International Journal of Infectious Diseases 15 (2011) e569–e575

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

# A double-blind study of the efficacy and safety of multiple daily doses of amikacin versus one daily dose for children with perforated appendicitis in Costa Rica☆

Víctor Pérez [a,b,*], Desirée Saénz [b], Juan Madriz [a], Michael Harhay [c], Juvenal Feoli [a], Maria Castro [a], Carla Odio [a]

[a] Intensive Care Unit, National Children's Hospital, San José, PO Box 1654-1000, Costa Rica
[b] School of Medicine, University of Costa Rica, San José, Costa Rica
[c] Public Health Consultant, Philadelphia, PA, USA

ARTICLE INFO

*Article history:*
Received 20 August 2010
Received in revised form 4 April 2011
Accepted 26 April 2011

**Corresponding Editor:** William Cameron, Ottawa, Canada.

*Keywords:*
Amikacin
ODD (once daily dosing)
MDD (multiple daily dosing)
Appendicitis
Costa Rica

SUMMARY

*Background:* There is evidence that aminoglycosides given in a single daily dose (once daily dose, ODD) are as effective and safe as multiple daily doses (MDD). However, the published pharmacokinetic and pharmacodynamic data are overly representative of pediatric populations in Europe and the USA, and not representative of low or middle-income countries such as Costa Rica, in which the patient population might differ from those in higher income settings.

*Methods:* A double-blind, randomized clinical trial of the efficacy and safety of ODD vs. MDD amikacin therapy was conducted for children aged 2–12 years with an intraoperative diagnosis of perforated appendicitis. One hundred patients were randomized following a one-to-one randomization to receive either amikacin 7.5 mg/kg every 8 h (MDD) or 22.5 mg/kg as a single dose (ODD). Patients in both groups were given clindamycin 10 mg/kg every 6 h. Efficacy was evaluated by the occurrence of intra-abdominal abscesses, documented by abdominal ultrasound, and therapeutic failure. Safety was determined by the presence of renal or cochlear toxicity.

*Results:* Fifty patients were enrolled in each group. There were no statistically significant differences in the incidence of intra-abdominal abscesses or therapeutic failures, or in the occurrence of cochlear or renal toxicity, between the MDD and ODD treatment groups.

*Conclusions:* In this patient population of Costa Rican children with perforated appendicitis, we found that amikacin ODD is as safe and effective as the MDD regimen. This could have implications for national health systems such as that in Costa Rica, as ODD is presumably a more economic option and may reduce the cost of antibiotic treatment in patients with perforated appendicitis. This would need to be confirmed through an economic analysis, which is outside the purview of this paper.



## 1. Introduction

Aminoglycosides are commonly used for the treatment of children with perforated appendicitis, despite their potential to cause ototoxicity and nephrotoxicity.[1,2] However, there is still debate, even in clinical settings where resources are not limited, as to whether these antibiotics should be given in multiple daily doses (MDD) or as a single daily dose (once daily dose, ODD). ODD has been shown to achieve higher peak plasma concentrations with relatively undetectable trough concentrations, and thus to exert a high concentration-dependent bactericidal activity, greater post-antibiotic effect, lower risk of adaptive resistance, and reduced accumulation in the inner ear and renal proximal tubules.[3–5] Recent systematic reviews of the efficacy and safety of giving aminoglycosides as an ODD to children and neonates have concluded that ODD is preferable to MDD, because ODD both minimizes costs and simplifies administration while remaining efficacious and safe.[6,7] However, most empirical data in these reviews are derived from well developed American and European clinical settings in pediatric populations.[8,9] As a result the promulgated standard of care may not be the same for other populations with potential metabolic differences in drug handling. As the healthcare systems in low- and middle- income countries continue to develop, it is critical that clinical investigation follows that of the countries that generally dominate the peer reviewed literature so that appropriate and cost-effective patient care evolves.

☆ Trial registration: Estudio 229-08-04-00017. Comparación de la eficacia y seguridad de la amikacina, administración única diaria contra tres dosis diarias en pacientes pediátricos con apendicitis aguda perforada.

* Corresponding author. Tel.: +506 22552239; fax: +506 22552239.
*E-mail address:* vperezh@hnn.sa.cr (V. Pérez).

1201-9712/$36.00 – see front matter © 2011 International Society for Infectious Diseases. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.ijid.2011.04.012

For example, although there are well designed studies comparing the two amikacin dosing regimens in the pediatric population,[10–13] we found only one other prospective study in the English language literature conducted in children with peritonitis.[14] As most systematic reviews use English search terms and peer review literature only, the above-mentioned populations are not represented in existing analysis. Thus, to further build the available empirical pharmacodynamic, pharmacokinetic, and outcome data, we undertook a prospective, double-blind, controlled study to compare the effectiveness and safety of ODD vs. MDD of amikacin in patients with perforated appendicitis in a patient population in a middle-income country, Costa Rica, for which little empirical data exist.

## 2. Methods

The protocol for this trial and supporting CONSORT checklist are available as supporting information (see Supplementary Information, appendices 1 and 2).

### 2.1. Participants

This was a prospective, randomized, double-blind, single-center study. The patient population consisted of 100 children aged between 2 and 12 years, with a diagnosis of perforated appendicitis in the operating room at the Department of General Surgery, National Children's Hospital in San José, Costa Rica. Fifty patients were assigned to each group following a one-to-one randomization.

Exclusion criteria included: known allergy to aminoglycosides, known impaired renal function, known hearing loss or vestibular disease, neutropenia, cystic fibrosis, neuromuscular disease, concomitant administration of furosemide or other nephrotoxic drugs, and history of treatment with aminoglycosides in the preceding 2 weeks. Informed consent was obtained from parents or legal guardians of the patients prior to enrollment.

### 2.2. Ethics

Original approval for this study protocol (attached in Supplementary Information, appendix 2) was granted by the ethics committees of the National Children's Hospital, COIBI-CCSS and Universidad de Costa Rica.

### 2.3. Study endpoints

Primary endpoints: For efficacy the objective was to determine if there was a statistically significant difference between the two therapeutic groups regarding the development of intra-abdominal abscesses and treatment failures. For safety the objective was to determine if there was a statistically significant difference between the two therapeutic groups regarding the development of nephrotoxicity and ototoxicity.

Secondary endpoints: We also assessed if there was a statistically significant difference between the two therapeutic groups of patients with respect to body temperature, leukocyte count, C-reactive protein (CRP) serum concentration, and hospital stay.

### 2.4. Study protocol

One hundred patients were assigned to either regimen using computer-generated random numbers kept by the pharmacists; the blinding was not broken until the end of the study. An interim analysis was done when 40 patients were enrolled in the study to look for significant differences in efficacy and safety between the two groups. At that point there were no differences. Using a computer-generated randomization program (http://www.randomizer.org), the patients were randomized into either the ODD arm, to receive 22.5 mg/kg every 24 h, or the MDD arm, to receive 7.5 mg/kg every 8 h; only the pharmacist was aware of the randomization assignment. The amikacin dose was calculated according to body weight in all cases and was not adjusted in any case.

VP (first author) was responsible for the random allocation sequence, the surgeon who performed the surgery (usually the pediatric surgical resident) enrolled the participants, and the pharmacist assigned the subjects to the intervention. Patients and care providers were kept blind to the intervention. Patients assigned to MDD received amikacin sulfate 7.5 mg/kg of body weight every 8 h as a 20-min infusion, without exceeding 500 mg per dose. Patients assigned to ODD received amikacin sulfate 22.5 mg/kg of body weight once daily over the same infusion time as MDD and not exceeding 1.5 g per dose. In the ODD group, the first amikacin dose was followed by two further doses of saline every 8 h in a volume equal to that of the corresponding amikacin dose. The color of the solution was the same and only the pharmacist who prepared the solution knew the intervention group. All study patients also received clindamycin 10 mg/kg, administered as an intravenous infusion over 20 min every 6 h. Patients with perforated appendicitis and localized peritonitis were given antibiotics for a minimum of 5 days and those with generalized peritonitis received antibiotics for at least 7 days. Antibiotic treatment beyond 7 days was administered to patients with a documented intra-abdominal abscess defined by the presence of one or more collections in the pre-rectal space, right iliac fossa, mid-abdomen, or retrovesical area, visualized by abdominal ultrasound.

### 2.5. Cultures

Samples of peritoneal exudates were obtained from all patients and sent for aerobic bacterial cultures. They were plated onto blood and MacConkey agar and only the predominant organism from each culture was reported. The minimum inhibitory concentration (MIC) for amikacin was determined for any bacteria grown from an intraoperative sampling, and the maximum concentration ($C_{max}$)/MIC ratio was calculated for each isolate.[15] Anaerobic cultures were not performed.

### 2.6. Amikacin serum concentrations

Amikacin peak and trough serum concentrations were measured on days 2, 4, 6, and 8 of therapy. After sampling, plasma was separated and frozen at −70 °C until processed (within 1 month). Amikacin concentrations were determined by fluorescence polarization immunoassay (Abbott Tax; sensitivity 0.8 μg/ml).

### 2.7. Renal function assessment

The serum creatinine concentration was determined prior to the start of therapy with amikacin and every 48 h thereafter until its discontinuation. Any abnormal value was followed until its return to the normal range according to age. Amikacin-related renal toxicity was defined as an increase in serum creatinine ≥0.4 mg/dl from the basal post-rehydration value before the first dose was administered.

### 2.8. Cochlear function

Cochlear function was assessed according to the age of the patient. Children younger than 4 years of age were screened through oto-acoustic emissions (OAE-DP), immittance, and free-field audiometry (behavioral observational audiometry, BOA). Children over the age of 4 years were assessed with conventional