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Measuring antibiotic levels and their relationship with the microbiome in chronic rhinosinusitis

J Siu[1], M D Tingle[2] and R G Douglas[1]

Departments of [1]Surgery and [2]Pharmacology and Clinical Pharmacology, University of Auckland, New Zealand

Review Article

Prof R G Douglas takes responsibility for the integrity of the content of the paper

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Author for correspondence:
Prof Richard George Douglas
Department of Surgery,
University of Auckland,
Private Bag 92019, Auckland 1142,
New Zealand
E-mail: richard.douglas@auckland.ac.nz
Fax: +64 9 377 9656

Abstract

Background. The evidence supporting the efficacy of antibiotic therapy in the treatment of chronic rhinosinusitis is not compelling. A limited number of studies show that the changes in the nasal microbiome in patients following drug therapy are unpredictable and variable. The evidence for the impact of oral antibiotics on the gut microbiota is stronger, possibly as a result of differences in drug distribution to various sites around the body. There are few studies on sinus mucosal and mucus levels of oral antibiotics used in the treatment of chronic rhinosinusitis. The distribution dependent effects of antibiotics on the sinonasal microbiome is unclear.

Conclusion. This review highlights that relative drug concentrations and their efficacy on microbiota at different sites is an important subject for future studies investigating chronic rhinosinusitis.

Introduction

The evidence for the clinical efficacy of antibiotics in the treatment of chronic rhinosinusitis remains inconclusive, with the exception of longer courses of macrolide antibiotics for some specific chronic rhinosinusitis phenotypes.[1] Although the exact role of bacteria in the pathogenesis of chronic rhinosinusitis is still being defined, it is conceivable that the lack of antibiotic efficacy may be due in part to insufficient levels in the sinonasal mucosa and mucus to inhibit the growth or kill bacteria residing in this niche. However, studies on the drug distribution into the sinonasal mucosa and mucus, or those evaluating the impact of antibiotics on the sinonasal microbiota are limited. In contrast, there is a wealth of knowledge concerning the impact of antibiotics on the gut microbiota. It is possible that deleterious effects of antibiotics on the gut microbiota may exceed their favourable impact on the sinonasal microbiota.

We believe that relative drug concentrations and their efficacy on microbiota at different sites is an important subject for future studies investigating chronic rhinosinusitis. This review aimed to evaluate the existing literature concerning the pharmacokinetics or activity of antibiotics in the sinonasal mucosa and mucus.

Role of bacteria in immunopathology

Chronic rhinosinusitis is considered to represent a spectrum of disorders with varying combinations of immunopathological mechanisms. Although the exact role of infection in the pathogenesis of chronic rhinosinusitis is unknown, bacteria probably contribute to the persistence and severity of chronic rhinosinusitis.[2]

Historically, chronic rhinosinusitis has been primarily categorised into two groups: chronic rhinosinusitis with nasal polyps and chronic rhinosinusitis without nasal polyps. Both types are characterised by epithelial disruption, ciliary dysfunction, mucus gland hyperplasia, bacterial overgrowth and biofilm formation.[3]

Bacteria may become pathogenic by acting as antigens and activators of pathogen-associated molecular receptors.[3] They can also secrete toxins which may have superantigen activity and immune adjuvants that stimulate non-specific adaptive immune responses.[3] *Staphylococcus aureus* is especially common in eosinophilic chronic rhinosinusitis, in which it is associated with a superantigen-mediated increase in T-cell type 2 cytokine secretions and immunoglobulin E (IgE) sensitisation.[4,5] Observations of improvement in individuals with chronic rhinosinusitis treated with doxycycline and macrolide antibiotics may be linked to the role of these antibiotics in reducing bacterial load and superantigen production, as well as their more direct anti-inflammatory effects.[1,3,6]

Despite the widespread use of antibiotics in the treatment of chronic rhinosinusitis, there is some evidence to indicate that antibiotics may be paradoxically implicated in the causation of this condition. Some evidence suggests that an imbalance of immunogenic bacteria against tolerogenic bacteria may promote the persistence of chronic

rhinosinusitis.[7–9] In addition, with repeated use of broad-spectrum antibiotics, there is concern that more resistant bacterial strains will emerge. These bacteria reside in biofilms, are extremely difficult to eradicate, and may form a nidus for future exacerbations.

Biofilms can alter antibiotic effectiveness, as the bacteria in their centre are less metabolically active and so less responsive to the cellular mechanisms that are central to the action of many antibiotics.[3] The gradients in hypoxia and pH created within the biofilms also aid survival of the core bacteria throughout treatment. Further defence mechanisms which promote bacterial persistence in biofilms include quorum sensing, and the ability of an organised multicellular complex that forms the biofilm to evade phagocytosis.[3]

A dose-dependent effect of topical tobramycin in penetrating and destroying biofilms in a rabbit model has been reported.[10] However, effective treatment requires much higher doses of antibiotics than usual, with up to a thousand-fold higher concentration than the predicted mean inhibitory concentration being necessary.[10] Although the goal of topical antibiotic therapy is to achieve higher local delivery of drugs while reducing systemic effects, the evidence for the effectiveness of topical antibiotics has not been proven.[11] It is likely that topical antibiotics in safe prescribed doses are usually ineffective against biofilms.[12]

Efficacy of antibiotics

Antibiotic intervention has not been proven to be generally effective in chronic rhinosinusitis, other than during acute exacerbations.[2,3] Although bacteria are ubiquitous in the sinuses of patients with chronic rhinosinusitis, definitive evidence for a primary infectious aetiology of this condition remains elusive. A few prospective studies have investigated the efficacy of short-term antibiotic use in chronic rhinosinusitis. The lack of placebo arms in these studies limits the interpretation of any clinical response, and overall they have not detected significant differences between the treatment arms.[13–15]

The international consensus statement recommends the use of oral macrolides as an option in the treatment of chronic rhinosinusitis on the basis that they have shown benefit in some studies in reducing endoscopy scores and improving symptoms in chronic rhinosinusitis patients.[16] Most studies of macrolide therapy in chronic rhinosinusitis patients without nasal polyps have shown a benefit over placebo, while limited data are available to determine the efficacy for chronic rhinosinusitis with nasal polyps. There is a paucity of evidence supporting the efficacy of non-macrolides in chronic rhinosinusitis.[16]

A meta-analysis of the efficacy of long-term macrolide therapy in chronic rhinosinusitis did not demonstrate evidence for a clinically significant impact across three studies included in the review.[1] A single study reported a significant difference in patient-reported outcomes after 12 weeks of treatment, favouring roxithromycin, but only in those patients with a normal serum total IgE level. However, these results are difficult to interpret, as the patient-reported outcome scale used was not validated and could be interpreted as biased in having more points to describe improvement than worsening.[17] Macrolides function by downregulating proinflammatory cytokines including interleukin 8, a potent neutrophil chemoattractant.[18] Thus, it is possible that patients in the high serum IgE subgroup (often with associated eosinophilic infiltration) may be less likely to benefit from macrolide therapy compared to those in the normal IgE subgroup.[18]

Analysis of drug molecules in nasal and paranasal tissues and secretions

A number of studies have examined antibiotic concentrations in the sinonasal tissues and/or mucus.[19–38] However, the majority of these studies have been performed in patients with acute sinusitis, acute exacerbations of chronic rhinosinusitis or upper respiratory tract infections. Furthermore, there are limitations in the interpretation and comparison of these studies, including small sample sizes, and heterogeneity of study populations, specific antibiotic and dosage regimens, nasal sampling methods, time of sampling in relation to the time of dose, and drug analysis methods.

The lack of clinical difference seen in chronic rhinosinusitis patients treated with oral antibiotics may be attributed in part to a sub-therapeutic level of drug penetration into sinonasal biofilms, in addition to the presence of growing antibiotic-resistant strains.[2,3,10] However, the extent to which drug distribution to the human sinonasal mucosa can contribute to the efficacy of oral antibiotics in patients with chronic rhinosinusitis remains largely undefined.

Predicting the efficacy of an antibiotic is complicated by its varying distribution across the body.[39] The total plasma concentration of a drug is not a reliable predictor of its clinical efficacy, as it may not always reflect the drug concentration and activity in the target site. Accordingly, the total plasma concentration of a drug is not an ideal pharmacokinetic parameter on which to base rational dosing. The effects of antibiotics also differ by body site. For example, the pharynx and saliva recover their initial microbial diversity after antibiotic therapy much more quickly than does the gut.[40,41] Macrolides are highly lipophilic and consequently penetrate well into tissue, especially bronchial secretions, prostatic tissue, middle-ear exudates and bone tissues.[42] Similarly, second-generation tetracyclines like doxycycline are also lipophilic and so penetrate well into most tissues, including respiratory tract tissue, with the highest concentrations in the liver, kidney and digestive tract. Biliary doxycycline concentrations are found to exceed those of serum by many folds, possibly reflecting higher active transport and secretion of the drug in the biliary tract.[43] Both the macrolide and tetracycline drug groups are found to penetrate poorly into cerebrospinal fluid and saliva.[42,43]

The analysis of drugs or their metabolites in tissue target compartments such as cerebrospinal fluid and mucus can improve our understanding of drug penetration and likely efficacy at the site of infection.[44] The collection of sinonasal tissues or secretions has been shown to be an appropriate approach in studies measuring drug concentrations in nasal secretions, nasal mucosa, paranasal sinus mucosa, ethmoid bone and septal cartilage after intranasal and oral dosing. These studies have provided useful information in the fields of toxicology and pathophysiology.[13,20,22–25,27,30–32,34,36–38,44,45] However, nasal tissue samples and/or mucus are much more difficult to obtain than blood or urine, and are much smaller in volume. Accordingly, special attention is required in the various stages of bioanalysis as compared to that required for conventional samples such as the blood and urine, and validation procedures need to be considered.[46]

Nasal secretions can be sampled by nose blowing, aspiration, absorption or washing techniques, and each of these

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has its own advantages, limitations and influences on the results obtained.[46] Notably, different collection techniques provide heterogeneous matrices and analyte concentrations, which limit comparison between studies.[46] A sample preparation stage is mandatory for drug elution, as biological samples are not directly compatible with quantification techniques such as high-performance liquid chromatography analysis.[46] Nasal secretions are protein-rich samples that require an efficient sample clean-up procedure.[36,47] Liquid–liquid extraction and solid-phase extraction procedures have been found to improve sensitivity by removing matrix interferences.[36,47]

It is essential that all bioanalytical methods for determining analytes in a specific biological matrix undergo validation to assure that they are reliable and reproducible.[45] As nasal and paranasal specimens tend to be smaller in volume as compared with blood or urine samples, they impose a need for the partial validation of a method based on a previously validated method applied to a different matrix.[45,46] While selectivity and sensitivity are key parameters, the linearity, precision and accuracy of the measured concentrations, and the stability of the analytes in the biological matrix, should also be assessed.[45]

The determination of drug levels in sinus secretions in the past was largely performed by microbiological assays such as agar and disc diffusion.[21,23,27,29,31,33,34] However, in light of technological advances and the development of new analytical methodologies and instrumentation, more efficient quantitative analysis can be performed by chromatography.[46] Novel sample preparation methods have improved the extraction of drug analytes from biological matrices so that less than 10 µl of nasal secretions may be adequate for analysis.

High-performance liquid chromatography is frequently used as a bioanalytical method, as it provides several advantages over others such as gas chromatography.[46] Nevertheless, few studies have used high-performance liquid chromatography to determine the concentrations of various antibiotics commonly used for chronic rhinosinusitis, particularly those from the macrolide and tetracycline groups, compared with fluoroquinolone drugs.[26,28,32,35]

Older studies have described the pharmacokinetic properties in the sinus secretion of doxycycline and roxithromycin, using microbiological assay techniques, with many reporting the concentration of sinus secretion drug levels at varying time points to be above reference mean inhibitory concentration levels for susceptible strains of pathogens.[21,23,27,29,31,33,34] Although sinonasal drug levels are suggested to be therapeutic by being above the mean inhibitory concentration level for susceptible strains,[21,23,27,29,31,33,34] the definitions of therapeutic concentrations are variable between studies.

Microbiome studies have largely not been performed in parallel, thereby hindering investigation of the relationship between drug levels and activity on an intrinsic level, and there is often a lack of clinical correlation. Microbial analysis, when performed, appears to only have occurred in the context of pathogens in acute sinusitis or exacerbations of chronic rhinosinusitis.[19,20,34,35]

Impact of antibiotics on sinonasal microbiome

There is increasing evidence to support the concept that a more diverse microbiome is associated with improved health outcomes and less disease burden.[48–50] Some studies have shown that treatments such as intranasal corticosteroids in the management of acute exacerbations of chronic rhinosinusitis may decrease nasal microbiome diversity.[51,52] A decrease in sinonasal bacterial diversity following a period of oral antibiotics and corticosteroids in patients with acute exacerbations of chronic rhinosinusitis has also been reported.[51] However, as no baseline steady-state sample was collected, the decrease in diversity may also be attributed to resolution of the acute exacerbation.[51]

In a previous study, we observed that the immediate effects of oral doxycycline or prednisone on bacterial communities and cytokines were unpredictable and highly variable between individuals.[53] This is supported by further studies of changes in bacterial communities following systemic medical therapies, which also have not shown significant differences in bacterial diversity or richness, and which have described unpredictable and complex community shifts.[54–56] Small changes in the relative abundance in a number of dominant taxa have been demonstrated, including trends of increase in staphylococcal species.[54–56] The effects of medical therapies on the sinonasal microbiome in chronic rhinosinusitis patients have yet to be correlated with clinical responses.

Impact of antibiotics on gut microbiome

Collateral harm from antibiotics is not limited to rising antibiotic resistance. Antibiotic use can account for 19 per cent of emergency department visits for adverse drug reactions; furthermore, the risks of adverse reactions with some antibiotics are reportedly comparable to those of insulin, warfarin and digoxin.[57] In a prospective study of antibiotic-associated suspected adverse drug reactions among 762 hospitalised patients, 269 patients suffered an adverse drug reaction.[58] The system organ classes most frequently affected with serious adverse effects were the gastrointestinal (50 per cent, 135 out of 269), neurological (24 per cent, 64 out of 269), body-general (10 per cent, 27 out of 269), and skin or appendages (6 per cent, 17 out of 269), among others.[58]

It is well known that antibiotics can cause lasting changes to the gut microbiome, including a loss in diversity, the emergence of new genome sequences, growing antibiotic-resistant strains and the upregulation of antibiotic resistance genes.[40,59,60] Dysbiosis of the microbiome has been causally implicated in a large number of metabolic, immunological and developmental disorders, and may affect susceptibility to the development of infectious diseases, which can impact a wide variety of systems.[61–65] Just as dysbiosis is implicated in the development of chronic rhinosinusitis, it is also implicated in inflammatory bowel disease – representing a spectrum of chronic inflammatory intestinal disorders – via a dysregulated immune response to host intestinal microflora.[61,65,66]

Complete recovery after short-term antibiotic treatment may still not be achieved for as long as four years following treatment.[40] Many of these perturbations in gut microflora have been evaluated in relation to susceptibility to enteritis with *Clostridium difficile* and *Salmonella typhimurium*.[39,67] However, few studies have described the changes in gut microflora associated with acute, short-term adverse gastrointestinal symptoms not necessarily linked to common pathogens. The patterns of disruption to the gut microbiome associated with chronic gastrointestinal diseases such as inflammatory bowel disease and irritable bowel syndrome have been determined. However, the extent to which these can be attributed to previous antibiotic exposure remains to be elucidated.[63,66]

Disruption to gut microflora has been frequently studied in relation to the use of broad-spectrum medications, such as clindamycin[67] and beta-lactam antibiotics for infections

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affecting various other systems,[59,68,69] or metronidazole and vancomycin used to treat *C difficile*.[50,64,70] On the other hand, there is a relative lack of data for tetracyclines[61] and macrolides.[40,59,69]

In a large cohort study of Finnish children, macrolides were shown to induce long-term alterations of microbiota; for instance, there were reductions in actinobacteria (mainly bifidobacteria), Firmicutes (mainly lactobacilli) and total bacterial diversity, and increases in the relative abundance of Bacteroidetes and Proteobacteria. These results are supported by a study investigating the long-term impact of a short-term course of clarithromycin and metronidazole on patients with *Helicobacter pylori* infection.[40] Doxycycline has been shown to reduce faecal bacterial concentrations of Bacteroidetes, Firmicutes and lactobacillus in a study with healthy volunteers.[33]

Antibiotics from different classes, such as tetracyclines and macrolides, are expected to cause unique patterns of microbiota alteration because of their differing spectra of activity and bacterial targets.[63] Accordingly, they may play different roles in the development of acute adverse gastrointestinal symptoms or acute gastrointestinal infection. By investigating the short-term changes in the gastrointestinal microbiome in parallel with the nasal microbiome with commonly prescribed medication for chronic rhinosinusitis, we can better understand the effects of current medical management, including their adverse effects. This will allow the future development and delivery of more targeted therapy for all chronic rhinosinusitis patients.

Conclusion

The temporal changes that occur in the microbiome with oral antibiotics used to treat chronic rhinosinusitis are still poorly understood, and it remains a challenge to correlate these with the clinical state. Although sinonasal drug distribution could well be a factor in the effectiveness of oral antibiotics, further research is required into the relationship between drug concentrations and temporal changes in the microbiome at a local level and its clinical significance. There is scope in using nasal secretions collected with sinus aspiration or absorption techniques to represent a target compartment in the sinonasal tissues of chronic rhinosinusitis patients, and in measuring drug concentrations of oral medications commonly prescribed for chronic rhinosinusitis, such as doxycycline and roxithromycin, around the steady state, via validated, accurate and precise methods such as high-performance liquid chromatography. The determination of the concentration of antibiotics in nasal secretions in relation to changes in the nasal microbiome of chronic rhinosinusitis patients is an area of great interest with regard to the clinical efficacy of oral antibiotics.

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Competing interests. None declared

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