Safety of Single Dose Gentamicin Compared with Multiple Dose Regimens

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Aim

Systematically review the frequency and type of adverse events associated with a single dose of intravenous or intramuscular gentamicin.

Background

Multi-drug resistant *Neisseria gonorrhoea* is a global concern¹⁻³, with resistance to third-generation cephalosporins and macrolides reported in many countries, including the UK⁴. Gentamicin, an aminoglycoside antibiotic, has been suggested as a potential treatment for gonorrhoea.⁵ Traditionally, gentamicin has been given as a multiple daily dose regimen, eight hourly over a number of days, guided by drug levels. Meta-analyses have shown that single-daily dosing of gentamicin offers an equal, if not improved, toxicity profile compared to multiple daily dosing.^{6,7} Subsequently single-daily dosing has now become the standard treatment regimen for many infections.⁸

However the safety of a one-off dose of gentamicin has not been reviewed. Such a review is necessary before gentamicin can be considered amongst outpatients with gonorrhoea, where monitoring and follow up are often challenging.

Method

- Systematic review protocol developed and registered (PROSPERO: CRD42013003229).

Studies were considered eligible for this review if they;

- recruited human participants, male or female, ≥16 years old
- used gentamicin intramuscularly or intravenously as a single one-off dose
- compared gentamicin to a control group (a group receiving either; placebo, no treatment, an antimicrobial regimen which did not include gentamicin or a regimen that includes gentamicin in conjunction with other antimicrobials.)
- monitored adverse effects

- The following were searched for records; The Cochrane Library, MEDLINE, EMBASE, British Nursing Index and Cumulative Index Nursing and Allied Health Literature (CINAHL), National Guideline Clearinghouse, NICE and SIGN, trial registers, conference abstracts and proceedings, dissertations and theses. Specific sources of drug information were searched, including pharmacovigilance data from regulatory authorities and a specific drug bibliographic database. In order to identify grey literature, the National Technical Information Service (NTIS) and OpenGrey were searched.
- Citation searching was carried out on included articles.
- Initial searches were carried out in the first week of February 2013. The following were searched for separately as text words in the title, abstract and as index terms, gentamicin, gentamycin, cidomycin, genticin, single, one-off, stat, once, one.

The separate searches were combined in the following way:

gentamicin OR gentamycin OR cidomycin OR genticin **AND** single OR one-off OR stat OR once OR one

Study selection

- Titles and, where available, abstracts were screened independently by one reviewer for relevance. 15% of records were randomly selected and screened independently by a second reviewer.
- Inclusion and exclusion criteria were applied independently by one reviewer to all full text articles. Due to the quantity of articles the application of the inclusion and exclusion criteria by a second reviewer was split between four independent reviewers.
- Data extraction, including risk of bias assessment, was carried out independently by two reviewers on all included studies
- Foreign language records were included and potentially relevant articles were translated and data extraction carried out in the same way as English language articles.

Results

Figure 1: PRISMA Flow Diagram for Systematic Review of adverse effects of Gentamicin

- 22 studies; one thesis, three clinical trial protocols and 18 journal articles.
- Two of the three trial protocols had not reported results at the time of writing, so have been excluded.
- Final 20 studies; 12 randomised controlled studies (two crossover designs), two cohort studies, three pharmacokinetic and three quasi experimental studies.
- 2042 participants received a single one-off dose of gentamicin across all included studies.
 - Age range 18-94 years old
 - Dose of gentamicin 1mg/kg to 280mg

- Indications for gentamicin across all studies;
 - prophylaxis prior to neurosurgery, emergency abdominal surgery, cystogram or prostatectomy.
 - treatment for gonorrhoea, urinary tract infections or acute pyelonephritis.

Table 1.	Gentamicin	Control
Reversible nephrotoxicity/ Creatinine rise	37 reports	4 reports (incomplete reporting)
Irreversible nephrotoxicity	1 report	0 (incomplete reporting)
Ototoxicity	3 reports	7 reports
Dizziness	7 reports	7 reports

Other reported adverse events were either equal between the groups, or a known adverse effect of an adjuvant medication e.g. red-man syndrome reported in a group receiving vancomycin and gentamicin.

Conclusions

- Single dose gentamicin is an infrequent cause of adverse events.
- <2% of 2042 participants reported reversible nephrotoxicity or creatinine rise.
- The quality of published studies was low, with often limited information about adverse event monitoring or reporting.

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