

What is the evidence of safety of gentamicin use in children?

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The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at: http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

This review addresses the question: *What is the evidence of safety of gentamicin use in children?*

Gentamicin is widely advocated throughout the WHO **Pocketbook of Hospital Care for Children** in the treatment of serious bacterial infection (including meningitis, pneumonia, and various contaminations with enteric flora).

Introduction:

Infection is the commonest cause of infant and child mortality worldwide [1]. As there is such overlap between the clinical presentations of bacterial infection, an empirical combination of antibiotics are often used to cover the commonest and most serious microorganisms. Gentamicin, an aminoglycoside, is relatively cheap and widely available, and is bactericidal against most aerobic Gram-negative and some Gram-positive organisms: as a result, it is often included in empirical treatments, as it is in the WHO Pocketbook. It is also particularly useful in the co-treatment of infection with streptococcus, Listeria species or Pseudomonas infections [2].

Aminoglycosides act by preventing bacterial protein synthesis, and act synergistically with antibiotics that prevent cell wall formation [2], reducing the problem of resistance, and increasing efficacy.

Aminoglycosides are not absorbed from the gastrointestinal tract so must be administered by injection. Most is excreted by the kidney unchanged and the therapeutic index is narrow, therefore if renal function is inhibited, toxicity can rapidly occur. On these grounds, serum levels should be monitored where possible.

Few alternatives to gentamicin are available, particularly in countries with limited resources, where more expensive drugs are not obtainable. In some instances, such as in the treatment of severe pneumonia, the WHO Pocketbook recommends chloramphenicol as an alternative, for which clinical outcome should be similar [3].

Gentamicin is associated with dose-related (trough serum concentrations $>2 \mu\text{g/ml}$ [4]) nephro- and ototoxicity [2]. Nephrotoxicity is usually reversible on termination of gentamicin treatment, but ototoxicity can lead to permanent sensori-neural deafness and vestibular disturbance. If serum Gentamicin levels are monitored, safety can be improved, but this is not always possible in countries where the pocketbook would be used. It is on these grounds that the safety profile of gentamicin needs to be established: what is the evidence of safety of gentamicin use in children?

Methodology

The PubMed Clinical Queries search strategy developed by Haynes RB et al was employed: Clinical Study category 'therapy'((gentamicin OR gentamycin) AND (child OR neonate OR infant OR paediatric OR pediatric)) AND (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])) identified 176 Randomized Control Trials (RCTs) and Reviews.

A keyword search (Gentamicin OR Aminoglycosides) AND (Child OR Infant OR Pediatric) AND (Safety OR toxicity) identified one further Systematic Review.

A MeSH search ("Gentamicins"[MeSH] OR "Aminoglycosides"[MeSH]) AND ("Child"[MeSH] OR "Infant"[MeSH] OR "Pediatric Nursing"[MeSH]) AND ("Safety"[MeSH] OR "toxicity"[Subheading]) identified another relevant review.

All abstracts were read, and articles sourced fully where relevant. Articles were excluded if the article did not concern paediatric patients, if the safety of gentamicin had not been investigated, if the research did not include systemic treatment, or if doses were altered on the basis of serum Gentamicin levels. Articles involving other aminoglycosides were included where deemed appropriate. Much of the available research into the toxicity of Gentamicin was in the comparison of multiple versus once daily dosing: only once daily figures were considered, as this is the dosing strategy recommended in the WHO Pocketbook.

Results

Using the methodology described 14 RCTs, 2 systematic reviews and 1 meta-analysis were identified as relevant. It should be noted that ototoxicity was measured by a variety of means (including brainstem evoked responses (BER), audiological testing and clinical impression), all of which are used to detect deafness. Nephrotoxicity was also defined differently between studies: either by reduced creatinine clearance, raised serum creatinine, or β -2-microglobulinuria. Each case of nephrotoxicity mentioned below will be defined according to the parameters set in each individual study.

A Cochrane systematic review identified no difference between oto- and nephrotoxicity in once daily and multiple daily dosing of gentamicin, but the figures for each were not given [5].

Trials that monitored nephrotoxicity are as follows: None was noted in 6 RCTs [6][7][8][9][10][11], and one reported a clinically insignificant but potential gentamicin-induced nephrotoxicity [12]. One meta-analysis reported primary nephrotoxicity in 1.6% and secondary nephrotoxicity in 4.4% [13]. Occurrence of

nephrotoxicity (1.2% and 15%) was found in a further 2 RCTs [14][15]. Another reported laboratory nephrotoxicity in 1.5%, but none was detectable clinically [16].

Assessment of ototoxicity: A systematic review of aminoglycosides reported that with the exception of one study, ototoxicity occurred less frequently in aminoglycoside-treated patients than it did untreated control patients. It concluded that the lack of reports on aminoglycoside-associated toxic effects in children suggests that these compounds are safe and well tolerated in this age group [17]. A meta-analysis reported ototoxicity in 2.3% of cases, with no evidence of disturbed vestibular function [13]. An RCT that looked at the effect on hearing concluded that aminoglycosides are unlikely to cause ototoxicity [18]. No ototoxicity was noted in 3 RCTs [6][14][15].

Two studies into ototoxicity over a longer timescale (4 years) concluded there was no hearing loss that could be attributed to the use of aminoglycosides [19][20]. One study emphasized the importance of long-term follow-up of hearing, as there is a high incidence of transient auditory abnormalities which lead to no higher incidence of sensori-neural deafness than those without antibiotic treatment [21].

Discussion

Many studies are relatively small scale but the consistency of results suggests they are reliable, particularly in the case of nephrotoxicity. Evidence relating to ototoxicity is less convincing: perhaps larger scale studies would need to be included, although none could be obtained in this instance. Research indicates that nephro- and ototoxicity are relatively uncommon, and is a risk worth taking in the context of a life-threatening infection.

Alternatives such as chloramphenicol and beta-lactams (such as penicillin) would need to be investigated in terms of safety before being used confidently as a first line treatment: chloramphenicol is known to cause agranulocytosis and 'grey baby syndrome' in newborns, and beta-lactams are recognised as causing hypersensitivity reactions as well as exhibiting high levels of resistance against them.

In all the studies reviewed, the duration for which aminoglycosides were administered was

relatively short (usually about a week): perhaps with longer administration toxicity is more likely to develop [12].

Summary

Based on the evidence available, short-term Gentamicin administration at the recommended doses is an appropriate antibiotic, even without serum Gentamicin level monitoring.

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