

The Bradford Hill Criteria and Zinc-Induced Anosmia

A Causality Analysis

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Objective: To apply the Bradford Hill criteria, which are widely used to establish causality between an environmental agent and disease, to evaluate the relationship between over-the-counter intranasal zinc gluconate therapy and anosmia.

Design: Patient and literature review applying the Bradford Hill criteria on causation.

Setting: University of California, San Diego, Nasal Dysfunction Clinic.

Patients: The study included 25 patients who presented to the University of California, San Diego, Nasal Dysfunction Clinic complaining of acute-onset anosmia after intranasal application of homeopathic zinc gluconate gel.

Main Outcome Measures: Each of the 9 Bradford Hill criteria—strength of association, consistency, specific-

ity, temporality, biological gradient (dose-response), biological plausibility, biological coherence, experimental evidence, and analogy—was applied to intranasal zinc gluconate therapy and olfactory dysfunction using published, peer-reviewed medical literature and reported clinical experiences.

Results: Clinical, biological, and experimental data support the Bradford Hill criteria to demonstrate that intranasal zinc gluconate therapy causes hyposmia and anosmia.

Conclusions: The Bradford Hill criteria represent an important tool for scientifically determining cause between environmental exposure and disease. Increased Food and Drug Administration oversight of homeopathic medications is needed to monitor the safety of these popular remedies.

Arch Otolaryngol Head Neck Surg. 2010;136(7):673-676

IN 1965, THE BRITISH MEDICAL statistician Sir Austin Bradford Hill¹ famously demonstrated the link between tobacco smoking and lung cancer by outlining 9 key criteria for establishing causal relationships between a specific factor and a disease. Now known as the Bradford Hill criteria, this tool has been widely used in science and law to determine causation when an association is observed between exposure to an environmental agent or a drug and a disease. Hailed as having “an enormous impact on epidemiologists and medical researchers,” these criteria revolutionized the scientific approach to defining the relationship between environment and disease.² Herein, we apply these criteria to intranasal zinc gluconate therapy and smell dysfunction to determine if the two are causally linked.

Intranasal zinc gluconate is a popular over-the-counter alternative therapy that is used for prophylaxis and treatment of the common cold. The efficacy of this inter-

vention is questionable, with a recent structured review demonstrating insufficient evidence to support any therapeutic effectiveness of zinc.³ Multiple randomized, double-blind, placebo-controlled trials have found that intranasal zinc is ineffective in preventing or reducing the duration of the common cold.^{4,5} A randomized control trial conducted by Mossad⁶ did find that zinc nasal gel therapy reduced the duration and symptom severity of the common cold when it was started within 1 to 2 days of illness onset; however, Mossad’s study was funded by the makers of the medication used in the study and therefore has potential bias.⁶⁻⁸ In addition to concerns regarding the efficacy of intranasal zinc therapy, increasing evidence indicates that this medication may be linked to severe, potentially permanent hyposmia and anosmia.⁹⁻¹² The Bradford Hill criteria are applied to intranasal zinc therapy and anosmia to evaluate a possible causal relationship between the two.

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METHODS

Each of the 9 Bradford Hill criteria—(1) strength of association, (2) consistency, (3) specificity, (4) temporality, (5) biological gradient (dose-response), (6) biological plausibility, (7) biological coherence, (8) experimental evidence, and (9) analogy—was applied to intranasal zinc therapy and anosmia using published peer-reviewed medical literature as well as our recent clinical experience at the University of California, San Diego (UCSD), Nasal Dysfunction Clinic. Relevant literature was identified by searching both the PubMed and Ovid/MEDLINE databases for articles published between 1951 and 2008. Manual searches of the reference lists of selected articles were also performed to identify additional publications.

RESULTS

The first criterion is *strength* of the association. In animals, the administration of 5% intranasal zinc sulfate is a commonly used research method to induce olfactory injury.¹³⁻¹⁵ In humans, the first reported cases involved more than 4700 Canadian school children who received intranasal 1% zinc sulfate in the 1930s in an attempt to prevent polio. Fifty-two children (approximately 1%) self-reported anosmia at 6 months.⁹ DeCook and Hirsh¹⁰ and Jafek et al¹¹ have published case reports of anosmia resulting from the intranasal application of zinc gluconate gel. We previously described a series of 15 patients who presented to the UCSD Nasal Dysfunction Clinic with anosmia after using intranasal zinc gluconate.¹² An additional 10 patients have since presented to the UCSD Nasal Dysfunction Clinic with zinc-induced anosmia. Seven of the patients were female. The mean age of the patients was 47.9 years (age range, 35-55 years). The mean time between the use of intranasal zinc and evaluation in the UCSD Nasal Dysfunction Clinic was 10.8 months (range, 2-24 months). All of the patients diagnosed as having zinc-induced anosmia or hyposmia reported sniffing deeply when squirting the gel into their nose. Within minutes of medication use, they observed a sensation of intense burning that typically lasted several hours. Patients localized the burning sensation either “at the bridge of the nose” or “between the eyes.” Loss of the sense of smell is typically perceived within 12 to 36 hours. Butanol threshold and odor identification testing confirmed hyposmia or anosmia in all patients. Three patients were found to be anosmic and 7 were hyposmic. Mean (SE) composite scores on the threshold and odor identification tests were 31 (8.1) and 37 (10.2) in the left and right nostrils, respectively. The mean (SE) University of Pennsylvania Smell Identification Test score was 17.1 (2.7). Follow-up via telephone 3 to 22 months after initial testing revealed subjective reports of minimal to no improvement in 6 patients and moderate improvement in 2 patients; 2 patients could not be contacted.

Only 3 of the 10 patients (30%) reported a concomitant upper respiratory tract infection (URTI). For these patients, postviral anosmia was considered in their differential diagnosis but was ruled out based on history. Whereas the smell loss in postviral anosmia is generally first noted when the cold resolves (typically several weeks after the URTI, when the URTI-associated rhinitis and nasal congestion resolve), the smell loss in zinc-induced anosmia is immediate and noted within minutes to hours of

the offending application. Seven patients (70%) used the zinc nasal spray prophylactically and never developed signs or symptoms of a URTI. The differential diagnosis for smell loss is extensive, but the history and examination results of these patients were not consistent with any of the other known causes. The only clear intervention in each of these cases was the use of the zinc nasal spray. Therefore, the strength of the association between the use of zinc nasal spray and rapid-onset anosmia is strong.

The next Bradford Hill criterion is *consistency*. As Bradford Hill¹ queried in his landmark speech, “Has it been repeatedly observed by different persons, in different places, circumstances and times?” Zinc-induced anosmia is uncommon, but it has been observed and reported in peer-reviewed medical journals by multiple individuals in different geographic locations and at different times. The circumstances have ranged from medical application (eg, polio prophylaxis) to self-administration as a homeopathic cold remedy. The first report is by Tisdall et al,⁹ with 52 cases. The second is by DeCook and Hirsh,¹⁰ with a single case. The third is by Jafek et al,¹¹ with 10 cases. The fourth is our own experience, with 25 cases.

The third Bradford Hill criterion is *specificity*, the meaning of which is clear. Zinc nasal spray has a unique, specific association with anosmia. It has not been shown to cause blindness, cancer, or any other ailments or symptoms.

The fourth criterion is *temporality*. For affected patients, the use of a zinc nasal medication causes immediate-onset burning; then, the loss of smell is generally perceived within minutes to hours. Most likely, the anosmia is immediate. The realization may not occur for several hours because the patients are immediately focused on the pain and realize the olfactory loss only when they smell or eat something later that day or the next.

The fifth criterion is *biological gradient*, or dose-response curve, which has been demonstrated in animals. Using a murine model, Hansen et al¹⁶ applied an intranasal irrigation of zinc sulfate in concentrations varying from 0.01% to 1.0%. The lowest concentration caused anosmia in none of 5 animals, and the highest dose caused anosmia in 11 of 11 animals. Intermediate doses had intermediate effects. Hansen and colleagues note, “One day after irrigation (concentrations investigated were between 0.05-1%) the ability of food finding, an olfactory cue, was decreased in a concentration-dependent manner.”

Unfortunately, this dose-response experiment is difficult to reproduce in humans. The obvious experiment is to administer the gel in different strengths and for different periods of time and then to measure the degree and duration of olfactory impairment. However, in addition to ethical concerns, there are simply too many variables. How much zinc reaches the olfactory epithelium is a function of the concentration of zinc, the distribution of the olfactory epithelium in the upper regions of the nasal cavity, the thickness of the epithelial mucosa, the time (duration) of the exposure, the nasal anatomy, the airflow pattern and strength of the sniff, where in the nose the gel is deposited, and perhaps the individual susceptibility to the chemical injury. Hence, we must rely on the dose-response information that is generated in animals, which clearly shows a dose-response curve to varying concentrations of zinc cation in rodents.

The sixth criterion is *plausibility*. Biochemically, zinc gluconate is a weak acid; at physiologic pH, it is proteolytic. The nasal instillation of zinc sulfate in the mouse, rat, and other animals has clearly produced at least temporary anosmia, likely via proteolytic destruction of the olfactory receptor cells. If the olfactory clefts are examined at autopsy, tissue damage is seen within a few days of treatment.¹⁷ One possible mechanism for this is through the inhibition of carnosine synthesis.¹³ Of note, Slotnick et al¹⁸ propose that zinc gluconate may be less toxic than zinc sulfate; therefore, they question whether the animal literature based on the sulfate salt can be applied to the issue in question. However, they do not cite any literature to support their claim, and their own study—which is partially funded by industry—is confounded by the use of different concentrations of zinc sulfate and zinc gluconate. Therefore, while the olfactory system of humans certainly differs from that of animals, it appears biologically and biochemically plausible that the zinc cation can cause similar damage to the olfactory epithelium in humans, resulting in temporary or permanent anosmia.

Coherence is the seventh criterion. According to Hill,¹ “The cause-and-effect interpretations of our data should not seriously conflict with the generally known facts of the natural history and biology of the disease.” Consider those individuals who used intranasal zinc when they were otherwise healthy and had no other reason to become anosmic. The Canadian children who received zinc sulfate to prevent polio in the 1930s had no reason to lose their olfaction from natural causes.⁹ The only intervention was the intranasal zinc therapy; therefore, the most likely explanation for their smell loss was the chemical injury of the zinc. The same can be said for those individuals who used zinc nasal spray prophylactically: they had no natural cause to lose olfaction, particularly the ones who did not develop a URTI. The sole intervention was the nasal zinc. The differential diagnosis reveals no alternate cause; therefore, the probable explanation for the smell loss is chemical injury due to the use of intranasal zinc.

The eighth criterion is *experimental evidence*. Putting aside the unfortunate human experiments of polio prophylaxis and homeopathic nasal zinc, the animal experiments clearly demonstrate that zinc cation causes anosmia. A 2009 publication by Lim et al¹⁹ further confirms that cationic zinc causes damage to mouse and human nasal tissue. However, to truly demonstrate causation, a large-scale randomized control trial conducted in accordance with the Food and Drug Administration (FDA) is needed to collect safety and efficacy data on these medications.

The ninth and final Bradford Hill criterion is *analogy*. Other airborne and topical compounds have been shown to cause temporary or permanent anosmia. Ammonia, chlorine, and cadmium have all been implicated as a cause of anosmia.²⁰ Also, chronic toxin-induced anosmia has been seen with the use of formaldehyde and paint solvent.^{21,22}

COMMENT

As outlined by Höfler² in his elegant application of counterfactual arguments to the Bradford Hill criteria, this approach does have certain limitations. In terms of our analy-

sis, potential bias, such as confounding or selection bias, may have been introduced by the observational nature of the 4 studies linking cationic zinc to anosmia. Furthermore, patients who present with olfactory loss typically have multiple potential pathogenetic factors in their history, which increases the complexity of the causal system to which we are applying the Bradford Hill criteria.

Nonetheless, based on our analysis, it appears evident that intranasal zinc can and does cause anosmia. Bradford Hill¹ eloquently coincides, “All scientific work is incomplete—whether it be observations or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.”

Given the rapid expansion of the homeopathic drug market into a multimillion-dollar industry, it is clear that more stringent FDA regulation is needed to monitor the safety of these popular remedies. Currently, only homeopathic drugs offered for treatment of “serious disease conditions” must be dispensed by a licensed practitioner. Conversely, homeopathic products intended solely for self-limiting diseases that are amenable to self-diagnosis can be sold over the counter, exempt from FDA regulations on expiration dating and laboratory determination of the identity and strength of each active ingredient. Also, these products are exempt from the rigorous premarket approval process that allopathic medications must go through before entering the market. Protecting our patients from the potential risks of intranasal zinc medications and other homeopathic drugs, especially ones with limited proven therapeutic benefit, should be a high priority of the FDA.

Submitted for Publication: May 19, 2009; final revision received February 5, 2010; accepted February 22, 2010.

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Author Contributions: Dr Davidson had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Davidson and Smith. *Acquisition of data:* Davidson. *Analysis and interpretation of data:* Smith. *Drafting of the manuscript:* Davidson and Smith. *Critical revision of the manuscript for important intellectual content:* Davidson and Smith. *Administrative, technical, and material support:* Davidson and Smith. *Study supervision:* Davidson.

Financial Disclosure: As the director of the UCSD Nasal Dysfunction Clinic since 1984, Dr Davidson has evaluated well over 2000 patients with anosmia. A few patients (<1%) have been involved in litigation, and Dr Davidson has been retained as an expert witness for both defense and plaintiff. Dr Davidson’s involvement in cases of zinc-induced anosmia have all been on behalf of the plaintiff. The Bradford Hill article was Dr Davidson’s idea and was not discussed with or supported by any law firm or other entity.

Additional Contributions: Barbara A. Stribling assisted in the preparation of the manuscript.

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