ClinicSearch

International Journal of Clinical Reports and Studies

Alan Kleinman *

Open Access

Review Article

Antibiotic Antagonism and Synergism

Alan Kleinman*

36514 Monarch Canyon Road Coarsegold, CA 93614

***Corresponding Author**: Alan Kleinman. 36514 Monarch Canyon Road Coarsegold, CA 93614

Received Date: December 16 2023 | Accepted Date: December 29 2023 | Published Date: January 05 2023

Citation: Alan Kleinman, (2023), Antibiotic Antagonism and Synergism, *International Journal of Clinical Reports and Studies*, 3(1); **DOI:**10.31579/2835-8295/045

Copyright: © 2023, Alan Kleinman. This is an open-access artic le distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Combination therapy to prevent the evolution of drug resistance can be complicated by the phenome-non of antibiotic antagonism, that is, one drug interferes with the action of other drugs being used. This paper will be used to explain the phenomenon of antibiotic antagonism when it is an important factor when treating infections, and strategies that can be used to counteract this effect.

Keywords: an atrial septal defect; crochet age' sign; electrocardiogram

Introduction

Selection pressures are stressors that kill or impair the reproduction of some or all members of a population. Different selection pressures can affect the actions of one another. A well- known example is thermal stress affecting the action of hypoxia. If someone falls through ice, the low temperature of the cold water or drowning can kill the person. However, the cooling effect of the water can slow the action of drowning and hypoxia. The lethality of deprivation of oxygen to the brain is slowed by the cooling action of the water so a person takes longer to drown in cold water than warmer water. Antibiotics are selection pressures. The principal concept when using a selection pressure such as an antibiotic to treat an infection is to kill the infectious agent. This is a time-dependent process.

Even in an extreme case such as a severely infected limb that is removed by a surgeon, the patient may still have some residual bacteremia or septicemia that is not removed by the surgeon, and further treatment or the patient's own immune system must defeat the infection. It takes time to drive the infection to extinction. Administration of a drug requires absorption of the drug, transport of the drug through the circulatory system, and diffusion of the drug to the site of action. Once the drug reaches the site of action and starts to affect the target bacteria, it takes time to kill the bacteria. Sometimes, one drug can interfere with the action of the other drug and this action is called antibiotic antagonism. A good medical definition of the process is given by "The Free Medical Dictionary" by Farlex. [1] 70

1. Denoting mutual opposition in action among structures, agents, diseases, or physiologic processes. Compare: synergism.

2. A situation in which the combined effect of two or more factors is smaller than the solitary effect of any one of the factors." 75

This concept was presented in the 1950s by a pediatrician and bacteriologist named Ernest Jaweds in his paper "Antibiotic Synergism and Antagonism" [2]. This work was primarily inspired because Dr. Jaweds was treating patients with bacterial meningitis. He was trying to find the most rapid treatment for this extremely severe infection. What he found was those certain combinations of drugs cause antagonism between one drug and another, delaying the treatment and resolution of the infection. This observation led to the study of antibiotic antagonism (and synergism) [3].

Antibiotic Antagonism and Synergism, a time-dependent phenomenon: What Jaweds discovered is that antibiotic antagonism and synergism is a time-dependent phenomenon. Antagonism and synergism are a rate-dependent process. It takes time for antibiotics to work and every given antibiotic has a given mechanism of action that may be different from any other drug. For example, one class of drugs (the penicillin class) affects cell wall production in a particular class of bacteria [4]. A different class of drugs (the macrolide class) affects protein biosynthesis [5]. Other classes of antibiotics can have different mechanisms of action. Combining different classes of antibiotics to treat an infection can give different rates of killing the bacteria. What Jaweds and his coworkers did was investigate this rate- dependent phenomenon for several different antibiotics. They did this by measuring the number of viable bacteria in a ml of solution as a function of time for a variety of combinations of antibiotics. This is an important factor in rapidly progressing infections. An infection of the central nervous system such as meningitis can cause much greater morbidity and mortality if treatment is delayed only a few hours. The rate of killing of bacteria can be done with time-kill kinetic testing. The following is given in reference [6].

"Bactericidal activity is defined as greater than 3 log10 -fold decrease in colony forming units (surviving bacteria), which is equivalent to 99.9% killing of the inoculum. The time-kill analysis can monitor the effect of various concentrations of an antimicrobial agent over time

in relation to the stages of the growth of the bacteria (lag, exponential, stationary phase). Time-kill kinetics assays for agents such as antiseptics require a shorter time-kill kinetics study and follow different methodology. In contrast to the multiple time points in a time-kill kinetics assay, the minimal bactericidal concentration (MBC) test is defined as a 99.9% or greater killing efficacy at a specified time." These types of studies take place over hours, usually about 24 hours. In the clinical situation, treatment of infections can take a wide time span. For example, osteomyelitis or infective endocarditis can take weeks or more to treat [7,8]. Treatment of Tuberculosis can require 4 or more months of treatment [9].

Chronic infectious diseases such as HIV require life-long treatment. These treatment protocols that are much longer than 24 hours can be a factor in the evolution of antimicrobial drug resistance.

The problem of drug resistance vs Antibiotic Antagonism: Antibiotic Antagonism does not exist in a vacuum. The evolution of drug resistance is a significant problem in the practice of medicine. How should the problem of antibiotic antagonism be addressed in the context of the evolution of antibiotic resistance? Is antimicrobial resistance a greater problem than antimicrobial antagonism?

The following factors should be considered when using antimicrobial agents. The rate at which a given infection causes morbidity to the patient is an important factor in a rapidly progressing infection such as meningitis. The damage that such an infection causes to the central nervous system makes antibiotic antagonism an important issue to consider. Delaying the eradication of such an infection can cause irreducible injury to the patient. Therefore, antibiotic antagonism should be considered in such cases.

121 If drug-resistant variants of a given agent are known to exist in a given environment (such as variants of community methicillin-resistant staphylococcus aureus), then one could expect a high probability of treatment failure to such an infection due to those drug-resistant variants and a second drug (or more) will be necessary to treat those drug-resistant variants. This problem can be alleviated by an awareness of the existence of these drug-resistant variants and microbial drug culture and sensitivity results of the microbial populations in the environment. This will allow the clinician to choose two (or more) antibiotics to treat the given infection and address the issue of the drug-resistant variants. If the infection is rapidly progressing such as meningitis, then the choice of drugs used needs to not antagonize each other.

When treating long-term or chronic infections where the microbe still can replicate, this introduces the possibility that a resistant variant can appear through the evolutionary process during the treatment. Even though resistant variants do not exist at the time of initiation treatment of the patient, a drug-resistant variant appears during the treatment of the patient. The probability of this happening is markedly reduced by the use of combination antimicrobial therapy as demonstrated by the successful treatment of HIV. 138

The infectious agent is not the only microbe in a patient: The clinician needs to consider that the microbe causing an infection in a patient is not the only microbe inhabiting the patient. There are colonizing microbes on the patient's skin, in the sinuses, and in the respiratory tract. And the gastrointestinal tract has a huge microbe load. In the process of a clinician treating an infection, the clinician is also applying selection pressure on the colonizing microbes. The colonizing microbes are not causing infection at the time of treatment but, under the right circumstances, these microbes can cause infection. The probability of selecting these resistant variants can be reduced by combination therapy. Time-kill studies do not take into account this possibility.

Discussion:

The occurrence of antimicrobial antagonism is a real phenomenon that occurs between certain classes of antimicrobial agents. This antagonism does not mean that one drug is an antidote for the other drug. It means that in some circumstances, one drug will briefly delay the killing effect of the other antimicrobial agent. This effect will have clinical significance in rapidly progressing infections such as meningitis and other rampant infections. This effect must be taken in the context of existing drug resistance and evolving drug resistance. If the drug combination chosen works synergistically, then, that should address this problem.

Conclusion:

The are many issues to consider when choosing an antimicrobial agent (or agents) to treat an infection. First, one must choose an agent (or agents) that is/are effective. The patient cannot be allergic to the chosen agent and needs to be able to tolerate the substance. One needs to know if the agents interfere with one another especially if you are treating a rapidly progressing infection. The patient's immune status is important as are other comorbidities. The existence of drug-resistant variants in the infectious agent population or the possibility of drug-resistant variants evolving during the treatment period must be considered.

The following quote is taken from reference [10], page 132, by Dr. Jaweds, et al. **"Antagonism** is sharply limited by time-dose relationships and is therefore a rare event in clinical antimicrobial therapy. Antagonism resulting in morbidity and mortality has been most clearly demonstrated in bacterial meningitis. It occurred when a bacteriostatic drug (which inhibited protein synthesis in bacteria) such as chloramphenicol or tetracycline was given with a bactericidal drug such as a penicillin or an aminoglycoside. Antagonism occurs mainly if the bacteriostatic drug reached the site of infection before the bactericidal drug, if the killing of bacteria was essential for cure, and if only minimal effective doses of either drug in the pair were present. Antagonism can be overcome by large execs amounts of one or both drugs in the pair—a common event clinically—and it very rarely affects the outcome of clinical therapy." 174 Antimicrobial antagonism is a real phenomenon but this phenomenon must be kept in perspective. It is only important clinically in specific circumstances but drug resistance is always a possibility in virtually all circumstances.

Reference

1. The Free Medical Dictionary, Farlex, last acess 11/13/2023,
2. E. Jawetz, M.D., Ph.D., J. B. Gunnison, M.A., and R. S. Speck, M.D., (1951). Antibiotic Synergism andAntagonism, The New England Journal of Medicine, December 20, , N Engl J Med 1951; 245:966-968,
3. Jawetz E, Gunnison JB, Speck RS, Coleman VR. (1951). STUDIES ON ANTIBIOTIC SYNERGISM AND ANTAGONISM: The Interference of Chloramphenicol with the Action of Penicillin. AMA Arch Intern Med.;87(3):349–359.
4. Penicillin, (2023). Wikipedia, Last Edited on 5 November, at 17:16 (UTC),

5. Macrolide, (2023). Wikipedia, Last Edited on 1 November, at 14:21 (UTC).
6. Emery PHARMA. Copyright © 2023 Emery Pharma. Time-Kill Kinetics Assay.
7. Fritz JM, McDonald JR. (2008). Osteomyelitis: approach to diagnosis and treatment. Phys Sportmed.2008 Dec;36(1): nihpa116823.
8. Tackling G, Lala V. (2023). Endocarditis Antibiotic Regimens. [Updated 2023 Apr 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing;
9. Centers for Disease Control and Prevention. Last Reviewed: March 22, 2023. Tuberculosis (TB), Treatment for TB Disease. U.S. Department of Health & Human Services.
10. Jawetz, E., Melnick, J.L., Adelberg, E.A., (1984.) Review of Medical Microbiology, 16th edition, Lange Medical Publications,

Ready to submit your research? Choose ClinicSearch and benefit from:

- fast, convenient online submission
- rigorous peer review by experienced research in your field
- rapid publication on acceptance
- authors retain copyrights
- unique DOI for all articles
- immediate, unrestricted online access

At ClinicSearch, research is always in progress.

Learn more https://clinicsearchonline.org/journals/international-journal-of-clinical-reports-and-studies

ClinicSearch

© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/. The Creative Commons Public Domain Dedication waiver (http://creativeco mmons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated in a credit line to the data.