Pilot on harmonising dosing recommendations for term and preterm neonates in the Netherlands (NeoDose project)

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INTRODUCTION

Many drugs are used off-label in term and preterm neonates, and dosing recommendations for many drugs are lacking in the Dutch Paediatric Formulary (DPF). This results in widely varying dosing regimens used across neonatal intensive care units (NICUs) in the Netherlands. The NeoDose pilot aimed to develop best-evidence national dosing recommendations for preterm (<37 weeks' gestational age (GA)) and term (≥37 weeks' GA) neonates. Because scientific evidence is scarce, this pilot started with a consensus-based approach.

METHODS

A priority drug list, containing the most frequently used drugs for neonates, was drafted. From this list 22 drugs were selected for further research within the NeoDose pilot. The pilot utilised a two-step approach: Firstly, consensus was established with all Dutch NICUs for neonatal dosing recommendations. Local treatment protocols were gathered, compared and discussed in face-to-face meetings, leading to consensus-based dosing recommendations. Secondly, we aimed to develop best-evidence dosing recommendations for five of these 22 drugs, selected by need.

RESULTS

Part One
For 21 of 22 drugs, local dosing guidelines differed significantly. Mostly concerning total daily dose, dose frequency and route of administration. Little or no distinction is made between treatment of preterm and term neonates. Approximately half of the final consensus-based dosing recommendations (45%) differ in some degree from all local protocols.

Part Two
The following five drugs were chosen for the development of best-evidence dosing recommendations: **acyclovir, ganciclovir, ibuprofen, hydrocortisone and dexamethasone**. Comparing the consensus-based dosing recommendations with the available evidence, almost half of the consensus-based doses were adjusted.

Table 1 Acyclovir	GA	No of different dosages	No of hospitals with protocol	Consensus-based dosage	(Best) evidence-based dosage
HSV and VZV infection	<37 wk	2	4	60 mg/kg/day in 3 doses	60 mg/kg/day in 3 doses
	≥37 wk	1	8	60 mg/kg/day in 3 doses	80 mg/kg/day in 3 doses

Example 1. Acyclovir: For acyclovir most hospitals applied the same dosing recommendation; only one hospital had a different dosing recommendation for preterm neonates. Consensus was easily achieved. However, when the evidence was listed, every NICU agreed on adjusting the consensus-based dosing recommendation for term neonates (Table 1). This decision was mainly based on the population pharmacokinetic study of *Sampson et al. 2014.*. This study showed that term neonates need a higher dosage and this dosage is incorporated in the Dutch Paediatric Formulary.

Example 2. Hydrocortisone: eight hospitals had a dosing protocol. Almost every protocol differed more or less from the others (Table 2). The final consensus-based dosing recommendation (in the light blue bar) differed also more or less from all local protocols (deviations in red). After listing of the evidence, this consensus-based dosing recommendation was maintained.

Table 2. Local NICU dose recommendations and final concensus-based dosing recommendation

NICU	Hydrocortisone protocol	NICU	Hydrocortisone protocol
AMC	3 mg/kg/day in 3 doses, for 5 days IV	Radboud UMC	2 mg/kg/day in 2 doses, for 3-5 days IV
MMC	3 mg/kg/day in 3 doses	UMC Utrecht	5 mg/kg/day in 4 doses
Erasmus MC	12-15 mg/m2/day in 3 doses	UMC Maastricht	5 mg/kg/day in 4 doses
VUMC	3-6 mg/kg/day in 2-4 doses, for 3-5 days IV	LUMC	3 mg/kg/day in 3 doses, for 5 days PO/IM/IV

Consensus-based dosing recommendation: 3-5 mg/kg/day in 3 doses IV, tapering guided by clinical parameters

CONCLUSIONS

This pilot showed successful development of consensus and best-evidence dosing guidelines for dosing of term and preterm infants. For more uniform use across the Netherlands and Europe, these new recommendations will be published in the Dutch, German, Austrian and Norwegian Paediatric Formulary. We now aim to expand our newborn dosing guidelines to other drugs using the same framework.

READ IT LATER?

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Reference: Sampson, M. R., B. T. Bloom, R. W. Lenfestey, B. Harper, A. D. Kashuba, R. Anand, D. K. Benjamin, Jr., E. Capparelli, M. Cohen-Wolkowiez, and P. B. Smith. 2014. "Population pharmacokinetics of intravenous acyclovir in preterm and term infants." Pediatr Infect Dis J 33 (1):42-9.