

# USE AND ABUSE OF STEROIDS IN UPPER AIRWAY ALLERGIC DISORDERS

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## ABSTRACT

Intranasal steroids (GCS) are an extremely effective treatment for the treatment of allergic rhinitis and its co-morbidities. They should be the first-line treatment for patients with allergic rhinitis who have nasal congestion as a predominant symptom. Prolonged use of intranasal GCS has not been associated with any significant systemic or local side-effects. The biggest challenge is to encourage our patients to use intranasal GCS regularly.

Allergic rhinitis (AR) and its comorbidities affect a significant part of the population. In the ISAAC study,<sup>1</sup> it was shown that AR affects between 10% and 15% of the population. There is an exponential increase in the prevalence of allergic diseases globally, particularly in industrialised countries. The reasons for this are not yet clear. This trend is expected to continue here as South Africa becomes more industrialised.

AR significantly affects the quality of life of patients. There are also many comorbidities associated with AR, i.e. otitis media, sinusitis and uncontrolled asthma. It is therefore important to manage AR appropriately to control symptoms, improve quality of life and prevent the comorbidities.

Glucocorticosteroids (GCS) have an important role to play in the management of upper respiratory allergic disorders. Their role in asthma is well established and forms the cornerstone of treatment for persistent asthma. GCS if used appropriately are effective and safe, but if used injudiciously can cause side-effects. This is especially important in relatively benign illness such as AR, otitis media and sinusitis. This review focuses on the role of GCS in the management of AR, sinusitis and otitis media.

## MECHANISM OF ACTION

GCS mediate their action by binding to cytoplasmic receptors in cells after passing through the cellular membrane. These activated receptors then interact with the regulator region of target genes inducing or inhibiting their transcription. The interaction of the activated glucocorticosteroid receptor (GR), with the transcription factor nuclear kappa B (NF- $\kappa$ B) and activated protein-1 (AP-1) leads to an inhibition of the expression of proinflammatory molecules, thus giving GCS their anti-inflammatory effects.<sup>2</sup> This effect also leads to the induction of transcription genes involved in bone metabolism, regulation of ocular pressure, gluconeogenesis, and regulation of the rennin-angiotensin pathway. These extra effects are responsible for the side-effects experienced with GCS.

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## ADVERSE EFFECTS

There are very few adverse effects of intranasal GCS. These are epistaxis, nasal irritation and rarely nasal septal perforation. It is extremely important to teach patients the correct use of their nasal sprays to minimise side-effects. Nasal biopsy studies have shown that even with prolonged use of intranasal GCS, there is no nasal mucosal atrophy.

Intranasal GCS have a very low systemic bioavailability. Small degrees of systemic absorption may however occur.

In a 30-year review on the safety of intranasal beclomethasone dipropionate (BDP) only one case of adrenal suppression was reported and the recommended dose of 400  $\mu$ g/day was not associated with any systemic side-effects such as osteoporosis.<sup>3</sup>

Studies with intranasal BDP in children have shown growth retardation of 0.9 cm of growth in 1 year but this has not been demonstrated in studies with fluticasone propionate or mometasone furoate.<sup>4,6</sup>

In many long-term studies with budesonide, fluticasone propionate, triamcinolone acetonide and mometasone furoate at recommended doses, no evidence of hypothalamic-pituitary-adrenal axis suppression was found.<sup>7-12</sup>

Strangely glaucoma has been reported with the use of inhaled steroids in asthmatics, but has not been reported with the use of intranasal GCS.

The adverse effects of systemic GCS are well known. In children in particular, oral and injectable GCS have clearly been shown to affect growth and should not be used for the treatment of upper airway allergic disorders.

## GCS IN AR

The classification of AR has changed in the last few years and is now classified as 'persistent allergic rhinitis' or 'intermittent allergic rhinitis' depending on the duration of symptoms.<sup>13</sup> These can be further divided into mild, moderate and severe depending on the degree they affect quality of life.

Treatment of AR with GCS was introduced in the early 1970s. The first GCS used to treat AR was BDP. This was used as a nasal spray for AR. More recently budesonide, fluticasone propionate, mometasone furoate and triamcinolone acetonide have become available. The newer-generation intranasal GCS have a better safety profile.

Intranasal GCS are the first-line treatment for both persistent and intermittent AR. They are the most potent and effective treatment for AR and their major advantage is that they are delivered directly to the target organ with almost no systemic absorption.

The ARIA guidelines recommend the use of intranasal GCS as first-line treatment for patients with AR with moderate to severe disease.<sup>14</sup>

They work by reducing allergic inflammation in the nasal mucosa and thereby reduce symptoms of AR.

They have been shown to reduce inflammatory cells, including a marked reduction of langerhans cells in the lamina propria, reduction of T-lymphocytes, and a marked reduction in nasal eosinophils in the lamina propria.<sup>15</sup> Intranasal steroids also reduce pro-inflammatory cytokines and mediators of the symptoms of AR such as histamine, leukotrienes, and typtase.

The clinical effect of this marked anti-inflammatory action is a reduction in nasal mucosal oedema with consequent improvement in nasal breathing. Intranasal GCS also significantly reduce symptoms of rhinorrhea, nasal itching and sneezing. They are more efficacious than oral and intranasal antihistamines.<sup>16,17</sup> In a comparative study intranasal GCS were more efficacious than oral leukotriene receptor antagonist alone and combined with antihistamines.<sup>18</sup> They are the preferred drug for nasal obstruction caused by allergic inflammation.

Intranasal GCS are largely available in aqueous forms in South Africa. They are also available as drops. However the intranasal drops contain a potent steroid solution, betametasone, which is not recommended for chronic use or for use in children. The aqueous formulations are extremely safe and can be used in children from 2 years of age. None of the intranasal GCS are registered for use in children under the age of 2 years.

The dose that is recommended in adults is 200 µg/day in each nostril and 100 µg/day/nostril in children. These doses can however be titrated according to the severity of the patient's symptoms. Intranasal GCS start working around 7-8 hours after administration and may take up to a few weeks to be fully effective. Once symptom control is achieved a lower maintenance dose can be used. A topical nasal decongestant may be used initially to allow better distribution of the intranasal GCS. These must however not be used for longer than 7 days to avoid rhinitis medicamentosa.

Adherence to intranasal GCS is a major problem. Patient education about AR, its complications as well as correct use of medication is a very important part of the management of patients with AR.

There are at present no studies clearly showing the benefit of a combination of intranasal GCS and oral antihistamine over the use of intranasal steroids alone. However patients who do not experience total symptom control with intranasal GCS may benefit from the addition of oral antihistamines.

The use of depot injections with GCS into the turbinates should be avoided because of the risk of serious side-effects such as blindness.

When rhinitis control is not achieved with large doses of intranasal GCS and addition of antihistamines, consideration should be given to the use of systemic steroids, as recommended by the ARIA guidelines. Short courses may be necessary to obtain control of refractory cases of AR when other treatment modalities have failed. These should however be avoided in children.

### Summary

Intranasal GCS are the first line of treatment for moderate to severe AR. They are an extremely effective and safe treatment for a very troublesome illness. There are no objective and clinically significant differences between the different new-generation intranasal GCS. The choice should therefore be based on cost considerations.<sup>19</sup>

### EFFECT ON AR COMORBIDITIES

A meta-analysis comparing intranasal GCS and oral antihistamines in relieving symptoms of allergic conjunctivitis in patients with AR found no difference between these two treatments. It was however shown that there were considerable variations in the results of the different studies.

There are studies that support the 'united airways' concept that clearly showed that treatment of AR improves asthma control.<sup>20-22</sup> A Cochrane review showed that in patients with AR and asthma the use of intranasal GCS showed some improvement in asthma control but could not clearly demonstrate objective and significant improvement in symptom scores, PEFR, FEV<sub>1</sub> and metacholine challenges.<sup>23</sup>

### Use of GCS for rhinosinusitis (RS)

RS is a significant health problem in the general population. There are no epidemiological data on the prevalence of RS in South Africa. In clinical practice it is a common reason for consultations to general practitioners, paediatricians and ENT specialists.

RS is an inflammatory disorder that simultaneously affects the nasal mucosa and the paranasal sinuses. The diagnosis is largely a clinical one based on the history and clinical examination, but sometimes requires special investigations. The differentiation between acute and chronic RS is based on the duration of symptoms. Acute RS (ARS) is the presence of symptoms of RS for more than 10 days but less than 12 weeks whereas chronic RS (CRS) is defined by the presence of symptoms for longer than 12 weeks.

In general the treatment of RS is medical with a minority of patients requiring surgical intervention. The medical treatment of ARS involves the use of appropriate antibiotics, restoration of the patency of the ostiomeatal complex to facilitate ventilation and drainage of the paranasal sinuses and alleviation of pain and fever associated with ARS.

The common organisms causing ARS are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. The antibiotics recommended for ARS are amoxicillin, amoxicillin/clavulanate or cephalosporins. It is important that antibiotics be used in appropriate doses and for optimal duration to achieve bacterial eradication.

Intranasal steroids used in combination with antibiotics have been shown to be effective in treating ARS. Studies have shown that intranasal steroids used in combination with antibiotics significantly reduce nasal obstruction and headaches when compared to antibiotics alone.<sup>24-26</sup> This has also been demonstrated with short courses of systemic GCS.<sup>27</sup>

### Use of GCS in nasal polyposis (NP)

Nasal polyps cause severe nasal obstruction, rhinorrhea and hyposmia. In children this is an extremely rare condition and is a feature of cystic fibrosis. In adults it may occur as an isolated condition or may be part of aspirin-sensitive asthma. The main form of treatment for nasal polyposis is surgical resection of the polyps. This provides immediate relief of symptoms.

The main role of intranasal GCS in nasal polyposis is symptomatic improvement of the condition and prevention of recurrence after surgical resection.

There is good evidence that treatment of NP with intranasal GCS results in a significant reduction of symptoms associated with NP.<sup>28-30</sup>

Regarding the postoperative role of intranasal GCS, there is now considerable evidence demonstrating the efficacy of intranasal GCS. In a placebo-controlled study reported by Karlsson and Rundcrantz,<sup>31</sup> it was shown in 20 postpolypectomy treated patients that treatment with BDP at a dose of 400 µg/day for a month followed by 200 µg a day for 2.5 years resulted in a significant reduction in polyp size and recurrence in the treated versus the placebo group.

In a study by Hartwig et al.<sup>32</sup> it was shown that 54% of budesonide-treated postpolypectomy patients were polyp-free after treatment compared with 13% receiving placebo.

In a similar study Virolainen and Puhakka<sup>33</sup> compared the effects of 400 µg/day of intranasal BDP with placebo in postpolypectomy patients. They found that 86% of the BDP-treated group were polyp-free compared with 60% of the placebo group.

There are now well-established data confirming the beneficial effects of intranasal GCS in NP. In South Africa fluticasone nasules are registered for the treatment of NP. These nasules contain high doses of fluticasone (500 µg).

There are no randomised placebo-controlled studies demonstrating the effect of systemic GCS in the treatment or prevention of recurrence of NP. There have been a few open studies which showed a beneficial effect. Caution should be exercised because of the risk of adverse effects from long-term use.

### **GCS in otitis media**

GCS are thought to have a beneficial effect in the management of otitis media by exerting an anti-inflammatory effect in the middle ear and eustachian tube. They may also increase the release of surfactant in the eustachian tube and reduce the size of the lymphatic tissue surrounding the eustachian tube. This allows better drainage through the eustachian tube and a decrease in the viscosity of the middle ear fluid. It may also facilitate the removal of fluid from the middle ear cavity by promoting transepithelial sodium transport in the middle ear epithelium.

### **GCS in acute otitis media**

There are no studies that support the use of GCS, either systemic or intranasal, in the management of acute otitis media.<sup>34</sup>

### **Use of GCS in otitis media with effusion (OME)**

The use of prednisone in OME is controversial. In a randomised placebo-controlled study by Mandel et al.<sup>35</sup> it was shown that in a group of children treated with or without a course of prednisone after a course of antibiotics, there was a significantly higher reduction in effusion in the steroid-treated group after 2 weeks. However after 4 weeks of treatment there was no significant difference in effusions in both groups. Hearing measurements were better in the steroid-treated group compared to the placebo group.

In another study by Lambert<sup>36</sup> which compared the effects of prednisone and placebo in a group of children with OME, no significant difference in hearing recovery was found between the groups.

Intranasal GCS have also been investigated in patients with OME. Tracy et al.<sup>37</sup> studied a group of children with OME treated with antibiotics alone or intranasal GCS combined with antibiotics. They reported an improvement in resolution of the effusions at 4 and 8

weeks in the combined group, but no difference at 12 weeks.

A systematic review on the role of GCS in OME concluded that oral or intranasal GCS led to a faster resolution of effusions in OME but the long-term results are the same with or without GCS.<sup>38,39</sup>

Results have been similar in patients with OME with and without AR.<sup>39</sup>

In conclusion the balance of evidence does not support the use of GCS in patients with OME. This applies to both patients with and without AR.

### **Declaration of conflict of interest**

The author declares no conflict of interest.

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