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Non-Interaction of Ketotifen and Theophylline in Children with Asthma - an Acute Study

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Summary. Six asthmatic children participated in an acute crossover randomized study. They received a single dose of aminophylline syrup 6 mg/kg after having received ketotifen syrup 1 mg b.i.d. or placebo for 8 days. Ketotifen did not significantly affect the heart rate, pulse pressure or such pharmacokinetic parameters of theophylline as peak serum level, time to peak, half life and AUC. Thus, ketotifen had no significant effect on the disposition of theophylline.

Key words: ketotifen, asthma; theophylline disposition, drug interaction, children

Ketotifen has been shown to inhibit the release of histamine and leukotriene from basophils and lung tissue, to antagonize histamine at H_1-receptors, to inhibit calcium uptake, to block the passive cutaneous anaphylactic reaction, to reverse isoprenaline-induced beta-adrenoceptor tachyphylaxis, and to inhibit both allergen-induced and drug-induced asthma [1]. Most double-blind placebo-controlled clinical trials of ketotifen have shown it to have a beneficial effect in the treatment of asthma [2, 3] equivalent to that of disodium cromoglycate [4-6], and at least as effective as theophylline [3].

Theophylline is one of the principal drugs for treating asthma and it has a low therapeutic index. Several drugs can interact with it; cimetidine [7], erythromycin [8], allopurinol [9], and propranolol [10] decrease theophylline clearance and increase its serum concentration, whereas isproterenol [11], terbutaline [12], phenobarbital [13], and phenytoin [14] decrease serum theophylline levels by increasing its clearance. The present study was undertaken to determine whether ketotifen affected the disposition of theophylline.

Materials and Methods

Six asthamatic children aged 8-14 years (mean 11.2 years), with a mean weight of 25.6 kg, participated in an acute study. The study was approved by the Helsinki Committee and the patients' parents gave their written informed consent. All subjects had atopic, perennial bronchial asthma. Subjects with acute asthmatic attacks, viral infection, febrile disease, liver or renal dysfunction, and those treated with corticosteroids, erythromycin, barbiturates, phenytoin or salicylates were excluded. All antiasthmatic medication was stopped 7 days prior to the study.

All subjects were given ketotifen syrup 1 mg p.o. b.d. (Zaditen, Wander, Berne, Switzerland) for 8 days followed by placebo, or vice versa. There was a wash-out period of 7 days between the ketotifen and placebo regimens. Compliance of 97% was shown by measurement of unconsumed syrup. On the eighth day of each regimen the subjects were hospitalized after an overnight fast. A single dose of aminophylline syrup 6 mg/kg p.o. (Elixophylline, Sam-On, Bat-Yam, Israel) was given together with ketotifen syrup or placebo and 50 ml water. Food was not allowed for 3 h from the time of administration of the theophylline. Tea, coffee, Coke or other caffeinated beverages were not permitted during the trial.

Heart rate, blood pressure and peak expiratory flow rate (PEFR) were recorded each time blood was collected during the following 8 h. PEFR was mea-

Table 1. Pharmacodynamic parameters before and after coadministration of theophylline with ketotifen or placebo (mean ± SD)

	Theophylline and ketotifen		Theophylline and placebo	
	Before	After	Before	After
Heart rate (beats/min)	91.7 ± 20	85.7 ± 9.7	90.0 ± 26.8	94.0 ± 33
Blood pressure (mmHg)	114/76 ± 15/17	110/75 ± 16/8	106/69 ± 17/9	107/75 ± 21/10
PEFR (l/min)	360.8 ± 81.8	386.7 ± 69.7	336.7 ± 72.8	358.3 ± 70

Table 2. Pharmacokinetic parameters of theophylline with and without ketotifen (mean ± SD)

	Ketotifen	Placebo
Serum Peak (μg/ml)	10.0 ± 3.4	9.4 ± 3.3
Time of peak (h)	0.9 ± 0.6	1.0 ± 0.6
$t_{½\beta}$(h)	8.5 ± 1.3	8.2 ± 2.1
AUC (μg/ml · h)	118.5 ± 20.5	111.6 ± 23.9

sured with a mini-Wright peak flow meter (Airmed Clement Clarke Int., England). Blood for serum theophylline assay was collected at 0, 0.5, 1, 2, 3, 4, 6 and 8 h, stored at −20 °C and assayed in duplicate by fluorescent immunoassay (TDX, Abbot Irving, Texas). Ketotifen added in vitro did not interfere with the theophylline assay (data not shown). The serum theophylline concentration - time curve from 0 to 8 h was plotted semilogarhithmically for each patient and pharmacokinetic parameters of theophylline, including elimination half-life $t_{½}$, serum concentration peak, time to peak and area under the curve (AUC), were obtained from the curve [Giabaldi and Perrier 1975]. Statistical significance was evaluated using Student's paired *t*-test.

Results

The pharmacodynamic parameters are summarized in Table 1. Ketotifen did not change heart rate or blood pressure. PEFR was significantly improved 1 h after theophylline administration both in placebo-treated ($p < 0.05$) and ketotifen-treated ($p < 0.005$) patients. There was no significant difference in PEFR between placebo- and ketotifen-treated patients.

The pharmacokinetic parameters of theophylline with and without ketotifen are shown in Table 2. Ketotifen did not alter the peak serum level, time to peak, elimination half life or the AUC of theophylline.

Discussion

The present study, like most previous investigations [2, 3, 6], showed little or no effect of ketotifen on PEFR. The major clinical benefit of ketotifen is the reduction of symptoms together with reduction of inhaler usage [2, 3]. Ketotifen has shown a significant additional improvement in combined symptom score and inhaler use in patients receiving ketotifen-theophylline versus placebo-theophylline [15]. The major clinical side-effect of ketotifen is drowsiness, which is infrequent on prolonged administration [3]. In this respect it differs from the predominant side effects of theophylline, which are headache or gastrointestinal symptoms. It appears that combination treatment with ketotifen and theophylline should be clinically useful in bronchial asthma.

There was no significant effect of ketotifen on theophylline disposition in the present acute study. The finding is similar to that in a study which showed no change in serum theophylline levels when ketotifen or placebo were administered for 12 weeks and theophylline was added for the last 8 weeks of each regimen [15]. Therefore, ketotifen may be given to asthmatic patients being treated with theophylline without affecting the disposition of the latter medicine.

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