Formoterol thrice weekly does not result in the development of tolerance to bronchoprotection

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BACKGROUND: Loss of bronchoprotection routinely follows regular treatment with β_2 -agonists. There are no data on the effects on bronchoprotection for thrice weekly use of a β_2 -agonist.

METHODS: A double-blind, randomized, placebo controlled crossover trial was conducted to investigate the effects of thrice weekly administration of 12 μ g of formoterol versus placebo on bronchoprotection against methacholine. As an expected positive control, formoterol 12 μ g once daily was also evaluated.

RESULTS: There was no significant difference versus placebo in the bronchoprotective effects of 12 μ g of formoterol administered on day 8, following daily treatment for seven days or treatment every other day (analysis of variance $P=0.34$). However, a nonsignificant trend towards lower concentration of methacholine that caused a 20% fall in forced expiratory volume in 1 s developed only following the daily formoterol dosing.

CONCLUSIONS: Thrice weekly dosing does not result in the development of tolerance to bronchoprotection against the direct acting stimulus methacholine.

Key Words: *Bronchoprotection; Formoterol*

Le formotérol trois fois par semaine ne provoque pas une tolérance à la bronchoprotection

HISTORIQUE : Une perte de bronchoprotection suit invariablement un traitement régulier aux β_2 -agonistes. Aucune donnée ne porte sur les effets de l'usage, trois fois par semaine, des β_2 -agonistes sur la bronchoprotection.

MÉTHODOLOGIE : Un essai croisé à double insu, aléatoire et contrôlé contre placebo a été mené pour explorer les effets, sur la bronchoprotection contre la méthacholine, de l'administration de 12 μ g de formotérol trois fois par semaine par rapport à un placebo. Afin d'obtenir un contrôle dont on prévoyait le résultat positif, l'administration quotidienne de 12 μ g de formotérol a également été évaluée.

RÉSULTATS : Par rapport au placebo, 12 μ g de formotérol administrés le huitième jour suivant un traitement quotidien pendant sept jours ou un traitement tous les deux jours (analyse de variance, $P=0,34$), ne modifiaient pas les effets bronchoprotecteurs de manière significative. Cependant, une tendance non significative vers une concentration plus faible de méthacholine, qui provoquait une chute de 20 % du volume expiratoire forcé en 1 s, se présentait après le dosage quotidien de formotérol seulement.

CONCLUSIONS : Une dose trois fois par semaine n'entraîne pas l'apparition d'une tolérance à la bronchoprotection contre la méthacholine par stimulation à action directe.

Tolerance to the bronchoprotective effect of both long and short acting β_2 -agonists has been well documented (1). Researchers have shown that protection is lost rapidly at standard doses and has a greater effect against indirect than against direct stimuli.

Formoterol, an immediate and long lasting β_2 -agonist, initially indicated as add-on therapy for patients whose lung function and symptoms are not adequately maintained with inhaled corticosteroid, has recently been approved as rescue therapy for acute bronchoconstriction. Like salbutamol, rescue use of formoterol is 'as needed' but should not exceed three times a week (2). At least one study has shown the development of tolerance with daily administration of 12 μ g of formoterol over a 14-day period (3). There are, however, no data determining the effects of thrice weekly administration. We therefore investigated thrice weekly administration of 12 μ g of formoterol versus placebo and included a daily 12 μ g treatment arm as an anticipated positive 'control' for the development of tolerance.

METHODS

Subjects

The study protocol was approved by the University of Saskatchewan BioMedical Ethics Committee, and 13 patients with mild to moderate asthma were enrolled into the study after providing consent and meeting eligibility criteria. Patients with a forced expiratory volume in 1 s (FEV_1) of less than 65% of the predicted volume or a concentration of methacholine that causes a 20% fall in FEV_1 (PC_{20}) of more than 8 mg/mL were not eligible. In addition, subjects had to be free of an upper respiratory infection for more than six weeks. Short acting β_2 -agonists were withheld for more than one week before enrolment, and no subjects had been using long acting β_2 -agonists. Atopic subjects avoided known allergen exposure for more than four weeks before and throughout the trial. Two participants were using a stable dose of inhaled corticosteroid, which they were allowed to continue using at the same dose for the duration of the study.

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TABLE 1
Baseline demographics

Subject	Sex	Age (years)	Height (cm)	Atopy	FEV ₁ (L)	FEV ₁ (% predicted)	Methacholine PC ₂₀ (mg/mL)	Concomitant medications	Status
1	F	36	168	No	3.01	93	5.0	None	Complete
2	F	24	163	Yes	2.77	82	0.27	None	Withdrawn
3	M	54	168	Yes	2.34	68	0.50	None	Complete
4	M	21	180	Yes	4.62	106	0.25	None	Complete
5	M	27	180	Yes	5.85	122	7.0	None	Complete
6	F	30	160	Yes	2.59	82	4.2	None	Withdrawn
7	M	35	183	Yes	4.26	94	2.0	None	Complete
8	M	27	180	Yes	4.03	92	0.25	None	Complete
9	M	36	173	Yes	3.13	82	0.25	FP 500 µg/day	Complete
10	F	17	163	No	2.98	96	3.6	BD 200 µg/day	Complete
11	F	18	168	Yes	3.95	106	2.6	None	Complete
12	F	23	160	Yes	2.68	83	0.07	None	Withdrawn
13	M	29	178	Yes	3.69	81	0.25	None	Complete

BD Budesonide; F Female; FEV₁ Forced expiratory volume in 1s; FP Fluticasone propionate; M Male; PC₂₀ Concentration of methacholine that causes a 20% fall in FEV₁

Methacholine bronchoprovocation challenge

Subjects underwent the tidal breathing method of Juniper et al (4). Briefly, subjects presented to the laboratory daily and were required to rest to ensure stable lung function. Three reproducible flow volume loops were then obtained according to the guidelines of the American Thoracic Society (5). Following diluent inhalation, doubling doses of methacholine were administered at 5 min intervals until FEV₁ manoeuvres, obtained at 30 and 90 s after 2 min inhalations, fell by 17% or greater. The decrease from the lowest FEV₁ after diluent inhalation to the lowest FEV₁ after methacholine inhalation was calculated. If the fall was 17%, 18% or 19%, then the PC₂₀ was obtained by extrapolation using a single-point algebraic formula (6). If the fall was greater than 20%, the PC₂₀ was interpolated using the standard algebraic formula (7). Starting concentrations were identical within a given subject and were at least two concentrations below the known PC₂₀ for a given subject. Bronchoconstriction was reversed with 20 to 40 µg of ipratropium bromide; in some cases spontaneous reversal was preferred.

Study design

This was a double-blind, placebo controlled, randomized cross-over trial. Three kits containing six blinded Turbuhalers (Astra Pharma, Mississauga), three for days 1, 3 and 5, and three for days 2, 4, 6 and 7 were prepared. Each kit contained three treatment regimens: formoterol plus formoterol; placebo plus placebo and formoterol (days 1, 3, 5); and placebo (days 2, 4, 6 and 7). Each treatment arm required visits to the laboratory at the same time of day (± 1 h) on days 1 through 5 and again on day 8. Consistent with the authors' previous investigations of beta-agonist tolerance (1), the washout duration between treatment periods was a minimum of seven days. Each visit consisted of baseline FEV₁ determination followed by administration of blinded study medication, with the exception of day 8, on which 12 µg of open-label formoterol was administered. FEV₁ was measured again 10 min after inhalation of blinded or unblinded (day 8) medication just before methacholine bronchoprovocation challenge. Subjects administered doses on their own on days 6 and 7 with a

Figure 1 Geometric mean concentrations of methacholine that caused a 20% fall in forced expiratory volume in 1 s (PC₂₀) for each treatment group (vertical axis) plotted for each day bronchoprovocation challenges were given (horizontal axis). Thrice weekly formoterol (closed triangle) PC₂₀ values differed significantly from placebo treatment (open circles) on days 1, 3 and 5. Day 8 PC₂₀ values were not significantly different. Note, however, the trend toward the development of tolerance in the daily formoterol group (closed circles). Error bars represent SEM

blinded inhaler provided to them on leaving the laboratory on day 5.

Statistical analysis

The primary end point, day 8 methacholine PC₂₀, was analyzed using a two-way (subject versus treatment) analysis of variance (ANOVA) (STATISTIX for Windows, Analytical Software, USA). Least significant difference comparison of means was used when the ANOVA generated a $P < 0.05$. Secondary end points, baseline FEV₁ and delta FEV₁ after treatment, were analyzed in the same manner. A paired t test was used for within-group post hoc analyses. This study had a greater than 90% power to detect a 0.5 concentration change in methacholine PC₂₀.

TABLE 2

Forced expiratory volume in the first second of exhalation (FEV₁) (mean $\pm$ SD) at baseline (before administration of 12 μ g formoterol) and 10 min after administration of 12 μ g formoterol, and the change in FEV₁ from baseline to 10 min after the dose (absolute Δ)

Day	Placebo			Daily formoterol			Alternate day formoterol		
	Baseline	10 min after dose	Absolute Δ	Baseline	10 min after dose	Absolute Δ	Baseline	10 min after dose	Absolute Δ
1	3.73 $\pm$ 0.97	3.71 $\pm$ 1.00	-0.02 $\pm$ 0.16	3.75 $\pm$ 0.93	4.08 $\pm$ 0.98*	0.34 $\pm$ 0.18	3.82 $\pm$ 1.01	4.07 $\pm$ 1.02*	0.26 $\pm$ 0.17
2	3.83 $\pm$ 0.98	3.78 $\pm$ 0.94	-0.05 $\pm$ 0.08	3.89 $\pm$ 1.01	4.05 $\pm$ 1.01*	0.16 $\pm$ 0.15	3.93 $\pm$ 1.00	3.91 $\pm$ 1.03	-0.02 $\pm$ 0.11
3	3.79 $\pm$ 0.99	3.74 $\pm$ 1.02	-0.04 $\pm$ 0.13	3.81 $\pm$ 0.95	4.07 $\pm$ 1.00*	0.25 $\pm$ 0.19	3.80 $\pm$ 0.98	4.08 $\pm$ 1.02*	0.28 $\pm$ 0.16
4	3.73 $\pm$ 0.96	3.72 $\pm$ 0.96	-0.003 $\pm$ 0.03	3.85 $\pm$ 0.97	4.08 $\pm$ 0.98*	0.21 $\pm$ 0.21	3.98 $\pm$ 1.05	3.99 $\pm$ 1.02	0.002 $\pm$ 0.08
5	3.77 $\pm$ 0.98	3.72 $\pm$ 0.98	-0.06 $\pm$ 0.10	3.90 $\pm$ 0.95	4.12 $\pm$ 0.99*	0.22 $\pm$ 0.18	3.79 $\pm$ 1.01	4.10 $\pm$ 1.05*	0.31 $\pm$ 0.18
8	3.80 $\pm$ 0.97	4.05 $\pm$ 0.99*	0.26 $\pm$ 0.23	3.76 $\pm$ 0.96	3.97 $\pm$ 0.96*	0.21 $\pm$ 0.17	3.68 $\pm$ 1.04	4.00 $\pm$ 1.02*	0.32 $\pm$ 0.27

*12 μ g formoterol

RESULTS

Safety

Thirteen subjects were enrolled (Table 1), 10 of whom completed the trial. One subject voluntarily withdrew before completing the second treatment arm because of the required time commitment, and two subjects were withdrawn because of worsening asthma. There were no other adverse events. Results are presented on 10 subjects with complete data.

Bronchoprotection

Daily geometric mean log PC₂₀ values for each treatment arm are shown in Figure 1. ANOVA of the primary end point showed no significant difference between the three treatment arms ($P=0.34$). Day 8 geometric mean PC₂₀ concentrations were 6.3 mg/mL, 9.2 mg/mL and 9.6 mg/mL for daily formoterol, thrice weekly formoterol and placebo, respectively.

Both formoterol treatment arms were significantly greater than placebo on days 1, 3 and 5, and not significantly different from each other. On days 2 and 4, placebo and placebo days for the thrice weekly formoterol were significantly lower than daily formoterol but not significantly different from each other.

Baseline FEV₁

The only significant difference (ANOVA, $P=0.012$) was on day 4. The mean baseline FEV₁ (Table 2) of the thrice weekly treatment arm (3.98 $\pm$ 1.05 L) 24 h after administration of 12 μ g formoterol (administered on day 3) was significantly greater than the mean for the placebo group (3.73 $\pm$ 0.96 L). ANOVA for the analogous day 2 baseline FEV₁ values indicated no significant difference between the three treatments ($P=0.23$; paired t test for placebo versus thrice weekly formoterol yielded $P=0.092$).

Bronchodilation

ANOVA of day 8 mean daily absolute delta FEV₁ (FEV₁ 10 min after treatment minus baseline FEV₁; Table 2) indicated a reduction in bronchodilation in the daily (0.21 $\pm$ 0.17 L) versus the every other day treatment (0.32 $\pm$ 0.27 L) at the 0.05 level. Subsequent paired t test for day 1 versus day 8 for delta FEV₁ within the daily treatment arm showed significant reduction in bronchodilation on day 8 ($P=0.0035$). There was, however, no significant difference in the post-formoterol FEV₁ on day 8 (ANOVA $P=0.62$, FEV₁ 3.97 to 4.05 L).

DISCUSSION

In our study the long acting beta₂-agonist formoterol taken once daily or once every other day over a seven-day period did not result in a loss of the protection afforded by a single 12 μ g dose against methacholine-induced bronchoconstriction. There is little in the literature with which to compare our findings; however, our findings do contradict the work of Lipworth et al (3), who found tolerance at various doses of formoterol, including 12 μ g administered once daily. Interestingly, the plot of our data for the daily formoterol group shown in Figure 1 develops a downward trend at day 4 and is lower by day 8, but this was not statistically significant. The conflict between our results and those of Lipworth and colleagues may be explained by differences in the duration of treatment or the method of analysis. We administered a 12 μ g dose for seven days, compared with a 12 μ g dose for 14 days in the Lipworth et al study. At least one other seven-day investigation has failed to show tolerance despite the population being 'at risk' for its development and despite twice the daily dose of formoterol (8). We also chose between-treatment (formoterol versus placebo) protection afforded by formoterol as our primary end point, compared with a within-treatment first dose versus last dose comparison, as used by Lipworth and colleagues. The development of a downward trend of PC₂₀ in our daily formoterol data may have significance with longer treatment duration, a larger sample size or both; a trend toward the loss of bronchoprotection following administration of 12 μ g formoterol twice a day for seven days has been previously documented (9). We did not consider concomitant administration or inconsistent administration of inhaled corticosteroid to be a contributing factor in the difference between our results and others' because inhaled corticosteroid administration does not prevent the development of tolerance (10), and oral prednisolone does not reverse established tolerance (11).

Our findings with respect to baseline FEV₁ (Table 2) suggest improvements in daily lung function with thrice weekly dosing. Baseline FEV₁ values for the every other day treatment arm deviate to significance from placebo on day 4. However, the same improvement was not evident on day 2. This phenomenon is perhaps the result of prolonged or residual bronchodilator action from the previous day, suggesting that the duration of action of formoterol may extend up to 24 h when administered in a dose of 12 μ g every other day. The same effect was not evident with daily treatment.

The acute bronchodilator properties of 12 µg formoterol, measured as the absolute delta FEV₁ from baseline to 10 min after treatment, were significantly less pronounced following 12 µg daily formoterol administration, signifying possible loss of bronchodilation, which was not seen with thrice weekly treatment. Of clinical importance is the timeframe in which this loss occurs with daily treatment. The most pronounced loss in the delta FEV₁ over the study period occurred with the second dose (Table 2). This partially recovered at the third dose, but the difference in delta FEV₁ remained significant when compared with the first dose (within-group paired *t* test). In fact, all measurements of delta FEV₁ were significantly lower than those of the first dose within the daily treatment group; the day 8 delta FEV₁ was significantly lower for daily versus

every other day treatments. However, post-formoterol FEV₁ values did not differ significantly (Table 2).

We have shown that the long-acting beta₂-agonist formoterol administered in a dose of 12 µg thrice weekly for a period of seven days does not result in the development of tolerance to the bronchoprotective effects against the direct-acting stimulus methacholine. Although statistical significance was not reached, there does appear to be a trend toward a loss in bronchoprotection when the same dose is administered daily.

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