Short Communication

PRESCRIBING PRACTICES FOR INTRAVENOUS AMINOGLYCOSIDES IN UK CYSTIC FIBROSIS CLINICS: A QUESTIONNAIRE SURVEY.

(Running title: A QUESTIONNAIRE SURVEY OF AMINOGLYCOSIDE PRESCRIBING)

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ABSTRACT

Background: Intravenous aminoglycoside antibiotics are widely used to treat pulmonary infection with *Pseudomonas aeruginosa* in individuals with cystic fibrosis (CF). Over the last decade evidence has accumulated showing that the choice of aminoglycoside and the dosing regimen may help reduce adverse effects such as nephrotoxicity.

Methods: We undertook an online survey to determine current practice in UK CF Centres.

Results: We received a response from 35/48 (73%) centres. A once daily regimen was used in 30/35 (86%) centres. Around one third had stopped using gentamicin in the last 10 years. In most cases respondents reported changing practice in response to new evidence or evidence based guidelines. Obstacles to introducing evidence based practice were identified both at the level of the CF Centre and the hospital trust.

Conclusions: A once daily aminoglycoside regimen is now used in the majority of UK CF Centres. Tobramycin is first line and many centres have stopped using gentamicin. Obstacles to evidence based practice remain in a minority of centres.

Key words: Cystic fibrosis; aminoglycosides; nephrotoxicity; once daily dosing; obstacles to evidence based practice.

INTRODUCTION

Aminoglycoside antibiotics are widely used for the management of pulmonary exacerbations in cystic fibrosis (CF) due to *Pseudomonas aeruginosa*. In the UK around one third of CF patients receive intravenous antibiotics in a year, for a median of 23 days[1]. Aminoglycosides are recommended as first line therapy[2] and so CF patients are vulnerable to adverse effects, such as nephrotoxicity. The risk of acute kidney injury (AKI) is greater in CF than in the general population (100 times greater in children) and most episodes are related to aminoglycosides[3]. There are a limited number of antibiotics which are active against *P. aeruginosa* and so clinicians will continue to use intravenous aminoglycosides. However there is good evidence that nephrotoxicity may be reduced by using a once daily regimen[4] and by avoiding the use of gentamicin[3]. This evidence has informed recommendations in treatment guidelines both in the UK[2] and the US[5]. Indeed the guideline recommendation on aminoglycoside use has been highlighted as one of the few which is evidence based[5]. We therefore chose to evaluate adherence to this recommendation as an example of guideline adherence in CF. A decade ago, we conducted a survey of aminoglycoside prescribing practices in UK CF centres which showed low uptake of these strategies[6]. We wanted to know whether practice has changed in the light of evidence from recent research and so we repeated this survey.

METHODS

We contacted the Centre Director for all UK CF centres by email (using a contact list provided by the UK Cystic Fibrosis Trust) and invited them to complete an online questionnaire (figure 1) which asked about aminoglycoside prescribing practices in their centre. Answers could be yes / no; choose one option; choose one or more options; or free text, depending on the context of the question. Invitation emails were sent in March 2013 and a follow up to non-responders was sent a month later. The online tool captured the email address of the respondent and so duplicate responses from the same centre could be identified. Where there was more than one response from the same centre, we used the first response only. The questionnaire (Q1-3) asked specifically about first line antibiotic therapy for *P. aeruginosa* (the commonest indication for aminoglycosides in CF). This was to avoid confusion with aminoglycosides given for other indications such as intravenous amikacin for infection with *Mycobacterium abscessus,* where a twice or three times daily regimen is recommended[2].

RESULTS

We received a response from 35/48 (73%) centres, of which 21/35 (60%) were paediatric and 14/35 (40%) adult. Replies came from centres in England, Scotland, Wales and Northern Ireland. All centres reported using an aminoglycoside as part of an intravenous antibiotic regimen for infection with *P. aeruginosa* (Q1) and all named tobramycin as their first line aminoglycoside (Q2).

Results for Q3-Q9 by paediatric and adult centre separately are given in table 1. A once daily aminoglycoside regimen was used by 30/35 (86%) centres; twice daily by 1/35 (3%), and three times daily by 4/35 (11%) (Q3). Twenty two centres said they had changed the dosing regimen for aminoglycosides in the last 10 years (Q4). Of these, 21 centres had changed from a three times daily regimen to once daily, and one centre had changed from three times daily to a twice daily regimen (Q5). When asked the reason for changing (Q6), 19 respondents cited the TOPIC study[7], 5 respondents the UK CF Trust Antibiotic Guidelines[2] and 2 gave other reasons (such as local laboratory data).

When asked if the specific aminoglycoside drug prescribed in the centre had changed in the last 10 years (Q7), 10/35 (29%) centres said they had made a change and 24/35 (69%) had not. (One did not reply to this question). Of the 10 centres who had changed the antibiotic used, all had stopped using gentamicin (Q8). The CF Trust Antibiotic Guidelines[2] were cited by 5 centres

as a reason for changing; the UK case control study of acute kidney injury[3] by 3 centres and 2 gave other reasons (Q9).

We received 11 free text responses (9 from paediatric centres) to Q10 "If you have tried to change your aminoglycoside or regimen, but have encountered difficulties, please describe these briefly in the box". Many of these were informative, raising issues which fell into the following themes (direct quotations from respondents have been used to illustrate these themes). Some respondents gave more than one reason.

- **Training issues (3 respondents).** *"Lots of delays when changing from TDS to OD Tobramycin due the training of nurses and parents…"*
- **Difficulty arranging infusions (3 respondents).** A once daily aminoglycoside dose is administered by infusion (usually over 30 minutes) whereas three times daily doses may be given by bolus. *"Problems with od antibiotics infusion in the community setting."*
- **Laboratory unwilling to provide tobramycin assay for monitoring plasma levels (4 respondents).** ***"****Lab will only run a gentamicin and not a tobramycin assay. They have agreed to send away tobra levels"*
- **Once daily prescribing for CF patients would be out of line with policies for other patients increasing the risk of a drug error (1 respondent).** *"Hospital policy for other aminoglycosides is 8 hourly - we discussed TOPIC findings several times but we felt that clinical risk of Tobra overdose to CF patients (receiving once daily) on same ward as medical patients (receiving TDS aminoglycosides) would be too great."*

DISCUSSION

We have shown a profound change in aminoglycoside prescribing practices, in UK CF Centres, over the last decade. At the time of our previous survey[6] a once daily aminoglycoside dosing regimen was used in 17% of UK CF Centres. Once daily dosing is now used in 86% of centres. The use of tobramycin has increased from 87% in our previous survey to its use in all centres currently. Just under one third of centres responding had stopped using gentamicin in the last 10 years. Appropriately, most respondents cite high quality evidence or evidence based guidelines as their reason for changing practice. Obstacles to implementing evidence based practice include practical issues (such as the need for an infusion device and training). However the need for hospital wide change (in the assay performed and in the use of once daily regimens in other patients) was a significant obstacle in some centres. This is disappointing, as the evidence suggests that a once daily regimen should be widely used amongst all patients receiving aminoglycosides (not just those with CF) - with few contraindications[8].

Our findings are in line with reported changes in practice in Australia which have shown an increase in once daily dosing from 54% in 1999[9] to 88% in 2009[10]. There are no recent surveys from the US, but once daily aminoglycoside dosing is now recommended in US CF Foundation Guidelines for managing pulmonary exacerbations[5].

Whilst our response rate was good (73% centres), 13 centres did not respond and it is possible that there was a systematic bias in the non-responders

(such as centres not following evidence based practice not wishing to respond). The qualitative data reported here are informative but are limited by the study design (an online questionnaire). Further valuable data, regarding obstacles to implementing evidence based practice, could be obtained from semi-structured interviews with key decision makers in UK CF Centres and their hospital trusts.

In the setting of a clinical trial, once daily aminoglycoside dosing for pulmonary exacerbations of CF results in less nephrotoxicity[7]. Whether the widespread adoption of a safer regimen in the UK will result in fewer cases of acute kidney injury amongst CF patients is not known. However, data on acute kidney injury, requiring dialysis, are recorded in the UK CF Registry, allowing trends to be monitored. Therefore it may become clear over the coming years if morbidity has been reduced in this vulnerable group of patients.

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CONFLICT OF INTEREST STATEMENT

ARS was the chief investigator of the TOPIC study and the case control study of aminoglycoside use and acute kidney injury in CF. ELC is employed as an Impact Researcher at the University of Nottingham.

ROLE OF THE FUNDING SOURCE

Both authors are employed by the University of Nottingham. No additional funding was obtained. The authors were exclusively responsible for the study design; collection, analysis and interpretation of data; writing the manuscript; and the decision to submit the manuscript for publication.

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