Characterization of medications used during therapeutic hypothermia in the NICU - A pilot project

Sandra Yin, B.Sc.(Pharm); Brandi Newby, B.Sc.(Pharm), ACPR; Katrina Assen, B.Sc.(Pharm), ACPR

Background

- Peripartum asphyxia can cause hypoxic ischemic encephalopathy (HIE)
- Therapeutic hypothermia:
  - Recommended by the Canadian Pediatric Society for ≥36 weeks gestational age with moderate to severe HIE
  - Initiated within 6 hours and continued for 72h at 34 +/- 0.5°C
  - Improves survival and neurodevelopmental outcomes up to 18 months
- Hypothermia can alter the PK/PD parameters of medications
  - Absorption: ↓ intestinal perfusion, ↓ GI motility
  - Distribution: ↓/↑ Vd
  - Metabolism: ↓ basal/ cerebral metabolic rate, CYP450 activity, blood flow to liver
  - Elimination: ↓ blood flow to kidneys
  - Changes have been described in some medications
    - Morphine- elevated concentrations observed
    - Phenobarbital and gentamicin- mixed results for requiring dose adjustments
- In addition, the asphyxia event can affect liver and renal function

Objectives

Part A:

- Determine the number and type of medications received by neonates undergoing therapeutic hypothermia
- Compare doses of medications used during therapeutic hypothermia and rewarming with standard neonatal doses
- Determine the number of dose adjustments required during therapeutic hypothermia and rewarming

Part B:

- Describe medication use and dosing regimens in level 3 NICUs across Canada during therapeutic hypothermia

Methods

- Part A: Chart review- medication use during 1st week of life
  - Within Fraser Health (FH)- July 1, 2010 to July 31, 2013
  - Patients with birth asphyxia, birth depression or HIE
  - Inclusion: Neonates receiving therapeutic hypothermia
  - Exclusion: < 36 weeks, transfer out of FH within study period
- Part B: Survey of medication use during hypothermia
  - Inclusion: Pharmacists from Canadian Neonatal Network NICUs
- Statistical analysis using descriptive statistics

Results

Part A

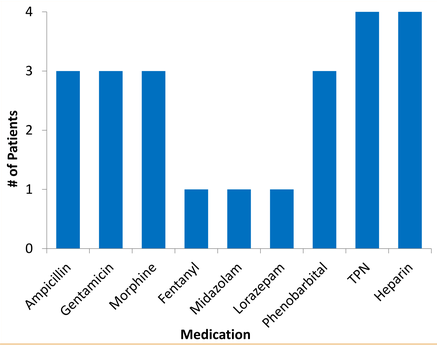
- 67 charts were identified
  - 10 charts were not available, 23 were < 36 weeks, 29 did not undergo hypothermia
  - 5 received therapeutic hypothermia
    - 1 excluded due to being transferred within 48 hours

Table 1: Characteristics of patients

Pt	GA (wks)	BW (kg)	Onset to cooling (h)	Cooling duration (h)	Rewarming period (h)	Ventilated?
1	37	3.05	1	83	11	Yes[a]
2	40+1	2.985	1.3	72	7	No
3	37+2	2.8	2.2	77	11	No
4	41	3.395	4.5	71	14	Yes[a]

[a]: Pt 1- for the first 11.6 h; Pt 4- for the first 7.3 h of hypothermia

Figure 1: Medication use during hypothermia and rewarming



Medications	Dose
Ampicillin	50 mg/kg/dose q8h
Gentamicin	2.5 mg/kg/dose q12h or **by levels** Levels pre 2nd, pre 3rd or after 22h
Morphine	**Started at and did not exceed 0.01 mg/kg/h**
Fentanyl	5 mcg/kg then 0.5 mcg/kg/h started after 50 min
Midazolam	Started at and did not exceed 0.01 mg/kg/h
Lorazepam	0.05-0.06 mg/kg/dose
Phenobarbital	20-25 mg/kg then 3.7-5 mg/kg/d started after 21-28 h **10 mg/kg for a mini-load**
TPN	Neonatal starter then neonatal standard starting pm of DOL1
Heparin	1 unit/h for arterial line

5 dosing regimens adjusted empirically (in bold): gentamicin (1), morphine (3), phenobarbital (1). **Note: Complete list of medications not depicted in figure.

Table 2: Adverse effects and dose adjustments

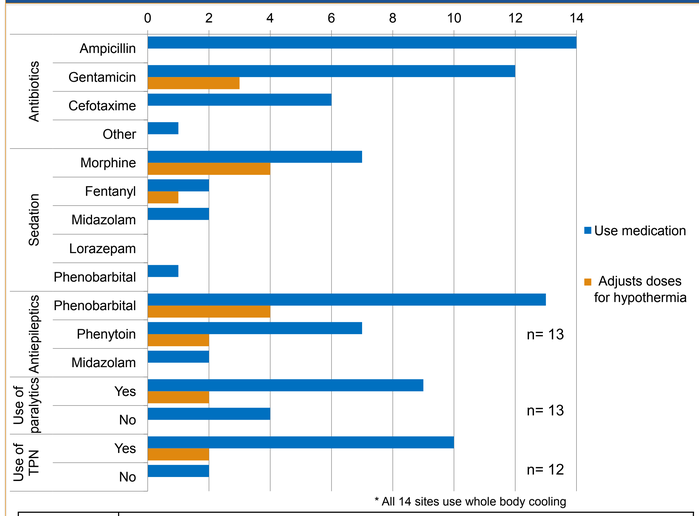
Pt	# Medications Used[a]	# Dose Adjustments	Adverse Events[b]	Details
1	12	2	Sedation[c]	• Increased sedation DOL2- midazolam infusion decreased, eventually held along with morphine - also received lorazepam 0.06 mg/kg x 1 and 0.05 mg/kg x 3 the previous day
			Seizure	• Occurred DOL5- phenobarbital initiated
2	11	1	↑ K^+	• Removed K^+ in TPN on DOL1
			Urinary retention	• Catheter inserted at 21 hours of life
3	5	0	-	-
4	12	2	↑ gentamicin levels	• Interval increased from q12h to q18h
			Urinary retention	• Catheter inserted at 8 hours of life
			Bradycardia	• Pre dose levels= 119 umol/L, decreased phenobarbital dose by 12%
			Seizure	• Occurred DOL4, phenobarbital mini loading dose 10 mg/kg

[a]: from birth until DOL7
[b]: adverse events recorded from initiation of therapeutic hypothermia to the end of DOL7
[c]: patient 1 was started on both morphine and midazolam at the same time

Part B

- 28 Canadian NICU sites were surveyed
  - 3 do not provide therapeutic hypothermia
  - 14 participated in the survey, of which 12 fully completed

Figure 2: Use of medications during therapeutic hypothermia in NICUs across Canada (n=14)



* All 14 sites use whole body cooling

Medication	Details of dose adjustment (n)
Gentamicin	adjust frequency (3), avoid use (1) note: Levels done prior 2nd dose (4), prior 3rd dose (5), 22-24h after dose (4)
Morphine	limit to 0.01 mg/kg/h (3), bolus dosing (1)
Fentanyl	bolus dosing (1), avoid use (2- due to neurotoxicitiy)
Phenobarbital	use lower dose (3), delays initiation of maintenance (1)
Phenytoin	use lower dose (1), delays initiation of maintenance (1), avoid use (1- due to cardiotoxicity)
Paralytics	lengthens interval (1), increases dose for rocuronium and decreases dose for pancuronium (1)
TPN	fluid restrict to 40 mL/kg/d on Day 1 and limit to 60 mL/kg/d, 1 K^+ free/restricted initially (1)

Dose adjustments also made based on renal function for: gentamicin, cefotaxime, morphine, midazolam, TPN

Conclusions

Part A

- Neonatal hypothermia in FH involved the use of 5 to12 medications including antibiotics, sedatives and antiepileptics
- Dosing regimens for gentamicin, morphine and phenobarbital were different than standard neonatal dosing
  - 5/40 (13%) medications were adjusted empirically
- 5/40 (13%) medications required dose adjustments for adverse events during the study period

Part B

- Medication use and dosing regimens during therapeutic hypothermia are variable in NICUs across Canada
  - Gentamicin, phenobarbital, morphine, phenytoin and/or TPN are empirically changed at some sites
  - Fentanyl, phenytoin and/or paralytics are avoided at some sites
- More information is required to guide empiric dos adjustments for medications used during therapeutic hypothermia

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