

Ratio of Sodium to Potassium Affects CV Risk

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COLORADO SPRINGS — The dietary intake ratio of sodium to potassium bears a much stronger association with subsequent development of cardiovascular disease than does consumption of either alone, according to new findings from the Trials of Hypertension Followup (TOPH) Study.

“We found that sodium and potassium

may have a joint effect on the development of cardiovascular disease, in keeping with a proposed biologic symmetry. In our data the ratio was the most important predictor,” Nancy R. Cook, Sc.D., reported at a conference of the American Heart Association.

She presented a 10- to 15-year follow-up of 2,275 participants in TOPH-I and -II, a pair of National Institutes of Health-sponsored randomized clinical trials of sodium reduction and other in-

terventions aimed at preventing hypertension in individuals who were prehypertensive at baseline.

There were 193 cardiovascular events—acute MI, stroke, revascularization procedures, or cardiovascular death—during follow-up.

A key feature of both studies was the periodic collection of 24-hour urine sodium and potassium excretions over several years.

“Most observational studies have had an

imperfect measure of exposure. It's very difficult to capture sodium on a food-frequency questionnaire because it's so much affected by what you add at the table or what's in processed food products. It really varies by product and brand. Also, a single urinary excretion may not reflect usual intake over a longer period of time,” noted Dr. Cook of Brigham and Women's Hospital, Boston, and the Harvard School of Public Health.

In the TOPH follow-up analysis, there was a significant, linear relationship with cardiovascular risk from lowest to highest quartile of the sodium to potassium excretion ratio.

After full statistical adjustment for numerous variables, including demographics, alcohol intake, body weight, physical activity, smoking status, and changes in those variables over the course of the study, individuals in the highest quartile of sodium to potassium ratio had a highly significant 50% increased risk

Individuals in the highest quartile of sodium to potassium ratio had a highly significant 50% increased risk of a cardiovascular event during follow-up.

of a cardiovascular event occurring during follow-up, compared with the patients in the lowest quartile.

For each unit increase in sodium to potassium ratio, future cardiovascular risk rose by 24%, she added.

The mean ratio was 2.9 in

both men and women in the study population as a whole. But it differed modestly by age and more profoundly by race. Black participants had lower potassium excretion levels than whites, leading to a much higher sodium to potassium ratio of 3.4.

Considered separately, neither sodium nor potassium excretion alone was significantly related to cardiovascular risk across quartiles.

Audience member Dr. Francesco P. Cappuccio observed that most of the Western world is now moving toward a generalized reduction in sodium intake at a population level in order to prevent cardiovascular disease. But the new TOPH analysis suggests an alternative approach may be better.

“Should we be looking into the use of salt substitutes in which sodium chloride is replaced by potassium in order to convey more cardiovascular protection? We know that increasing potassium intake through dietary means alone—eating more fruits and vegetables—is as hard as decreasing the salt in processed food,” said Dr. Cappuccio, professor of clinical sciences at Warwick Medical School, Coventry, England.

Dr. Cook replied that such an approach “would certainly be compatible” with the TOPH findings.

She noted that a small trial in Taiwan has demonstrated decreased cardiovascular mortality with the use of a potassium-based salt substitute, compared with ordinary table salt. ■

OMNARIS™ (ciclesonide)

Nasal Spray, 50 mcg

For intranasal use only

Rx only

BRIEF SUMMARY: Please see package insert for full prescribing information.

INDICATIONS AND USAGE

Seasonal Allergic Rhinitis

OMNARIS Nasal Spray is indicated for the treatment of nasal symptoms associated with seasonal allergic rhinitis in adults and children 6 years of age and older.

Perennial Allergic Rhinitis

OMNARIS Nasal Spray is indicated for the treatment of nasal symptoms associated with perennial allergic rhinitis in adults and adolescents 12 years of age and older.

CONTRAINDICATIONS

OMNARIS Nasal Spray is contraindicated in patients with a hypersensitivity to any of its ingredients.

WARNINGS

The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency. In addition, some patients may experience symptoms of corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticosteroids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, rapid decreases in systemic corticosteroid dosages may cause a severe exacerbation of their symptoms.

Patients who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in children or adults using corticosteroids. In children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

PRECAUTIONS

General

Intranasal corticosteroids may cause a reduction in growth velocity when administered to pediatric patients (see PRECAUTIONS: Pediatric Use). Rarely, immediate hypersensitivity reactions or contact dermatitis may occur after the administration of intranasal corticosteroids. Patients with a known hypersensitivity reaction to other corticosteroid preparations should use caution when using ciclesonide nasal spray since cross reactivity to other corticosteroids including ciclesonide may also occur.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or nasal trauma should not use a nasal corticosteroid until healing has occurred. In clinical studies with OMNARIS Nasal Spray, the development of localized infections of the nose and pharynx with *Candida albicans* has rarely occurred. When such an infection develops, it may require treatment with appropriate local therapy and discontinuation of OMNARIS Nasal Spray. Therefore, patients using OMNARIS Nasal Spray over several months or longer should be examined periodically for evidence of *Candida* infection or other signs of adverse effects on the nasal mucosa. Intranasal corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract, or in patients with untreated local or systemic fungal or bacterial infections; systemic viral or parasitic infections; or ocular herpes simplex.

If recommended doses of intranasal corticosteroids are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic steroid therapy, symptoms of hypercorticism may occur, including very rare cases of menstrual irregularities, acneiform lesions, and cushingoid features. If such changes occur, topical corticosteroids should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

The risk of glaucoma was evaluated by assessments of intraocular pressure in 3 studies including 943 patients. Of these, 390 adolescents or adults were treated for up to 52 weeks and 186 children ages 2 to 11 received treatment with OMNARIS Nasal Spray 200 mcg daily for up to 12 weeks. In these trials, no significant differences in intraocular pressure changes were observed between OMNARIS Nasal Spray 200 mcg and placebo-treated patients. Additionally, no significant differences between OMNARIS Nasal Spray 200 mcg and placebo-treated patients were noted during the 52-week study of adults and adolescent patients in whom thorough ophthalmologic assessments were performed including evaluation of cataract formation using slit lamp examinations. Rare instances of wheezing, nasal septum perforation, cataracts, glaucoma, and increased intraocular pressure have been reported following the intranasal application of corticosteroids. Close follow-up is warranted in patients with a change in vision and with a history of glaucoma and/or cataracts.

Information for Patients

Patients being treated with OMNARIS Nasal Spray should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Patients who are on immunosuppressive doses of corticosteroids should be warned to avoid exposure to chickenpox or measles, and if exposed, to obtain medical advice. Patients should use OMNARIS Nasal Spray at regular intervals since its effectiveness depends on its regular use (see DOSAGE AND ADMINISTRATION). In clinical trials, the onset of effect was seen within 24 to 48 hours with further symptomatic improvement observed over 1 to 2 weeks in seasonal allergic rhinitis and 5 weeks in perennial allergic rhinitis. Initial assessment of response should be made during this timeframe and periodically until the patients symptoms are stabilized.

The patient should take the medication as directed and should not exceed the prescribed dosage. The patient should contact the physician if symptoms do not improve by a reasonable time or if the condition worsens. For the proper use of this unit and to attain maximum improvement, the patients should read and follow the accompanying patient instructions carefully. Spraying OMNARIS Nasal Spray directly into the eyes or onto the nasal septum should be avoided. It is important that the bottle is gently shaken prior to use to ensure that a consistent amount is dispensed per actuation. The bottle should be discarded after 120 actuations following initial priming or after 4 months after the bottle is removed from the foil pouch, whichever occurs first.

Drug Interactions

Based on *in vitro* studies in human liver microsomes, des-ciclesonide appears to have no inhibitory or induction potential on the metabolism of other drugs metabolized by CYP 450 enzymes. The inhibitory potential of ciclesonide on CYP450 isoenzymes has not been studied. *In vitro* studies demonstrated that the plasma protein binding of des-ciclesonide was not affected by warfarin or salicylic acid, indicating no potential for protein binding-based drug interactions.

In a drug interaction study, co-administration of orally inhaled ciclesonide and oral erythromycin, an inhibitor of cytochrome P450 3A4, had no effect on the pharmacokinetics of either des-ciclesonide or erythromycin. In another drug interaction study, co-administration of orally inhaled ciclesonide and oral ketoconazole, a potent inhibitor of cytochrome P450 3A4, increased the exposure (AUC) of des-ciclesonide by approximately 3.6-fold at steady state, while levels of ciclesonide remained unchanged. Therefore, ketoconazole should be administered with caution with intranasal ciclesonide.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Ciclesonide demonstrated no carcinogenic potential in a study of oral doses up to 900 mcg/kg (approximately 20 and 10 times the maximum human daily intranasal dose in adults and children, respectively, based on mcg/m²) in mice for 104 weeks and in a study of inhalation doses up to 193 mcg/kg (approximately 8 and 5 times the maximum human daily intranasal dose in adults and children, respectively, based on mcg/m²) in rats for 104 weeks. Ciclesonide was not mutagenic in an Ames test or in a forward mutation assay and was not clastogenic in a human lymphocyte assay or in an *in vitro* micronucleus test. However, ciclesonide was clastogenic in the *in vivo* mouse micronucleus test. The concurrent reference corticosteroid (dexamethasone) in this study showed similar findings. No evidence of impairment of fertility was observed in a reproductive study conducted in male and female rats both dosed orally up to

900 mcg/kg/day (approximately 35 times the maximum human daily intranasal dose in adults based on mcg/m²).

Pregnancy: Teratogenic Effects

Pregnancy Category C

Oral administration of ciclesonide in rats up to 900 mcg/kg (approximately 35 times the maximum human daily intranasal dose in adults based on mcg/m²) produced no teratogenicity or other fetal effects. However, subcutaneous administration of ciclesonide in rabbits at 5 mcg/kg (less than the maximum human daily intranasal dose in adults based on mcg/m²) or greater produced fetal toxicity. This included fetal loss, reduced fetal weight, cleft palate, skeletal abnormalities including incomplete ossifications, and skin effects. No toxicity was observed at 1 mcg/kg (less than the maximum human daily intranasal dose based on mcg/m²).

There are no adequate and well-controlled studies in pregnant women. OMNARIS Nasal Spray, like other corticosteroids, should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Nonteratogenic Effects

Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

Nursing Mothers

It is not known if ciclesonide is excreted in human milk. However, other corticosteroids are excreted in human milk. In a study with lactating rats, minimal but detectable levels of ciclesonide were recovered in milk. Caution should be used when OMNARIS Nasal Spray is administered to nursing women.

Pediatric Use

The safety and effectiveness for seasonal and perennial allergic rhinitis in children 12 years of age and older have been established. The efficacy of OMNARIS Nasal Spray in patients 6 to 11 years of age for treatment of the symptoms of seasonal allergic rhinitis is supported by evidence from four adequate and well-controlled studies in adults and adolescents 12 years of age and older with seasonal and perennial allergic rhinitis, and one study in patients 6 to 11 years of age with seasonal allergic rhinitis. The efficacy of OMNARIS Nasal Spray for the treatment of the symptoms of perennial allergic rhinitis in patients 6 to 11 years of age has not been established (see CLINICAL TRIALS: Pediatric Patients Aged 6 to 11 Years). The efficacy of OMNARIS Nasal Spray in children 2 to 5 years of age has not been established. The safety of OMNARIS Nasal Spray in children 2 to 11 years of age was evaluated in 4 controlled clinical studies of 2 to 12 weeks duration (see CLINICAL PHARMACOLOGY: Pharmacodynamics, CLINICAL TRIALS, ADVERSE REACTIONS: Pediatric Patients).

Clinical studies in children less than two years of age have not been conducted. Studies in children under 2 years of age are waived because of local and systemic safety concerns.

Controlled clinical studies have shown that intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA)-axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA-axis function. The long-term effects of this reduction in growth velocity associated with intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for “catch-up” growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids, including OMNARIS Nasal Spray, should be monitored routinely (e.g., via stadiometry). The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of safe and effective noncorticosteroid treatment alternatives. To minimize the systemic effects of intranasal corticosteroids, each patient should be titrated to the lowest dose that effectively controls his/her symptoms.

Geriatric Use

Clinical studies of OMNARIS Nasal Spray did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Adult and Adolescent Patients Aged 12 Years and Older:

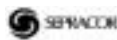
In controlled clinical studies conducted in the US and Canada, a total of 1524 patients ages 12 years and older received treatment with ciclesonide administered intranasally. The overall incidence of adverse events for patients treated with OMNARIS Nasal Spray was comparable to that in patients treated with placebo. Adverse events did not differ appreciably based on age, gender, or race. Approximately 2% of patients treated with OMNARIS Nasal Spray 200 mcg in clinical trials discontinued because of adverse events; this rate was similar for patients treated with placebo. Adverse events, irrespective of drug relationship, that occurred with an incidence of 2% or greater and more frequently with OMNARIS Nasal Spray 200 mcg (N = 546) than with placebo (N = 544) in clinical trials of 2 to 6 weeks in duration included headache (6.0% vs 4.6%), epistaxis (4.9% vs 2.9%), nasopharyngitis (3.7% vs 3.3%), and ear pain (2.2% vs 0.6%). In a 52-week long-term safety trial that included 663 adults and adolescent patients (441 treated with ciclesonide: 227 males and 436 females) with perennial allergic rhinitis, the adverse event profile over the treatment period was similar to the adverse event profile in trials of shorter duration. Adverse events considered likely or definitely related to OMNARIS Nasal Spray that were reported at an incidence of 1% or greater of patients and more commonly in OMNARIS Nasal Spray versus placebo were epistaxis, nasal discomfort, and headache. No patient experienced a nasal septal perforation or nasal ulcer during long-term use of OMNARIS Nasal Spray. While primarily designed to assess the long-term safety of OMNARIS Nasal Spray 200 mcg once daily, this 52-week trial demonstrated greater decreases in total nasal symptom scores with OMNARIS Nasal Spray versus placebo treated patients over the entire treatment period.

Pediatric Patients Aged 6 to 11 Years:

Two controlled clinical studies 2 and 12 weeks in duration were conducted in the US and Canada and included a total of 1282 patients with allergic rhinitis ages 6 to 11 years, of which 913 were treated with OMNARIS (ciclesonide) Nasal Spray 200 mcg, 100 mcg, or 25 mcg daily. The overall incidence of adverse events for patients treated with OMNARIS Nasal Spray was comparable to that in patients treated with placebo. Adverse events did not differ appreciably based on age, gender, or race. In clinical trials, 1.6% and 2.7% of patients treated with OMNARIS Nasal Spray 200 mcg or 100 mcg, respectively, discontinued because of adverse events; these rates were lower than the rate in patients treated with placebo (2.8%). Adverse events, irrespective of drug relationship, that occurred with an incidence of 3% or greater and more frequently with OMNARIS Nasal Spray 200 mcg (N = 380) than with placebo (N = 369) included headache (6.6% vs 5.7%), nasopharyngitis (6.6% vs 5.4%), and pharyngolaryngeal pain (3.4% vs 3.3%).

Pediatric Patients Aged 2 to 5 Years:

Two controlled clinical studies 6 and 12 weeks in duration were conducted in the US and included a total of 258 patients 2 to 5 years of age with perennial allergic rhinitis, of which 183 were treated with OMNARIS Nasal Spray 200 mcg, 100 mcg or 25 mcg daily. The distribution of adverse events was similar to that seen in the 6 to 11 year old children.



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