Attenuation of propranolol-induced bronchoconstriction by frusemide

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Abstract

Background – Inhaled propranolol causes bronchoconstriction in asthmatic subjects by an indirect mechanism which remains unclear. Inhaled frusemide has been shown to attenuate a number of indirectly acting bronchoconstrictor challenges. The aim of this study was to investigate whether frusemide could protect against propranolol-induced bronchoconstriction in patients with stable mild asthma.

Methods – Twelve asthmatic subjects were studied on three separate days. At the first visit subjects inhaled increasing doubling concentrations of propranolol (0.25–32 mg/ml), breathing tidally from a jet nebuliser. The provocative concentration of propranolol causing a 20% reduction in FEV₁ (PC₂₀FEV₁ propranolol) was determined from the log concentration-response curve for each subject. At the following visits nebulised frusemide (4 ml × 10 mg/ml) or placebo (isotonic saline) was administered in a randomised, double blind, crossover fashion. FEV₁ was measured immediately before and five minutes after drug administration. Individual PC₂₀FEV₁ propranolol was then administered and FEV₁ was recorded at five minute intervals for 15 minutes. Residual bronchoconstriction was reversed with nebulised salbutamol. **Results** – Frusemide had no acute bronchodilator effect but significantly reduced the maximum fall in FEV₁ due to propranolol: mean fall 18.2% after placebo and 11.8% after frusemide. The median difference in maximum % fall in FEV₁ within individuals between study days was 3.6% (95% CI 1.2 to 11.7).

Conclusions – Frusemide attenuates propranolol-induced bronchoconstriction, a property shared with sodium cromoglycate. Both drugs block other indirect challenges and the present study lends further support to the suggestion that frusemide and cromoglycate share a similar mechanism of action in the airways.

(Thorax 1997;52:861–865)

Keywords: asthma, frusemide, propranolol.

Beta adrenergic receptor antagonists remain an important therapeutic option in the treatment of hypertension and ischaemic heart disease. The potential for production of serious bronchoconstriction was recognised soon after their introduction¹ and occasional fatal reactions still occur. Inhaled propranolol causes dose-dependent bronchoconstriction in asthmatic

subjects by an indirect mechanism that has not been fully elucidated.² Propranolol-induced bronchoconstriction is believed to involve β_2 adrenoreceptor blockade since bronchoconstrictor activity is confined to its L-isomer.³ Propranolol-induced bronchoconstriction in humans is attenuated by anticholinergic agents,⁴ pilocarpine,⁵ vasoactive intestinal peptide,⁶ and by cromones.^{7,8}

Frusemide has been shown to antagonise the effects of a number of indirectly acting bronchoconstrictor stimuli in asthmatic patients. These include ultrasonically nebulised distilled water,⁹ hypertonic saline,¹⁰ exercise,¹¹ isocapnic hyperventilation of dry air,¹² sodium metabisulphite,¹³ bradykinin,¹⁴ 5'-adenosine monophosphate,¹⁴ salicylates,¹⁵ and early response to antigen.¹⁶ Sodium cromoglycate has also been shown to block all these challenges^{17–26} and it has been suggested that the mechanism of action of the two agents may be similar.

Since cromoglycate has been shown to attenuate propranolol-induced bronchoconstriction in asthmatic subjects,⁸ the aim of the present study was to determine whether frusemide shares this property.

Methods

SUBJECTS

Twelve subjects with stable mild asthma (eight women) were each studied on three separate occasions. Subjects were either members of hospital or medical school staff or patients recruited from outpatient clinics. All had a diagnosis consistent with the criteria of the American Thoracic Society.²⁷ Their demographic and clinical details are summarised in table 1. Their mean age (range) was 30 (22–45) years and mean (SD) baseline forced expiratory volume in one second (FEV₁) was 97 (12)% predicted.²⁸ Maintenance treatment consisted of inhaled β_2 agonists in all, inhaled corticosteroids in seven, and sodium cromoglycate in two subjects (table 1). No subject had had a respiratory infection, change in their medication, nor an exacerbation of asthma symptoms in the four weeks prior to the study. No subject was receiving systemic bronchodilator agents or corticosteroids. The study was approved by the Royal Postgraduate Medical School and Hammersmith Hospital Research ethics committee and written informed consent was obtained from each subject prior to entry into the study.

STUDY DESIGN

The study was of a randomised, crossover, double blind, placebo controlled design. Sub-

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Received 14 March 1997
Returned to authors
7 May 1997
Revised version received
23 June 1997
Accepted for publication
16 July 1997

Table 1 Demographic data of subjects

Subject no.	Age (years)	Sex	Atopy	Smoker	Treatment	FEV ₁ baseline (% predicted) (l)	PC ₂₀ FEV ₁ propranolol (mg/ml)
1	23	F	Yes	Yes	S, BUD	3.00 (94)	12.3
2	30	F	Yes	Never	S, BDP	3.48 (106)	11.1
3	31	M	Yes	Never	S	4.65 (103)	11.7
4	28	F	Yes	Yes	S, I, BDP, SCG	2.75 (84)	13.7
5	45	M	Yes	Never	T, BUD	2.85 (72)	7.3
6	28	F	Yes	Never	S, BDP	3.52 (103)	15.2
7	25	M	Yes	Never	S	4.37 (96)	7.5
8	34	M	Yes	Yes	S, SCG	5.12 (113)	10.0
9	22	F	No	Never	S, SM, BUD	3.71 (106)	13.8
10	27	F	Yes	Never	S	3.20 (93)	20.7
11	36	F	Yes	Never	Duovent, BDP	2.66 (85)	14.9
12	27	F	Yes	Never	S	3.34 (104)	12.4

S = salbutamol; T = terbutaline; I = ipratropium bromide; SM = salmeterol; BDP = beclomethasone dipropionate; BUD = budesonide; SCG = sodium cromoglycate; FEV₁ = forced expiratory volume in one second; PC₂₀FEV₁ = concentration of propranolol provoking a fall in FEV₁ of 20% or more. Atopy defined by clinical history.

jects attended the laboratory for a screening visit and two study visits, with a washout period of at least 48 hours between each attendance. Each subject completed the study within four weeks of screening. Subjects abstained from short acting bronchodilators for at least eight hours and from long acting bronchodilators and cromones for at least 12 hours prior to each visit. Inhaled corticosteroids were continued unchanged throughout the study period.

At screening a medical history was taken and a physical examination performed. Subjects then underwent propranolol challenge, and were included in the study if they had a provocative concentration of propranolol causing a 20% fall in FEV₁ (PC₂₀FEV₁ propranolol) of ≤ 32 mg/ml. Baseline FEV₁ at each study visit was required to be $\geq 65\%$ predicted and to not deviate by $>10\%$ from the screening value. If these criteria were not met an appointment was made for reattendance on another day.

On each study day baseline FEV₁ was measured. Subjects then received study drug (frusemide 40 mg or placebo) by nebuliser. Five minutes after nebulisation FEV₁ was measured and each subject's individually predetermined PC₂₀FEV₁ propranolol was then administered. FEV₁ was recorded at five minute intervals for 15 minutes. Salbutamol 2.5 mg was then administered by nebuliser and FEV₁ measured at five minute intervals for 30 minutes or until baseline FEV₁ was regained.

SPIROMETRY, DRUG DELIVERY AND PROPRANOLOL CHALLENGE

Spirometric measurements were made using a dry wedge bellows spirometer (Vitalograph, Vitalograph Ltd, Buckingham, UK) performed according to American Thoracic Society guidelines.²⁹

Study medication (Lasix for injection supplied by Hoechst Ltd, Hounslow, UK or placebo) was delivered via jet nebuliser (Ventstream, Medic-Aid, Sussex, UK) driven by medical air at a flow rate of 8 l/min with an output of 0.67 g/min.³⁰

Propranolol challenge was performed according to a standardised technique modified from that previously described.⁴ Anhydrous propranolol hydrochloride powder (Zeneca, UK) was dissolved in normal saline on the day of each study visit and diluted to provide

solutions of doubling concentrations from 0.25 to 32 mg/ml. Solutions were administered by tidal breathing for one minute via a Ventstream nebuliser driven by medical air at 8 l/min. Spirometric values were measured at baseline, three minutes after inhalation of saline, and three minutes after inhalation of each dose of propranolol. Doses were given at five minute intervals. Challenges were terminated when a 20% or greater fall in FEV₁ from the post saline value had been achieved or when the highest concentration of propranolol had been given. If there was a fall in FEV₁ of more than 15% but less than 20%, spirometric measurements were repeated after a further five minutes. The next concentration of propranolol was then administered only if FEV₁ remained above 80% of baseline. The provocative concentration of propranolol causing a 20% reduction in FEV₁ (PC₂₀FEV₁ propranolol) was determined by linear interpolation from the log concentration-response curve.³¹ Residual bronchoconstriction was reversed by nebulised salbutamol 2.5 mg plus ipratropium bromide 500 µg. Subjects were allowed to leave the laboratory when their FEV₁ had returned to at least 90% of baseline.

On the two study drug days an abbreviated propranolol challenge was performed with each subject receiving their individual PC₂₀FEV₁ propranolol as a single dose. Salbutamol alone was used to reverse residual bronchoconstriction.

DATA ANALYSIS

Results are expressed as mean (SD) using the value before frusemide/placebo administration as the baseline. Summary measures characterising the response to propranolol inhalation (maximum fall in FEV₁ as % baseline and area under the curve of fall in FEV₁ against time) and the rate of recovery following salbutamol administration (time to achieve 95% of baseline FEV₁) were compared for the active and placebo treatment days using the Wilcoxon signed rank test.³² Period and carryover effects were examined according to standard methods.³³

Results

Propranolol challenge was generally well tolerated although four subjects reported per-

Figure 1 Maximum fall in forced expiratory volume in one second (FEV_1) after propranolol (% baseline, individual data).

sistent mild wheeze, dry cough and/or increased requirement for inhaled β_2 agonist lasting for up to 12 hours following full propranolol dose-response assessment. One subject developed marked bronchoconstriction on the placebo day with a 58% fall in FEV_1 five minutes after propranolol inhalation. She was therefore immediately given nebulised salbutamol and ipratropium. This subject's recovery data are not included in the statistical analysis. There were no other adverse events reported after inhalation of single doses of propranolol. All subjects achieved at least 95% of baseline FEV_1 within the monitored recovery period following salbutamol administration.

Baseline FEV_1 did not differ significantly between the study days: mean (SD) 3.49 (0.81) l on the placebo day and 3.54 (0.87) l on the frusemide day. Neither frusemide nor saline administration significantly affected FEV_1 : mean (SD) FEV_1 after saline 3.49 (0.79) l, after frusemide 3.55 (0.89) l.

Administration of the individually determined $PC_{20}FEV_1$ at the placebo study visit resulted in a mean (SD) maximum percentage fall in FEV_1 from baseline of 18.2 (13.8)% (fig 1). This was not significantly different from the predicted 20% fall, despite the fact that the dose administered was only half the cumulative dose given during the full dose response. There was, however, considerable individual variation in the extent of bronchoconstriction resulting from this single dose of propranolol – less than 10% in three subjects and more than 30% in one – though all subjects had previously shown falls in FEV_1 of more than 20% at the screening visit. The maximum fall in FEV_1 following propranolol inhalation exceeded 20% in three subjects.

The early time course of propranolol-induced bronchoconstriction varied between individuals. One subject (no. 11, table 1) showed a 58% fall in FEV_1 five minutes after

Figure 2 Time course of absolute fall in forced expiratory volume in one second (FEV_1) after propranolol on frusemide and placebo days.

propranolol administration and was therefore given ipratropium bromide and salbutamol immediately. No specific distinguishing clinical features were identified to account for this subject's idiosyncratic response. In the other 11 subjects FEV_1 was followed for a full 15 minutes before bronchodilator treatment with salbutamol alone. Of these, five achieved maximum bronchoconstriction by five minutes and a further three by 10 minutes, while the remainder showed increased bronchoconstriction at the 15 minute time point.

The area under the curve of decrease in FEV_1 against time was less after frusemide than placebo (fig 2) but did not reach statistical significance ($p=0.051$, Wilcoxon), excluding subject 11 from the analysis. The mean (SD) maximum fall in FEV_1 following propranolol, expressed as % baseline, was 18.2 (13.8)% on the placebo day compared with 11.8 (9.4)% following frusemide (fig 1). This difference was significant ($p=0.02$), indicating that frusemide has a bronchoprotective effect against propranolol-induced bronchoconstriction. The median difference in maximum % fall in FEV_1 within individuals between study days was 3.6% (95% CI 1.2 to 11.7).

Once again there was considerable individual variation in the degree of bronchoprotection. One subject showed more than 80% protection but three subjects had no apparent bronchoprotection at all. These differences showed no apparent relationship to differences between subjects' age, sex, atopic or smoking status, or baseline $PC_{20}FEV_1$ propranolol.

Data for the recovery period were analysed for 11 subjects. The mean (SD) time taken for FEV_1 to return to at least 95% of baseline was 9 (10) minutes following frusemide which was not significantly different from 15 (11) minutes after placebo.

No period effect on the maximum percentage change in FEV_1 was identified.

Discussion

We have shown that pretreatment with nebulised frusemide attenuates the bronchoconstrictor response to inhaled propranolol in mild asthmatic subjects. This observation has not been previously reported. The degree of bronchoprotection afforded was approximately one third of the unattenuated propranolol-induced fall in FEV_1 , though there was

considerable variation between individuals. Frusemide, like sodium cromoglycate,⁸ thus provides partial bronchoprotection against propranolol-induced bronchoconstriction but fails to match the complete protection afforded by oxitropium.⁴

Inhalation of propranolol causes dose dependent bronchoconstriction in asthmatic subjects which is well tolerated. This study did not address the repeatability of the bronchoconstrictor effect of propranolol, which is known to be moderate or good.^{2,47} Inter-individual variation in propranolol response was seen, as mentioned above. Nevertheless, the randomised, crossover, placebo controlled design should take this into account. As in previous studies,⁴ protection against a single dose of propranolol was examined rather than constructing a full dose-response curve on each occasion, for convenience and simplicity.

The mechanism of propranolol-induced bronchoconstriction is unclear but it is distinct from that of agents that act directly on airway smooth muscle such as methacholine, as shown by the lack of correlation of sensitivity to the different agents within individuals and differences in the shapes of the dose-response curves.² Bronchoconstrictor activity is specific to the L-isomer of propranolol, suggesting that this effect is due to its activity as a β_2 adrenoceptor antagonist,³ and this is supported by the lesser bronchoconstrictor effects of more β_1 selective agents³⁴ and its antagonism by β_2 agonists.⁴ Human bronchial smooth muscle does not receive significant innervation from sympathetic autonomic nerves, suggesting that circulating catecholamines provide a tonic bronchodilator stimulus and that propranolol-induced bronchoconstriction results from its blockade.³⁵ This is supported by a report of bronchoconstriction following inhalation of propranolol in one heart-lung transplant recipient.³⁶ However, this may not be the full explanation of propranolol-induced bronchoconstriction in asthma, in view of the wide variety of inhaled agents that antagonise it and the very low background levels of circulating catecholamines in the plasma of resting subjects.³

Sympathetic nerves have been described within autonomic ganglia in the lungs and in close proximity to cholinergic nerves.³⁵ There is strong evidence for a role of the parasympathetic nervous system in propranolol-induced bronchoconstriction with blockade by atropine,³⁷ oxitropium bromide,⁴ and by presynaptic agonists such as pilocarpine.⁵ In guinea pigs ganglionic blockade with hexamethonium blocks propranolol-induced bronchoconstriction. Beta agonists have been shown to inhibit acetylcholine release from cholinergic nerves in human airways *in vitro*.³⁵ This has led to the suggestion that propranolol may cause bronchoconstriction by blockade of inhibitory presynaptic β_2 adrenoceptors on cholinergic nerves. This mechanism is consistent with the absence of propranolol-induced bronchoconstriction in normal subjects whose airways are less sensitive than those of asthmatic

subjects to the constrictor effect of acetylcholine.^{38,39}

Involvement of non-adrenergic non-cholinergic (NANC) nerves is suggested by the ability of vasoactive intestinal peptide to attenuate propranolol-induced bronchoconstriction. This effect is additive to that of ipratropium, suggesting that it is not mediated by cholinergic nerves.⁶ Finally, the cromones sodium cromoglycate and nedocromil sodium have been shown to attenuate propranolol-induced bronchoconstriction. It is likely that they are acting on airway nerves though the evidence regarding involvement of mast cells in propranolol-induced bronchoconstriction is conflicting.⁴⁰⁻⁴² Thus, propranolol-induced bronchoconstriction is likely to be mediated by a number of mechanisms, with airway nerves playing a prominent role. This may explain the wide interindividual variation in response to blockade of propranolol-induced bronchoconstriction by frusemide and other agents.^{2,42}

A wide variety of indirectly acting bronchoconstrictor stimuli are antagonised by frusemide.⁹⁻¹⁵ The exact mechanism of action by which frusemide exerts these effects remains unclear. It has been postulated to act upon chloride channels in the bronchial epithelium but the target cell of such an action has not been established. Alternative hypotheses include inhibition of activation of airway inflammatory cells and modulation of cholinergic and/or NANC nerves, possibly acting through the enhanced production of bronchoprotective prostanoids.⁴³ The results of the current study do not elucidate this further.

As with frusemide, the mechanism by which sodium cromoglycate exerts its bronchoprotective effects has not been fully established. Its ability to inhibit mediator release from mast cells has been demonstrated,⁴⁴ but it can also block activation of bronchial C fibres,⁴⁵ antagonise the actions of platelet activating factor,⁴⁶ and inhibit protein kinase C activity,⁴⁷ all of which could be relevant to its ability to attenuate indirectly provoked bronchoconstriction.

Our findings are consistent with the known properties of the agents studied and with the hypothesis that frusemide and the cromones provide bronchoprotection against indirect challenge by similar mechanisms. The inter-subject variability is consistent with multiple mechanisms of both propranolol-induced bronchoconstriction and frusemide bronchoprotection and is also seen with cromones.

Our observations do not provide any further insight into the mechanisms of action of the agents discussed, neither do they suggest a therapeutic role for frusemide in the treatment of established propranolol-induced bronchoconstriction. Frusemide did not demonstrate any bronchodilator activity, in keeping with previous studies,^{10,16} nor accelerate recovery of airway calibre following administration of salbutamol. The ability of frusemide to antagonise propranolol-induced bronchoconstriction was weak compared with that of β_2 agonists or anticholinergic agents which are the agents of

choice in treating bronchospasm induced by beta blockers in a clinical setting.

In conclusion, we have shown that inhaled frusemide attenuates the bronchoconstrictor response to propranolol. The effect is fairly weak and there is marked individual variation in its extent. These observations support the hypothesis that frusemide shares common mechanisms of bronchoprotection with the cromones.

Propranolol hydrochloride was kindly provided as anhydrous powder by Zeneca Ltd (Macclesfield, UK). Frusemide (Lasix) was kindly provided by Hoechst UK Ltd (Hounslow, UK).

This work was supported by a grant from Glaxo Wellcome.

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