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REVIEW

Hay fever and a single intramuscular injection of corticosteroid: a systematic review

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Abstract
Objectives: In severe hay fever, some patients are strongly affected despite the use of first-line therapy and are therefore treated with an intramuscular injection of systemic corticosteroid (i.m. SCS) in some countries. The aim of this paper was to explore the efficacy and side effects of a single i.m. SCS injection in hay fever in adults.
Data sources: PubMed, EMBASE, Cochrane Library.
Methods: Systematic review. Criteria for inclusion: hay fever or seasonal allergic rhinitis, adults, injectable steroids, clinical trials, English language. None of the clinical trials were excluded, since an important aim of the review was to identify any possible side-effects. Outcome measures: clinical effects, and clinical and physiological side-effects.
Results: 18 clinical trials met the inclusion criteria: nine double-blind RCTs (five placebo-controlled and four comparative RCTs), two single-blinded RCTs, and seven open trials. All studies were conducted before 1988. The efficacy of a single intramuscular injection of SCS was statistically significant in all five placebo-controlled trials and demonstrated considerable clinical benefit, lasting approximately from within the first day to four weeks. In the only two studies comparing i.m. SCS to nasal steroids a superior effect with i.m. SCS was demonstrated. The side-effects were few, both clinically and physiologically, with retained ability to respond to stress with hypothalamic-pituitary-adrenal activation.
Conclusions: The studies in this review were sound and their findings consistent: i.m. SCS therapy was shown to be efficient and safe for the treatment of hayfever in adults. This review shows no support for any concerns regarding serious tissue atrophy or other serious side-effects, any long-lasting suppression of plasma-cortisol, or any influence on stress reaction, following a single intramuscular injection of SCS.

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Contents

Introduction

The prevalence of hay fever (seasonal allergic rhinitis) is 10-20% in adolescence [1]. Generally, hay fever starts between the ages of 10 and 20 with peak severity in early adulthood and with a tendency to spontaneous remission [2].

The majority of hay fever patients are well treated by the use of first-line medication (an individual combination of nasal steroids, systemic and topical antihistamines, leukotrienes or cromones) [3]. However, a smaller group of patients with severe hay fever do not obtain symptomatic relief from first-line therapy and some of these patients—an estimated 12% of hay fever cases in Denmark [4] and 11% in the UK [5] — are given an intramuscular injection of systemic corticosteroid (i.m. SCS) at the onset of the allergy season. Other countries appear to use i.m. SCS less often [6].

International reports on allergic rhinitis rarely recommend i.m. SCS because of possible side-effects [7—10]. However, the only prior review on this topic established, ''that the reviewed data do not support the fear of a long-lasting suppression of hypothalamic-pituitary-adrenal (HPA) function from a single injection of i.m. SCS'', but states that, ''the lack of controlled studies has left us with uncertain guidelines'' [11].

A Danish register study of clinical side-effects from i.m. SCS [30] reported only a minute number of adverse effects. Within a 10-year period from 1985—94 a total of 26 side-effects were registered out of an estimated total sale of 330,000 i.m. SCS doses for hay fever; these consisted of two cases of subcutaneous atrophy, five local reactions and one change in skin pigmentation, while the remaining 18 cases were reversible minor problems.

Given the fact that i.m. SCS is used regularly in some countries, but that its use is discouraged by the international guideline recommendations, the aim of this systematic review was to evaluate the reported effects and side-effects of a single injection of i.m. SCS in patients with hay fever.

Methods

Search strategy

PubMed, EMBASE and Cochrane Library databases, in 2003. The search terms were: (hay fever OR allergic rhinitis) AND (injectable steroids OR systemic steroids OR depo-steroids) AND clinical trial. The search strategy in PubMed yielded 82 hits, of which eight articles included clinical trials with i.m. SCS [14—16,18—22]. From cross-referencing, we identified another ten studies meeting the search criteria. All studies were conducted before 1988. No further studies were found in EMBASE or the Cochrane Library.

Criteria for inclusion

Clinical trials including adults suffering from hay fever treated with a single, or several, dose(s) of i.m. SCS; English language.

Criteria for exclusion

Biochemical trials, reviews. None of the clinical trials were excluded, as an important aim of the review was to identify any possible side effects.

Quality of studies

The studies were divided into three groups according to their methodology: 1) double-blind randomised controlled trials (RCTs); 2) randomised single-blind trials; and 3) open trials.

Study characteristic

A summary of the 18 studies [12—29], giving data on 1362 participants, is presented in Table 1. Nine were double-blind RCTs [12—20], of which five were placebo-controlled [12—16] (including two combined placebo-controlled and comparative trials [15,16]) and four were double-blind comparative trials [17—20]. Two studies were single-blind RCTs [21,22] and seven were open studies [23—29] of which one was comparative [28]. Six studies were identified [12,18,23—25,28] which did not appear in the former review [11].

Different generic formulae were used (Table 2). Most studies used equipotent doses, i.e. methylprednisolone 80 mg, equivalent to triamcinolone 80 mg (which is equivalent to 100 mg oral prednisone). In two studies 40 mg triamcinolone was used [13,18]. In most studies a single depot injection of SCS was used. However, we included studies where some patients received more than one injection [12,23] to identify the side-effects.

Some studies explicitly included patients with severe hay fever [13,22,27]. Some of the older studies have their strength in size but failed in the homogeneity of the study population, including a minority of patients having coexisting or other allergic diseases such as asthma and urticaria [18,23,26].

The outcome variables

With one exception [26], the clinical results of the studies were based on the patients' subjective validation of the relief of hay-fever symptoms. In 11 studies a global satisfaction scale was used [12,13,15,17,18,23—25,27—29], rating the clinical effect on different scales, i.e. either as ''no symptoms, slight or moderate symptoms, severe symptoms'' [12,16], or ''restored/improved or unimproved'' [13] or using an ''excellent, good, poor or none effect'' scale [15]. Specific symptoms such as nasal blockage, nasal itching and eye symptoms were measured by grading them [14,16,19—22] and by counting the occurrence [14].

The clinical side-effects in the studies are summarised in Table 1. In terms of physiological side-effects, several studies evaluated a possible suppression of the HPA-axis caused by i.m. SCS [19,20,22,26,27,29], measured by the basal cortisol level or the stimulated plasma cortisol level (the stress response), the latter revealed either by an ACTH test or by a hypoglycemia test. Some studies measured the urine excretion of cortisol (as 17-ketosteroids), blood glucose and the occurrence of glycosuria, as well as weight and blood pressure.

Quantitative data-synthesis

A meta-analysis of the placebo-controlled studies has not been done and could potentially be misleading, because of the heterogeneity and the lack of definition of both the populations and outcome scales. In this review, the effects are best described in the placebo-controlled RCTs, while the clinical side-effects can best be looked at in the larger, open studies. The evidence of effect in the open studies must be interpreted with caution.

Results

Efficacy

In all the double-blind placebo-controlled trials [12—16] a statistically significant effect (from $p < 0.05$ to $p < 0.001$) and a considerable effect in symptom relief was shown (Table 1). Generally, the effect lasted from the first or second day until 3—5 weeks [12—16,19—29]. However, in one study the duration of the symptom relief was considerably less [18].

Compared to nasal steroids, i.m. SCS proved to be significantly superior to nasal beclomethasone ($p < 0.01$) [16], and equally effective when compared to nasal budesonide 400 mg even with increased use of supplementary medicine in the nasal steroid group [20]. Global satisfaction was not measured in either study [16,20].

Table 1 Overview of hay fever studies - efficacy and side-effects.

Ref.	Year	Author	N	Trials	Treatment	Efficacy	Effect duration	Clinical side effects	Physiological side effects
				RCT, double-blind:					
[12]	1960	Brown	95	Placebo	MP 80 mg × 3 vs placebo	Good; $P < 0.001$		Equally many	Glycosuria (1/90). Weight, blood pressure unaffected
[13]	1972	Axelsson	38	Placebo	TRI 40 mg *v* placebo	Good; $P < 0.001$ (16/17 *v* 2/21)	>20 d	Minor	Not measured
[14]	1987	Borum	24	Placebo	MP 80 mg *v* placebo, 2 seasons	Good; $P < 0.05$	>4 w	Not reported	Not measured
[15]	1969	Hermance	70	Placebo + comparative	DM 16 mg *v* DM 8 mg *v* placebo	Good; $P < 0.001$ (75% *v* 21%)	6 hours - 4 w	Minor, equally many	Not measured
[16]	1988	Laursen	30	Placebo + comparative	BMP 5 mg + BMP 2 mg *v* nasal Beclomethasone daily 4 w *v* placebo	Good; $P < 0.01$ *v* placebo & nasal Beclomethasone	4 w	Minor	Not measured
[17]	1968	Chervinsky	97	Comparative	MP *v* BM *v* DMP + DMA *v* DMA	Equally good; 3.6—4 on 5 scale	4 hours —12 d	Minor	Not measured
[18]	1971	McElhenney	220	Comparative	TRI 40 mg *v* DM 8 mg	Equally good, 70% good/excellent	8 hours - 4 d	Minor, equally many	Not measured
[19]	1987	Laursen	36	Comparative	BMD 5 mg + BMP 2 mg *v* T. Prednisone 7.5 mg daily 3 w	Equally good	>3 w	Minor	Plasma cortisol unaffected after 3 w, ACTH response unaffected after 3 w
[20]	1988	Pichler	30	Comparative	MP 80 mg *v* nasal Budesonide 400myg daily 3 w	Equally good	3 w	Minor, equally many	Plasma cortisol after 7 d. mean decrease 16.5%. ACTH test:equal in both groups
				RCT, single-blind:					
[21]	1979	Kronholm	42	Comparative	BMD 5 mg + BMP 2 mg *v* MP 80 mg	BMD + BMP better than MP; $P < 0.05$	3—5 w	Not reported	Urine cortisol unaffected
[22]	1980	Ohlander	59	Comparative	BMD 5 mg *v* BMP 3 mg *v* MP 40 mg	Equally good, 51/59 symptom free	1—4 w	Minor, equally many	
				Open:					
[23]	1964	Hefley	418		TRI 80 mg, total 949 i.m.SCS	75% good to excellent	>5 w	6%, incl. tissue atrophy	Urine cortisol depressed
[24]	1965	Marshall	20		MP 80 mg	90% complete relief	>4 w	No	Not measured
[25]	1968	Lewin	51		MP 80 mg	90% complete/substantial relief	3 w	Minor	Weight, blood pressure, urine glucose/protein unaffected
[26]	1970	Ganderton	8		MP 80 mg × 2 (interval 2 w)	3/8 improved	3 w	Major (uveitis, gastritis, cramps)	Plasma cortisol depressed <3 w; HPA affected in one person
[27]	1971	McMillian	18		TRI 80 mg	90% good to excellent	12-48 h—3 w	Minor	Plasma cortisol depressed <3 w
[28]	1973	Melotte	92	Comparative	TRI 80 mg *v* MP 80 mg	90% complete/substantial relief	90% >4 w	Minor	Not measured
[29]	1981	Hedner	14		MP 80 mg	90% excellent	1 d—3-4 w	No	Basal and stimulated plasma cortisol max.depressed 72% of control value. Plasma cortisol depressed <3w. Stress response maintained.
			1362						

Abbreviations: Generic formulas, see Table 2. v: versus, w: weeks, d: days.

Table 2 Different generic formulae of depot SCS.

Generic name	Equipotent doses
Betamethasone(BM)	5 + 5 mg = 2 ml
Diproprionate (BMD)	
Phosphate (BMP)	
Acetate (BMA)	
Methylprednisolone (MP)	80 mg = 2 ml
acetate	
Triamcinolone(TRI)	80 mg = 2 ml
Dexamethasone(DM)	16 mg = 2 ml
Phosphate (DMP)	
Acetate (DMA)	

Compared to oral steroids (7.5 mg oral prednisone daily for three weeks), a single injection of i.m. SCS (80 mg betamethasone) was equally effective in relieving symptoms for more than three weeks [19].

In six of the seven open studies [23—25,27—29] the efficacy of symptom relief was consistent, scoring good-to-excellent clinical effect in 90% of the participants [24,25,27—29] in five studies, and 75% of the participants [23] in one study, using one or two doses of i.m. SCS. However, in one open study with eight participants, only half of these improved [26].

In the comparison of different SCS-formulations there were no statistically significant differences in respect to efficacy, onset and duration in three of the studies [17,18,22]. A minor difference was found in one study [21], as betamethasone seemed significantly more effective than methylprednisolone.

In terms of steroid doses, 40 mg (1 ml) triamcinolone also seemed to be effective [13,18]. Dexamethasone 8 mg seemed to be as effective as 16mg but the higher dose provided longer duration of symptom relief [15].

Clinical side-effects

In the randomised double-blind placebo-controlled trials [12—16] there were no statistically significant differences in side-effects between the groups, not even in Brown's study with patients being given three consecutive i.m. SCS injections at one-weekly intervals [12] (Table 1). In the comparative studies, the clinical side-effects generally were regarded as minor and were similar with different SCS formulae [15—20].

In several studies, miscellaneous side-effects of minor importance were reported in a few participants, consisting of pain at the site of injections [12,19,25,28], menstrual irregularities [23], flushing [27], tiredness [18], nervousness [18] and blue skin marks [18]. One study reported subcutaneous atrophy [23]: out of 418 patients receiving 949 injections, 14 subcutaneous irritations with slight atrophy were identified, occurring only in the deltoid but not the gluteal muscle [23], and the atrophy sites filled in with time. One study with eight participants showed several side-effects, such as one person showing peptic ulcer symptoms, one showing peripheral cramps and one showing uveitis (the last diagnosis was explained as a reactivation of old tuberculosis, according to the author) [26].

Physiological side-effects

The basal plasma cortisol level was moderately depressed within one day following a single i.m. injection of SCS [27,29], with a mean decrease of 16.5% after seven days [20],or a mean decrease less than 20% when plasma cortisol was measured once a week for three consecutive weeks [29]. The plasma cortisol level was normalised after 2-3 weeks [19,22,26,27,29].

As regards the stimulated plasma cortisol by means of the ACTH test, Hedner established that a single i.m. SCS (2 ml methylprednisolone) caused only a partial suppression of the HPA-axis. None of the parameters (basal or stimulated plasma cortisol) ever fell below 72% of its control value, and therefore it was judged that ''the clinical significance of the suppression caused by one injection should be small'' [29].

Compared with oral prednisolone (7.5 mg/day for three weeks), and as assessed by the ACTH test, the HPA-axis was significantly less suppressed with i.m. SCS (2 ml betamethasone) [19]. Compared with nasal steroids (budesonide), the ACTH test induced an equally slight increase of cortisol level in both groups [20].

The blood glucose was slightly elevated in the first two days [22], regarded by the authors as being of no clinical significance. Glycosuria was identified in one out of 42 patients [12], but not detected in any of the 51 participants in another study [25]. No effect was reported on patients' weight [12,25] or blood pressure [12,25].

Discussion

It is remarkable that our search only identified studies published pre-1988. Generally, the methodological criteria of the older trials do not meet the scientific requirements of present-day studies. However, the studies seem to be both well designed

and properly carried out and the homogeneity of the results strengthens the findings of this review. Publication bias can never be excluded.

With regards to treatment benefit from an i.m. SCS injection, the most striking feature is the consistency we found in all the papers. The effect demonstrated in all the double-blind placebo-controlled trials [12—16] was statistically significant and clinically considerable, beginning after the first day of treatment and lasting about four weeks. When comparing different SCS formulations there were no statistically significant differences [17,18]. The evidence of the open studies must be interpreted with caution particularly because the first-line therapy offered at that time was less efficient compared with modern therapy. However, the trials support the conclusion, except for one study with a shorter duration of effect [18]. Nasal steroids are considered to be the most efficient modern first-line therapy [10]. In the two studies comparing i.m. SCS to nasal steroids, a superior effect was demonstrated with i.m.SCS [16,20], both in terms of symptoms [16] and in use of rescue medications [20]. Global satisfaction was not measured in either study [16,20]. The only study comparing i.m. SCS to oral steroids indicated equally good benefit [19].

A single i.m. injection of SCS produced few clinical side-effects and these were of minor importance. Merely the Hefley study [23] reported minor tissue atrophies due to 1.5% of the injections, and only in the deltoid muscle. The site of injection was thus recommended to be the gluteal muscles where no atrophy was seen [23]. In one study with eight participants there were extraordinary and marked side-effects [26]. As these side-effects were not reproduced in other studies, they might, as the author notes, have been due to coincidence.

The physiological effect on plasma cortisol indicated significant but minor and short-lasting depression and a persistent ability to respond to stress with HPA-activation [19,20,29], which is in accordance with a recent review [11].

The difference between this review and the recommendations of the international reports [7—10] concerning side-effects from SCS is striking and warrants some thought. The International Consensus Report on Rhinitis [7] discourages the use of SCS ''as they can produce severe side-effects, cannot be reversed, and suppress adrenal cortex function for long periods'', with only a single reference to Hedner & Persson [29]. However, Hedner & Persson concluded that a ''considerable ability to respond to stress with HPA activation persisted, and the clinical significance of the suppression caused by one injection should be small'' [29]. The other international reports [8—10] also question the use of i.m. SCS, and only recommend short courses (<three weeks) of oral steroids ''as a last resort'' [9,10]. The reasons given are: too few scientific studies [9,10]; the risk of tissue atrophy [9,10]; and the risk of long-term side effects [8]. However, no references are given to support these statements.

The lack of references in the international reports and guidelines pertaining to ''the fear of side-effects from SCS'' [7—10] is particularly disturbing and even casts doubt on the likelihood that such evidence exists.

Long-term treatment with SCS is known to cause increased risk of osteoporosis in a dose-related manner. If patients receive more than an average daily dose of 7.5 mg of prednisolone for more than six months, the risk of osteoporosis is generally believed to be increased. No studies have been published concerning the long-term risk of osteoporosis following a single, or a few, injections of i.m. SCS for a short period of years (personal communication). However, with a single yearly injection of 40—80 mg of methylprednisolone, or equivalent, for a limited number of years, the cumulated dose is far below the at-risk dose, and should be unlikely to influence bone structure. In any patient that receives SCS, calcium and vitamin D supplementation is recommended, but considering that the recipients typically are young healthy adults receiving SCS during the summertime when vitamin-D synthesis is high, this precaution is questionable.

In conclusion, we think that the number of sound and consistent (although relatively old) studies in this review support the findings that a single injection of i.m. SCS is an efficient and safe treatment for hay fever, provided that there are no contraindications (diabetes, osteoporosis, keratitis, tuberculosis).

This review shows no support for any concerns regarding long-lasting suppression of plasma-cortisol, the possibility of a longstanding influence on stress reaction, or the risk of serious tissue atrophy, following a single injection of i.m. SCS. Thus, in accordance with this review, the international reports and guidelines on hay fever seem to be too dismissive in their advice on the use of i.m. SCS.

We agree with other published reports on the lack of current evidence and wonder at this shortfall, which we propose to remedy with new trials that will include studies comparing i.m. SCS with first-line therapy.

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