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Nonantimicrobial Effects of Antibacterial Agents

R. Pasquale and J. Tan. *Clin Infect Dis 2005; 40:127–135*

The nonantimicrobial therapeutic activities derived from known side effects of antimicrobial agents are reviewed. For example, sulfonamide-related agents that lack antimicrobial activity are commonly used for hypoglycemic effect (sulfonylureas) and carbonic anhydrase blockade (acetazolamide).

Nonantibacterial effects of macrolides include gastrointestinal motility and immunomodulation. Clinical studies suggest that erythromycin and other 14-member macrolides act as motilin receptor agonists. Motilin, an amino acid peptide, is believed to play a role in controlling the cyclic bursts of contractile activity that occur in the gastrointestinal tract during the fasting state. Erythromycin and other macrolides also have beneficial immunomodulatory effects. These antibiotics have been found to be beneficial in the treatment of hypersecretory conditions, such as diffuse panbronchiolitis and cystic fibrosis.

Although the mechanism by which macrolides are effective in the treatment of hypersecretory conditions is not completely understood, several theories have been proposed. Macrolides reduce migration of neutrophils to the site of inflammation by suppressing neutrophil chemotactic activity in the lungs. By achieving high intracellular concentrations, macrolides can also directly or indirectly alter neutrophil function. In addition, macrolides have a direct effect on the cystic fibrosis transmembrane regulator gene. Finally macrolides demonstrate antioxidant effects. These immunomodulatory properties may be therapeutically beneficial to patients with chronic airway inflammation, including chronic sinusitis, chronic obstructive pulmonary disease and asthma.

Tetracyclines and their derivatives have effects on immunomodulation, neuroprotection and secretion of antidiuretic hormone. An important nonantimicrobial property that further supports the use of tetracyclines for periodontal and other disorders is their ability to inhibit matrix metalloproteinases (MMPs), probably as a result of zinc chelation from the active sites of MMPs. MMPs, which require zinc to be active, can play a vital role in the breakdown of the extracellular matrix physiologic function, including wound healing, bone resorption and mammary involution. Tetracyclines have also been reported to directly or indirectly decrease a variety of other inflammatory mediators, such as tumor necrosis factor, interleukin-l, neutrophil elastase, nitric oxide and reactive oxygen intermediates.

As a result of its inhibition of mitochondrial release of cytochrome *c* and reactive microgliosis, there is increased interest in the use of minocycline as a neuroprotective agent.

Demeclocycline is a tetracycline antibiotic with antibacterial activity similar to that of other tetracyclines. Its main clinical use is in the treatment of syndrome of inappropriate antidiuretic hormone secretion. This activity is believed to be secondary to its ability to inhibit both the formation and action of cyclic adenosine monophosphate in the collecting duct of the renal tubule.

Comment: Other antimicrobials could have side effects that are not clinically useful. Examples include osmotic diuresis with high dose β-lactam administration, neuromuscular blockade of aminoglycosides, dysglycemia of fluoroquinolones and serotonin syndrome with oxazolidinones.

Tularemia Associated with a Hamster Bite: Colorado, 2004

Centers for Disease Control and Prevention. *MMWR. 2005;53: 1202–1203.*

The Colorado Department of Public Health and Environment was notified about a 3-year-old boy diagnosed with tularemia associated with a pet hamster. Six hamsters that his family had purchased from a pet store in the Denver metropolitan area during the winter of 2004 died within 1 week of purchase. One hamster bit the child on the left ring finger shortly before it died. The child developed fever, malaise, painful left axillary lymphadenopathy and skin sloughing at the bite site 7 days later. Tissue culture of a left axillary lymph node excisional biopsy specimen yielded a *Francisella tularensis* isolate, and convalescent serology was positive at a titer of 4096. The patient improved after treatment with ciprofloxacin. No other risk factors for tularemia exposure were identified, including no other animal contact, no exposure to game meat and no known mosquito, tick or fly bites.

An unusual number of hamster deaths were reported at the pet store during January to February, but no carcasses were available for testing. However, 1 of 2 cats kept as store pets had a positive serologic test for *F. tularensis* at a titer of 256.

Similar to an outbreak of tularemia that involved 200 primates, a possible explanation for this infection is that infected wild rodents infested the store and spread the infection to hamsters by urinating and defecating through metal screens covering hamster cages (P. P. Callee, et al. *J Zoo Wildlife Med. 1993;24:459–468*).

Comment: Tularemia has not been associated previously with pet hamsters. Clinicians and public health officials need to be aware that pet hamsters represent a potential source of tularemia. In addition, because *F. tularensis* is a potential agent of biologic terrorism, clinicians should have a heightened awareness of this infection. (D. T. Dennis, et al. *JAMA. 2001;285:2761–2773*).

Association Between a Novel Human Coronavirus and Kawasaki Disease

F. Esper et al. *J Infect Dis. 2005;191:499–502.*

The authors identified evidence of a novel human coronavirus, designated "New Haven coronavirus" (HCoV-NH), in respiratory secretions from a 6-month-old infant with classic Kawasaki disease. To further investigate the possible association between HCoV-NH infection and Kawasaki disease, a case-control study was conducted. From November 2001 to May 2004, the investigators had archived specimens of respiratory tract specimens obtained from children younger than 5 years old. Of 53 children diagnosed with Kawasaki disease during the study period, 11 had archived respiratory specimens. Respiratory secretions from 8 (73%) of 11 children with Kawasaki disease and from 1 (4.5%) of 22 control subjects (children without Kawasaki disease

matched by age and the time when the specimens were obtained) tested positive for HCoV-NH by reverse transcriptase-polymerase chain reaction [Mantel-Haenszel matched odds ratio, 16.0 (95% confidence interval, 3.4–7.4), $P = 0.0015$]. Of the 3 HCoV-NH-negative specimens, 1 came from a child with atypical Kawasaki disease (fever plus 3 additional criteria and normal echocardiography) and 1 was obtained on day 11 of hospitalization. Coronary artery dilatation was noted in 3 patients, all of whom tested positive for HCoV-NH. These data suggest that HCoV-NH infection is associated with Kawasaki disease.

Comment by Steve Buckingham, MD, Memphis, TN: After decades of neglect, human coronaviruses became a subject of tremendous scientific interest as a result of the 2003 global epidemic of severe acute respiratory syndrome. Now comes the discovery that a previously unrecognized coronavirus (described for the first time in another article in the same issue of *The Journal of Infectious Disease*) may well be the long-sought etiologic agent of Kawasaki disease. The possibility that a respiratory virus might cause Kawasaki disease has been suggested previously. Evidence supporting this thought comes from the observations that: epidemics of the disease can occur, predominantly during the winter and spring; the disease is rare in young infants, which suggests protection by maternally derived antibodies; and the disease is rare in adults, which suggests widespread immunity to a common childhood infectious agent. This study presents evidence that strongly supports an association between HCoV-NH infection and Kawasaki disease; however, causality cannot be proved by a case-control study. For example, the possibility remains that Kawasaki disease results from the host's inflammatory response to numerous infectious agents, not solely HCoV-NH. The authors call for "prospective cohort studies, seroepidemiologic investigations, and investigations of inflamed tissue for the presence of virus. . . to determine the precise role played by HCoV-NH in the pathogenesis of Kawasaki disease." If further studies confirm that HCoV-NH is indeed the cause of Kawasaki disease, then the importance of this finding to the field of pediatrics cannot be overstated.