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AMINOGLYCOSIDES: OLD FRIEND…NEW FOE?

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Over a relatively short period,cystic fibrosis (CF) has gone from a disease of dying children to one where survival well into adulthood is expected. It was recently reported that by 2025, the adult CF population in Western Europe would increase by 75% (1). Although the reasons for improved survival are complex, one contributor is the aggressive use of antibioticsincluding aminoglycosides.However, aminoglycosides have well-recognised adverse effects, particularly nephrotoxicity and ototoxicity. Clear relationships between these effects and aminoglycoside concentrations or exposure have yet to be defined.

Acute kidney injury has been associated with longer courses of aminoglycoside therapyand is often reversible. The impact on renal function of cumulative exposure from the multiple coursesof aminoglycosides commonly encountered by patients with CF is less clear.Al-Aloul et al (2)identified a negative linear relationship between the lifetime number of aminoglycoside courses and creatinine clearance, particularly in the presence of IV colistin, whereas Pedersen et al (3) found no correlation between cumulative tobramycin dose and glomerular filtration rate, and Alghanem et al (4) found no change in aminoglycoside clearance over time in adultswho had received between 10 and28 courses.Variations in dosing and monitoring approaches, frequency and duration of individual courses and the presence of other risk factors confound the interpretation of the findings in these studies. It is also not clear whether multiple courses over a short time are more risky than the same number over several years.

Studies have also failed to clearly identify the level of exposure that would lead to an unacceptable risk of ototoxicity. Although hearing loss is more likely in patients who have received multiple courses of aminoglycoside therapy, the nature of this relationship is likely to be non-linear and linked to other factors, such as age and lung function (5). The precise prevalence of ototoxicity is unclear as data are limited, but in one series (n=153) of adult CF patients, 50.8% had some evidence of auditory impairment (6). We need more studies, not only to accurately quantify the problem, but also to identify the potential contribution of other potentially ototoxic drugs (e.g. azithromycin), other routes of administration (e.g. nebulised tobramycin) and to allow us to compare tobramycin, non-aminoglycoside IV antibiotics (e.g. colistin) and amikacin, since the risks of ototoxicity and nephrotoxicity may not be the same for these antibiotics. This is particularly important with the increasing use of amikacin to treat infections such as non-tuberculous mycobacteria.

So, what is the answer? Can we reduce the need for aggressive IV antibiotic policies in the era of multiple inhaled antibiotics - especially if the promise of better lung health with the early use of gene/protein modifying therapies is realised? When IV aminoglycosides cannot be avoided,

alternative dosing regimens and adjunctive therapies may be useful. The 'TOPIC' study proved that once daily dosing has equal efficacy to thrice daily dosing, with less nephrotoxicity for children (7), while the prospective, randomised study by Prayleet al in the current edition of the Journal challenges current practices regarding the timing of once-daily dosing (8). Despite no detectable difference in tobramycin clearance between morning and evening administration, the finding of a raised KIM-1 (a biomarker of nephrotoxicity) suggests that aminoglycoside doses may be bettergiven in the morning rather than at night. Perhaps more importantly, it encourages us to consider novel ways of administering old drugs to improve long term safety.

Another approach may be to use adjunctive therapy to mitigate the risks. In the current edition of the Journal, Fox et alinvestigate the co-administration of high doses of D-methionine and tobramycin to guinea pigs and found that methionine reduced tobramycin-induced ototoxicity without interfering with the anti-microbial effect (9). Previous studies with potentially 'protective' therapies, such as N-acetyl cysteine and aspirin, have highlighted the challenges of translating this approach into clinical practice;nevertheless,the principle holds promise.

A key issue for the future is the need for a more standardised approach to the monitoring of adverse effects, particularly ototoxicity. Collaboration with colleagues in audiological and renal medicine will be important to develop effective guidelines.There is increasing evidence to support the introduction of routine audiometric testing, both as a safety measure and to support further research into the relative importance of drug exposure, genetic susceptibility and ageing on the development of ototoxicity. The methods used to assess hearing and vestibular function are also important since standard pure tone audiometry may be unable to detect the minor changes in hearing identified by more sensitive techniques (5).

Unless there is a dramatic shift in antibiotic drug discovery, we will rely on aminoglycosides for the foreseeable future. Undoubtedly they have been a 'friend' of the CF community for a long time, however, this relationship is now under scrutiny….less a 'foe'…. more a matured relationship which needs re-adjustments to ensure we optimise their use to enhance both the quantity and quality of our patients' lives as they grow older.

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