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Population Pharmacokinetic Analysis of Fentanyl and Norfentanyl in Critically-III Children

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 IRB Approved

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Disclosure

- Sin Yin Lim
- Conflicts of interest: none
- Sponsorship: OU College of Pharmacy, OU Department of Pediatrics
- Propriety information or results of ongoing research may be subject to different interpretations
- Speaker's presentation is educational in nature and indicates agreement to abide by the non-commercialism guidelines provided

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Learning Objectives

1. Compare and contrast opioid agents given as continuous infusion for pain and sedation in critically-ill children
2. Identify 2 main factors associated with fentanyl clearance variability in children

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Opioid Agents for Pain & Sedation in Critically-III Children

Morphine	Fentanyl	Hydromorphone
<ul style="list-style-type: none"> • Active metabolites • Slower brain uptake • Longer half-life in neonates • May induce release of histamine, causing hypotension 	<ul style="list-style-type: none"> • 100x potency of morphine • Lipophilic; rapid distribution, quicker onset • Used in hemodynamically unstable patients • High doses may cause rigid chest syndrome 	<ul style="list-style-type: none"> • 5x potency of morphine • Faster onset than morphine • Useful when idiosyncratic reactions to morphine • Less likely to cause histamine release than morphine

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Fentanyl Dosing Uncertainty

- Dosing is highly variable among children
- Limited pharmacokinetic (PK) data in children
- Contribution of metabolic clearance by the formation of a primary metabolite, norfentanyl, to overall fentanyl clearance is largely undetermined

Objectives


1. Study fentanyl PK using a population PK approach
2. Characterize the PK of norfentanyl and determine its contribution to fentanyl clearance

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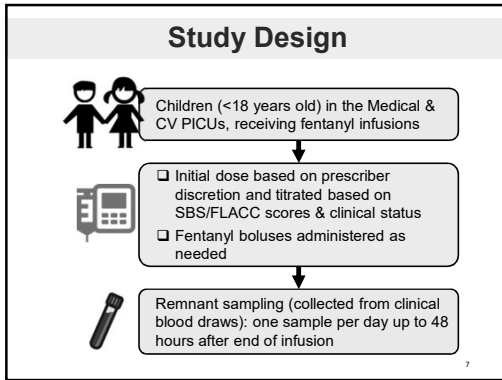
The Children's Hospital at OU Medical Center

Study Site

- Tertiary-care, academic pediatric hospital within a comprehensive health-system
- 314 bed inpatient facility:
 - > 13-bed Medical PICU
 - > 12-bed CV Surgical PICU
 - > 1000-1500 PICU admissions per year



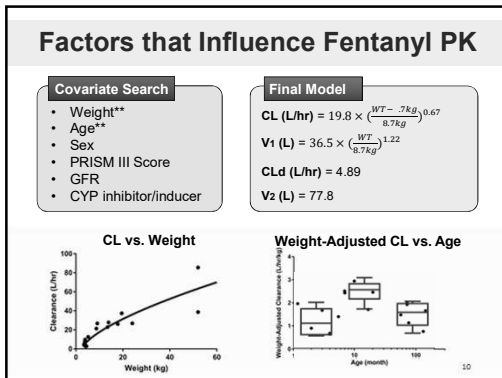
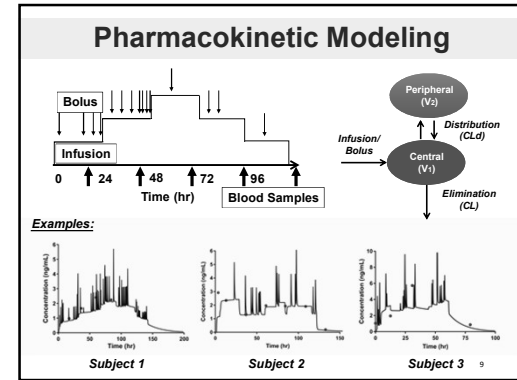
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Patient Baseline Characteristics

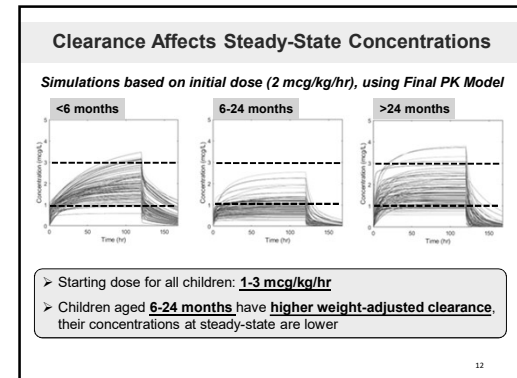
Characteristics (n=17)	Median (Range) or Number (%)
Female	10 (59)
Age (years)	0.83 (0.1-12)
Weight (kg)	8.7 (3.4-52)
Height (cm)	72 (46-163)
Medical PICU	10 (59)
PRISM III Score	3.2 (0.39-39)
Fentanyl Duration (days)	7 (3-35)

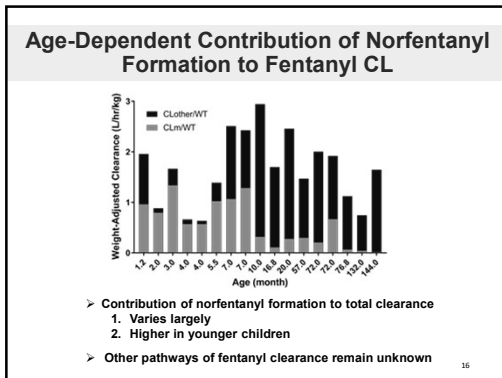
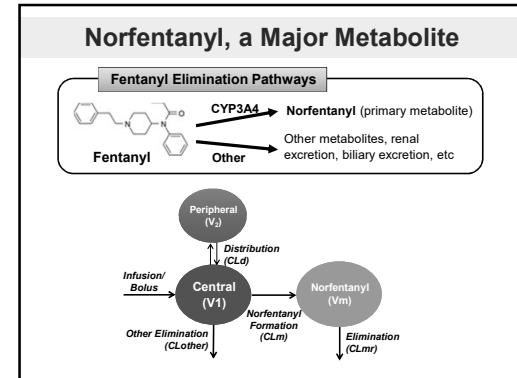
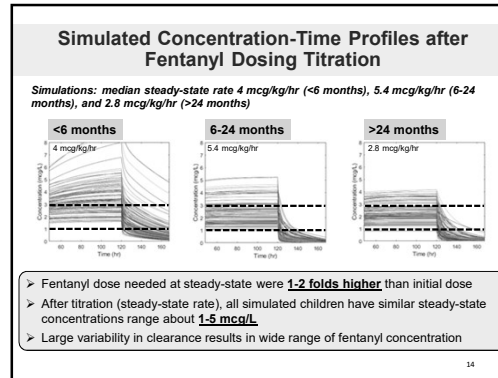
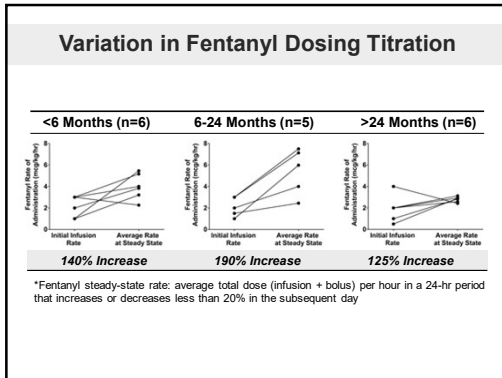
Other Sedatives Received	Number (%)
Dexmedetomidine	17 (100)
Midazolam	11 (65)
Ketamine	7 (41)
Propofol	2 (12)



PK/Dosing Variability in Three Age Groups

<6 Months (n=6)	6-24 Months (n=5)	>24 Months (n=6)
<i>Weight-Adjusted CL (L/hr/kg) ± SD</i>		
1.2 ± 0.55	2.4 ± 0.45	1.48 ± 0.48
<i>Observed Initial Fentanyl Infusion Rate (mcg/kg/hr), Median (Range)</i>		
2.5 (1-3)	2 (1-3)	2 (0.5-4)





Conclusions

- Large variability in fentanyl PK, mainly explained by **weight and age**
- Dosing requirement varies largely and appears to be weight- and age-dependent
- Titration of fentanyl based on sedation/pain scales as current practice; **reevaluation of initial dose** may be needed for children 6-24 months
- Contribution of norfentanyl formation to total CL is **higher in younger children**
- Further study on sources of fentanyl PK variability in children is needed, especially **elimination pathways** other than norfentanyl formation

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Primary Mentors

Self-Assessment Questions

1. Which of the following opioid analgesic agents has the highest potential to induce histamine release and cause hypotension in hemodynamically unstable patients?
 - A. Hydromorphone
 - B. Morphine
 - C. Fentanyl
 - D. Meperidine

2. Based on the population PK model from this study, which of the following patient factors have the highest association with fentanyl clearance in children?
 - A. Albumin and total bilirubin
 - B. Race and sex
 - C. Serum creatinine and liver function tests
 - D. Weight and age

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