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Efficacy and systemic tolerability of mometasone furoate and betamethasone sodium phosphate

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Abstract

This study evaluates the efficacy and systemic tolerability of licensed doses of mometasone furoate (Nasonex®) and betamethasone sodium phosphate (Betnesol®) in allergic chronic rhinosinusitis patients. It also assesses the diagnostic accuracy of morning salivary cortisol (MSC) concentrations to screen for adrenal suppression in these patients.

Forty-eight patients were prospectively randomized to two treatment limbs. Symptom scores and adrenal function assessments were performed immediately prior to commencement and at the end of treatment.

One (4 per cent) mometasone furoate and 14 (58 per cent) betamethasone sodium phosphate patients developed biochemical evidence of adrenal suppression. There were statistically significant ($p < 0.005$) reductions in symptom scores following treatment, but no significant difference ($p > 0.05$) between the drug groups regarding post-treatment symptom scores. As a screening tool for iatrogenic adrenal suppression, MSC had a sensitivity of 100 per cent and a specificity of 97 per cent.

This study demonstrates the high risk of developing adrenal suppression secondary to betamethasone sodium phosphate therapy. The salivary cortisol assay is an accurate tool for monitoring adrenal function and is ideally suited to the out-patient setting.

Key words: Hypersensitivity; Steroids; Disease Management; Adrenal Gland Hypofunction; Saliva; Toxicity Tests; Sensitivity and Specificity

Introduction

Several studies have reported adrenal suppression following topical intranasal glucocorticoid (TING) treatment.[1–8] These findings, which have precipitated warnings of caution from drug safety agencies, may discourage clinicians from prescribing TINGs.[9] We have previously reported evidence of adrenal suppression secondary to intranasal betamethasone sodium phosphate (Betnesol®) in allergic rhinosinusitis patients.[10] This preparation is only available in a non-metered dropper delivery system, and there is a tendency for patients to over-medicate.[11] However, detailed investigation of the relationship between betamethasone sodium phosphate over-medication and development of adrenal suppression in rhinology patients has not been performed. Although betamethasone sodium phosphate may be a more traditional agent in such patients, a new generation of glucocorticoid preparation, mometasone furoate (Nasonex®), has been made available as a metered dose administered once daily. Several studies have shown that mometasone furoate is an effective treatment in allergic rhinosinusitis and that it is rarely detectable in plasma after nasal administration because of its rapid and extensive metabolism.[12–19] It has been shown to have negligible systemic bioavailability (approximately 0.1 per cent) following intranasal administration and no effect on the hypothalamic–pituitary–adrenal (HPA) axis in adults, even when administered at up to 20 times the recommended daily dose of 200 µg (i.e. 4000 µg).[20]

The aims of this study were: (1) to compare the efficacy and tolerability of topical intranasal mometasone furoate and betamethasone sodium phosphate therapy in allergic rhinosinusitis patients treated for eight weeks; and (2) to assess the diagnostic accuracy of morning salivary cortisol (MSC) measurements (the index test) to correctly identify adrenal suppression in out-patients receiving TINGs, compared with the short Synacthen test (the reference test).

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Methods

Patients and baseline evaluations

Forty-eight adult (16 years and older) patients attending the rhinology clinic with a history of untreated chronic allergic rhinosinusitis were enrolled in a prospective, randomized clinical trial of eight weeks duration. Chronic rhinosinusitis was defined as 'an inflammation of the lining of the nose, characterized by one or more of the following symptoms: nasal congestion, rhinorrhoea, sneezing and itching'.[21] The allergic nature of the rhinosinusitis was suggested by the patient's history. Patients with nasal polyposis were excluded. Other exclusion criteria (concurrent or recent history of glucocorticoid or hormonal therapy; history of significant systemic medical conditions; and night-shift workers) were applied to avoid recruitment of patients with pre-existing HPA axis dysfunction. On the day of recruitment (day 0), each patient completed baseline rhinosinusitis disability index (RSDI)[22] and clinical HPA axis assessments. The latter included an endocrinological clinical history and examination. Patients then sampled saliva for baseline salivary cortisol assessment on two consecutive mornings (days 1 and 2) at home before commencement of TING therapy. The North Glasgow Hospitals University NHS Trust granted ethical approval.

Interventions

Patients were assigned to one of two treatment groups (mometasone furoate or betamethasone sodium phosphate) by computer-generated randomization. Patients in the mometasone furoate group administered an eight-week course of mometasone furoate 200 μg daily (two 50 μg sprays in each nostril applied daily in the morning), and patients in the betamethasone sodium phosphate group administered an eight-week course of betamethasone sodium phosphate 200 μg daily (two 25 μg drops in each nostril applied twice daily). Following drug assignment, a bottle of nasal steroid plus training in the correct method of drug administration were provided. During the study patients returned by mail their used, empty bottles to the clinic in exchange for a full, pre-weighed bottle repeat prescription. At the end of the study each patient returned their TING bottle for weighing. Total drug volumes administered by patients were calculated by collection and microbalance weighing of all used bottles.

Outcome measures

The primary outcome measures were symptomatic efficacy and systemic tolerability of the study TINGs. In the absence of a statistically significant difference in pre-treatment RSDI scores for the drug groups, the post-treatment RSDI for each drug group was used as the primary efficacy variable. The baseline clinical and biochemical HPA axis assessments were repeated at the end of the eight-week TING course to assess systemic tolerability. Patients collected saliva for cortisol measurement at the end of the eight-week TING course (days 57 and 58). On day 58 patients attended the rhinology clinic between 08.00 and 09.00 hours and completed the RSDI, clinical HPA assessment and the short Synacthen test (SST). The methodologies of the salivary cortisol assay and the SST were identical to those described in earlier publications.[10] Normal adrenal function was confirmed by an MSC concentration greater than 10.9 nmol/l in men and greater than 9.3 nmol/l in women. A normal SST was defined as: a baseline plasma cortisol concentration greater than 200 nmol/l; a 30-min post-Synacthen plasma cortisol concentration greater than 500 nmol/l; and a 30-min post-Synacthen cortisol increment greater than 200 nmol/l. Secondary outcomes included occurrence of adverse events other than HPA axis suppression and the percentage of the recommended dose (%RD) of intranasal glucocorticoid used by participants.

Power calculations and statistical analysis

Power calculations based on the findings of the earlier pilot study indicated the sample size required.[10] To detect a difference of at least 34 per cent in the incidence of adrenal suppression between the two groups, with a 0.05 two-sided significance level (α-error based on a chi-squared test) and a statistical power of 90 per cent, 24 participants were required in each group. Demographic details and descriptive statistics for each drug group were recorded and analysed. Mann–Whitney tests were performed to identify differences between the drug groups. Comparisons of group gender ratios were analysed using chi-squared and Fisher's exact tests. Spearman's correlation was used to investigate relationships between measures pre- and post-treatment. Statistical analysis was performed on an intention-to-treat basis using SPSS (Statistical Package for the Social Sciences, version 11.5) and all tests were performed at $p < 0.05$ significance level. Unless stated otherwise, the median and range values were reported.

Results

Patient demographics and baseline evaluations

All 48 patients who enrolled in the study completed the baseline assessments without difficulty. Normal baseline adrenal function, evaluated by clinical HPA axis assessment and salivary cortisol concentration, was confirmed in all patients prior to the commencement of TING therapy (Table I). There were no significant differences in the demographics, pre-treatment symptom scores (baseline RSDI scores) or pre-treatment adrenal function (baseline HPA parameters) of the two groups (Table I).

Outcomes

Efficacy of drugs. All 48 patients completed the post-treatment efficacy (RSDI) assessments without difficulty (Table I). Since there were no significant differences in the baseline RSDI scores for each drug group, the post-treatment RSDIs for each drug

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TABLE I

PATIENTS' DESCRIPTIVE STATISTICS

Patients	Drug		*p*
	Betamethasone sodium phosphate	Mometasone furoate	
n	24	24	
Sex			
Male	14	13	
Female	10	11	
Age (years)			
Median	41	48	
Range	16–66	16–79	
Baseline			
RSDI			
Median	32.5	33.0	
Range	11–64	0–65	
Salivary cortisol (nmol/l)			
Median	17.0	17.8	
Range	10.4–35.3	10.2–31.7	
Post-treatment			
RSDI			
Median	11.5	19.5	
Range	0–62	2–54	
Salivary cortisol (nmol/l)			
Median	5.6	17.7	<0.005
Range	1.6–25.3	10.2–39.2	
Baseline plasma costisol (nmol/l)			
Median	220	353	<0.05
Range	30–620	200–840	
Post-Synacthen plasma cortisol (nmol/l)			
Median	474	732	<0.005
Range	80–995	450–1112	
Percentage recommended dose			
Median	177	80	<0.005
Range	80–542	26–156	

Only statistically significant *p* values shown. RSDI = rhinosinusitis disability index; range = absolute range.

group were compared. There were statistically significant reductions in post-treatment RSDI scores (primary efficacy variable) for mometasone furoate ($p < 0.005$) and betamethasone sodium phosphate ($p < 0.005$). There was no significant difference between the drugs in respect of post-treatment RSDI scores ($p > 0.05$). Treatment failure (i.e. no change or worsening RSDI score following treatment) occurred in four betamethasone sodium phosphate patients and six mometasone furoate patients.

Systemic tolerability of drugs. Clinical and biochemical HPA axis assessments were completed in all 48 patients. Although there was no clinical evidence of adrenal suppression, we demonstrated biochemical evidence of adrenal suppression in both drug groups (Table I). Impaired salivary cortisol concentrations and SST responses were demonstrated in 14 (63 per cent) of the 24 betamethasone sodium phosphate patients and one (4 per cent) of the 24 mometasone furoate patients. This difference in the risk of iatrogenic adrenal suppression was statistically significant ($p < 0.005$). One betamethasone sodium phosphate patient had disparate biochemical results (impaired salivary cortisol and normal SST). All remaining nine betamethasone sodium phosphate patients and 23 mometasone furoate patients had normal salivary cortisols and SST responses.

Comparison of pre-treatment baseline parameters of the normal patients with the adrenally impaired patients in the betamethasone sodium phosphate group showed that the two groups were statistically similar ($p > 0.05$) in terms of age, gender ratio, pre-treatment RSDI scores and pre-treatment salivary cortisol concentrations (Table II). Compared with the normal betamethasone sodium phosphate patients, there was statistically significant impairment of post-treatment salivary cortisol ($p < 0.005$), post-treatment (pre-Synacthen) plasma cortisol ($p < 0.005$) and post-Synacthen plasma cortisol ($p < 0.005$) in the adrenally impaired betamethasone sodium phosphate patients. There was no significant difference between the two groups in respect of post-treatment RSDI scores ($p > 0.05$). There was significantly more over-dosage ($p < 0.005$) in the impaired group compared with the normal group (Table II). Eleven of 14 betamethasone sodium phosphate patients with adrenal suppression administered at least twice (200–542 %RD) the recommended dose. None of the nine betamethasone sodium phosphate patients with normal HPA axis function administered more than twice the recommended dose.

Patients in the mometasone furoate group administered doses that reflected the prescribed dose; this was statistically significant compared with the betamethasone sodium phosphate group (Table I). Since there was only one mometasone

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TABLE II

BETAMETHASONE SODIUM PHOSPHATE GROUP STATISTICS, ACCORDING TO SHORT SYNACTHEN TEST RESULT

Patients	Synacthen test result		*p*
	Normal	Impaired	
n	10	14	
Sex			
Male	5	9	
Female	5	5	
Age (years)			
Median	32.5	44.5	
Range	16–54	21–66	
Baseline			
RSDI			
Median	31	33	
Range	11–64	12–56	
Salivary cortisol (nmol/l)			
Median	17.6	17.0	
Range	15.0–35.3	10.4–31.0	
Post-treatment			
RSDI			
Median	7	12	
Range	0–62	4–50	
Salivary cortisol (nmol/l)			
Median	14.6	3.6	<0.005
Range	6.3–25.3	1.6–8.9	
Baseline plasma cortisol (nmol/l)			
Median	360	45	<0.05
Range	210–620	30–370	
Post-Synacthen plasma cortisol (nmol/l)			
Median	660	307	<0.005
Range	550–995	80–480	
Percentage recommended dose			
Median	124	253	<0.005
Range	80–181	91–542	

Only statistically significant *p* values shown. RSDI = rhinosinusitis disability index; range = absolute range.

furoate patient in the adrenally impaired group, no meaningful statistical comparisons could be made with the normal group.

Diagnostic accuracy of salivary cortisols. There was a significant positive correlation between post-treatment salivary cortisol and post-treatment (pre-Synacthen) plasma cortisol [Spearman's correlation 0.53 ($p < 0.005$)]. The ability of salivary cortisols to correctly identify normal and impaired adrenal function was assessed by cross-reference with the SST (reference) test. The sensitivity and specificity were 100 per cent (15 out of 15) and 97 per cent (32 out of 33), respectively (Table III). The diagnostic accuracy of salivary cortisol in this setting was 98 per cent.

Discussion

The number of patients studied met the requirements for a statistically meaningful analysis of results, based on power calculations. Significant symptomatic improvements were found following treatment for both drug groups. This study showed that mometasone furoate 200 µg, administered once daily in the morning, demonstrated symptomatic efficacy comparable to that achieved by betamethasone sodium phosphate 100 µg administered twice daily. Although the pooled data demonstrated favourable results for the drug groups, treatment failure occurred in six (25 per cent) mometasone furoate patients and four (17 per cent) betamethasone sodium phosphate patients.

Mometasone furoate proved to be a systemically well tolerated therapy, although one patient demonstrated biochemical evidence of borderline adrenal suppression. These findings support recent clinical studies which have shown that mometasone furoate is poorly absorbed following oral administration and is rapidly and extensively metabolized following intravenous administration.[18,19] Administration of mometasone furoate via the metered dose delivery system improves compliance and reduces the risk of overdosage. In contrast, betamethasone sodium phosphate users tended to

TABLE III

DIAGNOSTIC ACCURACY OF SALIVARY CORTISOL

Salivary cortisol	Actual condition of study population	
	Disease present	Disease absent
Positive	15 (true positives) *Sensitivity*	1 (false positive)
Negative	0 (false negative)	32 (true negatives) *Specificity*

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overdose, with clear evidence that administration of two or more times the recommended dose was associated with the development of adrenal suppression. Interestingly, development of adrenal suppression secondary to over-administration of betamethasone sodium phosphate did not result in improved symptomatic outcomes compared with the remaining patients. It is likely that the betamethasone sodium phosphate dropper delivery system contributed to over-administration and adrenal suppression. The prevalence of adrenal suppression in patients prescribed licensed doses of betamethasone sodium phosphate is a concern, and the issuing of warnings of caution regarding its use are justified. The findings in this study suggest that the risk of developing adrenal suppression secondary to betamethasone sodium phosphate is a high price to pay given that there is no statistically significant symptomatic gain compared with mometasone furoate.

- **In this paper patients with allergic rhinosinusitis were randomized to receive treatment with either mometasone or betamethasone**
- **Symptom scores and adrenal gland function were measured before and after eight weeks treatment**
- **There were statistically significant reductions in symptom scores in both groups following treatment**
- **Both groups of patients showed a degree of adrenal cortical suppression. A salivary screening test had a high sensitivity and specificity for monitoring such suppression**
- **The authors conclude that salivary screening for adrenal suppression is ideal in an out-patient setting**

Rhinosinusitis is a highly prevalent, benign disease and is commonly treated with drugs that have the potential to precipitate significant unwanted endocrinological effects. The intensity and persistence of the inflammatory response often necessitates prolonged treatment with TINGs.[23] A considerable number of clinicians encounter this problem, but very few have non-invasive, simple, cheap and accurate tools for identifying iatrogenic adrenal suppression in their patients. A widely accepted tool of HPA axis assessment was used to measure the validity of salivary cortisols to identify adrenal suppression. The results showed that salivary cortisol measurement is a sensitive screening tool for adrenal impairment in this setting. In particular, the positive predictive value of the test was 100 per cent, suggesting that patients with adrenal suppression secondary to TING use will be identified by this test. Only one patient had a disparate test result (subnormal salivary cortisol result but a normal Synacthen response). This is perhaps unsurprising as the ACTH dose used in standard SSTs is grossly supra-physiological and there are reports that this test can give false positive results.[24] Since salivary cortisol measurement provides a more physiological assessment, it is possible that it provides a more reliable indicator in borderline cases. Based on these findings, salivary cortisol measurements offer an extremely valuable out-patient screening test for adrenal suppression in patients prescribed TINGs, especially those receiving betamethasone sodium phosphate who commonly exhibit adrenal suppression.

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