Pediatr Nephrol (2009) 24:925–928
DOI 10.1007/s00467-008-1036-2

EDITORIAL COMMENTARY

# Cystic fibrosis, aminoglycoside treatment and acute renal failure: the not so gentle micin

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Received: 26 August 2008 / Revised: 30 September 2008 / Accepted: 2 October 2008 / Published online: 13 November 2008


**Abstract** Aminoglycosides have a wide spectrum of gram-negative anti-bacterial activities and are available at low cost, which makes them commonly used drugs, especially for patients with cystic fibrosis (CF), who often suffer from chronic lung infections from *Pseudomonas aeruginosa*. Unfortunately, this treatment seems to have resulted in an increased incidence of acute renal failure (ARF) in patients with CF. A recent case–control study investigated risk factors for ARF in CF patients and suggested intravenous use of gentamicin as the prime culprit. Moreover, in most cases, at least one other risk factor, such as CF-related diabetes, pre-existing renal failure, dehydration or concurrent use of other nephrotoxic drugs, was present. We comment on the renal handling of aminoglycosides and the possible mechanisms of toxicity, as well as strategies for risk minimisation.

**Keywords** Cystic fibrosis · Aminoglycoside · Gentamicin · Acute renal failure · Children

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## Introduction

Aminoglycosides (AGs) are commonly used in the treatment of gram-negative infections, because of their wide spectrum of anti-bacterial activities and comparatively low costs. They have good efficacy against *Pseudomonas aeruginosa*, which makes them especially useful in patients with cystic fibrosis (CF), who typically suffer from chronic lung infection from this bacterium. However, the use of AGs has possible side effects. In a recent case–control study Smyth et al. identified AG use as a key risk factor for the development of acute renal failure (ARF) in CF patients [1]. The study was based on a previous report by the same group in which they had identified 24 confirmed cases of ARF in CF patients, establishing the incidence of ARF, somewhat vaguely defined as "raised plasma creatinine for age", as approximately 100-times higher in children with CF (4.6–10.1 cases/10.000 CF patients per year) than the background incidence (7.5 cases/1,000,000 per year) in the UK [2]. Of these 24 cases, 21 were associated with acute AG exposure. The nephro- (and oto-) toxicity of aminoglycosides has long been known, but how does it occur and what can be done to prevent this complication?

## Mechanism of toxicity

Several mechanisms have been proposed for AG toxicity, including disruption of lysosomal function, induction of apoptosis via the calcium-sensing receptor and interference with protein synthesis (reviewed in [3]). The key mechanism of toxicity, however, appears to be related to its bacteriostatic effect: AGs bind to bacterial ribosomes, reducing fidelity of transcription and thus leading to errors in bacterial protein synthesis (reviewed in [4]). Human

mitochondrial ribosomes bear structural resemblance to bacterial ribosomes, consistent with the bacterial ancestry of mitochondria [5]. This makes mitochondrial function particularly prone to AG toxicity.

## Aminoglycosides and the kidney

AGs are non-protein bound drugs and, thus, are freely filtered by the glomerulus. Re-uptake can occur via megalin-mediated endocytosis in the proximal tubule [6]. This leads to increased concentration of AGs in proximal tubule cells and, therefore, the particular susceptibility of the kidney to AG toxicity [7]. Thus, mitochondrial dysfunction in the proximal tubule is the expected consequence of AG toxicity, and this is, indeed, concordant with the clinical findings: AG-induced kidney failure is typically non-oliguric, with evidence of proximal tubular dysfunction and damage (reviewed in [8]) and occasionally frank renal Fanconi syndrome [9]. Occasionally, more distant tubular segments are affected with a Bartter-like syndrome [10] or renal magnesium wasting [11].

An interesting point in the paper by Smyth et al. is the fact that not only acute AG use (within a week of ARF onset) but also previous administration in the preceding year were identified as risk factors. Duration of aminoglycoside therapy and cumulative exposure had previously been identified as risk factors for nephrotoxicity in the general population [12]. However, with the limitations of a case–control study, it is impossible to determine whether AGs may actually cause subclinical long-term damage, predisposing to subsequent ARF, or whether more frequent AG exposure just reflects more severely ill patients.

## Prevention of aminoglycoside-induced acute renal failure

So, what can be done to prevent AG-induced ARF? Avoidance of AG use would clearly eliminate this complication, but, given their antibacterial efficacy, their long track record of use and their low cost, this would not be practicable in clinical reality. Yet other measures can help.

## Dose monitoring

Toxicity is dose-dependent and related to glomerular kidney function. In their previous paper, Smyth's group showed that trough levels in their CF patients exceeded the recommended value of 2 mg/l in nine out of 21 patients with ARF [2], demonstrating the importance of meticulous dose monitoring.

## Dosage frequency

Once-daily administration of aminoglycoside has been shown to have good clinical efficacy in CF patients [13] but less toxicity than two- or three-times daily administration in animals [14] as well as humans [15]. This makes sense, as megalin-mediated AG uptake in the proximal tubule is saturable. Thus, the high plasma levels after a single dose may exceed the uptake capacity of the proximal tubule, so that, overall, less AG enters the proximal tubule cells. Yet, 19 of the 21 patients received three-times daily dosing [2].

## Mode of administration

In order to avoid systemic toxicity, one can administer AGs in nebulised form to treat pulmonary infections, which results in minimal systemic absorption yet satisfactory clinical efficacy for both gentamicin and tobramycin [16, 17]. Indeed, concurrent nebulised AG did not confer an increased risk for ARF in the study by Smyth et al. [1]. However, ARF in the context of inhaled tobramycin has been reported [18]. Thus, drug level monitoring may be advisable, even with this form of administration, especially before commencement of intravenous therapy of the same drug, to assess baseline systemic concentration.

## Choice of aminoglycoside

In their paper Smyth et al. demonstrated an association of ARF with exposure in the previous year to gentamicin, but not tobramycin [1]. Interestingly, they did not examine the choice of AG for the acute administration, but their previous survey showed that 18/21 cases of ARF were in the context of acute gentamicin exposure and 3/21 with tobramycin [2]. A concomitant survey of prescribing practices showed that, actually, more CF centres prescribed tobramycin than gentamicin, suggesting that the increased incidence of ARF with gentamicin reflected true increased nephrotoxicity of this drug rather than just prescribing patterns. And, indeed, there is previous evidence for increased toxicity of gentamicin in the general population [19]. Moreover, resistance to gentamicin has been found in the majority of *Pseudomonas aeruginosa* identified in patients with CF in the UK and many other countries, making it a poor choice not only because of side effects [20, 21].

## Risk factors for acute renal failure

Despite renal expression of cystic fibrosis transmembrane regulator (CFTR), the kidney itself seems to be primarily unaffected [22]. Nevertheless, patients with CF do have an increased risk for kidney-related problems such as stone disease or ARF, because of secondary complications: increased salt loss through sweat promotes dehydration [23]; intestinal fat malabsorption due to pancreatic enzyme deficiency leads to hyperoxaluria [24]; moreover, diabetes mellitus-related nephropathy [25] and chronic infections with potential immune complex deposition [26] are well recognised risk factors. Some of these obviously become more prominent with the increasing life expectancy of CF patients. Smyth et al. also investigated the presence of such risk factors, specifically pre-existing renal disease, concurrent use of other nephrotoxic drugs, CF-related diabetes mellitus, sepsis and dehydration. At least one of those risk factors was present in 18 of the 24 patients but only 7 of the 42 controls [1]. This is not surprising and highlights the cumulative effect of various nephrotoxic pathways. Several of those risk factors may simply potentiate the toxicity by decreasing glomerular filtration rate (GFR), as the resultant, prolonged, slow and steady delivery of AG to the luminal re-uptake receptors will enhance AG re-uptake. This could explain, for instance, the additive toxicity of non-steroidal anti-inflammatory drugs, which should be avoided. Lung infections and subsequent deterioration of lung function are still the one and major problem in most patients affected by CF, and concomitant administration of several potentially nephrotoxic antibiotics such as colistin, vancomycin and aminoglycosides is sometimes required to treat acute exacerbations of chronic lung infections. However, this should be carefully considered with respect to nephrotoxicity. The use of pre-drug hydration has not been studied systematically for AG treatment. However, this has been shown to be extremely successful for other nephrotoxic drugs such as cisplatin and makes intuitive sense also for AG use [27]. Thus, once-daily dosing regimens as well as GFR-appropriate dosing, checked by drug level measurements, and adequate hydration should be a prerequisite for AG treatment, particularly for children with CF.

## Genetic susceptibility to aminoglycoside toxicity

The ototoxicity of AG has been linked to a particular mitochondrial 12S rRNA gene mutation, m.1555A>G, which facilitates the binding of AGs to mitochondrial ribosomes [28]. Whilst there are no reports of concomitant renal failure in those patients with aminoglycoside-induced deafness, there have been no studies investigating this, and there is no reason to exclude a priori pathogenicity of this mutation in the kidney. If proven, a simple genetic test could identify those patients at risk for toxicity and in whom AG use should be considered carefully.

## Conclusion

There has been a steady improvement in the life expectancy of patients with CF over the past decades [29–31]. Part of this improvement comes from the establishment of early and improved diagnostics [32, 33] and the aggressive treatment of chronic lung infections, often using AGs. The study by Smyth et al. highlights that this approach is not without risk. Importantly, it shows potential strategies that minimise this risk, consistent with previous studies: that co-administration of other nephrotoxic medications should be avoided; adequate hydration should be ensured, and dosing should be once daily with meticulous attention to drug levels. Moreover, given the resistance pattern to gentamicin and its apparent increased nephrotoxicity, the use of tobramycin, instead of gentamicin, seems justified. Recommendations for the more frequent use of tobramycin also have implications for the treatment of patients that do not suffer from CF.

Studies are needed to investigate a potential link between the mitochondrial m.1555A>G mutation and nephrotoxicity and whether a test for this mutation could identify patients at particular risk. Unfortunately, by the time the nephrologist is called to the bedside, the damage has usually already been done. This emphasises the need to communicate these issues with our colleagues providing care to CF patients. Significant progress in the treatment of patients with CF has been accomplished. Further improvements are possible; a multi-disciplinary approach, by pulmonologists, nephrologists, pharmacists and others, can make this happen. Studies like the one by Smyth et al. will help to ensure a continued and needed discussion.

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