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INFLUENCE OF IBUPROFEN ON THE PHARMACOKINETICS OF ISONIAZID

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ABSTRACT

The influence of ibuprofen (400 mg orally) on the phannacoknetia of isoniazid (500 mg orally) was evaluated in healthy human subjects (n=30). Subjects participated in a two way crossover trial, the first dosing condition was isoniaiad alone (control), and the second doing condition was ibuprofen with isoniazid. The conceention of isonimid from the serum samples were determined by HPL C The pharmacokinetic paanmtem show a significant ($P<0.05$) increase in the area under the serum concentration/time curve (AUC) in both fast and slow acetylators of iw.azid, with a significant increase in the maximum serum concentration (C_{max}) of isommaid (only in slow acetylators with no effect on fast acetylators), a significant increase in the elimination half-life (t ½), and the time for the maximum drug concentration (T_{max}) (only in fast acctylators with no effect on slow acetylators).

INTRODUCTION

Isoniaad (isonicatinyl hydrazide) is widely used as a chemotherapeutic agent for the treatment of tuberculosis (Fox, 1972; 1975). Detailed pharmacokinetic analyses of isoniazid and its metabolites have indicated that acetylation is quantitatively the most important pathway for the metaboism of isoniazid (Barclay, 1953; Ellard, 1972; Wendell, 1979). Several studies have found isoniazid acetylation to be reduced by p-aminosalisylic acid (PAS), leading to elevated isoniazid plasma concentration and to prolonged serum isoniazid half-life (Bell, 1957; Hnngren, 1970; Jenne, 1961; Mitchell, 1957; Tiitineo, 1986; Wendell, 1979). There are further oxidative steps in the metabolism of isoniazid, and in some animal experiments isoniazid itself has been demonstrated to influence the rytochrome P450 oxidative enzyme system (Hoglund, 1987). Since the major metabolic pathway of ibuprofen in man involves a series of microsomal oxidative reactions (Hermann, 1985; Mills, 1973), one would predict that the pharmacokinetic parameters of isoniazid might be changed by the co-administration of ibuprofen, as it could interfere with the metabolic reactions of isonizaid.

MATERIALS AND METHODS

Subject Selection

Thirty healthy subjects (male) between 21 to 27 years of age participated in this study. All were healthy, ambulatory adults with no evidence of medical

diseases, and no one was taking any medicine. Subjects participated in a two way crossover trial, the two ways of dosing were as follows:

1. The control subjects *were* orally given 500 mg of isoniazid (5 xlOO mg Isonex; Pfizer) alone.

2. In the next round the same subjects received 500 mg isoniazid in combination with 400 mg of ibuprofen (Brufen, Boots).

All drugs were given in fasting state (after an overnight fast, with an unlimited take of water). After the drug adminiaration, the subjects remained fasting for 25 hours. Venous blood samples (5 ml) were drawn in Vacutainer serum tubes at 0, 0.25, 0.5, 1,2, 4, 6 and 8 hours interval. Serum was separated within 30 minutes and stored at -20°C till analysis. At least one week interval between each trial was given to every volunteer.

High Performance Liquid Chromatography (HPLC) Assay of Isoniazid

Isoniazid concentration in all human serum samples was determined by reversed-phase liquid chromatography using a method described by Moulin 1981. This consisted of a Rheodyne model 7161 injector (fitted with 20 υl loop), a Hitachi-4200 variable wavelength monitor, a Hitachi D-2000 Chromato- integrator and a stainless column (250 mm x 4 mm I.D.) packed with reverse phase Lichrosorb ODS (104, Hiber packed). Methanol (5%) in O.1M KH_2PO_4 (95%, pH 6.9), after degassing with helium, was used as a mobile phase at a constant flow rate of 1 ml/min.

Phamracokinetic and Statistical Analysis

The slope (ß) of the terminal log-linear phase of serum isoniazid concentration-time curve was determined by feathering method. This was used to calculate the apparent elimination half-life (t ½*)* of isoniazid. The AUC until the final detectable concentration was determined by the trapezoidal method. Maximum drug concentration time (T_{max}), was obtained from the plasma concentration data during 8 hours dosage intervals. The results are given as Mean ± S.E.M. Statistical analysis employed Student's t-test for paired data; $P < 0.05$ was taken as significant and P 0.001 as highly significant.

RESULTS

The serum isoniazid concentration in a representative subject in each of the two dosing condition are shown in Figure 1a, 1b, 2a. The Pharmacokinetic

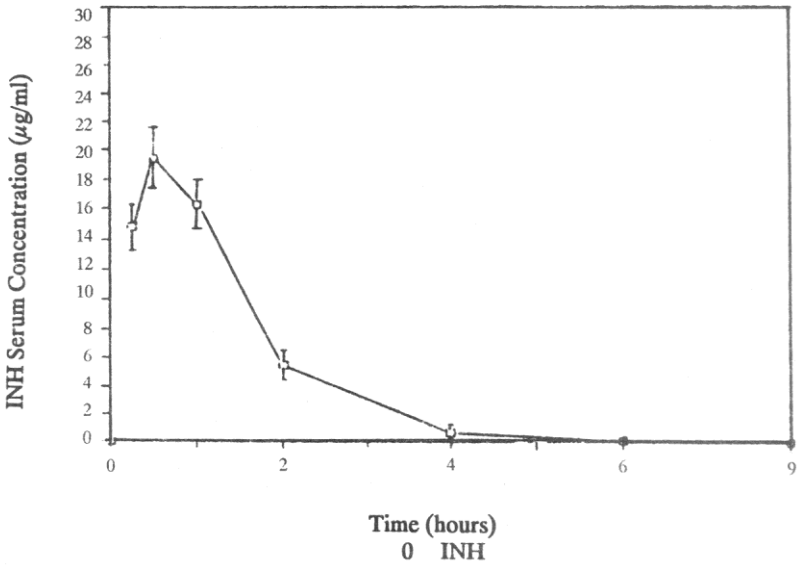

Figure 1a: Serum concentration (Mean ± S.E.M.) of isoniazid in fast acetylators following an oral administration of 500 mg of the drug.

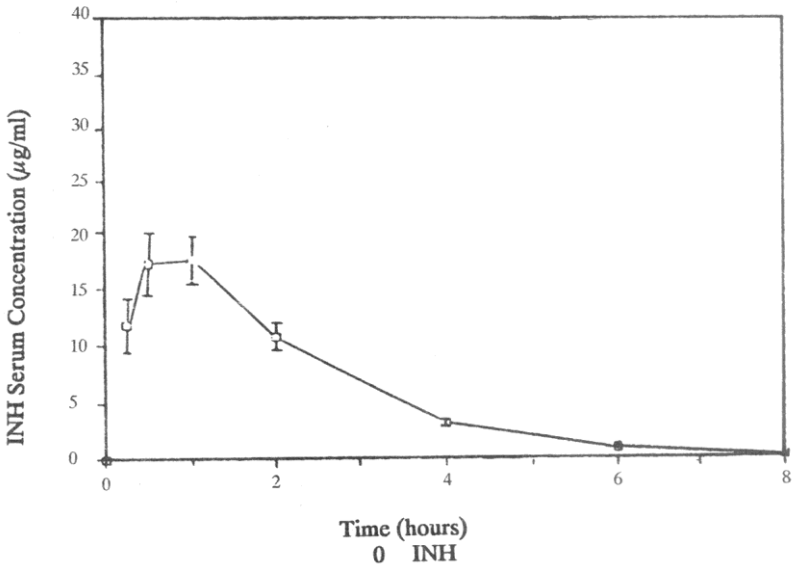

Figure 1b: Serum concentration (Mean ± S.E.M.) of isoniazid in slow acetylators following an oral administration of 500 mg of the drug.

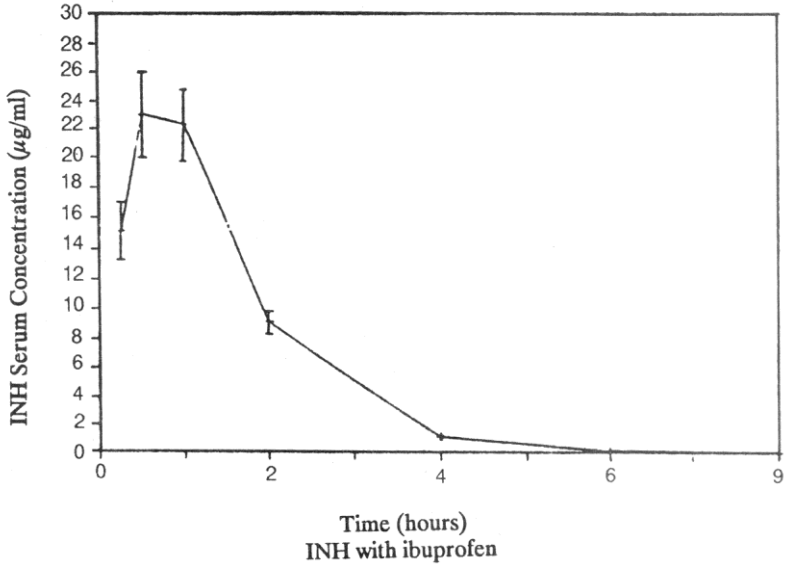

Figure 2a: Serum concentration (Mean ± S.E.M.) of isoniazid in combination with ibuprofen in fast acetylators after oral administration of 500 mg and 400 of the drugs respectively.

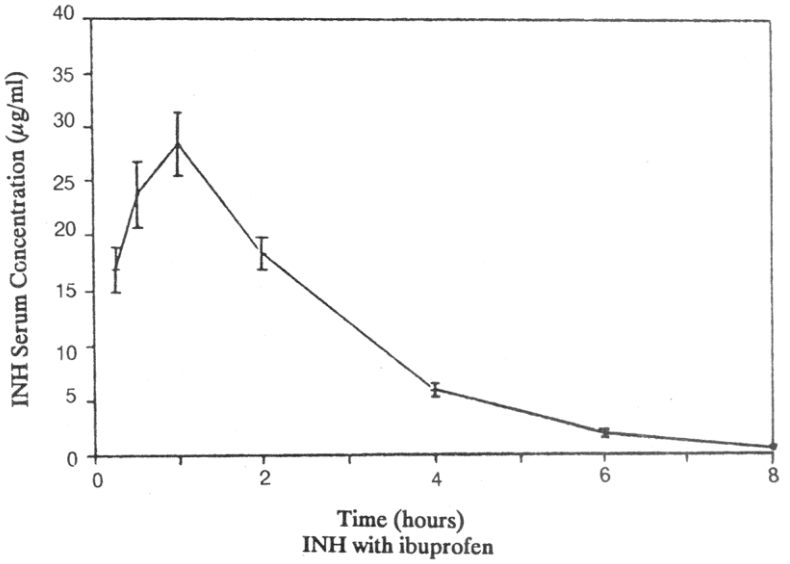

Figure 2b: Serum concentration (Mean ± S.E.M.) of isoniazid in combination with ibuprofen in fast acetylators after oral administration of 500 mg and 400 of the drugs respectively.

parameters show a highly significant ($P < 0.001$) increase in the area under the serum concentration time curve (AUC) in fast acetylators (32.8 ± 52.73 and 54.49± 23.95) with a significant increase in the AUC in the slow acetylators (47.21 ± 534 and 78.5 ± 17.58). A significant increase in the C_{max} of isoniazid in slow acetylators (15.24 ± 32.86 and 29.40 ± 3.64) has been observed, while in fast acetylators it was insignificant. A significant increase in the elimination half-life [t½] (0.61 ± 0.01 and 056± 30-.03) and t_{max} (0.47 ± 0.03 and 056±0.03) was observed only in fast acetylators as shown in Table 1.

Table 1

Effect of ibuprofen on pharmacokinetic parameters of isoniazid

	Control	ibuprofen treatment	t-value
Elimination t 1/2 (hr)			
(fast acetylators)	0.61 ± 0.01	0.68± 0.03	2.21*
(slow acetylators)	1.29 ± 0.11	1.29± 0.14	0.00
C_{max} (μg/ml)			
(fast acetylators)	20.20± 24.19	24.7± 3.07	1.19
(slow acetylators)	15.24± 2.86	29.4± 3.64	3.06*
AUC (μg.hr/ml)			
(fast acetylators)	32.85± 2.73	54.49± 3.95	4.51**
(slow acetylatos)	47.21± 5.34	78.51± 7.58	3.38*
T_{max} (hr)			
(fast acetylators)	0.47± 0.03	0.56± 0.03	2.21*
(slow acetylators)	0.69± 0.08	0.77± 0.06	0.8

Data are $\bar{X}$ ±S.E.
*P < 0.05 significant.
**P < 0.001 highly significant.

DISCUSSION

Isoniazid is widely prescribed in the treatment of tuberculosis (Fox, 1972; 1975). Its main metabolic pathway is *N*-acetylation in man (Barclay, 1953; Ellard, 1972; Wendell, 1979). Since the major metabolic pathway of ibuprofen in man involves a series of microsomal oxidative reactions (Hermann, 1985; Mills, 1973) and in some animals isoniazid itself has been demonstrated to influence oxidative enzyme system (Hoglund, 1987), these metabolic oxidative reactions

were used for the metabolism of ibuprofen which affected the N-acetylation pathway of isoniazid, as in the case of para-aminosalirylc acid (Bell 1957). Inhibition of the hepatic cytochrome mixed-function oxidase activity for the metabolism of isoniazid is thus an evidence to reduced isoniazid oxidation and to cause a highly significant increase in the AUC (about 56.8%) in fast acetylators and a significant increase (about 66.29%) in slow acetylators after co-administration of ibuprofen. This study, therefore, suggests that ibuprofen influences the bioavailability of isoniazid in both fast and slow acetylators, and that the dose of isoniazid should be reduced during the co-administration with ibuprofen.

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