yebenes JG (1992) Clinical and pharmacokinetic effects of a diet rich in insoluble fiber on Parkinson disease. *Clin Neuropharmacol* **15**:375–380.
- Dunne A (1985) JANA: A new iterative polyexponential curve stripping program. *Comput Med Programs Biomed* **20**:269–275.
- Düsterberg B, Kühnz G and Tauber U (1986) Half-lives in plasma and bioavailability of ethinylestradiol in laboratory animals. *Arzneim-Forsch Drug Res* **36**:1187–1190.
- Eastwood MA (1992) The physiological effect of dietary fiber: An update. *Annu Rev Nutr* **12**:19–35.
- Fernández N, García JJ, Diez MJ, Terán, MT and Sierra M (1993) Rapid high-performance liquid chromatographic assay of ethinylestradiol in rabbit plasma. *J Chromatogr* **619**:143–147.
- Fernández N, Sierra M, Diez MJ, Terán MT, Sahagun AM and García JJ (1996) Pharmacokinetics of ethinylestradiol in rabbits after intravenous administration. *Contraception* **53**:307–312.
- Fotherby K (1990) Interactions with oral contraceptives. *Am J Obstet Gynecol* **163**: 2153–2159.
- Gibaldi M and Perrier D (1982) Multicompartment models, in *Pharmacokinetics* (Swarbrick J, ed). Marcel Dekker, New York, NY.
- Godsland IF, Cook D and Wynn V (1992) Clinical and metabolic considerations of long-term oral contraceptive use. *Ann J Obstet Gynecol* **166**:1955–1963.
- Goldin BR, Adlercreutz H, Gorbach SL, Warram, JH Dwyer, JT Swenson and Woods MN (1982) Estrogen excretion patterns and plasma levels in vegetarian and omnivorous women. *N Engl J Med* **307**:1542–1547.
- Goldzieher JW (1994) Pharmacokinetics and metabolism of ethinyl estrogens, in *Pharmacology of the Contraceptive Steroids* (Goldzieher JW and Fotherby K, eds). pp 127–151, Raven Press, New York, NY.
- Howie BJ and Shultz TD (1985) Dietary and hormonal relationships among vegetarian Seventh-Day Adventist and non-vegetarian men. *Am J Clin Nutr* **42**:127–134.
- Hümpel M, Nieuweboer B, Wendt H and Speck U (1979) Investigations of pharmacokinetics of ethinylestradiol to specific consideration of a possible first-pass effect in women. *Contraception* **19**:421–432.
- Kappas A, Anderson KE, Conney AH, Pantuck EJ, Fishman J and Bradlow HL (1983) Nutrition-endocrine interactions: Induction of reciprocal changes in the  $\Delta^1$ - $\alpha$ -reduction of testosterone and the cytochrome P-450-dependent oxidation of estradiol by dietary macronutrients in man. *Proc Natl Acad Sci USA* **80**:7646–7649.
- Kirk JK (1995) Significant drug-nutrient interactions. *Am Fam Physician* **51**:1175–1182.
- Kritchevsky D (1988) Dietary fiber. *Annu Rev Nutr* **8**:301–328.
- Masterson BJ (1988) Oral contraceptive agents: Current status. *Ann J Surg* **155**: 619–627.
- McGilveray IJ, Midha KK, Skelly JP Dighe S, Dolouiso JT, French IW, Karim A and Burford R. (1990) Consensus report from "Bio International '89": Issues in the evaluation of bioavailability data. *J Pharm Sci* **79**:945–946.

- Melander A and McLean A (1983) Influence of food intake on presystemic clearance of drugs. *Clin Pharmacokinet* **8**:286–296.
- Metzler CM and Weiner DL (1989) *PCNONLIN User's Guide, Version 3.0* Statistical Consultants, Lexington, KY.
- Retuert PS and Yazdani-Pedram M (1992) Studies on the compatibility of diethylpropion hydrochloride with carboxy methyl cellulose and other dietary fibers. *Farmaco* **47**:649–660.
- Richter WO, Jacob BG and Schwandt P (1991) Interaction between fiber and lovastatin. *Lancet* **338**:706.
- Ritchel WA (1987) Methodology of bioavailability assessment. *Science Techniques et Pratiques Pharmaceutiques* **3**:286–301.
- Scheppach W, Burghardt W, Bartram P and Kasper H. (1990) Addition of dietary fiber to liquid formula diets: The pros and cons. *J Parenter Enteral Nutr* **14**:204–209.
- Silk DBA (1989) Progress report: Fibre and enteral nutrition. *Gut* **30**:246–250.
- Uusitupa M, Sodervik H, Silvasti M and Karttunen P (1990) Effects of a gel forming dietary fiber, guar gum, on the absorption of glibenclamide and serum lipids in patients with non-insulin-dependent (type 2) diabetes. *Int J Clin Pharmacol Ther Toxicol* **28**:153–157.
- Welling PG (1977) Influence of food and diet on drug absorption. *J Pharmacokinet Biochem* **5**:291–334.
- Yamaoka K, Nakagawa T and Uno TJ (1978a) Application of Akaike's information criterion (AIC) in the evaluation of linear pharmacokinetic equations. *J Pharmacokinet Biopharm* **6**:165–175.
- Yamaoka K, Nakagawa T and Uno TJ (1978b) Statistical moments in pharmacokinetics. *J Pharmacokinet Biopharm* **6**:547–558.

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