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Therapeutic effect of capsaicin nasal treatment in patients with mixed rhinitis unresponsive to intranasal steroids.

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Short title: Capsaicin nasal treatment in patients with mixed rhinitis

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Keywords: capsaicin treatment, idiopathic rhinitis, non-allergic rhinitis, mixed rhinitis, nasal hyperreactivity

Summary: Capsaicin nasal spray is effective in a broader group of idiopathic rhinitis (IR) patients than the strictly selected ones as described before (Van Gerven et al., JACI 2014 and 2017). The time interval of patients seeking a second treatment is shorter in mixed rhinitis patients than in strictly selected IR patients.

Abbreviations:

HC: healthy controls

INS: intranasal steroids

IR: idiopathic rhinitis

MR: mixed rhinitis

NAR: non-allergic rhinitis

NANIR: non-allergic non-infectious rhinitis

NHR: nasal hyperreactivity

SPT: skin prick test

TRE: therapeutic response evaluation

TRPV1: transient receptor potential cation channel subfamily V, receptor 1

Therapeutic response of capsaicin nasal treatment in patients with mixed rhinitis unresponsive to intranasal steroids.

Abstract:

Literature is convincing regarding the efficacy of capsaicin nasal treatment in idiopathic rhinitis (IR). However, up to 50% of IR patients do not meet the strict inclusion criteria of the trials conducted so far. As a consequence, the efficacy of capsaicin is unknown in a significant number of IR patients that do not meet the strict inclusion/exclusion criteria (1)(2). 'Mixed rhinitis' (MR) patients have more than one major etiologic factor involved in the mucosal pathology. We have no idea about the efficacy of capsaicin nasal spray in these patients nor about the time interval to seek a second application. We report here that capsaicin nasal spray is effective in a broader group of IR than the purely selected ones described before, that subjective nasal hyperreactivity is a good predictor of positive outcome and that the time interval for seeking a second treatment is likely to be shorter in MR patients than in the strictly selected IR patients.

Text:

At present, multiple studies have reported on the efficacy of capsaicin nasal treatment in idiopathic rhinitis (IR), with moderate to total symptom relief in up to 70-80% of patients (3)(4)(5)(6)(7). We reported on the molecular mechanisms underlying the efficacy of capsaicin nasal treatment, providing the first evidence for a reduction of nasal hyperreactivity (NHR) and reduced expression of the nociceptive cation channel TRPV1 in IR by capsaicin (1). More recently, we could demonstrate electrophysiological evidence for an increased

chemical sensitivity in IR patients compared to healthy controls. The enhanced chemical sensitivity in IR was decreased by capsaicin treatment, along with a reduction of self-reported NHR and nasal symptoms (2).

Idiopathic rhinitis is a subgroup of non-infectious, non-allergic rhinitis (NANIR) for which no clear international definition is available (8). NANIR involves a heterogeneous group of patients suffering of persistent rhinitis without clinical signs of infection (discolored secretions) and without systemic signs of allergic inflammation (allergen-specific IgE in blood and/or positive SPT results). This group is often defined in short as non-allergic rhinitis (NAR)(8). Other subgroups of NAR can be defined by thorough patient history and include drug-induced rhinitis, rhinitis of the elderly, hormonal rhinitis, occupational rhinitis and gustatory rhinitis.

All previously included IR patients met strict criteria: age between 18 and 60 y, non-smoking, negative skin prick tests (SPT) for the 18 most frequent regional airborne allergens, no clinical sign of endonasal infection or anatomical nasal deformity, no present/past history of chronic rhinosinusitis with/without nasal polyps, and self-reported unresponsiveness to intranasal steroids (INS) with a minimal duration of proper treatment for 4 w (1)(2). In clinical practice however, a significant portion (up to 50%) of IR patients do not meet the criteria of the 'strictly selected IR' population and are not included in the reported trials (1)(2). These patients are often defined as 'mixed rhinitis' patients (MR), as the treating physician considers that more than one etiologic factor is involved in the rhinitis phenotype (9)(10).

As we need insight into the efficacy of capsaicin nasal treatment in everyday clinical practice, we here report on a prospective comparison in efficacy between the strictly-selected IR patients that participated into the trial (N=28) and those IR patients (N=24) that did not meet these inclusion criteria due to *age* (≥ 60 y) (25%), *smoking* (4%), *a positive skin prick test to clinically irrelevant allergens e.g; birch pollen allergy but symptoms all year long* (42%; 30% monosensitized, 70% polysensitized), *an anatomical deformity* (17%; 2 patients with septal perforation, 1 with a mild septal deviation and 1 with a nasal valve problem) and/ or an occasional episode of acute *rhinosinusitis* (13%).

We compared the patient characteristics between the strictly selected IR patients (N=28) and MR patients (N= 24) as shown in Table 1. All patients were non-responsive to INS. Patients were evaluated for the presence of NHR, which was defined as the induction of nasal symptoms by exposure to changes in temperature and humidity, strong odors and/or other irritants that lasted for at least 5 minutes (11). We found NHR to be key feature for both IR patient populations as it was present in 89% and 75% of the patients of the strictly-selected IR group and the MR group, respectively. Notably, 46% percent of the strictly-selected IR patients and 45% of the MR patients underwent nasal surgery in the past because of minor anatomical abnormalities (mainly septoplasty and/or reduction of the inferior turbinates). However, the surgical corrections had no influence on the rhinitis symptoms, reflecting the unmet therapeutic need for these patients.

All patients were treated with capsaicin 0.1 mM nasal spray as described previously (1)(6) and the therapeutic response, defined as self-reported symptom reduction, was evaluated at 12 w after treatment. In brief, all MR patients were treated with capsaicin 0.1 mM nasal spray 5 consecutive times on a single day with 1 hour intervals (2 puffs in each nostril, 0.4 ml/puff). The nasal mucosa was anaesthetized prior to the first 2 applications by cocaine 5% nasal spray. To ensure effective local anaesthesia, an interval of 15 minutes was

maintained between the cocaine and capsaicin application. The therapeutic response evaluation (TRE) was quantified according to the following criteria: no improvement (0% symptom relief), minor improvement (>0 - $<30\%$ symptom relief), moderate improvement (≥ 30 - $<60\%$ symptom relief), major improvement (≥ 60 - $<100\%$), symptom-free (100% symptom reduction). Patients had to fill in the TRE at the consultation at 12 w after treatment. The distribution of patients towards reduction of the symptoms was less favorable for the MR population compared to the IR (Figure 1A and B). However, 68% of the MR patients showed a therapeutic response, which is slightly lower, but not statistically significantly different than for the strictly-selected IR patients (Fisher's exact test) (79%). Thirty-two percent of MR patients reported a major symptom reduction. Interestingly, as suggested recently (2), the presence of NHR seemed to be a good predictor for the success of capsaicin treatment. Mixed rhinitis patients with self-reported NHR had significant better TREs compared to the patients with no NHR ($P = 0.039$).

Moreover, patients were instructed to attend the outpatient clinic when symptoms recurred in a sufficient degree in order to justify a second treatment with capsaicin. In the strictly-selected IR population, 25% underwent a second treatment after a mean interval of 14 m (range: 4-29 m), while 29% of MR patients sought a second treatment after a mean interval of 7 m (range: 3-12 m). We hypothesize that the interval for seeking a second treatment correlates with the time needed for re-innervation and TRPV1 expression on afferent nerves (1). Thus, the shorter interval in the MR cohort might reflect the contribution of other etiologic factors such as intermittent infection or additional seasonal allergy, old age and smoking to the pathology. Of note, 75% of IR patients do not seek a second treatment, probably related to a multitude of reasons.

We here report on the efficacy of capsaicin 0.1 mM nasal spray in MR patients. The limitations of this short communication are the fact that the treatment is not placebo-controlled and that only a limited amount of outcome parameters are available. Both are the direct consequence of the fact that the MR patients were actually "excluded" from other trials and were not the subject of a proper trial design as such. However, this brings us directly to the major strength of these data; the evaluation of this well-defined drug in a more "real-world" clinically relevant environment. Another shortcoming on this topic is the lack of consensus in literature on the definition of both IR and MR which makes it difficult to compare results between studies and to draw firm conclusions.

In conclusion, the capsaicin nasal spray is effective in a broader group of IR than the purely selected ones described before (1)(2). The subjective NHR is a good predictor for the chance of success of capsaicin treatment. The time interval for seeking a second treatment is likely to be shorter in MR patients than in strictly selected IR patients.

Accepted Article

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Legends:

Table 1: Patient characteristics.

Figure 1: Therapeutic response evaluation (TRE) at 12 weeks after capsaicin treatment in strictly selected IR patients (n=28) (A) and mixed rhinitis patients (n=24) (B).

Table 1. Patient Characteristics.

Patient Characteristics	Strictly selected IR patients (N = 28)	Mixed rhinitis patients (N= 24)
Average age (range)	41 y (21 y- 60 y)	53 y (24 y- 83 y)
Age > 60 y	0%	25% (N = 6)
Gender (M)	50% (N = 14)	67 % (N = 16)
Non-responsive to INS	100% (N = 28)	100% (N = 24)
Smokers	0%	4% (N = 1)
Allergy (+ SPT)	0%	42% (N = 10)
Infection (NE)	0%	13% (N = 3)
Concomitant nasal anatomical deformities	0%	17% (N = 4)
Previous nasal surgery	46% (N = 13)	46% (N = 11)
Subjective NHR	89% (N = 25)	75% (N = 18)
Major symptom	50% nasal obstruction (N = 14) 43% rhinorrhea (N = 12) 7 % sneezing (N = 2)	42% nasal obstruction (N = 10) 50% rhinorrhea (N = 12) 8% itch (N = 2)

