

Original article

Steroid sparing effects of intranasal corticosteroids in asthma and allergic rhinitis

Background: Treating allergic rhinitis may have a downstream anti-inflammatory effect on the lower airways. We conducted a dose ranging study in asthma and persistent allergic rhinitis to evaluate if intranasal corticosteroids exhibit a sparing effect on the dose of inhaled corticosteroid.

Methods: Twenty five participants were randomized to receive two weeks of 100 µg/day (Low dose) or 500 µg/day (High dose) of inhaled fluticasone propionate both with intranasal placebo; or inhaled fluticasone 100 µg/day with intranasal fluticasone 200 µg/day (Combined) in a double-blind cross-over fashion.

Results: Low dose fluticasone produced a shift of 1.20 doubling-dilutions (95% CI, 0.63, 1.77); Combined fluticasone, 1.79 doubling-dilutions (95% CI, 0.77, 2.80) and high dose fluticasone, 2.01 doubling-dilutions (95% CI, 1.42, 2.61) in methacholine PC₂₀ from respective baselines. There was a significant difference between high and low doses: 0.82 doubling dilutions (95%CI, 0.12, 1.50) but not between combined and low dose 0.58 doubling dilutions (95% CI, -0.78, 1.95). Combined treatment alone produced improvements in peak nasal inspiratory flow ($P < 0.001$), rhinitis quality of life ($P = 0.004$) and nasal NO ($P = 0.01$); reduced blood eosinophil count ($P = 0.03$), and serum eosinophil cationic protein ($P = 0.02$). All treatments significantly improved tidal NO, FEV₁ and asthma quality of life.

Conclusions: High-dose fluticasone was superior to low dose fluticasone for methacholine PC₂₀, demonstrating room for further improvement. Combined treatment was not significantly different from low dose fluticasone and we could not demonstrate a steroid sparing effect on methacholine PC₂₀. Combined treatment alone produced improvements in upper airway outcomes and suppressed systemic inflammation but not adrenal function.

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Asthma and allergic rhinitis (AR) frequently coexist and are considered to be different manifestations of the same inflammatory disease continuum (1–3). Braunstahl and colleagues elegantly demonstrated the presence of significant naso-bronchial crosstalk with their experiments on segmental bronchoprovocation (4, 5). Epidemiological studies have indeed shown the adverse impact of AR on asthma control, hospitalization, and quality of life (6–9). Equally, treating AR has been shown to reduce the frequency of asthma related visits to the emergency department and inpatient hospitalization (7, 9–11). Likewise, the beneficial effects of intranasal corticosteroids in AR on bronchial hyperresponsiveness have also been reported, suggesting a downstream anti-inflammatory effect (10, 12).

However, whether adding intranasal corticosteroids to patients with concomitant asthma and persistent allergic rhinitis (PAR) allows a reduction in the dose of inhaled corticosteroid required to achieve control, has to the best of our knowledge not been investigated in a prospective

randomized fashion. We have therefore evaluated the steroid sparing effect of intranasal fluticasone on the dose of concomitant inhaled fluticasone by carrying out a dose response study between 100 and 500 µg/day of inhaled fluticasone (both with intranasal placebo) vs 100 µg/day of inhaled fluticasone with 200 µg/day of intranasal fluticasone, using bronchial methacholine challenge as the primary outcome. We also measured other surrogates of lower and upper airway inflammation, airway calibre, quality of life, and systemic adverse effects.

Methods

Participants

Patients were recruited from our database of volunteers with the following inclusion criteria: males and females, 18–65 years, asthmatics with FEV₁ ≥ 60% on ≤ 1000 µg beclometasone dipropionate equivalent units (BDP) with concomitant PAR as evidenced by symptoms and a positive skin prick test to at least one perennial

aeroallergen, and a methacholine $PC_{20} < 4$ mg/ml. Assessment of asthma and PAR were based on current GINA and ARIA guidelines respectively (1, 13). Patients with nasal polyposis $\geq$ grade 2, deviated nasal septum $\geq 50\%$, oral corticosteroids within 3 months and respiratory tract infection within the preceding 2 months were excluded.

Study design

A single centre, randomized, double blind, double-dummy, three-way crossover design was employed. The Tayside committee for medical research ethics fully approved the study protocol. Patients attended a screening visit at which suitability was assessed using strict inclusion and exclusion criteria and written informed consent was obtained. Participants who were on ≥ 400 μ g BDP had their corticosteroid dose tapered by half at weekly intervals till a dose of ≤ 400 μ g BDP and ≤ 200 μ g intranasal BDP was attained. Thereafter participants who were clinically stable had their medications stopped and were provided intranasal fluticasone placebo nasal spray and inhaled HFA-fluticasone placebo via pMDI to enter the placebo run-in period for 2 weeks (double-dummy). Stability was assessed based on peak flow variability, symptom scores and reliever use. Participants on long acting beta-agonists, leukotriene receptor antagonists, or anti-histamines, had these discontinued prior to placebo run-in and HFA-salbutamol and intranasal sodium cromoglicate were provided as rescue therapy.

The screening visit was followed by six study visits (Fig. 1), each separated by a minimum of 2 weeks. The 2-week inhaled and intranasal corticosteroid free washout period between study treatment visits was designed to exceed the five elimination half lives of fluticasone ($t_{1/2}$: 14 h). The washout period was extended by a further week in participants whose pretreatment baseline methacholine PC_{20} were not within one doubling-dilution to obviate a carryover effect. Participants received the following treatments in a randomized assignment order: (i) One puff of inhaled fluticasone propionate Evohaler pMDI 50 μ g twice a day (total fluticasone dose 100 μ g) and one puff of inhaled placebo twice a day with placebo intranasal spray two squirts each nostril once a day. (ii). One puff of inhaled fluticasone propionate Evohaler pMDI 50 μ g twice a day

(total daily fluticasone dose 100 μ g) and one puff of Placebo twice a day with intranasal fluticasone propionate (Flixonase®) 50 μ g two squirts in each nostril once a day (total intranasal fluticasone daily dose 200 μ g). (iii) One puff of inhaled fluticasone propionate Evohaler 250 μ g twice a day (total daily fluticasone dose 500 μ g) and one puff of inhaled placebo twice a day with placebo intranasal spray two squirts each nostril once a day. The above treatments were designed to reflect dosages used in current clinical practice and allowed us to construct a putative dose response relationship to demonstrate assay sensitivity between the three treatment arms using doubling dilution shift in methacholine PC_{20} as the primary outcome. Standard instructions were given for inhaler and spray use and technique was checked at each visit.

Measurements

All measurements were made at post run-in baseline and after each 2 week treatment and washout period. All study visits took place at 8.30 a.m. at the research unit.

Airway inflammation, hyperresponsiveness and systemic absorption

Exhaled tidal NO, alveolar NO, bronchial flux and nasal NO measurements were recorded prior to any pulmonary or nasal function measurement by Niox® Nitric oxide analyser (Aerocrine AB, Solna, Sweden) using ATS criteria (14). Bronchial provocation testing using methacholine was performed using the five breath dosimeter technique in accordance with ATS recommendations to determine the PC_{20} threshold at baseline, after each treatment period, and after a corticosteroid free washout using log-linear interpolation (15). Estimation of PC_{20} for subjects who did not attain a reduction in FEV_1 of 20% (i.e. those with a 15–19% fall in FEV_1) was derived using single point log-linear interpolation formula ($20 \times \text{concentration}/FEV_1 \text{ fall}$) (16). Adrenal suppression from systemic absorption of the inhaled and intranasal corticosteroid treatment was assessed by measuring overnight 10 h urinary free cortisol and creatinine ratios as described previously in literature (17).

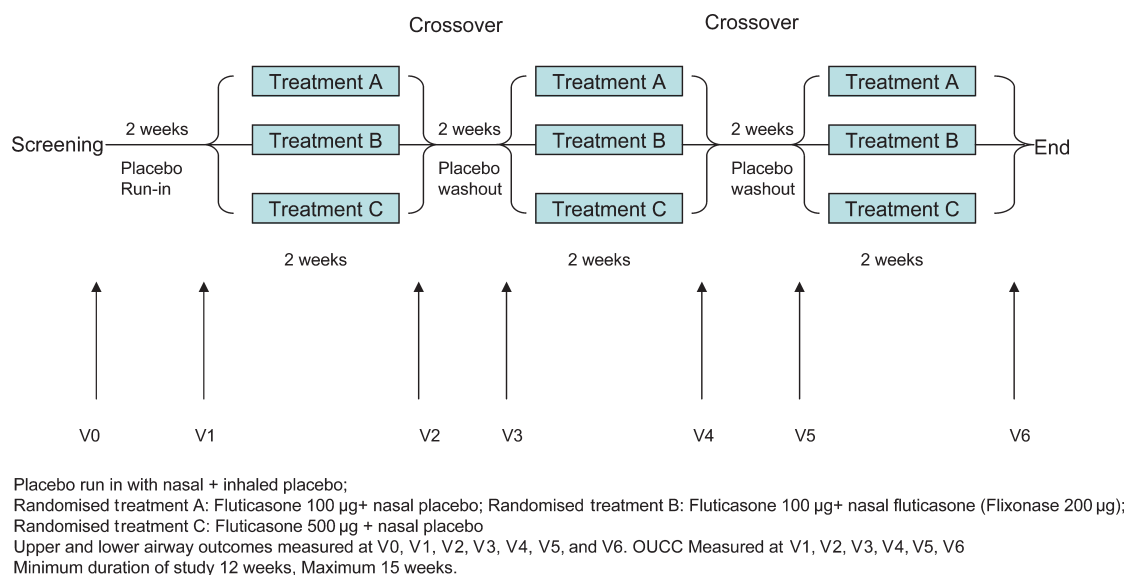


Figure 1. Study design.

Nasal and bronchial airway calibre

All patients received appropriate instructions at the initial screening visit and were required to demonstrate good technique in recording their peak nasal inspiratory flow (PNIF) using the In-Check® PNIF meter (Clement Clarke International Ltd, Harlow, UK). The morning PEF was recorded by using the Mini-Wright peak flow meter (Clement Clarke International Ltd). The technique was then further reassessed and reinforced, prior to each study visit. Peak nasal inspiratory flow and PEF measurements were recorded daily on a domiciliary basis. Spirometry was performed according to the ATS criteria.

Quality of life

Instructions for recording Juniper mini asthma and mini rhino-conjunctivitis quality of life questionnaires were provided at screening (18, 19).

Assays

All assays were performed in duplicate in a blinded fashion. The serum ECP was measured using an enzyme linked immunoassay technique (UniCAP; Sweden Diagnostics UK Ltd, Milton Keynes, UK) with an intra-assay co-efficient of variation of 3.3%. Blood Eosinophil count was analysed using the Sysmex XE 2100 Hematology auto analyser. The urinary cortisol was measured using a commercial radioimmunoassay kit (DiaSorin Ltd, Wokingham, Berkshire, UK), which has no cross reactivity with fluticasone. The intra assay coefficient of variation was 4% and the inter assay coefficient of variation was 8%. Urinary creatinine was measured on a Cobas-Bio auto analyser (Roche Products, Welwyn Garden City, UK). The intra assay and inter assay co-efficient of variation was 4.6% and 3% respectively.

Statistical analysis

SPSS version 14 (SPSS Inc., Chicago, IL, USA) was used to carry out the statistical analysis. A sample size of 24 completed patients was estimated to give 80% power to detect a one doubling-dilution shift (minimal important difference or MID) in methacholine PC₂₀ value (primary endpoint) assuming a 0.84 within-patient SD for this outcome. The sample size estimations were supported by prior studies from our department and external data published to assist sample size calculations (20–22). Datasets were analysed for patients who completed the crossover study per protocol. Data were assessed for normality using visual inspection, Q–Q plots and with previous consideration for literature, and if appropriate non-Gaussian data was logarithmically transformed prior to analyses. Comparisons were made using an overall repeated measures ANOVA (adjusted for baselines) with Bonferroni correction for multiple comparisons ($P < 0.05$, two tailed) and subject, treatment and sequence as factors.

Results

Fifty participants were screened of which 37 were randomized into the trial. Twenty five subjects completed the study per protocol. Ten subjects withdrew because of personal reasons or illness unrelated to asthma and one subject had an exacerbation of asthma during washout prior to final

randomized trial intervention and hence withdrawn. One additional subject was excluded from analysis as his methacholine PC₂₀ was > 4 mg/ml at baseline and hence should not have been permitted to continue in accordance with the trial protocol. Thus data from these 25 subjects were included in the final per-protocol analysis (Table 1). There was no significant difference in baseline and washout values for the primary outcome with respect to treatment or sequence (data not shown) thus ruling out a carryover effect. Similarly, there were no significant differences in the pretreatment baselines for all secondary outcomes except exhaled nitric oxide and rhinitis quality of life. Treatment effects are therefore presented as differences from respective pretreatment baselines.

Lower airway outcomes

For the primary outcome measure of methacholine PC₂₀, all three treatments conferred significant improvements from respective pretreatment baseline (Table 2). Low dose fluticasone produced a 1.20 doubling-dilution shift (95% CI, 0.63, 1.77; $P < 0.001$); Combined fluticasone, a 1.79 doubling-dilutions (95% CI, 0.77, 2.80; $P = 0.001$) and high dose fluticasone, 2.01 doubling-dilutions (95% CI, 1.42, 2.61; $P < 0.001$) in methacholine PC₂₀ from their respective baselines. There was a significant difference between high and low doses: 0.82 doubling-dilutions (95% CI, 0.12, 1.50; $P = 0.02$), showing there was room for further improvement. However there was no significant difference between combined and low dose treatments showing no additivity conferred by intranasal fluticasone: 0.58 doubling-dilutions (95% CI, –0.78, 1.95, $P = 0.82$) (Table 3).

Combined treatment with low dose fluticasone and intranasal fluticasone was not significantly different to high dose treatment. Tidal NO was significantly suppressed by all three treatments to a similar degree compared to baseline. Low dose fluticasone led to a 0.65-fold change (35% reduction) 95% CI, 0.54–0.78; $P < 0.001$, Combined treatment a 0.60 geometric mean fold change (40% reduction) 95% CI, 0.51–0.72; $P < 0.001$ and high dose fluticasone a 0.56-fold change (44% reduction) 95% CI, 0.45–0.69; $P < 0.001$. Exhaled NO arising from the medium sized airways (bronchial flux) was also significantly suppressed by all three treatments to a similar degree (i.e. 32%, 36%, 43%, reductions by low, combined and high dose respectively). None of the treatments significantly reduced the alveolar component of exhaled NO.

All three treatments showed small but statistically significant improvements in asthma quality of life score, which were not clinically relevant as compared to the minimal important difference of 0.5 units. There were small, but statistically significant improvements in FEV₁ or peak flow with all treatments, while FEF_{25–75} showed a small significant improvement with high dose fluticasone alone (Table 2).

Table 1. Patient demographics at baseline

Subject	Age	Sex	ICS dose (µg)	SPT	FEV ₁ % pred	FEF _{25–75} % pred	PNIF l/min	FENO ppb	Nasal NO ppb	OUCC µM/MM	PC ₂₀ mg/ml
2	47	F	0	G,H	83	67	105.71	36.23	723.17	11.57	2.44
3	46	M	0	G,C	98	95	103.57	24.33	851.9	3.31	0.86
6	23	F	800	G,H,D,C	85	53	88.57	37.7	754.93	4.13	1.86
7	39	M	800	G,H	59	29	192.86	22.3	731.47	7.58	0.11
9	41	F	800	G,H,C	96	78	66.43	48.9	1431.97	14.09	2.76
10	22	M	800	C	91	52	67.14	66.13	–	17.36	0.25
11	53	F	400	G,H, D,C	91	51	64.29	94.07	771.53	13.82	0.04
13	44	F	400	G, T, H,C	112	79	191.43	21.6	886.3	9.86	0.28
14	41	F	500	G,T,H, F,D,C	66	75	107.14	108.23	961.23	12.44	0.18
15	29	M	0	G,T,H	97	38	124.29	206.97	745.63	16.96	2.93
16	35	F	800	H,G	66	94	111.43	46.3	948.17	3.44	0.16
17	25	F	400	G,H,C	106	67	57.14	58.13	1474.4	9.48	3.93
18	39	M	0	G,W,H, D,C	80	51	67.14	47.87	708.6	20.8	0.68
19	57	F	1000	G,H,A,C,D	96	39	132.86	19.83	1098.93	5.2	4
20	62	M	500	H,G,C	69	52	134.29	25.7	694.3	10.17	0.44
21	38	M	0	G,H,C	69	50	210	27.77	815	9.8	0.27
22	42	M	500	G,T,H	81	60	130	40.5	1271.67	9.48	0.8
24	49	F	0	H	86	33	111.43	25.17	664.77	4.16	0.57
25	38	M	800	G,T,H,C	63	90	180	170.67	1054.07	8.59	0.42
26	21	M	400	C,H	106	44	200	124.8	1181.03	10.93	2.48
27	49	F	0	H,G	79	53	210	38.87	829.67	3.55	0.87
30	45	F	400	G,T,H,C,D	99	68	138.57	64	1114.4	8	0.18
31	41	M	0	G,H,D,C	91	85	100	109.3	752.13	3.83	0.74
33	20	F	400	G,H,C	100	45	130	67.03	1097.5	9.56	1.68
35	42	F	400	G,H,D,C	65	67	65.71	55.07	888.5	11.59	0.04
Mean (SEM)			*400 (0-800)		85.36 (3.04)	60.33 (3.93)	123.6 (9.81)	50.75† (1.14)	910 (1.04)	8.41† (1.11)	0.58† (0.16)

FEV₁, forced expiratory volume in 1 s; FEV₁%, percentage predicted forced expiratory volume in 1 s; FEF_{25–75}%, percentage predicted expiratory flow rate over the middle half of forced vital capacity manoeuvre; PNIF, peak nasal inspiratory flow rate; ICS, beclomethasone dipropionate equivalent dose of inhaled corticosteroid; PC₂₀, Provocation concentration of methacholine causing a 20% decline in FEV₁; OUCC, overnight urinary cortisol-creatinine ratio; SPT, skin prick test; H, house dust mite; G, grass pollen; T, tree; D, dogs; C, cats; F, feathers; W, weeds.

*Median (interquartile range).

†Geometric mean and (standard error of geometric mean).

Upper airway outcomes

Peak nasal inspiratory flow significantly improved from baseline only by combined treatment [mean difference 23.4 l/min, 95% CI (14.29–32.54); $P < 0.001$], and this was different from low or high dose inhaled fluticasone (Table 3). Nasal NO levels were significantly suppressed from baseline only by combined treatment (Mean –123 ppb, 95% CI –204 to –41.17; $P = 0.01$), which was significantly different compared to high dose or low dose (Table 3). The rhinitis quality of life questionnaire showed significant statistical and clinically relevant improvements from baseline (Table 2) in overall scores with combined treatment only [0.57 units, 95% CI (0.20–0.94), $P = 0.004$], which was significantly different from high dose inhaled fluticasone (Table 3) as compared to the MID of 0.5 units.

Systemic markers of inflammation and bioactivity

Serum eosinophil cationic protein and blood eosinophil count were significantly suppressed from baseline by combined treatment alone as: geometric mean fold

change of 0.77, 95% CI (0.63 to 0.97), $P = 0.02$ and arithmetic mean change of –59 cells/µl, 95% CI (–113 to –5), $P = 0.03$, respectively. Systemic bioactivity as assessed by overnight and early morning urinary cortisol creatinine ratios were not suppressed from baseline by any of the three treatments (Tables 2 and 3).

Discussion

For the primary outcome of methacholine PC₂₀, our results showed that, while all three randomized treatments significantly improved airway hyperresponsiveness compared to baseline, there was no difference when comparing combined low dose inhaled fluticasone with intranasal fluticasone vs low dose inhaled fluticasone alone. Thus we were unable to demonstrate any steroid sparing effect per se on lower airway outcomes by adding intranasal steroid to low dose steroid. Crucially we also demonstrated a significant dose response effect between low and high dose fluticasone alone, showing there was room for further improvement by adding in intranasal fluticasone to low dose inhaled fluticasone.

Table 2. Effect of treatments on the upper and lower airway indices from respective pre-treatment baseline

Lower airway outcomes	Baseline	High dose	Difference 95% CI, <i>P</i>	Baseline	Combined (LD+NFP)	Difference 95% CI, <i>P</i>	Baseline	Low dose	Difference 95% CI, <i>P</i>
Methacholine PC ₂₀ *	0.64 (0.81)	2.57 (0.93)	2.01 (1.42, 2.61) <i>P</i> < 0.001	0.47 (0.98)	1.63 (0.95)	1.79 (0.77, 2.80) <i>P</i> = 0.001	0.76 (0.80)	1.75 (0.92)	1.20 (0.63, 1.77) <i>P</i> < 0.001
FE _{NO} † Ppb	51.16 (1.15)	28.58 (1.13)	0.56 (0.45, 0.69) <i>P</i> < 0.001	49.71 (1.16)	29.68 (1.13)	0.60 (0.51, 0.72) <i>P</i> < 0.001	39.07 (1.15)	25.04 (1.14)	0.65 (0.54, 0.78) <i>P</i> < 0.001
CA _{NO} † ppb	2.71 (1.31)	2.31 (1.15)	0.85 (0.44, 1.65) <i>P</i> = 0.61	1.84 (1.05)	2.42 (1.05)	1.31 (0.71, 2.44) <i>P</i> = 0.36	1.83 (1.31)	2.46 (1.26)	1.34 (0.68, 2.63) <i>P</i> = 0.37
Bronchial flux† (ml/s)	2.27 (1.17)	1.30 (1.15)	0.57 (0.42, 0.77) <i>P</i> = 0.001	2.19 (1.17)	1.42 (1.14)	0.64 (0.50, 0.83) <i>P</i> = 0.002	1.95 (1.15)	1.34 (1.15)	0.68 (0.57, 0.82) <i>P</i> < 0.001
PEF l/min	446.97 (23.98)	466.24 (24.72)	19.27 (8.48, 30.06) <i>P</i> = 0.001	432.02 (23.05)	457.35 (23.05)	25.32 (12.77, 37.87) <i>P</i> < 0.001	448.39 (23.83)	459.04 (24.06)	10.64 (−1.06, 22.35) <i>P</i> = 0.07
FEV ₁ , predicted	85.70 (3.20)	91.16 (3.08)	5.45 (1.95, 8.96) <i>P</i> = 0.004	86.87 (3.21)	88.91 (3.01)	2.04 (0.009, 4.07) <i>P</i> = 0.049	86.5 (3.14)	90.83 (3.19)	4.33 (1.44, 7.22) <i>P</i> = 0.005
FEF _{25–75} %, predicted	60.12 (3.89)	66.41 (4.69)	6.29 (0.77, 11.80) <i>P</i> = 0.02	60.62 (4.31)	63.08 (4.20)	2.45 (−1.03, 5.94) <i>P</i> = 0.15	62.95 (4.30)	66.00 (4.54)	3.04 (−0.24, 6.32) <i>P</i> = 0.07
Asthma quality of life units	5.82 (0.21)	6.07 (0.20)	0.25 (0.02, 0.48) <i>P</i> = 0.03	5.78 (0.18)	6.11 (0.18)	0.33 (0.10, 0.55) <i>P</i> = 0.006	5.91 (0.20)	6.22 (0.14)	0.31 (0.05, 0.57) <i>P</i> = 0.01
Upper airway outcomes									
N _{NO} Ppb	1002.2 (54.27)	1043.54 (69.65)	41.33 (−24.88, 107.54) <i>P</i> = 0.72	923.33 (70.89)	800.33 (42.31)	−123.00 (−204.83, −41.17) <i>P</i> = 0.01	927.23 (57.50)	993.25 (88.65)	66.03 (−199.89, 67.82) <i>P</i> = 0.10
PNIF l/min	127.23 (8.78)	126.20 (10.18)	−1.02 (−9.81, 7.75) <i>P</i> = 0.81	123.57 (9.89)	146.99 (10.49)	23.41 (14.29, 32.54) <i>P</i> < 0.001	128.99 (9.52)	130.66 (11.55)	1.67 (−8.93, 12.28) <i>P</i> = 0.74
Rhinitis quality of life units	1.70 (0.20)	1.44 (0.20)	−0.25 (−0.70, 0.19) <i>P</i> = 0.25	1.02 (0.20)	1.60 (0.18)	0.57 (0.20, 0.94) <i>P</i> = 0.004	1.54 (0.21)	1.64 (0.25)	0.09 (−0.24, 0.47) <i>P</i> = 0.57
Systemic markers									
ECP† (μg/l)	16.21 (3.00)	14.12 (1.63)	0.87 (0.56, 1.34) <i>P</i> = 0.53	17.37 (2.81)	13.49 (2.18)	0.77 (0.63, 0.97) <i>P</i> = 0.02	15.49 (3.59)	15.85 (2.56)	1.02 (0.77, 1.38) <i>P</i> = 0.82
Peripheral‡ blood eosinophils (cells/μl)	351.90 (46.20)	326.66 (44.74)	−25.23 (−79.0, 28.6) <i>P</i> = 0.34	369.0 (52.62)	310 (45.74)	−59.04 (−113, −5.03) <i>P</i> = 0.03	321.42 (37.35)	341.42 (46.62)	20 (−17.2, 57.2) <i>P</i> = 0.41
OUCC† (nM/mM)	8.64 (1.09)	8.46 (0.84)	0.97 (0.79, 1.21) <i>P</i> = 0.84	8.07 (0.96)	7.55 (1.00)	0.93 (0.72, 1.20) <i>P</i> = 0.59	8.74 (1.06)	8.25 (0.91)	0.94 (0.71, 1.25) <i>P</i> = 0.67
EMUCC† (nM/mM)	12.76 (1.2)	14.44 (1.18)	1.13 (0.78, 1.62) <i>P</i> = 0.49	16.49 (1.17)	15.98 (1.23)	0.96 (0.69, 1.36) <i>P</i> = 0.85	15.32 (1.19)	15.47 (1.16)	1.01 (0.72, 1.41) <i>P</i> = 0.95

FEV₁%, percentage predicted forced expiratory volume in 1 s; PC₂₀, Provocation concentration of methacholine causing a 20% decline in FEV₁; FE_{NO}, exhaled tidal nitric oxide; CA_{NO}, alveolar nitric oxide; N_{NO}, nasal nitric oxide; FEF_{25–75}%, percentage predicted expiratory flow rate over the middle half of forced vital capacity manoeuvre; PNIF, peak nasal inspiratory flow rate; PEF, peak expiratory flow rate; ECP, Serum eosinophil cationic protein; OUCC, Overnight cortisol creatinine ratio; EMUCC, Early morning cortisol creatinine ratio.

Data presented as arithmetic mean (SEM) with corresponding mean differences, 95% Confidence Interval (CI), *P* except where otherwise indicated.

*Results expressed as geometric mean (SE) and differences expressed as doubling dilution shift.

†Results expressed as geometric mean (SE) and differences expressed as geometric mean fold changes, 95% CI, *P*.

‡Peripheral eosinophil count (absolute change in cell count).

P-values and 95% CI are two tailed.

Table 3. Comparison of differences in clinical outcomes between treatments

Variable lower airway outcomes	Combined vs high dose Difference, 95% CI <i>P</i>	Combined vs low dose Difference, 95% CI <i>P</i>	High dose vs low dose Difference, 95% CI <i>P</i>
Methacholine PC ₂₀	0.22 (−1.18, 1.62), <i>P</i> > 0.99	0.58 (−0.78, 1.95) <i>P</i> = 0.82	0.82 (0.12, 1.50), <i>P</i> = 0.02
Tidal nitric oxide, ppb	0.92 (0.69, 1.21), <i>P</i> > 0.99	1.07 (0.86, 1.33) <i>P</i> > 0.99	1.16 (0.87, 1.56) <i>P</i> = 0.81
Alveolar nitric oxide, ppb	0.64 (0.21, 1.97) <i>P</i> = 0.95	1.01 (0.31, 3.31) <i>P</i> > 0.99	1.57 (0.42, 5.78) <i>P</i> > 0.99
Bronchial flux (nl/s)	0.88 (0.57, 1.34) <i>P</i> > 0.99	1.06 (0.75, 1.49) <i>P</i> > 0.99	1.20 (0.84, 1.71) <i>P</i> = 0.56
PEF (l/min)	−6.04 (−25.15, 13.06) <i>P</i> = 1	−14.68 (−32.46, 3.10) <i>P</i> = 0.13	−8.63 (−24.71, 7.44) <i>P</i> = 0.53
FEV ₁ % predicted	3.41 (−0.97, 7.81) <i>P</i> = 0.17	2.29 (0.98, 5.56) <i>P</i> = 0.25	−1.12 (−4.9, 2.6) <i>P</i> > 0.99
FEF _{25–75} % predicted	3.83 (−5.94, 13.61) <i>P</i> = 0.96	0.58 (−5.07, 6.24) <i>P</i> > 0.99	−3.25 (−9.85, 3.35) <i>P</i> = 0.64
Asthma quality of life units	0.07 (−0.29, 0.44) <i>P</i> > 0.99	0.01 (−0.37, 0.39) <i>P</i> > 0.99	−0.06 (−0.41, 0.28) <i>P</i> > 0.99
Upper airway outcomes			
Nasal nitric oxide ppb	−164.33 (27.35, 301.32) <i>P</i> = 0.01	−189.03 (−317.73, −60.33) <i>P</i> = 0.002	−24.70 (−152.70, 103.30) <i>P</i> = 0.14
PNIF (l/min)	−24.45 (−37.30, −11.58) <i>P</i> < 0.001	−21.75 (−37.61, −5.88) <i>P</i> = 0.005	2.70 (−10.35, 15.75) <i>P</i> > 0.99
Rhinitis quality of life units	0.83 (0.04, 1.62) <i>P</i> = 0.03	0.48 (−0.06, 1.02) <i>P</i> = 0.09	−34 (−1.18, 0.49) <i>P</i> = 0.89
Systemic outcomes			
ECP (μg/l)	0.89 (0.49, 1.61) <i>P</i> = 1	0.76 (0.47, 1.22) <i>P</i> = 0.46	0.85 (0.47, 1.53) <i>P</i> > 0.99
Peripheral eosinophil count (cells.μl)	33.81 (−67.68, 135.30), <i>P</i> > 0.99	79 (−13.68, 171.78), <i>P</i> = 0.11	45.23 (−14.08, 104.56), <i>P</i> = 0.18
Overnight urinary cortisol creatinine ratio (nM/mM)	1.04 (0.73, 1.48), <i>P</i> > 0.99	1.008 (0.62, 1.63) <i>P</i> > 0.99	0.96 (0.58, 1.58), <i>P</i> > 0.99
Early morning urinary cortisol creatinine ratio (nM/mM)	1.14 (0.61, 2.22), <i>P</i> > 0.99	1.02 (0.51, 2.15) <i>P</i> > 0.99	0.89 (0.48, 1.65) <i>P</i> > 0.99

FEV₁ %, percentage predicted forced expiratory volume in 1 s; FEF_{25–75} %, percentage predicted expiratory flow rate over the middle half of forced vital capacity manoeuvre; PNIF, peak nasal inspiratory flow rate; PEF, peak expiratory flow rate; PC₂₀, Provocation concentration of methacholine causing a 20% decline in FEV₁; ECP, Serum eosinophil cationic protein.

Differences expressed as geometric mean fold changes, 95% Confidence Interval (CI), *P* except PC₂₀ (doubling dilution shift), peripheral eosinophil count (absolute change in cell count).

Nasal nitric oxide, Airway calibre and QOL outcomes expressed as arithmetic mean differences, 95% CI, *P*.

P-values and 95% CI are bonferroni corrected to allow multiple pair wise corrections.

This is to our knowledge the first randomized dose response study to prospectively investigate the putative sparing effects of intranasal corticosteroids on the dose of inhaled corticosteroid in patients with concomitant asthma and PAR. In this regard, it is pertinent to mention the study by Dahl et al. (23), who did not demonstrate superiority of combined intranasal (200 μg/day) and inhaled fluticasone (500 μg/day) over inhaled fluticasone alone (500 μg/day). Their patients had mild asthma and

seasonal intermittent allergic rhinitis, with well preserved baseline lung function. They showed that treatment with 500 μg of inhaled fluticasone significantly improved morning PEF (primary outcome) by only 13 l/min, but pointedly did not improve methacholine PD₂₀. Unsurprisingly the addition of intranasal fluticasone to this dose of inhaled fluticasone did not result in further improvements in PEF or methacholine PD₂₀ or sputum eosinophils. This is because 500 μg/day of inhaled fluti-

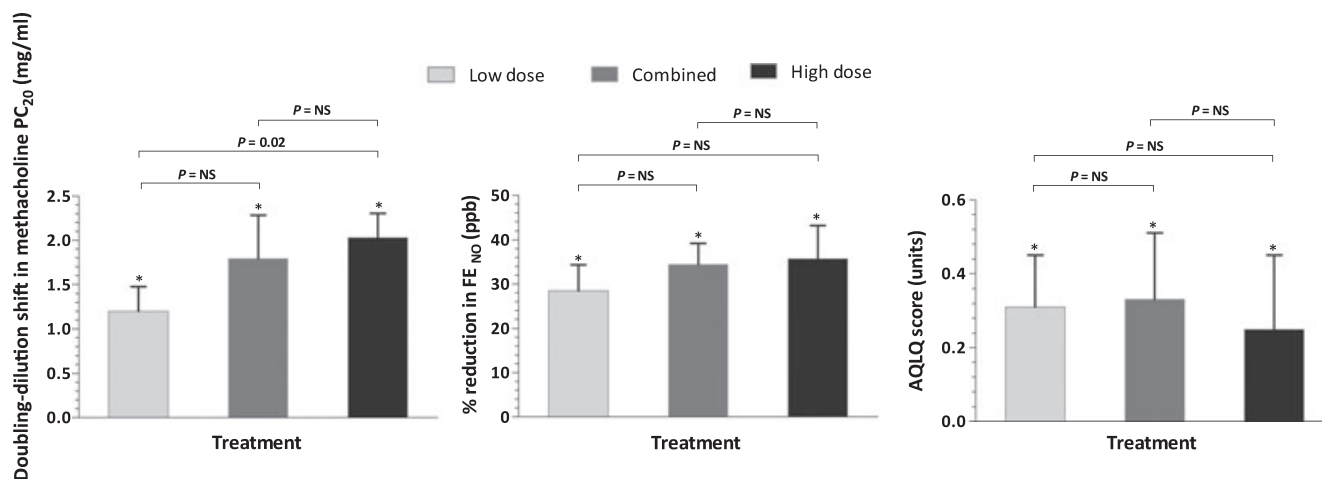


Figure 2. Comparison of treatment effects on lower airway outcomes: Methacholine PC₂₀, exhaled tidal NO and asthma quality of life with low dose, combined and high dose fluticasone. *Significant (*P* < 0.05) change from respective baseline.

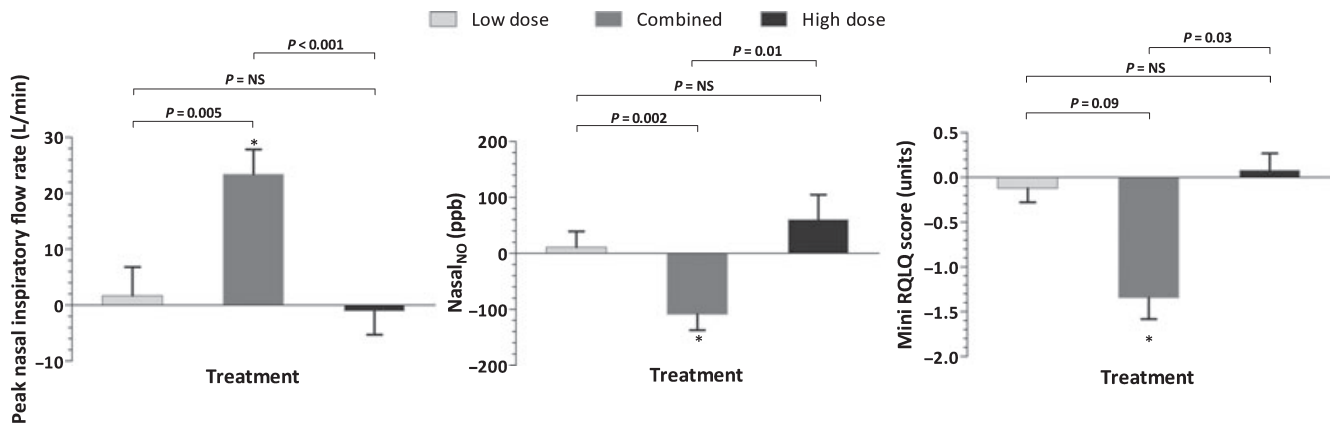


Figure 3. Comparison of treatment effects on upper airway outcomes: Peak nasal inspiratory flow, Nasal NO and rhinitis quality of life with low dose, combined and high dose fluticasone. *Significant ($P < 0.05$) change from respective baseline.

casone would be on the top of the dose response curve for all of these outcomes in mild asthmatics. In other words there was clearly no room for further improvement in terms of being able to show potential additivity with intranasal fluticasone to 500 $\mu\text{g}/\text{day}$ of inhaled fluticasone. Similarly, the study by Nathan et al. (24) once again in seasonal intermittent AR and asthma and also powered on PEF, showed no further improvement with intranasal fluticasone, as prior treatment with fluticasone propionate/salmeterol, 100/50 μg bid had fully optimized their already preserved lung function.

In this respect, our study is unique in that we looked at a lower dose of 100 $\mu\text{g}/\text{day}$ of inhaled fluticasone. Importantly, we were able to show that there was room for further improvement between 100 μg vs 500 $\mu\text{g}/\text{day}$ of inhaled fluticasone with a significant difference in the primary outcome of methacholine PC_{20} (Fig. 2). We did not demonstrate any significant difference between combined therapy vs low dose inhaled fluticasone (amounting to 0.58 doubling-dilutions) and thus were unable to conclude any significant additivity for the effect of intranasal fluticasone on airway hyper-responsiveness. It is, however, important to note that our study was powered to detect a one doubling-dilution difference in PC_{20} (within subject SD = 0.84) and as such may have missed differences smaller than the biological variability of this instrument. It could also be hypothesized that this might be a reflection of the type of challenge itself. Indeed, previous data have shown that sputum eosinophils are increased after adenosine monophosphate but not methacholine challenge (25). Hence, future studies looking for additivity with intranasal corticosteroid might be better advised to employ indirect challenges which reflect eosinophilic inflammation more closely in asthma.

As expected, only the combined treatment improved upper airway outcomes including PNIF, nasal NO and rhinitis quality of life (Fig. 3). From this we can infer that the apparent lack of additivity of intranasal corticoste-

roid on lower airway hyper-responsiveness cannot be attributed to a lack of topical efficacy on the upper airway.

The suppression of the blood eosinophil count and serum ECP by combined therapy but not high dose inhaled fluticasone is an interesting observation, given that combined therapy did not at the same time suppress urinary cortisol/creatinine. This systemic disconnect in turn suggests that the addition of intranasal fluticasone may have had a facilitatory effect on local eosinophil trafficking through the nose which was not associated with direct systemic absorption of fluticasone from the upper airway. This locally driven effect of intranasal fluticasone per se on systemic eosinophil markers is also supported by the lack of suppression by high dose inhaled fluticasone on the same systemic eosinophil makers.

We recognize the limitations of our study. Firstly, the dose response in PC_{20} when comparing 100 μg vs 500 $\mu\text{g}/\text{day}$ of inhaled fluticasone was not mirrored by other markers such as exhaled NO, spirometry or asthma specific quality of life. Perhaps this is unsurprising given that we selected our patients *a priori* on the basis of being methacholine responsive, rather than having impaired lung function. Secondly, it is possible that a longer duration of treatment may have detected a further improvement in PC_{20} . However, it has been shown previously with inhaled fluticasone that after 2 weeks treatment, the shift in PC_{20} is near maximal as compared to after 6 weeks (26). We chose to strike a pragmatic balance between the duration of treatment using a three-way crossover design, along with the risk of losing asthma control during the steroid free washout periods. Thirdly, it is important to consider any potential carryover effects when employing a crossover design, as in the present study. In terms of any potential carryover effect on the primary outcome between the three randomized treatment arms, our crossover analysis did not show any difference ($P > 0.05$) pretreatment baseline values, which is important when calculating the shift in PC_{20} from

respective pretreatment baseline values. Finally, it is possible that one might show an additive effect of intranasal fluticasone on the lower airway in patients with more severe asthma. However, as this was an initial proof of concept study, we selected participants *a priori* on the degree of airway hyper-responsiveness. Indeed, we have clearly shown that our chosen primary end point had sufficient sensitivity in terms of there being room for improvement.

In summary, our results showed that for the primary outcome of methacholine PC₂₀, the shift in methacholine PC₂₀ with high dose fluticasone was significantly superior to low dose fluticasone demonstrating potential for improvement over and above low dose inhaled fluticasone alone. While combined treatment with intranasal and low dose inhaled fluticasone resulted in a significant improvement in methacholine PC₂₀ from

baseline, there was no difference when comparing with low dose inhaled steroid alone. Thus, we were unable to demonstrate any steroid sparing effect per se on lower airway outcomes by adding intranasal steroid to low dose steroid. However, as expected, combined treatment did improve upper airway outcomes and suppressed systemic eosinophilic inflammation which inhaled steroid alone did not. Further long-term studies are required to look at combined therapy on exacerbations.

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