

The effects of mometasone furoate and strontium chloride in a rat model of allergic rhinitis

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Abstract

Neurogenic inflammation plays a role in the pathophysiology of allergic rhinitis. Highly effective in reducing the sensory irritation caused by some substances, strontium salts directly affect C-type nerve fibers. The aim of this study was to compare the efficacy of mometasone furoate and strontium chloride on early-phase symptoms in a rat model of allergic rhinitis. Wistar albino rats ($n = 24$) were randomly divided into three groups: the mometasone group, receiving 1 μg mometasone furoate (2 $\mu\text{l}/\text{site}$); the strontium 3% group, receiving 3% strontium chloride (2 $\mu\text{l}/\text{site}$); and the strontium 5% group, receiving 5% strontium chloride (2 $\mu\text{l}/\text{site}$). To induce significant nasal symptoms of allergic rhinitis, 5 μmol of histamine dihydrochloride (HDC) (2 $\mu\text{l}/\text{site}$) was administered. Symptoms of allergic rhinitis were recorded as frequencies of sneezing and nasal rubbing during a 15-minute interval. On days 1 and 2, respectively, 0.9% sodium chloride (NaCl) (2 $\mu\text{l}/\text{site}$ to each nasal cavity) and HDC were administered in all of the study groups. On days 3 and 4, the study drugs were administered 10 and 30 minutes before the administration of HDC. On day 5, the study drugs were administered 10 minutes after the administration of HDC. The results of the present study revealed that when strontium chloride or mometasone furoate was administered 30 minutes before the onset of symptoms, a significant decrease was observed in sneezing and nasal rubbing. The number of sneezing occurrences was significantly lower and the number of nasal rubbing occurrences was higher in the strontium 3% group compared to the groups in which mometasone fu-

roate and 5% strontium chloride were administered after onset of symptoms. Recent studies have investigated the efficacy and safety of strontium chloride nasal drops compared with common pharmacologic treatments of allergic rhinitis. These studies have revealed that allergic rhinitis can be successfully and safely treated with strontium-chloride-containing products, thus offering a potential new treatment strategy.

Introduction

Allergic rhinitis (AR) is clinically characterized by the symptoms caused by immunologically mediated (most often IgE-dependent) inflammation after exposure of the nasal mucous membranes to offending allergens.¹ Allergic reactions developing in AR patients exposed to allergens have two patterns based on time sequence. The first pattern is the *early reaction*, when sneezing and rhinorrhea develop within 30 minutes and disappear. The other pattern is the *late reaction*, when nasal obstruction occurs approximately 6 hours after exposure to allergens and subsides slowly.

The early reaction is the response of mast cells to the offending allergens. Nasal symptoms are induced by stimulated mast cells through secretion of chemical mediators such as histamine, prostaglandins, and leukotrienes. These neurotransmitters play an important role in the pathogenesis of AR through vasodilation and cell aggregation by causing an increase in secretion and changes in smooth-muscle tone.²

When cytotoxic proteins are released from eosinophils, they destroy respiratory epithelium and cause nerve endings to be exposed. Thus, sensory nerve fibers are excited by nonspecific stimuli, and both sensory afferent and surrounding efferent fibers are stimulated. This is called a *retrograde axonal reflex*, which results in secretion of neuropeptides such as substance P and neurokinin A from the sensory nerve fibers, as well as

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contraction of smooth muscles, mucous secretion by goblet cells, and plasma exudation from capillaries. This process is called *neurogenic inflammation*.^{3,4}

It is known that neurogenic inflammation plays a role in the pathophysiology of AR and thus, despite their well-known side effects, intranasal corticosteroids are the indispensable first-line treatments because of their anti-inflammatory effects.⁵

In 1999, Hahn reported that strontium salts are highly effective in reducing the sensory irritation caused by some substances and hypothesized that strontium salts directly affect C-type nerve fibers.⁶ When we completed a literature review, we found no study on the use of strontium chloride in the treatment of AR. The aim of the present study was to compare the efficacy of mometasone furoate and strontium chloride on early-phase symptoms of AR in a rat model.

Materials and methods

Ethical considerations. The experiments were carried out according to the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23, revised 1996). The study protocol was approved by the Institutional Review Board and Local Ethics Committee for Animal Experiments of Cumhuriyet University School of Medicine.

Experimental animals. In this study, a randomized experimental protocol was used. The study was conducted with 24 male Wistar albino rats that were 16 to 18 weeks old and had an average body weight of 220 to 240 g. The rats were fed with standard pellet chow and water *ad libitum* under standard laboratory conditions (12 h light/dark cycles, $24 \pm 2^\circ\text{C}$, and 35 to 60% humidity).

The rats were randomly divided into three groups: the mometasone group ($n = 8$), receiving 1 μg mometasone furoate (2 $\mu\text{l}/\text{site}$); the strontium 3% group ($n = 8$), receiving 3% strontium chloride (2 $\mu\text{l}/\text{site}$); and the strontium 5% group ($n = 8$), receiving 5% strontium chloride (2 $\mu\text{l}/\text{site}$).

Drugs and chemicals. Histamine dihydrochloride (HDC), a positive control medication known to cause allergic symptoms, and strontium chloride were obtained from Sigma Chemical Co. (St. Louis, Mo.). These reagents were dissolved in saline. Sodium chloride (NaCl) 0.9% (a negative control agent known not to cause allergic symptoms) was purchased from Delta Vital (Istanbul), and mometasone furoate (Nasonex Aqueous Nasal Spray) was purchased from Schering-Plough (Kenilworth, N.J.). The purity of all chemical reagents was at least analytical grade. Drugs were administered

in a volume of 2 μl to each nasal cavity of the rats with a micropipette.

Evaluation of the nasal symptoms in rats and the experimental procedure. The mouse AR model of Kusaka et al.⁷ was used as a basis for our study. In our study, which was conducted in rats for the first time, it was shown that the administration of 5 μmol HDC (2 μl site) elicited significant nasal symptoms, such as sneezing and nasal rubbing.

Before the experiment was started, each rat was kept in an observation cage for 10 minutes for adaptation to the environment. After this adaptation process, drug applications were made. In every step of the experiment, nasal symptoms in the rats (sneezing and nasal rubbing) were counted for 15 minutes. On all days of the experiment, the method described above was followed.

On the first day of the experiment, 2 μl of 0.9% NaCl was administered via micropipette to each nasal passage of every rat, and nasal symptoms were counted and recorded. On the second day of the experiment, 5 μmol HDC (2 $\mu\text{l}/\text{site}$) was administered via micropipette to each nasal passage of each rat and, again, nasal symptoms were counted. Symptoms occurring on the first and second days of the experiment were compared statistically, and it was shown that the rat model we developed was comparable to the mouse AR model of Kusaka et al.⁷ Then the test protocol was started.

To determine how the drugs would affect nasal symptoms when applied before contact with allergen, the mometasone group was given mometasone furoate (1 $\mu\text{g}/\text{site}$) 10 minutes before the administration of HDC on day 3 of the experiment, and 30 minutes before the administration of HDC on day 4; nasal symptoms of every rat were counted and recorded. Strontium chloride 3% (2 $\mu\text{l}/\text{site}$) and strontium chloride 5% (2 $\mu\text{l}/\text{site}$) were administered to the strontium 3% group and the strontium 5% group, respectively, before the administration of HDC. Nasal symptoms of every rat were counted and recorded.

To assess the effect of medication on the nasal symptoms after the rats' nasal passages were exposed to HDC, the drugs, at above-mentioned doses, were administered again on day 5, 10 minutes after the administration of HDC (2 μl , 5 $\mu\text{mol}/\text{site}$), and nasal symptoms were counted and recorded once more.

At the end of the experiment, all the rats were euthanized with sodium thiopental.

Statistical analysis. The data were analyzed using the Statistical Package for Social Sciences for Windows v. 14.0 (SPSS, Inc.; Chicago). To evaluate the data, the univariate chi-square test and McNemar test were used. Level of significance was set at $p < 0.05$.

Results

Days 1 and 2. The results related to the frequency of sneezing and nasal rubbing on the first and second days of the experiment were as follows: When nasal symptoms were counted for 15 minutes after the administration of 0.9% NaCl, the values of nasal rubbing showed a statistically significant difference between the mometasone group and the strontium 3% group and between the strontium 3% group and the strontium 5% group ($\chi^2 = 15.57$, $p = 0.001$; $p < 0.05$). This difference was associated with the fact that the frequency of nasal rubbing was higher in the mometasone group than in the strontium 3% and 5% groups.

When the groups were compared in terms of sneezing frequency after the administration of HDC, sneezing frequency showed no statistically significant difference ($\chi^2 = 1.94$, $p = 0.379$; $p > 0.05$). There was a statistically significant difference between the mometasone group and the strontium 3% group and between the mometasone group and the strontium 5% group in terms of frequency of nasal rubbing ($\chi^2 = 8.71$, $p = 0.013$; $p < 0.05$). This difference, which emerged when the groups were evaluated after the administration of HDC, was associated with a low frequency of nasal rubbing in the mometasone group.

When the groups were compared in terms of symptoms after 0.9% NaCl nasal spray and HDC, there was a statistically significant difference (table 1). Consequently, these results show that HDC elicits allergy-like symptoms in mice and rats.

The statistically significant differences in the number of symptoms such as nasal rubbing and sneezing showed that the Kusaka et al mouse experimental model⁷ was suitable for rats. After the appropriateness of the experimental model was established, the results obtained on days 3, 4, and 5 of the experiment are given below.

Day 3. Changes in symptoms were caused by HDC 10 minutes after administration. When the groups were compared in terms of the frequency of nasal rubbing before the administration of HDC, the results were not statistically significant ($\chi^2 = 5.87$, $p = 0.053$; $p > 0.05$).

When the groups were compared in terms of sneezing frequency after the administration of HDC, the difference was statistically significant ($\chi^2 = 19.91$, $p = 0.001$; $p < 0.05$). This difference was associated with the fact that sneezing frequency in rats in the mometasone group was lower than in the other groups. There was no statistical significant difference in sneezing frequency in rats in the strontium 3% and 5% groups.

Similarly, when the groups were compared in terms of the frequency of nasal rubbing after the administration of HDC, a statistically significant difference was determined between the groups ($\chi^2 = 12.68$, $p = 0.002$; $p < 0.05$). This statistical difference was associated with the fact that frequency of nasal rubbing was lower in mometasone group than in the other groups; there was no statistically significant difference in nasal rubbing in rats in the strontium 3% and 5% groups.

Within-group comparisons carried out in terms of sneezing frequency before and after the administration of HDC revealed statistically significant differences in the mometasone group ($p < 0.001$), the strontium 3% group ($p < 0.001$), and the strontium 5% group ($p < 0.001$). This difference was caused by the increase in sneezing frequency in all groups after the administration of HDC.

Within-group comparisons carried out in terms of the frequency of nasal rubbing before and after the administration of HDC revealed statistically significant differences in the mometasone group ($p < 0.001$), and the strontium 3% ($p < 0.001$) and the strontium 5% group ($p < 0.001$) (table 2). This difference was caused by the increase in nasal rubbing in all groups after the administration of HDC.

Day 4. When the changes in nasal symptoms caused by HDC 30 minutes after the medication was administered were evaluated, the results were as follows: When the groups were compared in terms of the frequency of nasal rubbing before the administration of HDC, the results were not statistically significant ($\chi^2 = 6.17$, $p = 0.124$; $p > 0.05$). When the groups were compared in terms of sneezing frequency after the administration of HDC, the differences between the mometasone group and the

strontium 3% group and between the mometasone group and the strontium 5% group were statistically significant ($\chi^2 = 6.33$, $p = 0.0042$; $p < 0.05$). These differences were associated with the fact that sneezing frequency was lower in mometasone group than

Table 1. Frequency of sneezing and nasal rubbing in study rats for 15 minutes after the administration of NaCl and HDC

Group	Sneezing		p Value	Nasal rubbing		p Value
	0.9% NaCl	HDC		0.9% NaCl	HDC	
Mometasone	3	58	$p = 0.001$	33	66	$p = 0.008$
Strontium 3%	1	67	$p = 0.001$	11	101	$p = 0.001$
Strontium 5%	8	74	$p = 0.001$	13	98	$p = 0.001$

Key: NaCl = sodium chloride; HDC = histamine dihydrochloride.

Table 2. Frequency of sneezing and nasal rubbing in rats that were administered the study medications 10 minutes before being administered HDC (number of times over 15 minutes)

Group	Sneezing		p Value	Nasal rubbing		p Value
	Medication	HDC		Medication	HDC	
Mometasone	0	70	$p = 0.001$	16	40	$p = 0.001$
Strontium 3%	3	134	$p = 0.001$	5	79	$p = 0.001$
Strontium 5%	3	107	$p = 0.001$	10	64	$p = 0.001$

Key: HDC = histamine dihydrochloride.

the other two groups. In terms of the sneezing frequency after the administration of HDC, there was no statistically significant difference between the strontium 3% group and the strontium 5% group. There was a statistically significant difference between the groups in terms of the frequency of nasal rubbing after the administration of HDC ($\chi^2 = 0.400$, $p = 0.819$; $p > 0.05$).

Within-group comparisons carried out in terms of the sneezing frequency before and after the administration of HDC revealed statistically significant differences in the mometasone group ($p < 0.001$), the strontium 3% group ($p < 0.001$), and the strontium 5% group ($p < 0.001$). Intragroup comparisons in terms of the frequency of nasal rubbing before and after the administration of HDC revealed statistically significant differences in the mometasone group ($p < 0.001$), the strontium 3% group ($p < 0.001$), and the strontium 5% group ($p < 0.001$) (table 3). Since the increase in frequency of nasal rubbing was lowest in the strontium 3% group compared to the other groups, it can be interpreted that the administration of strontium 3% was statistically more effective.

Comparative evaluation of the results obtained on the third and fourth days of the experiment. When all the groups were compared in terms of both the sneezing frequency and the frequency of nasal rubbing, a statistically significant difference was found ($p < 0.001$).

Day 5. When the frequencies of sneezing and nasal rubbing were counted for 30 minutes, and the changes in nasal symptoms were evaluated after administering mometasone furoate (1 µg/site) to the mometasone group, 3% strontium chloride (2 µl) to the strontium 3% group, and 5% strontium chloride (2 µl) to the strontium 5% group via the micropipette to each nasal cavity 10 minutes after the administration of HDC, the results were as follows: When the three groups were compared in terms of sneezing ($\chi^2 = 4.82$, $p = 0.089$; $p > 0.05$) and nasal rubbing ($\chi^2 = 0.27$, $p = 0.871$; $p > 0.05$) for the initial 10 minutes following the medication, 10 minutes after the administration of HDC, it was found

that the results were not statistically significant.

Evaluation of the nasal symptoms for the next 20 minutes revealed no statistically significant difference in terms of the frequency of sneezing ($\chi^2 = 4.68$, $p = 0.097$; $p > 0.05$); the difference in the frequency of nasal rubbing was significant

between the mometasone group and the strontium 3% group and between the strontium 3% group and the strontium 5% group ($\chi^2 = 11.62$, $p = 0.003$; $p < 0.05$). The lowest nasal rubbing was observed in the mometasone group. Therefore, it can be interpreted that the administration of mometasone was statistically more effective. On the other hand, there was a statistically insignificant difference between the mometasone group and the strontium 5% group.

When the three groups were compared in terms of total number of symptoms during a period of 30 minutes following administration of medication, the differences between the mometasone group and the strontium 3% group and between the strontium 3% group and the strontium 5% group were statistically significant in terms of the frequency of sneezing ($\chi^2 = 7.81$, $p = 0.020$; $p < 0.05$), whereas no statistically significant difference was found between the mometasone group and the strontium 5% group.

These results indicated that a lower frequency of sneezing was observed in rats administered 3% strontium. Therefore, it can be interpreted that the administration of strontium 3% was statistically more effective. Similarly, when the groups were compared in terms of nasal rubbing, the differences between the mometasone group and the strontium 3% group and between the strontium 3% group and the strontium 5% group were statistically significant ($\chi^2 = 7.09$, $p = 0.029$; $p < 0.05$), whereas there was not a statistically significant difference between the mometasone group and the strontium 5% group. The results indicated that a lower frequency of nasal rubbing was observed in rats administered 5% strontium. Therefore, it can be interpreted that the administration of 5% strontium was statistically more effective.

On the fifth day of experiment, when the number of sneezes during the initial 10 minutes and next 20 minutes were compared, the difference was not statistically significant in the mometasone group; on the other

Table 3. Frequency of sneezing and nasal rubbing in rats that were administered the medications 30 minutes before being administered HDC (number of times over 15 minutes)

Group	Sneezing		p Value	Nasal rubbing		p Value
	Medication	HDC		Medication	HDC	
Mometasone	4	30	$p = 0.001$	28	37	$p = 0.001$
Strontium 3%	1	52	$p = 0.001$	24	32	$p = 0.001$
Strontium 5%	0	48	$p = 0.001$	12	36	$p = 0.001$

Key: HDC = histamine dihydrochloride.

hand, a statistically significant decrease was found in the strontium 3% group and the strontium 5% group ($p < 0.001$).

A statistically significant increase or decrease was not observed during the follow-up period in the mometasone group in terms of sneezing, but a statistically significant decrease was observed in the strontium 3% and strontium 5% groups. In terms of nasal rubbing, the differences in the mometasone group and the strontium 5% group were not statistically significant; on the other hand, there was a statistically significant increase in the strontium 3% group ($p < 0.001$).

Discussion

We found in the present study that strontium chloride had comparable therapeutic efficacy to that of mometasone furoate in a rat AR model which, to the best of our knowledge, we are showing for the first time in the literature. The present study investigated the effect of strontium chloride at two concentrations (3% and 5%).

The aim of our study was to investigate whether 3% and 5% strontium chloride had an effect on early-phase reactions in AR, such as sneezing and nasal rubbing. For this purpose, we divided the test procedure into two main sections: administration of strontium chloride before onset of the symptoms and administration of strontium chloride after onset of symptoms.

There are a number of pharmacologic treatments for AR, such as oral and topical antihistamines, leukotriene receptor antagonists, intranasal glucocorticoids, and cromoglicic acid.⁸ Intranasal steroids are the gold-standard treatment for this disease, and nasal steroids are preferred in patients having persistent symptoms because they are more effective on all nasal symptoms.^{9,10}

Clinical effects of the topical steroids commonly used to control inflammation in rhinitis and sinusitis can be related to prevention of the accumulation of inflammatory cells in the airway, selective suppression of local cytokine production, inhibition of mediator release,

and structural repair of the nasal mucosa.¹¹ The topical administration of corticosteroids is an established and effective treatment for AR, but its mode of action remains unknown.¹² In general, many AR patients are still unsatisfied with the control of symptoms, complain about incom-

plete relief of symptoms, and suffer from unwanted side effects.¹³⁻¹⁵ Therefore, the increasing interest in the use of new treatment strategies for treating rhinitis is not surprising.

Neurogenic inflammation is known to have a role in the pathogenesis of AR, and strontium chloride has been shown to have a positive effect on neurogenic inflammation. Topical strontium, formulated in water-soluble salts such as chloride or nitrate, has been shown to inhibit sensory irritation^{6,16} and reduce histamine-induced itching.¹⁷

The exact mechanism underlying the antipruritic effect of strontium salts is not well understood. Due to similar size, charge, and chemical characteristics between strontium chloride and Ca^{2+} ions, strontium ions could compete with calcium for receptor binding and transport via calcium channels, which could ultimately lead to inhibition of calcium-dependent depolarization of C-type nerve fibers. Indeed, strontium ions can interact with calcium-sensing receptors (CaSR), a G-protein coupled receptor in C-type nerve fibers.¹⁸

Actions of strontium on the nervous system, especially at the level of synapse, have been reported. Strontium can substitute for calcium to trigger neurotransmitter release, and it has been employed as an experimental tool to investigate this process.¹⁹ Studies on the squid giant synapse,²⁰ neuromuscular junction,²¹⁻²⁵ and central synapses^{26,27} have shown that strontium triggers a “desynchronized” neurotransmitter release with a reduced peak and prolonged duration. Therefore, it is suggested that strontium chloride is less effective than Ca^{2+} in triggering exocytotic transmitter release.^{28,29} However, it is unclear whether the antipruritic action of strontium is mediated by effects of disrupting synaptic transmission, neurotransmitter release, or depolarization.

Itching and sneezing are two of the main bothersome symptoms of AR, in addition to nasal obstruction and rhinorrhea. Apparently, activation of the central and peripheral nervous system plays a major role in the

pathophysiology of this process. Sensory nerves of the afferent trigeminal system, including myelinated A δ fibers and thin, nonmyelinated C-type fibers transmit signals induced by the nasal mucosa based on stimulation, and they generate motor reflexes such as itching and sneezing. These nerves can be stimulated by products of allergic reactions and external physical and chemical irritants. Via axon reflex, inflammatory neuropeptides including the tachykinins, substance P, and neurokinin A, and the calcitonin-gene-related peptide are released, thus leading to vasodilatation, increased vascular permeability, glandular activation, leukocyte recruitment, and differentiation of immune cells including mast cells, eosinophils, lymphocytes, and macrophages.⁵

As size, charge, and chemical characteristics of strontium chloride and Ca^{2+} ions are similar, strontium ions may be able to compete with calcium for receptor binding and transport via calcium channels, which may ultimately lead to inhibition of calcium-dependent depolarization of C-type nerve fibers. While planning the present study, we anticipated that strontium chloride would compete with Ca^{2+} and bind to CaSR, which would in turn decrease the secretion of Substance P and the AR symptoms such as itching and sneezing.

The results of the present study showed a significant decrease in sneezing and nasal rubbing when strontium chloride or mometasone furoate was administered 30 minutes before onset of the symptoms. The sneezing was significantly lower and nasal rubbing was higher in the strontium 3% group compared to the mometasone group and the strontium 5% group.

The efficacy of strontium salts (strontium ranelate) for preventing fracture in osteoporosis is well established. According to current knowledge, strontium ranelate is an appropriate treatment for patients without ischemic heart disease, peripheral arterial disease, and/or cerebrovascular disease, uncontrolled hypertension, or a history of these diseases.³⁰ Further studies on the safe use of the other strontium salts (e.g., strontium chloride) are required.

It is thought that when administered before onset of symptoms, the efficacy of strontium chloride is greater, with an action equal to that of mometasone furoate; on the other hand, treatment with 5% strontium chloride implemented after onset of the symptoms had results similar to those of mometasone furoate, and it would not be appropriate to comment on why 3% strontium chloride, which was more efficacious on sneezing compared to mometasone furoate, had an insufficient effect on nasal rubbing without conducting histochemical studies. There are two questions:

1. *As strontium chloride is as efficacious as mometasone furoate when administered before onset of the symptoms, would the efficacy of strontium chloride change with longer-term administration?*

2. *Is the reason that 3% strontium chloride administered after onset of the symptoms is not as effective as 5% strontium chloride on nasal rubbing associated with the dose differences?*

Results from this rat model suggest that strontium chloride may provide symptomatic relief during the management of allergic rhinitis, which warrants further investigation. However, we believe that the histochemical changes, side effects, the amount entering the systemic circulation, optimum administration dose, and duration and efficacy of long-term strontium chloride administration should be investigated in future studies. For this reason, we plan to compare the long-term use of strontium chloride and its dose-dependent efficacy.

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