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Research Paper

Discrepancies between predicted and observed rates of intravenous gentamicin delivery for neonates

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Abstract

Objectives This study aimed to investigate intravenous infusions as used in the neonatal intensive care setting, to determine the effect of gentamicin dose (mg), gentamicin concentrations (mg/ml), flow rate (ml/h) and flush volume (ml) upon the length of infusion time.

Methods Intravenous infusions were set up to simulate administration of gentamicin to neonates. Dextrose (10%, w/v) was administered as the primary intravenous fluid at 3.8 or 18.7 ml/h. Gentamicin doses (0.5 mg/0.2 ml, 2 mg/0.2 ml, 2.5 mg/1.0 ml, or 10 mg/1.0 ml) were delivered into the intravenous line at a T-connection using a Graseby pump over 35 min. This was followed by a saline flush of 1 or 2 ml over a further 35 min. At the end of each experiment a 2 ml 0.9% saline bolus was given. Analysis of gentamicin collected at 5-min intervals was by an HPLC method.

Key findings The experiment demonstrated that under the infusion conditions neonates weighing 2.5 kg would receive only 80% of the drug at 60 min, increasing to 90–95% by 75 min. In extremely low birth weight neonates (0.5 kg), even lower percentage of gentamicin recovery occurred. At 60 min only 60% of the intended gentamicin dose had been delivered and this increased to only 70% by 75 min.

Conclusions The delivery of gentamicin administered by intravenous infusion is substantially extended in extremely low birth weight neonates. This appeared to be primarily due to the small volumes and low infusion rates used in these patients.

Keywords drug delivery; gentamicin; intravenous infusion; neonatal

Introduction

The efficacy and safety of medicines in neonates depends upon predictable drug delivery. This is especially relevant for aminoglycosides like gentamicin that are used frequently to treat bacterial infections in the neonatal population. A lack of appreciation of extended duration in drug delivery in neonates can result in a lower than expected maximum drug blood concentration (C_{max}) of aminoglycoside. This may be much lower than what is required for optimal antimicrobial therapy. Adjustments of drug dosage based on an incorrect C_{max} value could easily place patients at risk, either for toxicity if the dose is increased (in response to low blood concentrations) or for therapeutic failure if the dose is decreased (in response to high blood concentrations).[1]

Duration of an infusion is an important pharmacokinetic parameter in delivery of intravenous drugs to neonates.[2,3] The physical properties of the intravenous line, including flow dynamics (specific gravity, laminar and turbid flow) or position of tubing relevant to the patient (which can lead to the drug being trapped within the line) can influence delivery of the drug to the patient. Additionally, the use of inline filters and other components that contribute to the dead space within the intravenous line may unintentionally extend the duration over which the drug is delivered to the patient.[4] Such variations in drug delivery may be wrongly attributed to inter-patient differences in drug disposition, sample collection and/or analysis.[5,6]. Fluid restrictions and a need to administer several medications may further contribute to limiting the intravenous infusion rate.[7,8] It has been reported in neonatal patients that significant portions of a drug dose may never reach the patient, due to retention in the intravenous line.[9] Therefore, it is

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important to distinguish between infusion into the intravenous line and infusions into the bloodstream.

We have investigated intravenous infusions of gentamicin as used in the neonatal intensive care setting, to determine the effect of gentamicin dose (mg), gentamicin concentration (mg/ml), flow rate (ml/h) and flush volume (ml) upon the length of infusion time.

Materials and Methods

Gentamicin infusion experiments

Experiments were designed to approximate the clinical administration of intravenous gentamicin to neonates (Table 1). The dose was administered via an intravenous infusion set up over 30–35 min using a Graseby syringe pump driver. The effused volumes were collected from the end of the intravenous line at 5-min intervals. The end time of 35 min was chosen as the Graseby syringe driver does not always deliver the entire gentamicin volume within the 30-min time frame. This reflected current clinical practice in the neonatal intensive care unit at Dunedin Hospital, where the flush is not administered until the entire gentamicin dose has been delivered into the line.

A Baxter Colleague Volumetric neonatal infusion pump (Baxter Healthcare, Deerfield, Illinois, US) was used to deliver dextrose 10% (Baxter Viaflex, Sydney, NSW, Australia). This was used as the primary infusion solution in the simulated infusions using flow rates of either 3.8 (the flow rate for a 0.5-kg neonate receiving 180 ml/kg per day) or 18.7 ml/h (the flow rate for a 2.5-kg neonate receiving 180 ml/kg per day). A Graseby syringe driver (Graseby Medical, Watford, Hertfordshire, UK) was used to deliver the gentamicin sulfate injection (Mayne Pharma, Mulgrave, Victoria, Australia). The selection of the gentamicin dose (mg) was based on administering 4 mg/kg to a neonate with a weight of 0.5 or 2.5 kg; a range of doses (2–10 mg) were investigated in the study. A dose of 0.5 mg gentamicin was included to increase the scientific rigour of the investigation. Gentamicin sulfate injection was diluted with dextrose 10% to 0.5 mg in 0.2 ml, 2 mg in 0.2 ml, 2.5 mg in 1.0 ml, or 10 mg in 1.0 ml. Solutions were drawn up in 1 or 2-ml syringes, placed in the Graseby syringe driver and infused into the intravenous line at a Smart site (Alaris, Dublin, Ohio, US) over 35 min.

The intravenous line included: a Baxter syringe T-piece Smart site luerlock (luer valve volume 0.25 ml); a Medex Rem 160 3-way stopcock; a BD connector plus 3 (BD Connecta, Stockholm, Sweden); an inline filter (0.2 μm, internal volume 0.3 ml; PALL Posidyne Neo in-line Filter, East Hills, New York, US); a Baxter T-connector extension set (15.3 cm long, Baxter Healthcare, Deerfield, Illinois, US) and an Insyte IV catheter (Becton Dickson, Sandy, Utah, US), 22G (1.00IN, 0.9 × 25 mm, 35 ml/min) (Figure 1).

Following the 35-min gentamicin infusion, a flush of either 1 or 2 ml 0.9% normal saline (Baxter Viaflex, Sydney, NSW, Australia) was given over 35 min again using the Graseby syringe pump. At 75 min, a final 2 ml 0.9% normal saline bolus flush was administered over 2 min to recover any remaining gentamicin in the intravenous line. Solutions were collected at 5-min intervals from the peripheral end of the intravenous line for 75 min into 5 ml polypropylene tubes and stored at −20°C. Infusion experiments were performed in triplicate for each combination of variables. A data collection form was used to record sample volumes during each infusion.

HPLC analytical method for gentamicin

Gentamicin was derivatised with 9-fluorenylmethyl chloroformate (FMOC-Cl, Fluka BioChemika, Buschs, Switzerland) and measured by reversed phase-high performance liquid chromatography (HPLC) with fluorescence detection

Table 1 Outline of infusion experiments

Experiment 1	Experiment 2	Experiment 3	Experiment 4
Gentamicin phase 35-min infusion Gentamicin dose: 0.5 mg (0.2 ml)	Gentamicin phase 35-min infusion Gentamicin dose: 0.5 mg (0.2 ml)	Gentamicin phase 35-min infusion Gentamicin dose: 2.5 mg (1.0 ml)	Gentamicin phase 35-min infusion Gentamicin dose: 2.5 mg (1.0 ml)
Flush phase 35-min infusion Normal saline 1 ml Final line flush = 1-ml flush	Flush phase 35-min infusion Normal saline 2 ml Final line flush = 1-ml flush	Flush phase 35-min infusion Normal saline 1 ml Final line flush = 1-ml flush	Flush phase 35-min infusion Normal saline 2 ml Final line flush = 1-ml flush
Flow rate: 3.8 ml/h (Dextrose 10%)	Flow rate: 3.8 ml/h (Dextrose 10%)	Flow rate: 18.7 ml/h (Dextrose 10%)	Flow rate: 18.7 ml/h (Dextrose 10%)
Experiment 5	**Experiment 6**	**Experiment 7**	**Experiment 8**
Gentamicin phase 35-min infusion Gentamicin dose: 2 mg (0.2 ml)	Gentamicin phase 35-min infusion Gentamicin dose: 2 mg (0.2 ml)	Gentamicin phase 35-min infusion Gentamicin dose: 10 mg (1.0 ml)	Gentamicin phase 35-min infusion Gentamicin dose: 10 mg (1.0 ml)
Flush phase 35-min infusion Normal saline 1 ml Final line flush = 1-ml flush	Flush phase 35-min infusion Normal saline 2 ml Final line flush = 1-ml flush	Flush phase 35-min infusion Normal saline 1 ml Final line flush = 1-ml flush	Flush phase 35-min infusion Normal saline 2 ml Final line flush = 1-ml flush
Flow rate: 3.8 ml/h (Dextrose 10%)	Flow rate: 3.8 ml/h (Dextrose 10%)	Flow rate: 18.7 ml/h (Dextrose 10%)	Flow rate: 18.7 ml/h (Dextrose 10%)

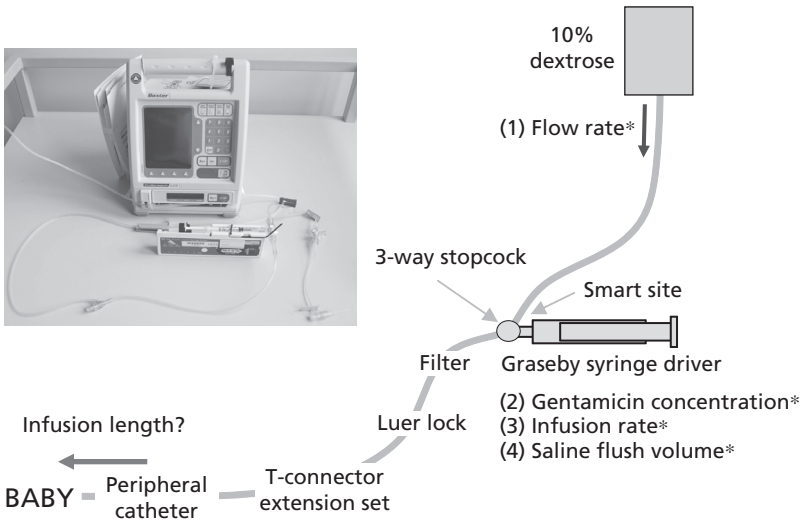

Figure 1 Neonatal intensive care unit infusion line setup for delivery of intravenous gentamicin. *The four study variables were flow rate, gentamicin concentration, infusion rate and saline flush volume.

(λ_{exc} = 260 nm; λ_{em} = 315 nm).[10,11] Separation was carried out on a C18(2) Luna 5 μm, 150 × 4.6 mm i.d. column with a C18 guard column (Phenomenex, Auckland, New Zealand) maintained at a temperature of 30°C using a Thermasphere TM TS-130 column heater (Phenomenex, Auckland, New Zealand). The mobile phase was a mixture of acetonitrile (HPLC grade, Merck, Darmstadt, Germany) and deionised water at a volume of 90 : 10, v/v. Deionised water was produced using a Millipore system (MilliQ, Billerica, Massachusetts, US). The mobile phase was degassed by vacuum filtration through a 0.2-μm filter and then online through a Degassex DG-4000 (Phenomenex, Auckland, New Zealand). The flow rate for all analyses was 1.0 ml/min.

Gentamicin sulfate (Sigma Aldrich, Munich, Germany), used as the analytical standard, was a mixture of the three major components designated as C1, C1a and C2. The estimated ratios of the three major components by HPLC were C1 < 45%, C1a < 35% and C2 < 30% (Sigma Aldrich, Munich, Germany). Tobramycin injection, 80 mg/2 ml (Mayne Pharma, Melbourne, Victoria, Australia) was used as the internal standard (IS) at 0.5 μg/ml in water. Standards of gentamicin sulfate in 10% w/v dextrose were prepared over the concentration range 2–100 μg/ml. Gentamicin standards and solutions from the infusion study were derivatised as follows. A 20-μl sample of the standard or infusion solution was mixed with 980 μl of a 1 : 1, v/v, solution of acetonitrile and borate buffer (0.2 M, pH 8.9) and a 20-μl sample of the IS (tobramycin 0.5 μg/ml). These solutions were derivatised by the addition of 200 μl FMOC-Cl solution (2.5 mM in acetonitrile), then vortexed and incubated for 20 min at 25°C. Following incubation, 50 μl 0.1 M glycine (SigmaUltra, Munich, Germany) was added to stop the derivatisation reaction and resulting solutions were analysed by reversed phase-HPLC as described above.

The reverse phase-HPLC analysis undertaken analysed three components of gentamicin sulfate: C1, C1a and C2. However, only calibration curves for the C1a component were used for quantitation of total gentamicin sulfate in each analysed sample. C1a had a retention time of 16.02 min, followed by C2 at 18.57 min and C1 at 20.83 min. The IS (tobramycin) had a retention time of 7.13 min. The assay was linear over the range 2–100 μg/ml for gentamicin sulfate (n = 5, R^2 > 0.99) and there was no evidence of curvature. The limit of quantification (CV% < 15%) for gentamicin sulfate was 0.1 μg/ml (CV% 9.8). At concentrations of 3, 15 and 75 μg/ml the intraday and interday variability was expressed as the % relative standard deviation. The intraday variability ranged from 0.5 to 9.7% and interday variability ranged from 2.7 to 9.2%.

Statistical analysis of infusion data

The mean percentage of gentamicin dose recovered in each experiment was displayed graphically using Axum v.7 (MathSoft 2000). Least-squares linear regression was used to estimate the rate of gentamicin infusion (coefficient, %/min) and the time lag (x-intercept, min) before appearance of the drug at the end of the peripheral catheter using Stata v.8.0 (2005).

Effects of gentamicin dose, gentamicin concentration, 10% dextrose flow rate, infused saline flush volume on percentage of gentamicin recovered at 60 and 75 min were investigated by univariate regression analysis. Variables determined to be statistically significant (P < 0.05) in the univariate analysis were included in a stepwise multivariate regression. Stata (v.8, 2005) was used to perform the univariate and multivariate analyses. The data was also investigated for any high correlations between the percentage of gentamicin recovered at 60 and 75 min in relation to the gentamicin dose (mg/ml), flow rate (ml/min) and flush volume (ml) using Stata (v.8, 2005).

Results

The variables that changed between experiments included the dose of gentamicin, concentration of gentamicin, the

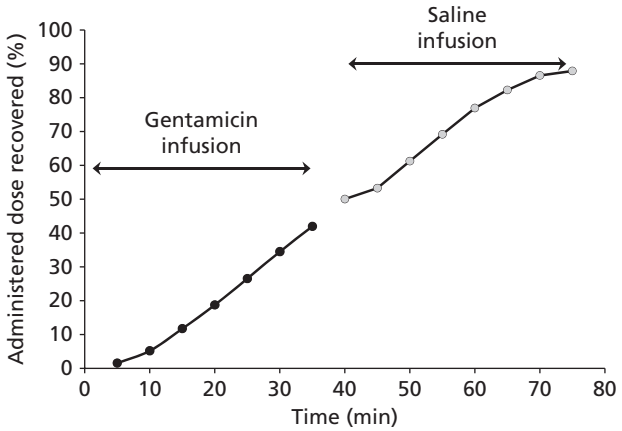

Figure 2 Example of infusion of gentamicin sulfate and saline flush from experiment 7. •, Gentamicin sulfate 10 mg/ml (35 min); ◦, saline flush 1 ml (35 min). Primary infusion 10% dextrose, flow rate 18.7 ml/h.

flow rate of 10% dextrose and the volume of saline flush as per Table 1. There were 24 infusions run, with each infusion divided into a gentamicin phase and normal saline flush phase (Figure 2). The gentamicin phase included samples collected during the 35-min gentamicin infusion (t = 0–35 min) while the normal saline flush phase included the samples collected during the 35-min normal saline flush infusion (t = 40–75 min). The time taken to change the syringe in the Graseby pump between phases was standardised at 5 min (t = 35–40 min). Cumulative gentamicin delivery over the 75 min approximated to a zero-order process ($R^2 > 0.97$) and a summary of the least-squares variables is given in Table 2. Additionally, the percentage of the intended dose recovered at 60 and 75 min is tabulated in Table 2. The lag-time was longer in the experiments reflecting administration to extremely low birth weight infants compared with larger neonates (Table 2).

In the experiments designed to simulate administration to larger neonates (experiments 3, 4, 7 and 8; Figure 3a), a higher percentage of administered dose was recovered at 60 and 75 min compared with administration to extremely low birth weight neonates (experiments 1, 2, 5 and 6; Figure 3b). Under the current infusion set up, neonates weighing 2.5 kg potentially received only 80% of the intended dose by 60 min and this increased to approximately 90–95% by 75 min (Table 2). For example, a 2.5-kg neonate given 10 mg in 1 ml gentamicin, with a dextrose flow rate of 18.7 ml/min, would receive an estimated delivered percentage of 74.6 ± 2.2 (with a 1 ml saline flush) and 80.2 ± 1.2% (with a 2-ml saline flush) by 60 min and 86.0 ± 1.7 (with a 1-ml saline flush) and 92.6 ± 1.2% (with a 2-ml saline flush) by 75 min.

In extremely low birth weight neonates (0.5 kg), the simulated infusions (experiments 1, 2, 5 and 6; Figure 3b) suggested these infants would receive an even lower percentage of the intended dose by 60 min. In these experiments, when a 2-mg gentamicin dose in 0.2 ml was infused into the intravenous line, with a dextrose flow rate of 3.8 ml/h and followed by a 1-ml saline flush, only 61.1 ± 1.9 and 74.9 ± 1.9% gentamicin was delivered by 60 and 75 min, respectively. The recovery for a lower 0.5-mg gentamicin dose was 61.7 ± 4.3% at 60 min, but this did increase when the saline flush volume or 10% dextrose flow rate was increased.

The univariate analysis indicated gentamicin dose (mg), gentamicin concentration (mg/ml), dextrose flow rate (ml/h) and saline flush volume (ml) significantly ($P < 0.05$) affected the percentage of gentamicin recovered from the intravenous line at 60 and 75 min. Results from a multivariate stepwise analysis of the percentage of gentamicin recovered at 60 min showed that a combination of these variables in the analysis produced a construct of 52.92 (2.5 SE), (47.7 to 58.13, 95% CI), $P < 0.001$ and R^2 0.89. A similar result was obtained for the gentamicin recovered at 75 min with a construct of 62.79 (2.4 SE) (57.7 to 67.7, 95% CI), $P < 0.001$ and R^2 0.91 (Table 3).

The correlation between flush volume (ml) and the percentage of gentamicin recovered at 60 and 75 min was r = 0.22 and r = 0.24, respectively. The highest correlation was seen between the volume of the concentration administered (mg/ml) and the percentage of gentamicin recovered (r = 0.87 at 60 min and r = 0.89 at 75 min). The correlation coefficients between the percentage of gentamicin recovered and the independent variables were less than 0.9.

Table 2 Summary of gentamicin recovery and least-square variables from intravenous infusions

Experiment	Gentamicin dose (mg)	Gentamicin volume (ml)	Saline flush volume (ml)	Dextrose 10% flow rate (ml/min)	Recovery (%) 60 min	Recovery (%) 75 min	Least-squares linear regression		
							Slope (%/min)	Lag-time (min)	R^2
1	0.5	0.2	1	3.8	61.7 ± 4.3	68.7 ± 5.0	1.03 ± 0.08	5.7 ± 1.2	>0.98
2	0.5	0.2	2	3.8	71.4 ± 4.0	76.8 ± 3.4	1.16 ± 0.06	7.4 ± 1.4	>0.97
3	2.5	1.0	1	18.7	82.7 ± 0.7	96.2 ± 0.9	1.39 ± 0.02	2.2 ± 1.1	>0.99
4	2.5	1.0	2	18.7	85.2 ± 0.8	97.2 ± 0.5	1.45 ± 0.01	5.5 ± 0.8	>0.98
5	2.0	0.2	1	3.8	61.2 ± 1.9	74.9 ± 1.9	1.10 ± 0.03	8.4 ± 0.4	>0.98
6	2.0	0.2	2	3.8	60.5 ± 2.1	78.7 ± 1.1	1.15 ± 0.04	12.9 ± 0.8	>0.95
7	10	1.0	1	18.7	74.6 ± 2.2	86.0 ± 1.7	1.28 ± 0.03	4.5 ± 0.4	>0.99
8	10	1.0	2	18.7	80.2 ± 1.2	92.6 ± 1.2	1.39 ± 0.02	5.1 ± 0.3	>0.98

Least-square variables: infusion rates (slope) and lag-time. Values are mean ± SD, $n = 3$.

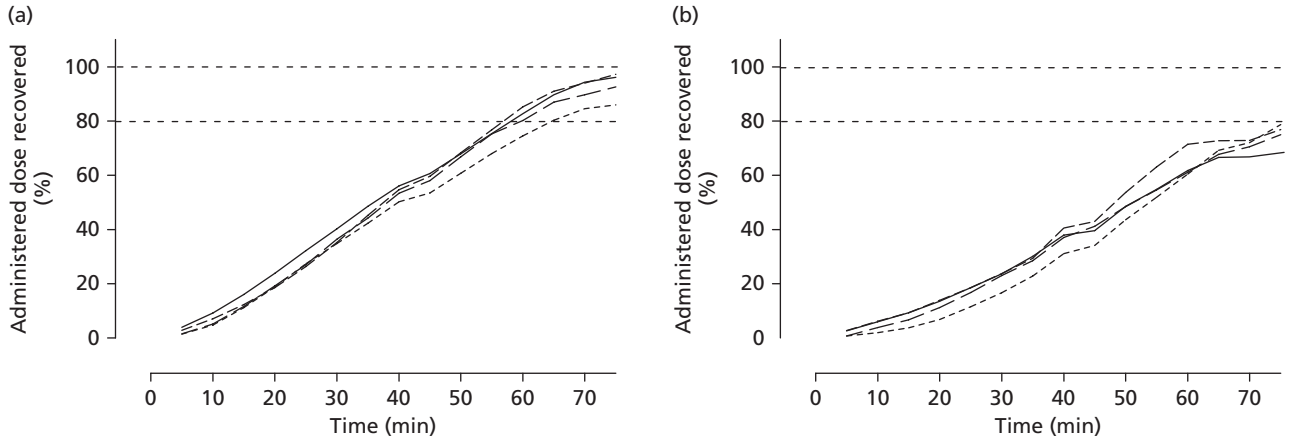

Figure 3 Mean administered dose recovered (%) for all gentamicin infusion experiments. (a) Gentamicin (10 and 2.5 mg) infusions for premature neonates. (b) Gentamicin (2 and 0.5 mg) infusions for extremely low birth weight neonates. Experiments 1 (b; —) and 2 (b; - · - ·): gentamicin dose 0.5 mg in 0.2 ml, flow rate 3.8 ml/h and saline flush of 1 and 2 ml, respectively. Experiments 3 (a; —) and 4 (a; - · - ·): gentamicin dose 2.5 mg in 1 ml, flow rate 18.7 ml/h and saline flush of 1 and 2 ml, respectively. Experiments 5 (b; - - -) and 6 (b; ····): gentamicin dose 2 mg in 0.2 ml, flow rate 3.8 ml/h and saline flush of 1 and 2 ml, respectively. Experiments 7 (a; - - -) and 8 (a; ·····): gentamicin dose 10 mg in 1 ml, flow rate 18.7 ml/h and saline flush of 1 and 2 ml, respectively. $n = 3$.

Table 3 Results of stepwise multivariate regression for percentage of gentamicin recovered following intravenous infusion

Variable ($n = 24$)	Coefficient	Standard error	95% CI	*P* value
Recovered at 60 min*				
Gentamicin dose (mg/ml)	–0.99	0.26	–1.54 to –0.44	0.001
Flow rate (ml/h)	1.47	0.13	1.2 to 1.74	<0.001
Flush volume (ml)	4.26	1.42	1.29 to 7.24	0.007
Construct	52.92	2.50	47.7 to 58.13	<0.001
Recovered at 75 min**				
Gentamicin dose (mg/ml)	–0.84	0.25	–1.37 to –0.32	0.003
Flow rate (ml/h)	1.51	0.12	1.25 to 1.77	<0.001
Flush volume (ml)	4.88	1.37	2.02 to 7.74	0.002
Construct	62.79	2.40	57.7 to 67.7	<0.001

*Recovered at 60 min ($R^2 = 0.89$) and **recovered at 75 min ($R^2 = 0.91$). CI, confidence interval.

Discussion

Gentamicin is one of the most widely monitored drugs in clinical practice because its efficacy and toxicity are reported to correlate with blood concentration.[12] It is also known that substantial variability can exist in the serum concentration of aminoglycosides in patients receiving the same intravenous doses.[13] Dosing modifications are generally made based on the measured concentrations. Routine practice in the Dunedin Hospital neonatal intensive care unit is to take a blood sample at 60 min after starting the gentamicin infusion, when it is assumed that the entire gentamicin dose has been administered. Therefore, it is expected that the concentration at this time should reflect the peak serum concentration. The gentamicin concentrations are measured 30 min after completion of the intravenous infusion to avoid taking the peak during the infusion. If clinicians are basing dosing changes on misleading measurements, then neonates may potentially be under or over dosed with gentamicin, leading to an increased risk of treatment failure or alternatively adverse effects (ototoxicity and nephrotoxicity).[8,14]

This study has shown that current infusion guidelines led to slower than expected delivery of gentamicin to the bloodstream. The infusion rate chosen for the primary intravenous line was high (180 ml/kg per day) so in clinical practice gentamicin could be given into slower intravenous lines and the infusion would be considerably slower than that reported here. A gentamicin dose of 2 mg represents a standard dose for a 0.5-kg neonate and at the standard gentamicin concentration of 10 mg/ml this means a dose volume of 0.2 ml. These small drug volumes together with the slow primary infusion rate combine to slow delivery of the drug into the bloodstream.

The effects of the individual intravenous infusion parameters (varying gentamicin dose, gentamicin concentration, flow rate and flush volume) were investigated using a univariate analysis and it was found that all individual parameters had a significant effect on the percentage of drug recovered. It was determined that the lag time was longer when a smaller gentamicin dose and lower flow rate was used, leading to a lower percentage of recovery. The subsequently performed stepwise multivariate regression

analysis confirmed the significance of each of the variables. The flow rate (ml/h) of the carrier fluid was the most significant variable in the multivariate analysis, with $P < 0.001$ at 60 and 75 min. There was a high correlation between the dose administered (mg/ml) and the percentage of gentamicin recovered, supporting the hypothesis that delivering small drug volumes (0.2 ml) at low carrier fluid infusion rates (3.8 ml/h) dramatically affected the residence time of the drug in the intravenous line. This was consistent with reports that have determined that in delivering drugs in the neonatal setting the physical variables associated with an intravenous infusion, such as low infusion rates (2 ml/h) and delivery of small drug volumes (<1 ml), could significantly increase the actual infusion duration.[15–18]

There is also a need to consider if the drug becomes trapped in the dead space.[19] The estimated dead space in the experimental infusion set up was 0.8 ml; this volume of dead space represents a volume greater than the volume of the intended dose of drug in neonatal practice. The site of administration and the infusion method directly affects the proportion of dead space, the amount of drug remaining in the infusion set, and thus the quantity of drug delivered to the patient.[9] The results from this study did confirm that the volume of the saline infusion administered after gentamicin influenced the amount of drug recovered and decreased the period of time it took for the drug to reach the peripheral catheter. Highest dose recovery occurred in the intravenous infusions simulating infusion of gentamicin to larger neonates (2.5 kg). In contrast, the infusions simulating delivery to extremely low birth weight neonates resulted in the percentage of dose recovery at 60 min being as low as 57%. The administration of the 2-ml saline flush in comparison with the 1-ml flush improved the amount of drug recovered up to 76%. The impact of variables such as inline filters, dead space and extension tubing were not explored in this study and they need investigating to determine what affect these might have on the duration of drug delivery to neonates. Future experiments need to be undertaken to identify any additional physical characteristics associated with the delayed drug delivery in the infusion line identified in this study.

The results from this study suggested that delivering gentamicin by slow intravenous infusion to extremely low birth weight neonates may not be appropriate and that administration by intravenous bolus should be investigated further. Additionally, there are potentially consequences for other drugs given in low infusion volumes via similarly set up neonatal infusions. However, increasing the flush volume or giving a saline bolus flush to neonates following drug administration may not be appropriate depending on the clinical picture. In neonates, it is common for small volumes of concentrated drug solutions to be administered at low infusion rates to avoid volume overload.[20] Hence, a larger flush volume might not be desirable. Extremely low birth weight neonates have a very narrow range of fluid tolerance and flow rates in the primary intravenous line may be as low as 0.1–2 ml/h.[20,21] Potential for fluid overload occurs if multiple intravenous drug and electrolyte treatments are required and is further exacerbated when drug dilution is recommended before administration.[22]

Conclusions

This study indicated that not all gentamicin was administered to the bloodstream by the predicted 60-min interval. The intravenous infusion administration of gentamicin under the current set up was neither efficient nor effective and this had significant clinical implications. The delivery of gentamicin administered by intravenous infusion was substantially extended in extremely low birth weight neonates. This finding was most likely due to the low infusion rates that are typically used to administer gentamicin to these neonates. These findings have direct implications for the interpretation of the value of C_{max} for aminoglycoside in neonates. Furthermore, when low rate infusions were used, it may have been more appropriate to administer gentamicin as a bolus dose rather than an infusion.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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