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Effect of piperine on bioavailability and pharmacokinetics of propranolol and theophylline in healthy volunteers

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Summary. The effect of piperine on the bioavailability and pharmacokinetics of propranolol and theophylline has been examined in a crossover study. Six subjects in each group received a single oral dose of propranolol 40 mg or theophylline (150 mg) alone or in combination with piperine 20 mg daily for 7 days. An earlier t_{max} and a higher C_{max} and AUC were observed in the subjects who received piperine and propranolol. It produced a higher C_{max}, longer elimination half-life and a higher AUC with theophylline.

In clinical practice, the enhanced systemic availability of oral propranolol and theophylline could be exploited to achieve better therapeutic control and improved patient compliance.

Key words: Piperine, Propranolol, Theophylline; pharmacokinetics, drug interaction.

Black pepper (Piper nigrum Linn.), long pepper (P. Longum Linn.) and their major alkaloidal component, piperine (1-peperoyl piperidine), have been reported to enhance the blood levels of several drugs in experimental and clinical studies [1–3].

In the present experiment, the influence of piperine on kinetic profiles of propranolol and theophylline has been studied. A major kinetic problem with propranolol is its high first pass metabolism and consequent poor systemic availability. Sharp peaks and troughs in the steady state levels and short dosing intervals also contribute to poor therapeutic control in theophylline therapy. Any pharmacological intervention that enhanced the bioavailability of either drug and produced sustained levels for a longer period should be advantageous.

Subjects and methods

Twelve nonsmoking subjects (18–45 y; 45–66 kg), judged to be healthy on the basis of clinical examination, and routine blood chemistry and urine analysis, were admitted to the study after obtaining their written consent. All participants were advised to abstain from alcohol and drugs other than those investigated for one week prior to and during the period of study. On separate occasions 6 of the subjects received a single oral dose of either a tablet of propranolol 40 mg or of theophylline 150 mg. Each of these treatments was preceded by piperine 20 mg daily for 7 days. One week was permitted as a washout period between the two treatments. Venous blood samples were collected at 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 h and 0, 0.25, 0.5, 0.75, 1, 2, 4, 8, 12 and 24 h after propranolol and theophylline administration respectively. Plasma propranolol levels were estimated by a spectrofluorimeteric method [4] and theophylline levels in serum were analysed by EMIT [5].

Pharmacokinetic analysis

The plasma concentrations of the drugs at the different time intervals were plotted on a semilogarithmic scale. The kinetics were seen to be most appropriately described by a one compartment model for theophylline and a two compartment model for propranolol. Elimination constants were derived from the slope of the terminal log-linear portion of the concentration decay curve [6]. The area under the serum concentration-time curve AUC(o–t)/AUC) was calculated according to Gibaldi [7]. The pharmacokinetic parameters from the two groups were analysed by the paired 't' test and $P = 0.05$ was taken as the minimum level of significance.

Results and discussion

The mean plasma concentration-time curves of propranolol alone and in combination with piperine are depicted in Fig. 1. It shows a gradual ascent to a maximum (45 ng · ml^{-1}) at 2 h in contrast to the steeper upward slope and higher C_{max} (90 ng · ml^{-1}) after propranolol plus piperine. The decay of propranolol with or without piperine was similar. There was a highly significant increase in the systemic availability and AUC of propranolol under the in-

fluence of piperine, whilst its elimination kinetics was not changed (Table 1).

The time-concentration curves of theophylline (Fig. 1) behaved in a manner similar to that of propranolol. However, the decay curve of the theophylline-piperine combination was comparatively steeper than that of theophylline alone. The significant alterations in theophylline kinetics due to prior administration of piperine were a higher C_{max}, a longer elimination half-life and a larger AUC (Table 1).

The possibility that piperine had enhanced the bioavailability of propranolol by increasing its absorption cannot be excluded out. The piperine-induced increase in the elimination half-life, C_{max} and AUC of theophylline can be explained on the basis of the finding of Atal et al. [8] of reversible inhibition of drug metabolising enzymes. The present authors have previously reported piperine-induced enhancement of the systemic availability of phenytoin as a consequence of its accelerated absorption.

Propranolol is extensively used in clinical practice for various cardiac and noncardiac conditions and theophylline constitutes the mainstay of bronchodilator therapy. Both drugs need to be used on a chronic basis but suffer from the drawback of a short duration of action, which necessitates frequent dosing. The rigours of multiple dosing decrease patient compliance and limit the efficacy of the regimens. Long acting (LA) preparation of propranolol and sustained action formulations (SA) of theophylline have been introduced with the aim of prolonging the duration of the therapeutic response. Although there has been some success with the SA preparations, experience of LA propranolol has been disappointing due to extremely low serum levels of the β-adrenoceptor blocker [9]. On the basis of the present data it is suggested that steady state levels of both the drugs would be likely to be maintained within a therapeutic range for at least 12 h if they were co-administered with piperine. It would be useful to determine the effect of piperine co-administration on the steady state concentrations of propranolol and theophylline.

The enhancement of systemic availability of propranolol and theophylline by piperine assumes additional significance from the fact that the toxicological potential of the latter has been reported to be extremely low [10]. The ability of piperine to enhance the bioavailability of co-administered drugs, as reported in this and previous studies [3], can be considered from a different perspective. In Ayurvedic materia medica, pepper products enjoy a unique place, as these plant extracts are an ingredient of almost all the formulations used by practioners of this system, even though there is no convincing explanation for such extensive use. It is tempting to speculate that concomitant Piper administration may be intended as a enhancer of bioavailability of drugs in the Indian System of Medicine, which does not employ the parenteral route of drug administration.

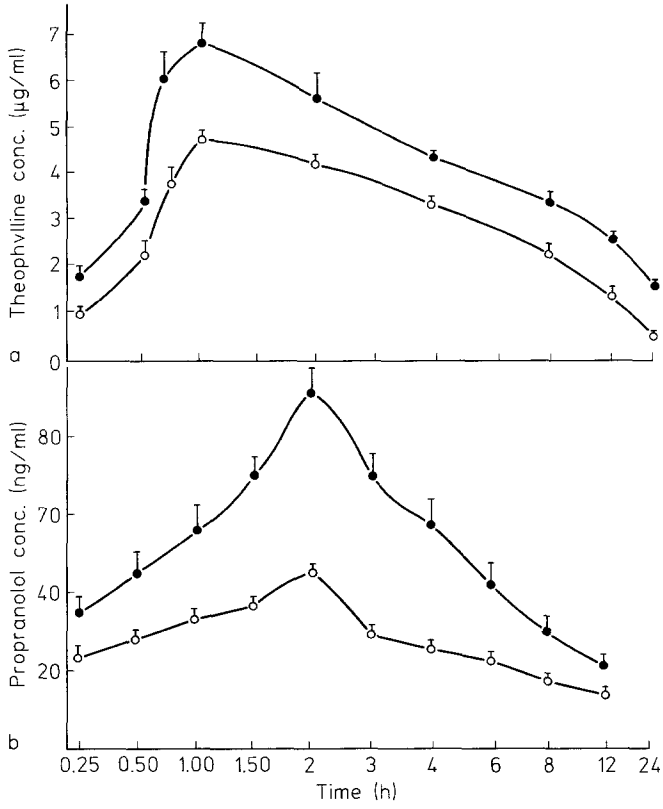

Fig. 1. a. Mean plasma concentrations of propranolol (o---o) and propanolol + piperine (●---●). **b** Mean serum concentrations of theophylline (o---o) and theophylline + piperine (●---●)

Table 1. Mean with (SEM) pharmacokinetic parameters of propranolol and theophylline after oral dosing in the absence and presence of piperine

Parameter	Propranolol	Propranolol + piperine	Theophylline	Theophylline + piperine
C_{max}	45.0[a]* (3.24)	92.0[a]* (5.46)	4.55[b] (0.19)	7.36[b]* (0.40)
$t_{1/2}$ (h)	9.05 (1.59)	9.38 (1.51)	6.58 (0.23)	10.75 (0.33)
AUC (0–∞)	561[c] (65.7)	1140[c]* (175)	43.8[d] (3.3)	85.7[d]* (2.7)

[a] (ng·ml^{-1}); [b] (μg·ml^{-1}); [c] (ng·ml^{-1}·h^{-1}); [d] (μg·ml^{-1}·h^{-1})
* $P < 0.001$

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