Pharmacokinetic Contributions to Postantibiotic Effects
Focus on Aminoglycosides

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Summary

The postantibiotic effect (PAE) refers to a period of time after complete removal of an antimicrobial during which there is no growth of the target organism. The PAE appears to be a feature of most antimicrobial agents and has been documented with a variety of common bacterial pathogens. Various factors influence the presence or duration of the PAE including the type of organism, type of antimicrobial, concentration of antimicrobial, duration of antimicrobial exposure, antimicrobial combinations, and inoculum and medium used.

β-Lactams demonstrate a PAE against Gram-positive cocci, but produce only a short PAE with Gram-negative bacilli. Antimicrobial agents that inhibit RNA or protein synthesis have a PAE against Gram-positive cocci and Gram-negative bacilli.

In vivo studies of aminoglycosides suggest that area under the plasma concen-
The postantibiotic effect (PAE) refers to the time period after complete removal of an antimicrobial during which there is no growth of the target organism.\(^1\) This suppression of bacterial growth that occurs following short exposure to antimicrobial agents is not a new phenomenon.\(^2\) In 1946, Parker and Marsh\(^3\) demonstrated that staphylococci exposed to benzylpenicillin (penicillin G) for 30 minutes and transferred to a penicillin-free medium did not resume normal growth for 3 hours. These investigators noted that there appeared to be a time-concentration relationship in the production of this effect. Higher concentrations of the penicillin and/or longer exposure of the organism to the antimicrobial resulted in greater bacterial killing and a longer time for resumption of normal growth. Subsequently, Eagle\(^4\) reported that benzylpenicillin induced a PAE against various Gram-positive cocci and that these organisms, after exposure to benzylpenicillin, were extraordinarily susceptible to the defence mechanisms of the body.

Even at this early stage, researchers postulated that the PAE would greatly increase the knowledge of the theoretical basis for the administration of antimicrobial chemotherapy. With its potential for increasing our knowledge in this area, it is surprising that this important area of research was not extended to other organisms and antimicrobials. In fact, it was not until the last 15 years that other antimicrobials and Gram-negative bacteria were investigated.\(^5,6\) Today, investigators and clinicians realise that the PAE is an important pharmacodynamic parameter with an essential influence on the design of antimicrobial dosage regimens.

In this paper we review the factors that affect the PAE. More importantly, we focus on aminoglycosides and discuss how the PAE has been an important pharmacodynamic parameter in redesigning aminoglycoside dosage regimens.

1. Factors Affecting the Postantibiotic Effect (PAE)

Although several methods have been used to follow bacterial growth kinetics following drug removal, the PAE is best quantitated by calculation from growth curves. The viability curves of a standard staphylococcus species during a 2-hour exposure to benzylpenicillin and after drug removal either by washing, dilution or inactivation are illustrated in figure 1. The PAE is quantified by the following equation:

\[
PAE = T - C
\]

where \(T\) is the time needed for the bacterial count [measured in colony-forming units (cfu) per ml] in the test culture to increase \(1 \log_{10}\) above the count observed immediately after drug removal, and \(C\) is the time required for the count in an untreated control culture to increase by \(1 \log_{10}\) above the count observed just after completion of the same procedure used on the test culture.\(^7,8\) PAE is usually expressed in hours.

The PAE is a feature of most antimicrobial agents and has been documented with a variety of common bacterial pathogens. However, several factors influence the presence or duration of the PAE and are discussed in more detail in sections 1.1 to 1.9.

1.1 Type of Organism

The majority of published data with Gram-positive cocci include *Staphylococcus aureus*, although data are available for *Streptococcus pneumoniae*, *S. faecalis*, *S.agalactiae* and *S. pyogenes* (table I). The majority of published data with Gram-ega-