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Short communication

Effect of ketanserin, a new blocking agent of the 5-HT_2 receptor, on airway responsiveness in asthma

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Most of the antihypertensive drugs have a liability for adverse effects in asthma. Since there are few available data on the effect of ketanserin, a new antihypertensive drug which is a type-2 serotonin receptor antagonist, on human respiratory function, we have tested whether this drug can modify bronchial hyperresponsiveness to methacholine in asthmatic patients. The protective effect of intravenous ketanserin (0.14 mg/kg) was small, but significant.

Key words: ketanserin; $5HT_2$ receptors; bronchial asthma; methacholine induced bronchoconstriction.

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Most agents in the treatment of hypertension must be used with caution in asthmatic patients.

The daily use of diuretic drugs to control mild hypertension may result in increased sputum viscosity, thereby impairing mucokinesis; patients with asthma who have profuse, viscous sputum are at risk of mucostasis (11).

All drugs with significant beta-blocking properties have been reported to cause either attacks of asthma or to render such attacks more resistant to therapy with beta-agonist drugs (3). Alpha-methyldopa is reported to cause delayed wheeze, rhinitis and dyspnea following dust exposure, usually in an occupational setting. The mechanism is unclear since the onset of symptoms usually follows months of exposure, but neither precipitins, nor positive prick tests have been observed (4). Recent experience with the angiotension-converting enzyme (ACE) inhibitors (captopril and enalapril) suggests that these drugs may sometimes cause cough (10) and, less frequently, exacerbation of chronic asthma or the appearance of serum-sickness-like syndrome with dyspnea (8).

Ketanserin is a new antihypertensive drug which is a type-2 serotonin receptor antagonist. There are few available data on the effects of ketanserin on human bronchi *in vivo*. We have shown that it can elicit mild bronchodilation in chronic airway obstruction (2). The aim of the present investigation was to investigate whether ketanserin affects the methacholine challenge in asthmatic subjects.

METHODS

The study comprised 18 well-characterized, stable, moderately severe asthmatic patients. All subjects satisfied the criteria for the definition of asthma as stated by the American Thoracic Society (1). Nine children (8 boys and 1 girl) and nine adults (4 men and 5 women) were studied (Table 1). Informed consent was obtained from subjects or their parents. All patients received mantenance bronchodilator therapy for control of their bronchospasm, but none required regular oral or inhaled corticosteroids.

Each subject had long-acting theophylline preparations discontinued for 24 h and beta-agonists for 12 h prior to testing. All patients attended the lung function laboratory on 3 different days within 2 weeks at the same time of

Table 1

Mean (±SE) changes in FEV_1 after intravenous administration of placebo or ketanserin (0.14 mg/kg)

FEV_1 l			
Placebo		Ketanserin	
Basal	After 30 min	Basal	After 30 min
2.71	2.80	2.62	2.83
0.31	0.32	0.29	0.31

day (between 9 and 12 a.m.). On day 1 (pilot day), a methacholine inhalation test was done in order to characterize airway responsiveness. Methacholine inhalation was then repeated on 2 different days after saline (placebo) or ketanserin pretreatment. Drugs were injected intravenously in a volume of 5 ml in 3 min 30 min before the beginning of the provocation test. At the ketanserin sessions, 0.14 mg/kg of ketanserin (Sufrexal, Janssen, Rome, Italy) were administered.

Inhalation tests were done with the delivery of the aerosolized methacholine solution by a breath-activated dosimeter (Mefar, Brescia, Italy). Cumulative methacholine doses were 40, 80, 120, 200, 400, 600, 800, 1200, 1600, 2000, 2400 and 2600 μg.

FVC and FEV_1 were measured by electrical integration of a signal from a pneumotachygraph (Fleisch No. 3) (Pneumodata, Cosmed, Rome, Italy) with an on-line computer for immediate availability of data.

Dose-response curves were constructed with FEV_1 on the ordinate as the percentage of the lowest post-saline value, and the cumulative methacholine dose was expressed logarithmically on the abscissa. The results were presented as the cumulative dose of methacholine producing a 20% decrease in FEV_1 (PD_{20}), which was obtained from the log dose-response curve by linear interpolation of the last two points.

Values of PD_{20} FEV_1 after treatments were compared by a two-way analysis of variance, with a P value < 0.05 considered significant.

RESULTS

There was no statistically significant difference ($P > 0.05$) between average values of FEV_1, even if this functional variable increased more after ketanserin than after placebo (Table 1).

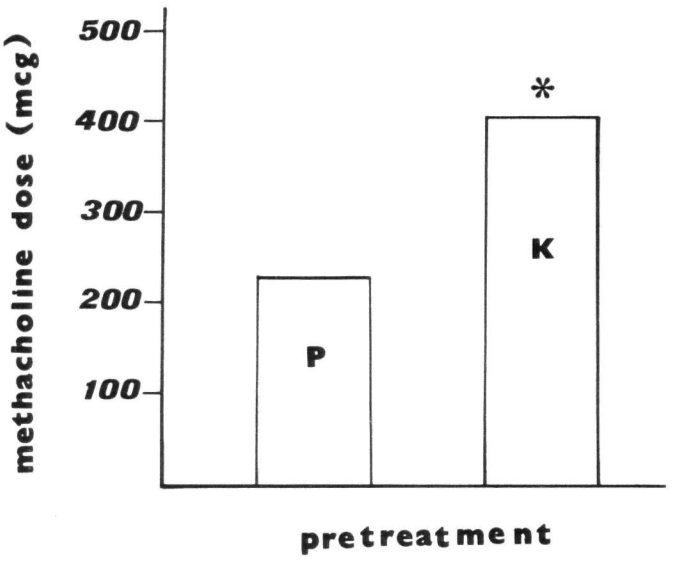

Fig. 1. Methacholine PD_{20} FEV_1 after intravenous administration of placebo (P) or ketanserin (K) (0.14/mg/kg). Values are geometric means. *Significant difference between ketanserin and placebo ($P < 0.05$).

Some inhibition of methacholine-induced bronchoconstriction has been obtained in 14 of 18 studied patients after ketanserin administration. This protective effect was small, but significant (Fig. 1). In three of the nine adults and one of the nine children who underwent ketanserin in pretreatment, however, no change in responsiveness to methacholine was observed.

DISCUSSION

In this study we have shown a marginal effect of ketanserin on methacholine-induced bronchoconstriction. The interpretation of the results is difficult. It has been demonstrated that ketanserin has no anticholinergic effect (Awouters, unpublished observations). It is possible that its influence on bronchial responsiveness may be due to the bronchodilator effect of ketanserin itself, but it could be speculated that this effect is associated with a release of catecholamines from the adrenal medulla (7), or with its antihistaminic activity (6). It may also be possible that ketanserin interferes with efferent cholinergic traffic by means of 5-HT receptor blockade at the cholinergic neuroeffector junction, since serotonin can facilitate the release of acetylcholine in autonomic ganglia (5).

At the present, it remains uncertain whether ketanserin exerts its action because it possesses alpha$_1$-antagonistic properties. It is unlikely, however, that intravenous injection of 10 mg ketanserin causes alpha$_1$-adrenoceptor blockade in man (9).

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