function; and vision (clinical examination and global motion perception). Primary outcomes were neurosensory disability (cognitive, language or motor score below -1 SD or cerebral palsy or blind or deaf) and processing problem (executive function or global motion perception worse than 1.5 SD). Data are mean (SD), n (%), or relative risk (RR), 95% confidence interval.

Results 184 children were assessed; 90/118 (76%) randomised to dextrose and 94/119 (79%) to placebo gel. Mean birth weight was 3093 (803) g and gestation 37.7 (1.6) wk. 67 children (36%) had neurosensory disability (1 severe, 9 moderate, 57 mild) with similar rates in both groups (dextrose 35 (39%) vs placebo 32 (34%), RR 1.14, 0.78–1.67). Processing difficulty was also similar in both groups (dextrose 8 (10%) vs placebo 16 (18%), RR 0.52, 0.23–1.15).

Discussion Neurosensory disability is common amongst children treated for neonatal hypoglycaemia. Treatment with dextrose gel does not change the incidence of disability or processing problems.

REFERENCE

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Pharmacology, Pharmacokinetics, Pharmacodynamics

O-105 PROSPECTIVE EVALUATION OF REMIFENTANIL DURING INSURE IN PRETERM NEWBORNS: UNPREDICTABLE EFFECTS AND SIDE EFFECTS

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Background and aims Premedication for neonatal intubation should provide fast and adequate sedation with a minimum of side-effects. Aim of this study was to evaluate effect and safety of remifentanil as premedication during INSURE in preterm neonates.

Methods Remifentanil was prospectively studied using increasing dosages (Table 1). Outcome measures were adequate sedation, defined as adequate sedation score, good intubation conditions and absence of side-effects, and duration of respiratory depression. To exclude degradation or dilution errors as explanation for observed variability in response, pharmaceutical analysis was performed after simulated preparation.

Abstract O-105 Table 1 Protocol of remifentanil for the 2 study periods

	Period 1 (n = 5)	Period 2 (n = 9)
Site of administration	Intravenously	Intravenously
Period of administration	In 30 seconds	In 30 seconds
Starting dose	1 µg/kg	2 µg/kg
		Dose 2: 3 µg/kg
	Dose 2: 1 µg/kg	Dose 3: 4 µg/kg
Repeated doses	Dose 3: 1 µg/kg	Dose 4: 5 µg/kg
Sedative in case of failure	Propofol 1–2 mg/kg	Propofol 1–2 mg/kg

Results The study was terminated after inclusion of 14 patients. A dose of 1 ug/kg did not provide adequate sedation in 80% of patients. Higher dosages also resulted in inadequate sedation in 89% of patients and were frequently associated with chest rigidity (36%). Duration of respiratory depression was reported in 6 patients, with a median of 18 min (mean 16.5 min, range 5 seconds to 30 min). Pharmaceutical analysis showed a concentration of the active substance of 80 to 112% of the expected concentration, indicating adequate stability and preparation.

Conclusion Remifentanil intravenously over 30 seconds frequently not provides adequate sedation and has a high risk of chest wall rigidity in preterm neonates. Also, duration of respiratory depression is quite long for use during INSURE.

O-106 POPULATIONPHARMACOKINETIC MODEL OF THE ANTIMICROBIAL EXCIPIENT METHYL PARABEN ADMINISTERED IN ROUTINE CLINICAL PRACTICE TO NEONATES

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Introduction Parabens are widely used as antimicrobial preservatives in medicines given to neonates. Some concerns have been raised about the potential of paraben toxicity. To date there have been no studies of the circulating concentrations of methyl paraben (MPB) in babies. This study aimed to describe the relationship between dose of MPB administered and circulating concentrations using a population pharmacokinetic model.

Methods Neonates in 4 UK and 1 Estonian neonatal units who were prescribed paraben-containing medications were recruited with parental consent. Parabens were assayed in timed, dried blood spots using LCMSMS. The limit of quantification was 20ng/mL.

Results 180 babies provided 841 samples of which 382 (45%) were below the limit of quantification. The mean (range) of observed blood MPB concentrations was 28.4 (10–874) ng/ml. The final kinetic model for MPB included first order absorption and two compartment disposition. Clearance was related to postnatal age (PNA). The model parameters are shown in the Table.

Discussion Routine use of MPB as an excipient in medicinal formulations does not lead to markedly high circulating blood concentrations of MPB in neonates. We cannot exclude accumulation from these data. These findings will contribute to safety

Abstract O-106 Table 1

Parameter	Estimate	% Relative Standard Error
Clearance if PNA <21 days (L/hr)	0.57	9.57
Clearance if PNA ≥21 days (L/hr)	0.88	7.19
Central volume (L/1.6kg)	1.84	7.55
Peripheral Volume (L)	12.2	12.0
Residual (proportionate) Error (%)	44.5	4.7

assessments and regulatory advice and may indicate that current levels of MPB in formulations are acceptable for young children.

O-107 PROSPECTIVE VALIDATION OF A MODEL-BASED DOSING REGIMEN FOR AMIKACIN IN PRETERM AND TERM NEONATES

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Background and aims An essential step in drug dosing optimalisation is prospective validation of newly proposed dosing regimens. Based on a recently published population pharmacokinetic (PK) model, a neonatal amikacin dosing regimen was developed. The aim of the current study was to prospectively validate this model-derived dosing regimen.
Methods Routine amikacin therapeutic drug monitoring (TDM) concentrations were prospectively collected. To test efficacy of the dosing regimen, early observed TDM results (i.e. prior to and 1 h after the second intravenous amikacin dose) reaching target concentrations (trough <3 mg/L, peak >24 mg/L) were defined. To test stability and accuracy of the model, all observed concentrations were compared with the predicted concentrations and a normalised prediction distribution error (NPDE) was performed. Monte Carlo simulations were used to evaluate amikacin exposure.
Results In total, 1195 TDM results of 579 neonates [median gestational age 34 (range 24–41) weeks, postnatal age 2 (range 1–30) days] were included. Sixty percent of the early trough levels was below 3 mg/L, 90.4% of the peak levels reached 24 mg/L. Comparable parameter estimates were obtained between the final PK model and the prospective dataset. No trend was seen in the NPDE *versus* time and the NPDE *versus* predicted concentrations. Based on the Monte Carlo simulations, peak concentrations above 24 mg/L were reached in almost all patient subgroups.
Conclusions After 14 years experience of amikacin dosing optimalisation in (pre)term neonates, a model-based dosing algorithm was prospectively validated confirming its efficacy, stability and accuracy over the entire neonatal population.

O-108 PHARMACOKINETICS OF MELATONIN IN PRETERM INFANTS

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Background Evidence from neonatal studies is critical in understanding developmental variations in drug pharmacokinetics and can guide dosing adjustments. Melatonin has been shown previously in a single dose study to have slow clearance and prolonged half-life in preterm infants.
Aim To determine the melatonin pharmacokinetic profile in preterm infants on exogenous supplementation and to determine the melatonin concentrations in donor and maternal breast milk.
Methods The study was part of an exploratory; double-blinded randomised placebo controlled trial evaluating the neuroprotective effect of melatonin in preterm infants less than 31 weeks gestation. Infants in the melatonin arm (n = 29) received an intravenous infusion 0.1 mcg/kg/hr for 2 h once daily for 7 days starting by 48 h after birth. The placebo group (n = 28) received same volume of saline. Plasma and milk melatonin concentrations were analysed by radioimmunoassay. Population pharmacokinetics was carried out using NONMEM.
Results The median plasma melatonin levels on day 4 was 152pg/ml in the melatonin group and was 0pg/ml in the saline group. On nonlinear mixed effect modelling, using first order conditional estimation with interaction, the clearance was 0.05L/hr with a half-life of 15.61 h. Effect of covariates: gender and race were not significant in this study unlike previously reported. Mean melatonin concentrations in donor breast milk were 63pg/ml, higher than that of maternal breast milk even on day 4 (16.6 pg/ml).
Conclusions Preterm infants have delayed clearance and prolonged half-life of melatonin. This data can be used for simulation of future dose studies in preterm infants.

O-109 NEBULIZED ADRENALINE IN 3% HYPERTONIC SALINE SOLUTION IN BRONCHIOLITIS: IS SAFE?

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Background and aims The use of nebulized adrenaline in the treatment of infants with acute bronchiolitis, has been related to increased cardiac rate. On the other hand, bronchoconstriction episodes requiring bronchodilators have been reported with the use of nebulized 3% hypertonic saline solution (3%SSH) without bronchodilators. We aimed to analyse the safety of nebulized adrenaline and nebulized 3% HSS in the management of infants hospitalised for acute moderate bronchiolitis.
Methods Randomised, double-blind, controlled trial. 185 hospitalised infants (2.11 ± 2.23 months (mean ± SD) received nebulized 3%HSS (7ml) either with 3 mg of adrenaline (group SSH3%+A; n = 94) or 3 ml of placebo (group SSH3%+P; n = 91), in addition to routine therapy. Nebulizations were initially administered every four hours and adjusted thereafter according to clinical response. The principal outcomes measures were cardiac rate (CR) and frequency rate (FR) up to the median of stay, nebulization requirements and need of transfer to the PICU.
Results There was not statistically significant differences in the cardiac frequency (p = 0.76, 0.48 and 0.73, respectively) and frequency rate (p = 0.88, 0.07 and 0.24, respectively) in 3 days of median of stay, nebulizations rates (p = 0.89), PICU's admission (p = 1). No other adverse events were reported.
Conclusion In acute bronchiolitis for moderately ill hospitalised infants, nebulized adrenaline and nebulized 3%HSS are safe.

Abstract O-109 Table 1

	CR(1d)	CR(2d)	CR(3d)	FR(1d)	FR(2d)	FR(3d)	Neb
3%HHS+P	143	143	142	49	49	48	4.13
3%HHS+A	141	142	142	49	47	46	4.17
p	0.76	0.48	0.73	0.88	0.07	0.24	0.89