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Multiple Uses of Antibiotics

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In the feature article "Intracellular Activity, Potential Clinical Uses of Antibiotics" Robert M. Rakita (*ASM News*, 64, 570, 1998) discusses the three-way interaction of the pathogens, host defense cells, and antimicrobial agents, especially inside the neutrophils and macrophages. The preparation of newer macrolide and quinoline antibiotics try to achieve higher intracellular levels with greater antimicrobial activities and with minimal cellular damage. The goal being the control and elimination of the infecting bacteria.

What is often over-looked is the broad cellular reactions of antibiotics in addition to their antimicrobial and clinical response. Inhibiting a pathogen's growth with antibiotics usually includes the inhibition of cellular protein synthesis while its elimination depends on its intracellular location and the host's immune responses. Many more conditions can effect the reactivity of pathogens and antibiotics in the complex host tissues than in the controlled in-vitro Tissue Cell Cultures. The variable tissue pathogenicity also contributes to the variable antibiotic sensitivity requiring adjustments for each pathogen and their tissue location.(1)

Prior to the availability and application of antibiotics for the control of diseases, gold salts, arsenicals, sulfa drugs and other various chemicals were used to ward off the offending bacterial pathogens without killing the patient. The clinical application of antibiotics started in the early '40's when penicillin became available during WWII as the first miracle drug from a penicillium mold. A few years later when the broad spectrum tetracycline antibiotics became available their clinical use spread like a gold rush. The bacterial sensitivities and potential clinical application of the new antibiotics were extensively used by clinics and laboratories. The choice of antibiotics was made after the isolation and identification of the infecting agent. The development of allergies and toxicities to some antibiotics limited their use in some patients. Microcidal penicillins inhibit bacterial cell wall synthesis, whereas the tetracyclines (macrolides) are micro static inhibiting protein synthesis and the growth of the wall-less bacteria such as mycoplasmas.

The initial use of high dosage antibiotics in some chronic disease patients may cause a flare or clinical worsening with a serologic rise in antibody titer to a suspected microbial agent such as mycoplasmas. A temporary flare of symptoms following antibiotic treatment is often referred to as a Jarisch Herxheimer reaction. The flares often occur in joints or areas that have been quiet or dormant since the arthritis was first observed. Knowing this the patients are encouraged by the temporary worsening following their antibiotic treatment. The delayed reaction resulting from the release of microbial antigen into the sensitized host tissue as in a "Graft vs. Host" reaction that is not a drug sensitivity. Similarly the occurrence of physical &/or mental stress could also initiate clinical worsening with a rise in microbial antibody titer. The flare reaction could also result from the released microbial antigen complexing with its circulating antibodies to promote Complement Fixation. The antibiotics, tetracyclines, can also act like the immunosuppressant steroids by blocking the formation of the antibiotic+antigen complex that initiates inflammation. Many clinical disorders are considered Immune Complex Diseases of infectious origin, such as rheumatoid arthritis and Lupus, resulting from the activation of complement and proteolytic destruction of tissues with the deposition of Immuine Complex on the kidneys and other tissue cell membranes.

The tetracycline antibiotics are potent metal chelating, complexing, agents and comparable in action to the clinical use of the chelating agents ethylenediaminotetraacetate, EDTA, and penicillamine. Consequently the mode of antibiotic administration, Intravenous or Oral (between meals), could have an affect on the composition of their absorption state and thus their reactivity. When complexed with divalent trace metals (Cu, Zn, Mg, Se, etc.) The antibiotics become antioxidants or electron scavengers. As such the metal antibiotic complex becomes antiinflammatory neutralizing free oxygen radicals. By combining with metaloproteins and metaloenzymes such as collagenase, antibiotic therapy can inhibit collagen tissue destruction. If used excessively in high doses the antibiotics, as protein synthesis inhibitors, could also inhibit the synthesis and function of essential cellular proteins and not just the pathogens.

Because of their immunosuppresive actions the macrolide antibiotics can block and limit the immune complex (Antibody + Antigen) formation and thus stop the complex induced inflammation. In cases with low pathogenic activity, such as mycoplasmas, pulsed antibiotic therapy with lower doses over longer periods has proven more effective and with fewer side effects. Tissue cells will survive intermittent (pulse) treatment of tetracyclines but not constant exposure even at lower doses. In the chronic immunologic disorders of probable infectious etiology high daily antibiotic doses are not essential or effective for the less virulent agents.

Bioassays for antibiotic levels in blood and tissues measures the antimicrobial action that would not explain their other activities based on intracellular concentration.

Although suspected of infectious origin the clinical trials of minocycline antibiotic in rheumatoid arthritis was based primarily

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on its inhibitory action of the metalloenzyme, collagenase, that destroys the connective tissues and joint cartilage causing the inflamed joints.

The effectiveness of treatment with minocin antibiotic was based primarily on the eradication of arthritis inflammation rather than infectious agents. The maximum effectiveness of the antibiotic treatment was found in the duration of therapy indicating a slow healing process that has to balance cell growth versus inhibition of protein synthesis and microbial growth by the multiple antibiotic actions. Growth inhibiting antibiotics may control mycoplasma or microbial growth for an indefinite period until the neutralizing antibodies and immune system process their elimination.

Antibiotics can be used in the identification of the infectious bacterial agent(s). In cases where the agent can not be isolated and identified or the DNA can not be matched it is possible that antibiotic therapy will cause the release of the microbial antigen to initiate a specific antibody response. The serologic measure of a change or response in the serum antibody level to a bacterial infection would indicate its presence. The sero conversion or the increase in antibody titer, resulting from the administration of a vaccine would indicate the host's immune responsiveness to a particular antibiotic therapy. The specificity and sensitivity of the serologic response depends on the test used, such as: growth inhibition, neutralization, agglutination (ELIZA), complement fixation, immunoblotting.

A rise in serum antibody level during the acute to convalescent phase on antibiotic therapy would indicate a concurrent infection or the antigen release from a persisting silent infection. A similar positive sero conversion with a rise in antibodies could be observed in a patient following physical or mental stress. No rise in antibody titer to a vaccine, infection or stress would indicate an immunodeficient agammaglobulinemia subject with limited antibody production and immune defence. In rheumatoid arthritis and other infectious diseases that initiate the anti-antibody response (rheumatoid factor) RF the antibody levels are inversely related causing an apparent decrease or negative sero conversion. Following antibiotic treatment when the mycoplasma antibody level increases, the RF test results will be lower.

The use of generic antibiotics may have the same antimicrobial potency while their systemic action in the host may varay significantly. For example in the treatment of RA the generic minocycline is reportedly less effective than minocin. In some patients this difference in antibiotic action could result from patient differences.