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Research Paper

Impact of antibiotics on smell dysfunction

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Abstract *Objective:* Viral or bacterial respiratory infections can cause long-lasting olfactory dysfunction. Antibiotic therapy is indicated in severe cases; however, it is unclear whether antibiotic use produces a positive, negative, or null effect on olfactory function. This retrospective study sought to determine whether antibiotic use has an influence on odor identification and detection threshold test scores of patients with smell dysfunction secondary to upper respiratory infections (URIs), lower respiratory infections (LRIs), or rhinosinusitis.
Methods: Data from a total of 288 patients presenting to the University of Pennsylvania Smell and Taste Center were evaluated.
Results: Patients with a URI etiology who had taken bactericidal antibiotics had lower detection thresholds than did patients who had not taken antibiotics ($P < 0.023$; analysis of covariance with age and time since infection onset as covariates). Moreover, thresholds were lower for bactericidal antibiotic users than for bacteriostatic antibiotic users with either URI ($P = 0.023$) or rhinosinusitis ($P = 0.028$) etiologies. No meaningful influences of antibiotics on the odor identification test scores were evident.
Conclusions: These findings, which need to be confirmed in prospective double-blind studies, suggest that bactericidal antibiotic therapy may be beneficial in mitigating, at least to some degree, chronic decrements in smell sensitivity due to URIs and rhinosinusitis.

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Introduction

The use of antibiotics in treating respiratory tract infections is common in medical practice, even in cases where viral infections are most likely.[1] In general, antibiotic therapy is not recommended in initial treatment for upper respiratory tract infections (URIs); on the contrary, avoidance of prescribing antibiotics in these patients is encouraged, largely to prevent antibiotic resistance. In chronic rhinosinusitis, which adversely influences smell function in approximately three-quarters of patients,[2] bacterial infection or colonization may directly induce inflammation or serve as a disease modifier of a preexisting inflammatory state.[3] Therefore, antibiotic therapy is generally indicated to lower bacterial burden in such cases.

A standard classification of antibiotics differentiates bactericidal antibiotics, which specifically kill bacteria, from bacteriostatic antibiotics, which impede bacterial growth. However, overlap exists between these two classes of antibiotics.[4] While bactericidal antibiotics strongly and directly attack bacteria, the milder bacteriostatic antibiotics rely on phagocytosis and intracellular killing.[5] Ocampo et al[6] quantified death rates of both these classes of antibiotics and showed a substantial increase in killing rates for bactericidal antibiotics compared to those of bacteriostatic antibiotics. Although Nemeth et al[7] found minimal differentiation of efficacy between bactericidal and bacteriostatic antibiotics for abdominal infections, soft tissue infections, and pneumonia, differentiation has not been established for URIs that impact olfactory function. Importantly, interactions between viruses and bacteria are known to occur within the upper respiratory tract, decreasing or increasing the potency of some antibiotics in complex microbial communities.[8] In addition to antibacterial and anti-inflammatory effects, the bacteriostatic antibiotic minocycline has anti-apoptotic effects, delaying, for example, photoreceptor degeneration in the retina of the *Prph2*$^{Rd2/Rd2}$ (*rds*) mouse.[9]

The efficacy of antibiotics in improving smell function has been previously found to be negative, both when used for bacterial and viral infections. Van Zele et al,[10] in a double-blind, placebo-controlled, multicenter study, found no influence of doxycycline treatment on self-reported olfactory loss in 14 chronic rhinosinusitis patients with bilateral nasal polyps. Videler et al[11] administered azithromycin to 29 chronic rhinosinusitis patients (62% with nasal polyps) and a placebo to 31 such patients (42% with polyps). A 12-odor smell identification test was administered at the beginning of the treatment period and at 6 and 12 months during the treatment period. No influence of azithromycin was found. More recently, Reden et al[12] administered, in a randomized double-blind placebo-controlled study, either minocycline ($n = 26$) or a placebo ($n = 29$) to patients whose olfactory dysfunction was due to an upper respiratory infection. No influence of the antibiotic on tests of odor identification, detection, and discrimination was observed.

Taking a somewhat different tact, Ramakrishnan et al[13] examined, in a study of 434 medically refractory chronic rhinosinusitis patients, whether the number of days of reported antibiotic use in the 90 days before endoscopic nasal sinus surgery was related to pre-surgical scores on a 12-item smell identification test. No meaningful differences in the olfactory test scores were evident among the groups who had used no antibiotics ($n = 163$) or had used antibiotics for 1–14 days ($n = 102$), 15–28 days ($n = 69$) or more than 29 days ($n = 100$).

The purpose of this retrospective study was to assess, in a comparatively large number of subjects presenting with complaints of chemosensory disturbances, the potential influences of bactericidal or bacteriostatic classes of antibiotics on odor identification and detection threshold test scores of individuals whose olfactory dysfunction followed URIs, rhinosinusitis, or lower respiratory infections (LRIs). This study is the first to differentiate between the potential effects of bactericidal and bacteriostatic antibiotics on smell function and, unlike previous studies, focused on a patient group specifically seeking help for their chemosensory disturbance.

Materials and methods

Subjects

Data from 288 patients who had used or not used antibiotics at the time of their infection and whose chronic smell problem was attributed to URIs, LRIs, or rhinosinusitis were evaluated. The data were obtained from the clinic database of the University of Pennsylvania Smell and Taste Center from 1990 to 2013 (Table 1). This retrospective use of our clinic database information was approved by the Institutional Review Board of the University of Pennsylvania's Office of Regulatory Affairs.

In order to minimize the effect of other major etiologies such as head trauma or surgery, we included only data from patients who had URI, LRI, or rhinosinusitis as their principle etiologies. To minimize the confounding effect of the use of multiple types of antibiotics by the same patient, only patients who had used the same antibiotic during their treatment period were included in the sample.

In addition to detailed chemosensory testing described below, information regarding each person's current health, medical history, and chemosensory complaint was obtained from the patient's intake interview, physician reports, and an intake questionnaire completed by the patient prior to their visit to the Center. Medical information included a history of physician visits and physical examinations, as well as, in some cases, specific test results. The questionnaire was comprised of seven sections: (1) General Information (e.g., questions regarding demographics, referral source, and drinking and eating habits); (2) Medical History (listing of major illnesses and injuries, hospital admissions, and medications taken in the year prior to and since symptom onset); (3) History of Present Illness (report of the problem, in the patient's own words, including date of onset, duration, antecedent conditions, and treatments received); (4) Smell Symptoms (questions concerning problems with the sense of smell, general nasal health and abnormal nasal sensations, including nasal obstruction, rhinorrhea, and postnasal drip); (5) Taste Symptoms (questions related to problems with the sense of taste, general oral health, and abnormal oral sensations); (6)

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