The Advantage of Bactericidal Drugs in the Treatment of Infection

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Introduction

Bactericidal antibiotics are generally thought to be superior or even required therapy in three settings: treatment of endocarditis and meningitis, and in neutropenic patients. The advantage of bactericidal drugs in the treatment of bacterial infection is clear in concept but would benefit from a better understanding of the nature of bactericidal and bacteriostatic drugs, and careful clinical study. The demarcation between slowly bactericidal and bacteriostatic drugs can be unclear, and some drugs are classified as both bactericidal and bacteriostatic, depending on the bacteria and test conditions. In addition, there is clearly a time gradient within the drugs classified as bactericidal, with some drugs rapidly bactericidal, whereas others are only marginally different from the drugs classified as bacteriostatic. The generation of drug resistance in bacteria is more closely linked to mechanism of action than to the classification of bactericidal versus bacteriostatic. Conclusive clinical comparisons of bactericidal versus bacteriostatic drugs in controlled settings are rare and generally not powered to conclusion. This is based in part on the reluctance to use bacteriostatic drugs in some serious settings, and partially on the inability of trial design to capture subtle outcome differences in speed of response in less serious settings in which bacteriostatic versus bactericidal comparisons could be made. However, bactericidal drugs are the primary choice in the treatment of serious infections in which failure to rapidly resolve infection has serious consequences.

In Vitro Classification of Bactericidal Drugs

The classification of a drug as bactericidal or bacteriostatic is based entirely on in vitro performance. The most common method is to determine the ratio of minimum bactericidal concentration (MBC) to minimum inhibitory concentration (MIC). The MIC value usually is determined in broth and is the concentration of drug to inhibit growth of the test bacteria as determined by a turbidity measurement after incubation of the bacteria in broth and drug. The MIC value is determined by a readout of the bacteria in the presence of drug. The MBC is a more rigorous test and is the concentration of drug that kills a significant proportion of bacteria during incubation in broth. The MBC is determined by dilution plating of the surviving bacteria onto solid or liquid media in the absence of additional drug. A drug that produces a MBC/MIC ratio of 4 or less is considered bactericidal.

A second method used to classify drugs as bactericidal is based on the speed of bactericidal action through a time-kill experiment. Cidality is defined by a reduction in the bacterial cell count of at least 3 $\log_{10}$ within 24 hours of incubation with the drug. This method produces continuous data in the form of hours to achieve a 3 $\log_{10}$ kill. In this experiment, drug and a known concentration of bacteria are incubated together in broth and dilution plated onto solid agar at various time points. The proportion of survivors is determined, and the time to achieve a significant kill is calculated. There is generally a good correlation between the MBC/MIC method and the time-kill method for the classification of drugs as bactericidal or bacteriostatic.

Some antibacterials, such as fluoroquinolones, aminoglycosides, and the newly approved lipopeptide, daptomycin, are bactericidal under nearly all test conditions [1–3]. Against susceptible bacteria, the β-lactams are nearly always bactericidal (with activity against the enterococci a notable exception), as are the glycopeptides [1]. Linezolid usually is considered bacteriostatic but may just meet the criteria for cidality against certain pathogens under certain conditions, and vancomycin may be bacteriostatic against some susceptible *Staphylococcus aureus* isolates [4]. The macrolides, tetracyclines, and trimethoprim-sulfonamide combination are bacteriostatic under normal test conditions [5–7]. To further complicate this classification, some of these drug classes are considered to be bactericidal and bacteriostatic against susceptible bacteria, depending on the bacteria species and test conditions.

There is a significant range in the degree of bactericidal activity for the antibacterial drugs. For example, daptomycin is rapidly bactericidal and achieves a 3 $\log_{10}$ bacterial kill in 30 to 60 minutes against *S. aureus* in vitro [3]. In contrast, vancomycin can require 14 to 24 hours of incubation to

achieve bactericidal activity against *S. aureus* [8]. Fluoroquinolones are intermediate in speed of cidality and generally are more rapidly bactericidal than β-lactams or vancomycin [9]. Although daptomycin and vancomycin can be classified as bactericidal, daptomycin achieves cidality much more rapidly, with an advantage of more than 13 hours.

Bactericidal Drugs and Resistance

In theory, bactericidal drugs would be less likely to induce resistance than would bacteriostatic drugs based on the premise that dead bacteria cannot mutate. The duration of the pharmacokinetic "window" between the MIC value (at which the bacteria are only inhibited) and the mutant prevention concentration (or bactericidal concentration at which bacteria are irreversibly unable to replicate) can influence the incidence of resistance [10]. The selection of resistance has more to do with the mechanism of action than the classification of cidality. Drug resistance likely will occur with some frequency when single mutation in the binding site results in significantly decreased susceptibility, such as alteration of the S12 ribosomal protein resulting in streptomycin resistance. The β-lactams, fluoroquinolones, macrolides, and oxazolidinones all show significant loss in potency against alterations in the bacterial target site. Resistance through the production of degrading enzymes such as β-lactamases or through intracellular drug export pumps also affects bactericidal and bacteriostatic drugs. Decreases in *S. aureus* susceptibility to vancomycin have been slow to develop, possibly because of the multiple steps apparently involved in alteration of the cell wall. However, the recent identification of two isolates of *S. aureus* with vancomycin resistance has raised concern regarding the transfer of resistance elements between enterococci (with a higher level of vancomycin resistance) directly to *S. aureus* [11].

Does Bactericidal Activity In Vitro Translate to Clinical Advantage?

Endocarditis, meningitis, and infections in neutropenic patients are three clinical settings in which bactericidal drugs are commonly thought to be superior. However, the difficulty in conducting clinical trials in these settings and the serious consequences of treatment failures severely limit comparative clinical data of bactericidal versus bacteriostatic drugs. In these settings, the speed of response is perceived as a critical factor. Bacterial endocarditis or meningitis infections that persist for even a few additional days can cause irreversible damage to critical areas of the body, resulting in poor outcome. In these settings, the use of bactericidal drugs is the first option.

In the treatment of enterococcal endocarditis, the use of the bactericidal combination of aminoglycoside plus penicillin was superior to the bacteriostatic treatment with penicillin alone [12]. The widespread use of gentamicin in combination therapies with vancomycin or semisynthetic penicillins for treatment of endocarditis is mainly based on the in vitro improvement in bactericidal activity. The treatment of methicillin-resistant *S. aureus* (MRSA) in endocarditis is difficult because vancomycin and linezolid are very slow on the cidality scale or may even be considered bacteriostatic. Daptomycin is rapidly bactericidal versus MRSA and is undergoing study for treatment of *S. aureus* (including MRSA)–associated endocarditis.

In the treatment of meningitis, successful therapy depends on rapid sterilization of the cerebrospinal fluid (CSF) and modulation of the inflammatory response that can be exacerbated by the rapid lysis of infecting bacteria. In an older study of neonates with gram-negative meningitis, treatment with a single bactericidal drug (cefotaxime) yielded more rapid sterilization of the CSF and a higher survival rate [13] than indicated by data generated previously with combination therapy with ampicillin and gentamicin [14]. In a 1951 study of *Streptococcus pneumoniae* meningitis [15], the use of penicillin produced better survival rates than the combination of penicillin plus chlortetracycline, possibly because the use of the bacteriostatic protein synthesis inhibitor chlortetracycline inhibited the bactericidal activity of penicillin. These older studies highlight the difficulty in obtaining comparative clinical data regarding the efficacy of bactericidal versus bacteriostatic drugs for the treatment of meningitis.

Infections in neutropenic patients are a third setting in which bactericidal antibacterials are a first choice of therapy. Most often, these patients are immunosuppressed from cancer therapy or because of HIV infection. Immunosuppressed patients can contribute less to infection resolution from their own immune system. Early trials from the 1970s demonstrated that the bactericidal combination of β-lactams plus aminoglycosides was superior to treatment with aminoglycoside alone [16,17]. Most of the recent studies in neutropenic patients have used bactericidal drugs, alone or in combination, unless there is specific intolerance. Experiments in neutropenic mice have tended to demonstrate the greater difficulty in treatment of immunosuppressed patients and the value of bactericidal antibiotics [18]. Rapid elimination of the bacterial infection is the preferred option when there is a significant impairment in the immune response.

The value of bactericidal drugs in other less serious clinical situations conceptually should lead to superior clinical outcomes, even if the consequences of failure are not as dramatic. However, capturing the subtle differences in outcome, such as speed of response, eradication of pathogen, or induction of resistance, can be challenging. Recent clinical data in treatment of otitis media and pharyngitis have indicated the value of bacterial eradication and bactericidal drugs [19,20]. In these settings, multiple factors including adverse event profiles of the drugs should be considered. Nevertheless, the value of bactericidal drugs for treatment of moderate bacterial infections is clear, even in infections with typically nonlethal outcomes.

Conclusions

Bactericidal drugs potentially have a significant advantage in the treatment of infection. Conceptually, bactericidal drugs should result in faster resolution of infection and better outcomes, especially in situations of moderate and severe infections with serious outcomes. Clinical data demonstrating the superior activity of bactericidal drugs or even advantages of rapidly versus slowly bactericidal drugs are much more difficult to obtain. Clinical trials are designed to maximize efficacy of all arms. In these settings, bactericidal versus bacteriostatic trials are rare. However, there is an acceptance of the value of bactericidal drugs in the treatment of moderate and serious infections. The potential comparative advantage of bactericidal drugs relating to the treatment of mild/moderate infections is largely based on small case studies. Additional investigation of the performance of bactericidal drugs in a variety of experiment and clinical settings could optimize the established use of bactericidal drugs. Therapy with rapidly bactericidal drugs should be considered as a first option in infection settings in which treatment failure is of serious consequence or speed of response is important.

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