Aminoglycoside nephrotoxicity

Introduction

Since the discovery of streptomycin in 1944, aminoglycosides have endured as indispensable agents in the antimicrobial armamentarium. This is despite their well described potential for serious nephrotoxicity and otoxicity and the emergence of other classes of antibiotics with similar antibacterial spectrums. The major aminoglycoside antibiotics in clinical use worldwide include gentamicin, tobramycin, amikacin, netilmicin, neomycin, isepamicin and arbekacin. These agents remain in clinical use against gram negative infections largely because of their dependable efficacy. Several attributes render these antibiotics particularly effective. First, aminoglycosides exhibit a concentration-dependent bactericidal activity [1, 2]. Unlike the β-lactams, the bactericidal activity of aminoglycosides depends more on their concentration rather than the duration of antimicrobial exposure. Furthermore, the bactericidal efficacy increases with increasing
Aminoglycosides also exhibit a post-antibiotic effect meaning they continue to kill bacteria even after the aminoglycoside concentration has fallen below the bacterial minimum inhibitory concentration. Another useful attribute of aminoglycosides is their synergism with antibiotics that inhibit bacterial cell wall biosynthesis, such as β-lactams and vancomycin. Finally, aminoglycosides have relatively predictable pharmacokinetic characteristics that allow them to be dosed to minimize their inherent toxicities. However, despite this predictable pharmacokinetic profile, aminoglycosides always retain their potential for serious toxicity. Moreover, aminoglycoside toxicity can occur despite the maintenance of serum levels in the therapeutic range. The purpose of this section is to describe the nephrotoxicity associated with the clinical use of aminoglycoside antibiotics.

Epidemiology of aminoglycoside nephrotoxicity

Numerous individual studies and meta-analyses have shown the incidence of aminoglycoside nephrotoxicity is quite variable with a reported range of from 0 to 50% [3-24]. There are several explanations for this marked variability in incidence. First, the various studies differed in the parameters used to define nephrotoxicity. Some studies used increases of serum creatinine as the threshold for nephrotoxicity; others used a percentage increase of serum creatinine from a baseline value as the guide. In addition, not all of the studies used the same aminoglycosides or treated similar patient populations. This is significant since aminoglycosides differ in their nephrotoxic potential. Smith et al. noted renal impairment in 26% of patients who received gentamicin, but only 12% of patients who received tobramycin [11]. Not surprisingly, an elderly cohort of patients with extensive co-morbid disease or the critically ill had a much greater incidence of nephrotoxicity as compared to a cohort of healthier subjects [19, 20, 95]. The studies reviewed also differed in the type of infections treated and the duration of aminoglycoside therapy administered [4]. Finally, whether a study utilized a conventional pharmacokinetic monitoring program or a once daily aminoglycoside (ODA) regimen was important since ODA programs may attenuate the risk of nephrotoxicity [3]. Despite this variability, however, an overall incidence of nephrotoxicity of from 5 to 10% of patient courses has been reported in the majority of studies [19, 95].

Risk factors for aminoglycoside nephrotoxicity

Several risk factors can predispose a patient to nephrotoxicity after an aminoglycoside is administered. Aminoglycosides differ in their inherent nephrotoxic potential, so the choice of a specific agent can be clinically important. This inherent aminoglycoside nephrotoxicity appears to be related to the degree to which an aminoglycoside concentrates in the renal cortex after administration. Streptomycin does not concentrate in the renal cortex and is the least nephrotoxic aminoglycoside. Conversely, neomycin concentrates to the greatest degree in the renal cortex and is the most nephrotoxic [2]. As a result, neomycin is not used as a systemic agent. Differences in the nephrotoxicity of gentamicin and tobramycin remain controversial. However, one early study demonstrated less nephrotoxicity with tobramycin as compared to gentamicin [11]. In contrast, amikacin appears to have similar nephrotoxic potential as gentamicin [17]. Netilmicin has been shown to have less nephrotoxic potential than tobramycin [26]. When considered as a group, gentamicin appears to have the greatest nephrotoxic potential followed in decreasing order of nephrotoxicity by tobramycin, amikacin and netilmicin [30].

Other aminoglycoside-related factors that have been shown to predispose patients to nephrotoxicity include prolonged duration of therapy and elevated serum aminoglycoside levels [9, 20, 21, 22, 29]. Studies have shown that patients treated with aminoglycosides for longer than one week have a greater incidence of nephrotoxicity. In one study, 3.9% of elderly patients treated for seven or fewer days developed nephrotoxicity compared to 30% of patients treated for 8 to 14 days and 50% treated for more than 14 days [22]. Both elevated peak and serum trough levels have been shown to increase the incidence of nephrotoxicity. Koo et al demonstrated that a peak serum level of greater than 12mg/dL increased the incidence of nephrotoxicity in elderly patients [9]. A trough greater than 2.5 mg/dL was also shown to be an important cause of nephrotoxicity in another study of elderly patients [21].

Patient-related factors can have a significant impact on the risk of aminoglycoside nephrotoxicity. Bertino et al. observed that advanced age, ascites, male gender,