Extended-interval Dosing of Gentamicin in Premature Neonates Born at <32 Weeks' Gestation and >7 Days of age

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ABSTRACT

Purpose: Extended-interval dosing (EID) regimens of gentamicin have been validated for treating confirmed or suspected early- and late-onset sepsis in preterm infants in the first week of life. Despite the marked changes in volume of distribution and renal clearance in preterm infants after the first few days of life, few studies have validated EID regimens of gentamicin in this population. The objective of the study was to evaluate an EID regimen of gentamicin in infants born at <32 weeks' gestational age and aged >7 days.

Methods: This observational study of an EID regimen was conducted in 39 infants. Dosing interval was based on the serum drug concentration at 22 hours after the administration of the first dose of 5 mg/kg. Gentamicin peak (5–12 μg/mL) and trough (<2 μg/mL) levels were compared to those in a historical control group of 39 infants who received traditional-interval dosing (TID) of 2.5 mg/kg of gentamicin with dosing intervals of 8, 12, or 24 hours.

Findings: There were no differences in birthweight, gestational age at birth, postmenstrual age, weight at the start of gentamicin administration, postnatal age, small for gestational age status, antenatal corticosteroid use, or postnatal indomethacin exposure between the 2 groups. In the EID group, dosing intervals were 24 hours in 30 infants, 36 hours in 6 infants, and 48 hours in 3 infants. Compared with the TID group (n = 39), the EID group had a significantly higher peak level (median, 9.0 vs 4.7 μg/mL) and a significantly lower trough level (median, 0.7 vs 1.1 μg/mL) (both, $P < 0.001$). On regression analysis, the postmenstrual age was correlated significantly with trough levels in the EID group. There was no adverse effect on renal function in either group. On follow-up, 1 infant in the EID group and 2 infants in the TID group had evidence of sensorineural hearing loss.

Implications: In infants born at <32 weeks' gestation and >7 days of age, an EID gentamicin regimen, with a dosing interval based on a single concentration measurement at 22 hours after the administration of the first dose, achieved therapeutic peak and trough levels and performed significantly better than did a TID regimen in reaching target peak and trough levels. Larger-scale trials are needed for assessing the clinical efficacy (treatment failure/success) of these regimens. (*Clin Ther*. 2017;39:1233–1241) © 2017 Elsevier HS Journals, Inc. All rights reserved.

Key words: >7 days, extended interval, gentamicin, peak and trough levels, preterm.

INTRODUCTION

Gentamicin is an aminoglycoside antibiotic agent and is among the antibiotics most commonly used for the treatment of confirmed or suspected early- and late-onset sepsis in neonates. Gram-negative organisms are major causative pathogens in sepsis in neonates, and gentamicin forms a part of first-line antimicrobial treatment in neonatal intensive care units (NICUs) in North America and Europe.[1,2] Extended-interval dosing (EID) gentamicin regimens employ larger doses with longer intervals, while traditional-interval dosing (TID) regimens employ lower doses with shorter

Accepted for publication May 10, 2017.
http://dx.doi.org/10.1016/j.clinthera.2017.05.343
0149-2918/$ - see front matter

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Table I. Gentamicin dosing interval based on concentration at 22 hours after administration.

Concentration at 22 h, μg/mL	Dosing Interval, h
≤1.2	24
>1.2–2.6	36
2.7–3.5	48
≥3.6	Hold next dose, repeat concentration measurement in 24 h. Base dosing interval on time to achieve a concentration of <2 μg/mL.

Adapted from Neofax.[11]

intervals between doses. EID regimens are especially efficacious in neonates, particularly premature neonates, compared with older children and adults, as neonates have a greater volume of distribution and a lower glomerular filtration rate. The higher dose in EID regimens helps to achieve target therapeutic peak levels in the greater volume of distribution, and the longer interval helps to achieve target therapeutic trough levels, as the rate of gentamicin elimination is dependent on the glomerular filtration rate. Importantly, aminoglycosides, including gentamicin, possess distinct pharmacokinetic and pharmacodynamic properties that are augmented by an EID regimen. These include concentration-dependent bacterial killing, postantibiotic effect (PAE), and avoidance of the toxicity associated with elevated trough levels.[3,4] Given their inherent advantages, EID regimens are widely used in NICUs worldwide. Although there are variations in dose and dosing intervals, findings on EID regimens have been reported in studies from North America, Thailand, Europe, Australia, and India.[3]

Most EID regimens have been validated for use in the first week of life in neonates.[5] However, profound changes take place in the glomerular filtration rate and volume of distribution after the first week of life. These changes are more pronounced the more premature the infant. Renal blood flow is only 3% of the cardiac output in the fetus but increases to 10% by the end of the first week of life.[6] Glomerular function improvement after birth correlates positively with gestational age and postnatal age, while tubular function, as assessed by fractional excretion of sodium, correlates negatively with the same factors.[7,8]

Gentamicin is distributed in the extracellular fluid compartment, and following birth, neonates lose 8% to 10% of their body weight with contraction of the extracellular fluid compartment. This decrease is greater the more premature the infant, with body weight loss of as much as 15%.[9] We have validated, in extremely preterm (born at ≤28 weeks' gestational age) infants, an EID regimen for use in the first week of life employing a dose of 5 mg/kg and a dosing interval based on the gentamicin concentration measured at 22 hours after the first dose.[10] The objectives of this study were to validate the same EID regimen in preterm (born at <32 weeks' gestational age) neonates aged >7 days and to compare the peak and trough gentamicin levels to those in a TID regimen.

PATIENTS AND METHODS

The Conjoint Health Research Ethics Board at the University of Calgary (Calgary, Alberta, Canada) approved the study protocol. An EID regimen was introduced in the NICUs in Calgary in 2009, following an audit of TID that revealed a considerable number of subtherapeutic gentamicin levels. A simple EID regimen was chosen, with an initial dose of 5 mg/kg and a dosing interval based on a gentamicin concentration measured at 22 hours after the first dose (Table I). Details of the dosing regimen were published previously.[10] Briefly, a fixed dosing interval was not chosen, as gentamicin pharmacokinetics can be variable in preterm neonates of varying gestational and postnatal ages.[3,12–18] Although NeoFax[11] recommends a dosing interval based on a level measured at 24 hours after the administration of the first dose of gentamicin, results would be delayed at a dosing interval of 24 hours. Hence, NeoFax recommends a dosing interval

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