

IV Acetaminophen in Children: Is there evidence for safety and efficacy?



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Disclosures

- I was the local PI at CHOP for a safety trial of IV acetaminophen in children sponsored by Cadence Pharmaceuticals (CPI-APA-352):
A phase III multi-center, open-label, prospective, repeated dose, multi-day study of the safety and efficacy of intravenous acetaminophen in pediatric inpatients
- IV acetaminophen (Acetavance®) has not been approved for use by the FDA

Objectives

- Pharmacokinetics of enteral acetaminophen (APAP) in children
- Metabolic pathways of APAP
- Pharmacokinetics of IV APAP in children
- Safety of IV APAP
- Administration guidelines for IV APAP
 - Dosing
 - Technical considerations

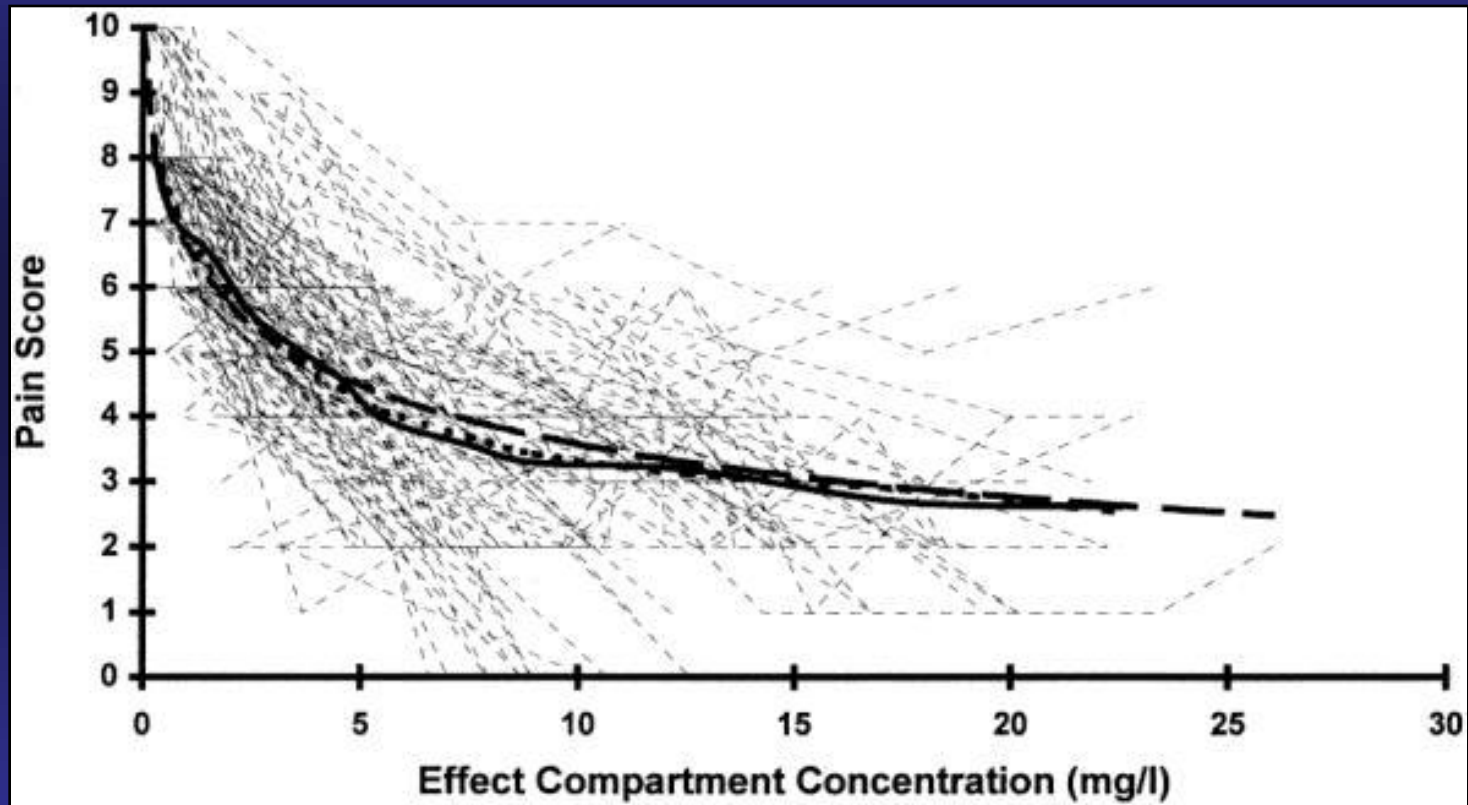
Postoperative Analgesia

- Opioids only drugs approved for IV analgesia in children
- Opioids associated with adverse effects
 - PONV
 - Pruritus
 - Constipation
 - Prolonged PACU stay
- NSAIDS not approved; risk of bleeding
- Enteral acetaminophen effect delayed, unpredictable blood levels

Pharmacokinetics of Enteral Acetaminophen

- Wide range of blood levels seen with both oral and rectal administration
- Variability among preparations
 - Elixir, solution, suppository, etc.
- Concentration:response relationship well established for fever (10 mg/L) but not for pain

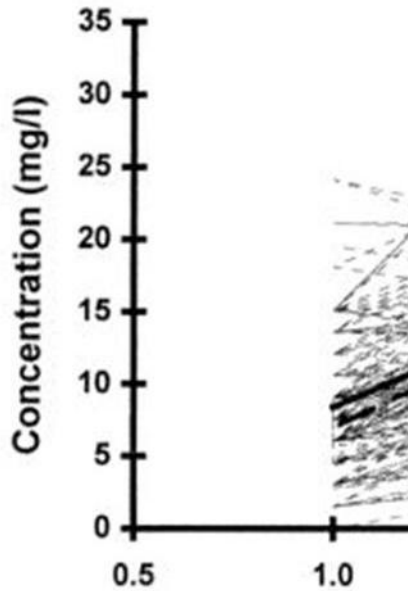
10 mg/L may be effective concentration for pain relief



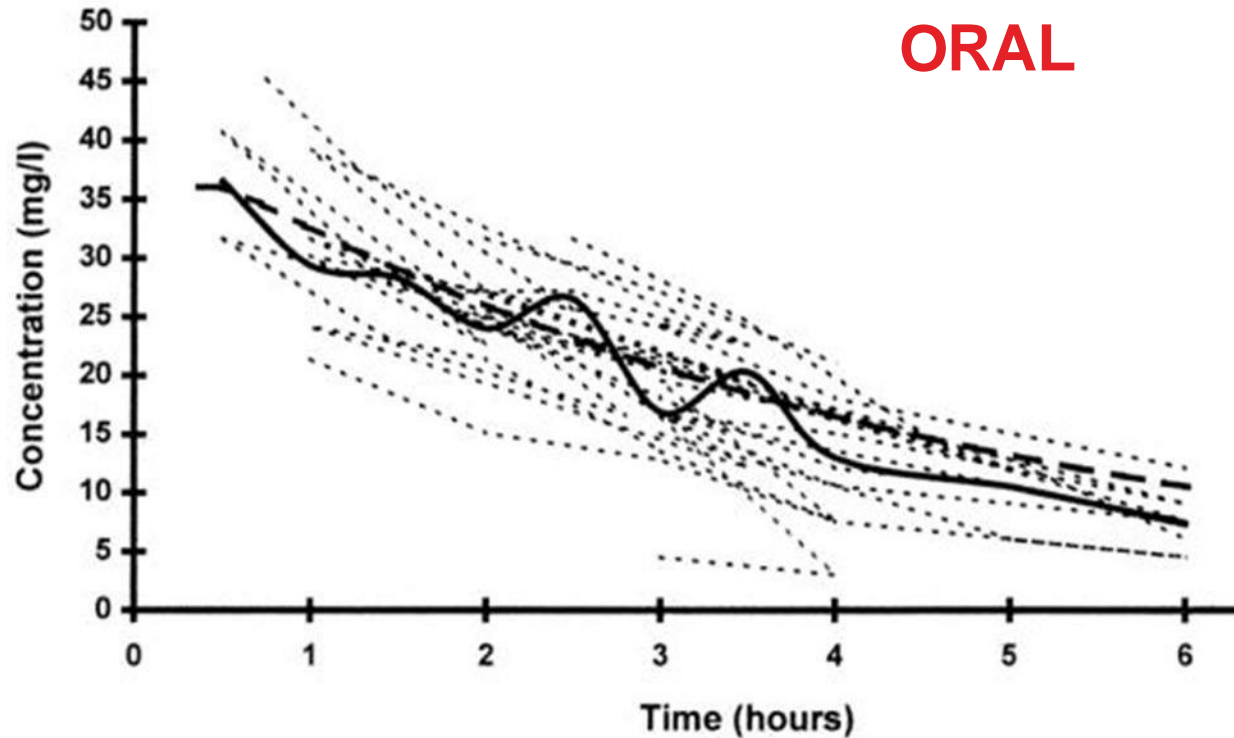
Anderson BJ, Anesthesiology 1999

Variability in blood levels: enteral

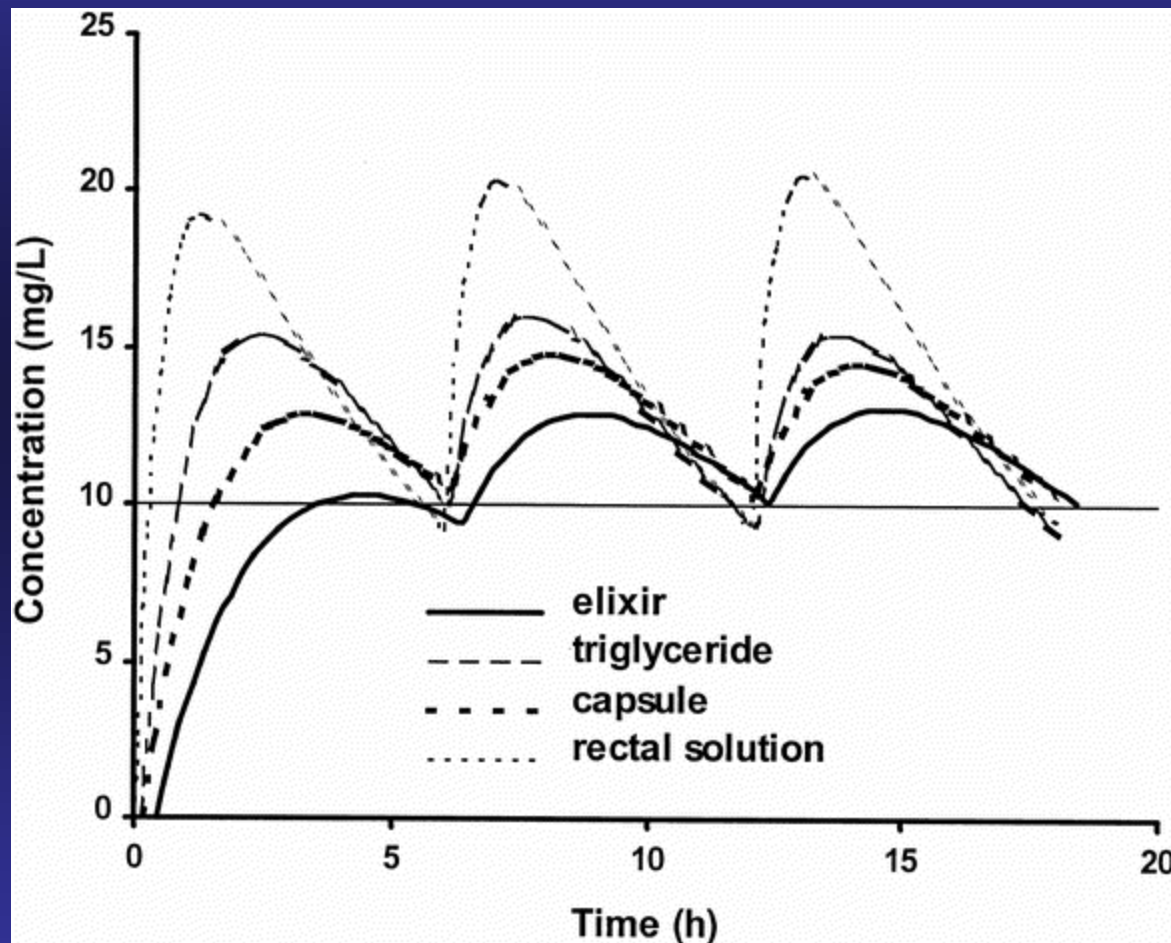
RECTAL



ORAL



Plasma levels depend on mode of administration



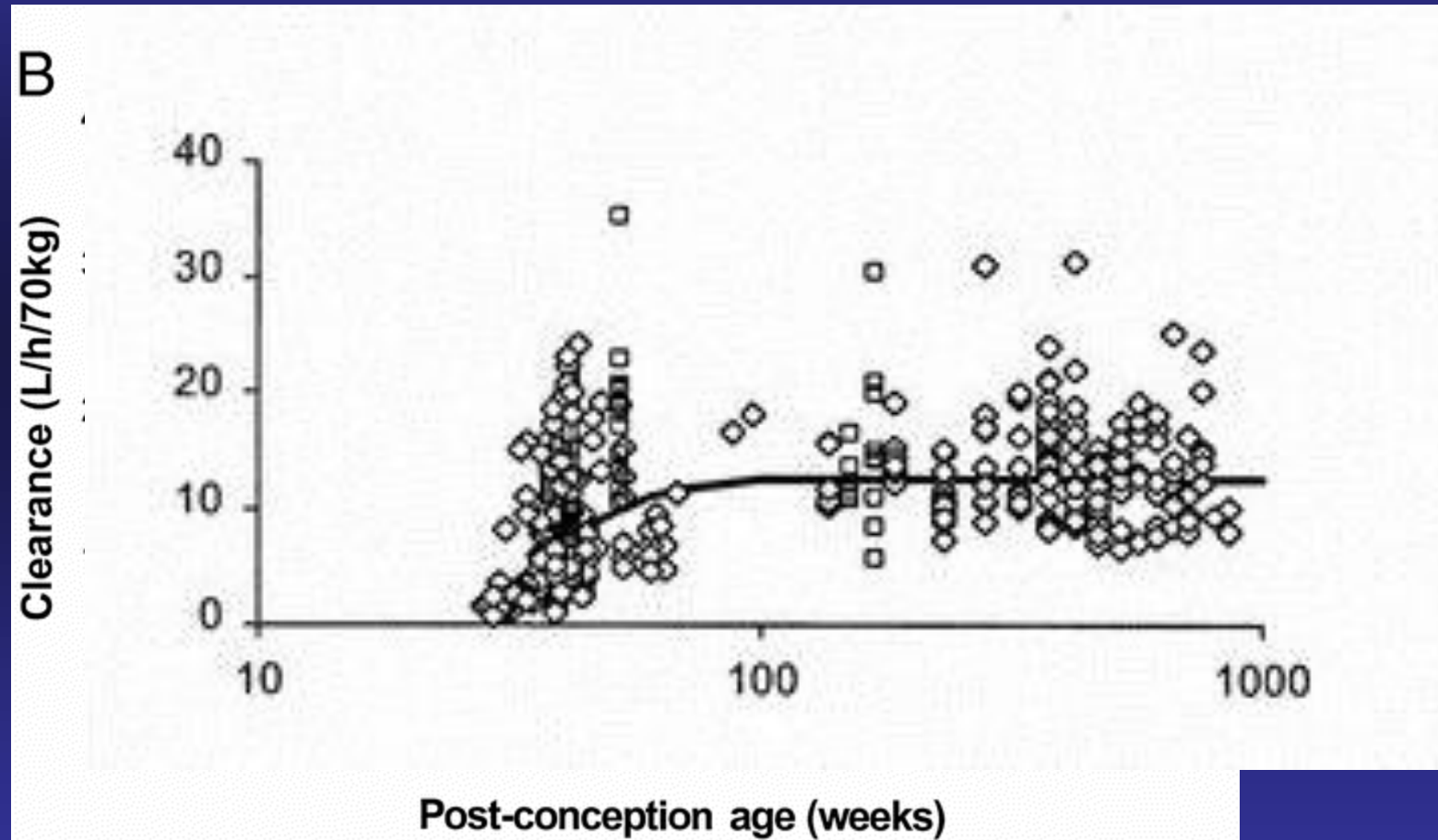
Anderson BJ et al, Anesthesiology 2002

Pharmacokinetic differences in neonates and infants

- Longer elimination half life in neonates:
 - as high as 11 hours in 28 to 32 weeks GA
 - 4.8 hours in 32 to 36 weeks
 - 3.5 hours for term neonates
 - approximately 2 hours in infants and older children and 2 to 3 hours in adults
- Higher percentage of excretion of unchanged acetaminophen in neonates (25%) compared with older children and adults (3 to 5%)

Arana A, Morton NS, Hansen TG. Treatment with paracetamol in infants. *Acta Anaesthesiol Scand* 2001

Acetaminophen clearance increases slightly with PCA and postnatal age



Acetaminophen: PK

- Reduced dosing and/or longer dosing interval to get similar plasma concentrations in neonates, even longer dosing interval in preterm neonates (q8h)
- Daily maximum for rectal dosing = daily maximum for oral dosing
- Maximum daily dosing:
 - full term: 60-80 mg/kg/day
 - 28 - 32 weeks: ? 45 mg/kg/day

Dosing regimens to achieve a target plasma concentration of 10mg/L

	Loading Dose (mg/kg)	Maintenance Dose (mg/kg)	Dosing Interval (h)	Daily Maintenance (mg · kg ⁻¹ · da
Oral dosing regimens				
30 weeks	25	12	12	24
34 weeks	25	15	8	45
40 weeks	25	15	6	60
60 weeks	25	15	4	90
Rectal dosing regimens				
Triglyceride suppository				
30 weeks	35	15	12	30
34 weeks	35	20	8	60
40 weeks	35	20	6	80
60 weeks	35	20	4	120
Capsule suppository				
30 weeks	30	12.5	12	25
34 weeks	30	17.5	8	52.5
40 weeks	30	17.5	6	70
60 weeks	25	15	4	90
Solution				
30 weeks	40	20	12	40
34 weeks	45	25	8	75
40 weeks	45	30	6	120
60 weeks	45	25	4	150

A Prospective, Multi-Center, Randomized,
Open-label, Single and Repeated Dose,
48-hour Study of Intravenous
Acetaminophen in Pediatric Inpatients to
Determine Pharmacokinetics and Safety in
Acute Pain and Fever (CPI-APA-102)

PI: A Zuppa, CHOP

Objectives

1. To define single and multiple-dose PK of IV acetaminophen at various dosing regimens in pediatric inpatients
2. To assess the safety of repeated doses of IV acetaminophen under various dosing regimens in pediatric inpatients

Study Design

- Randomized, open-label, multicenter study in pediatric inpatients at 5 centers in U.S.A.
- Population pharmacokinetic analysis of plasma acetaminophen in blood collected over 2 days
- Safety evaluated in terms of liver function tests (LFTs), vital signs, adverse event (AE) recording, and concomitant medications
- Urinary metabolites measured

Main Inclusion Criteria

- Pediatric inpatients stratified by age:
 - Full-term neonates (≤ 28 days and PCA of 37 weeks)
 - Infants (29 days to < 2 yrs old)
 - Children (2 yrs to < 12 yrs old)
 - Adolescents (12 yrs to ≤ 16 yrs old)
- Analgesic treatment for acute pain or
- Antipyretic treatment for fever
- IV access required for the duration of the study
- Free of other physical, mental, or medical conditions that made study participation inadvisable

Main Exclusion Criteria

- Not able to comply with plasma sampling requirements
- Known sensitivity to acetaminophen or inactive excipients of IV acetaminophen
- Use of acetaminophen in 12 hours prior
- Significantly impaired liver or renal function
- Any of the following in 48 hours prior:
probenecid, disulfiram, isoniazide, St. John's wort, skullcap, chaparral, comfrey, germander, jin bu huan, kava, pennyroyal, or valerian

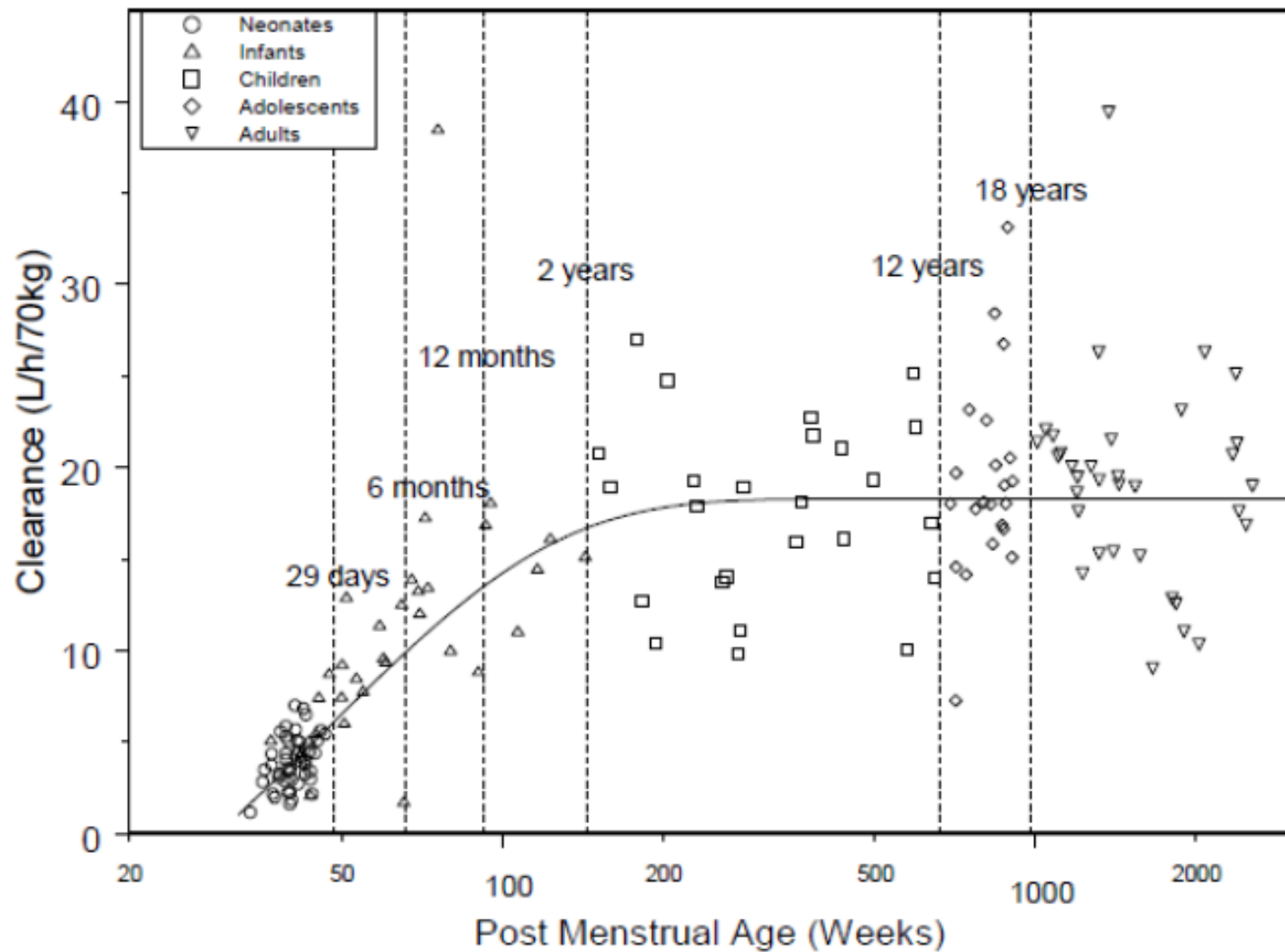
Treatments

- Repeated doses as 15 minute infusions
- Full-term neonates randomized to:
 - 12.5 mg/kg q6h or 15 mg/kg q8h
 - (maximum daily dose for neonates was 50 mg/kg)
- Infants, children, and adolescents randomized to:
 - 12.5 mg/kg q4h (maximum of 660 mg/dose) or
 - 15 mg/kg q6h (maximum of 1 g/dose)
 - (maximum daily dose 75mg/kg or 4 g, whichever was less)

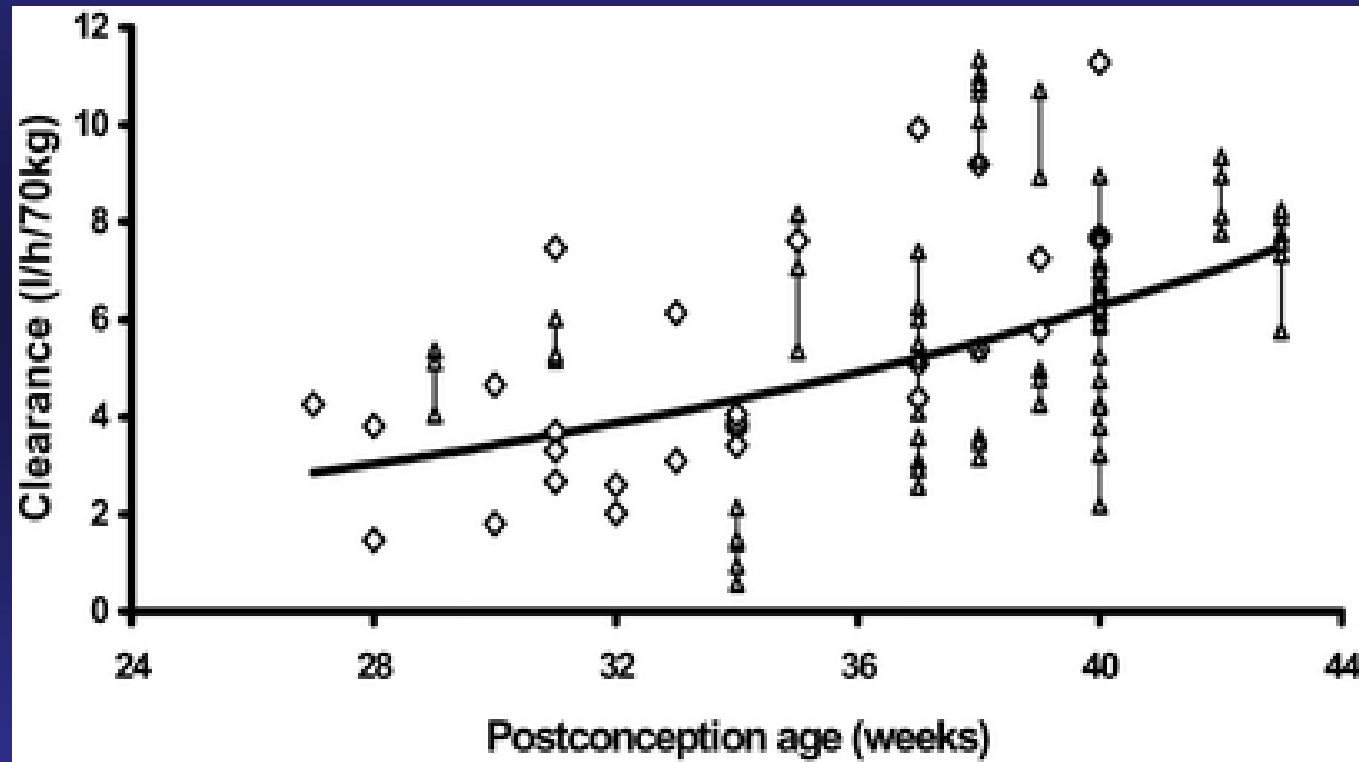
PK Parameters Across Age Strata

- Median terminal elimination half-life
 - comparable across infants, children, and adolescents
 - longer in neonates (3.9/4.2 hours for 12.5/15 mg/kg, respectively) than in infants, children, and adolescents (median values 2.4 to 2.9 hours)
- Differences in median C_{\max} values across age strata for a given dose were negligible
- C_{\max} appeared to increase in a dose proportional manner

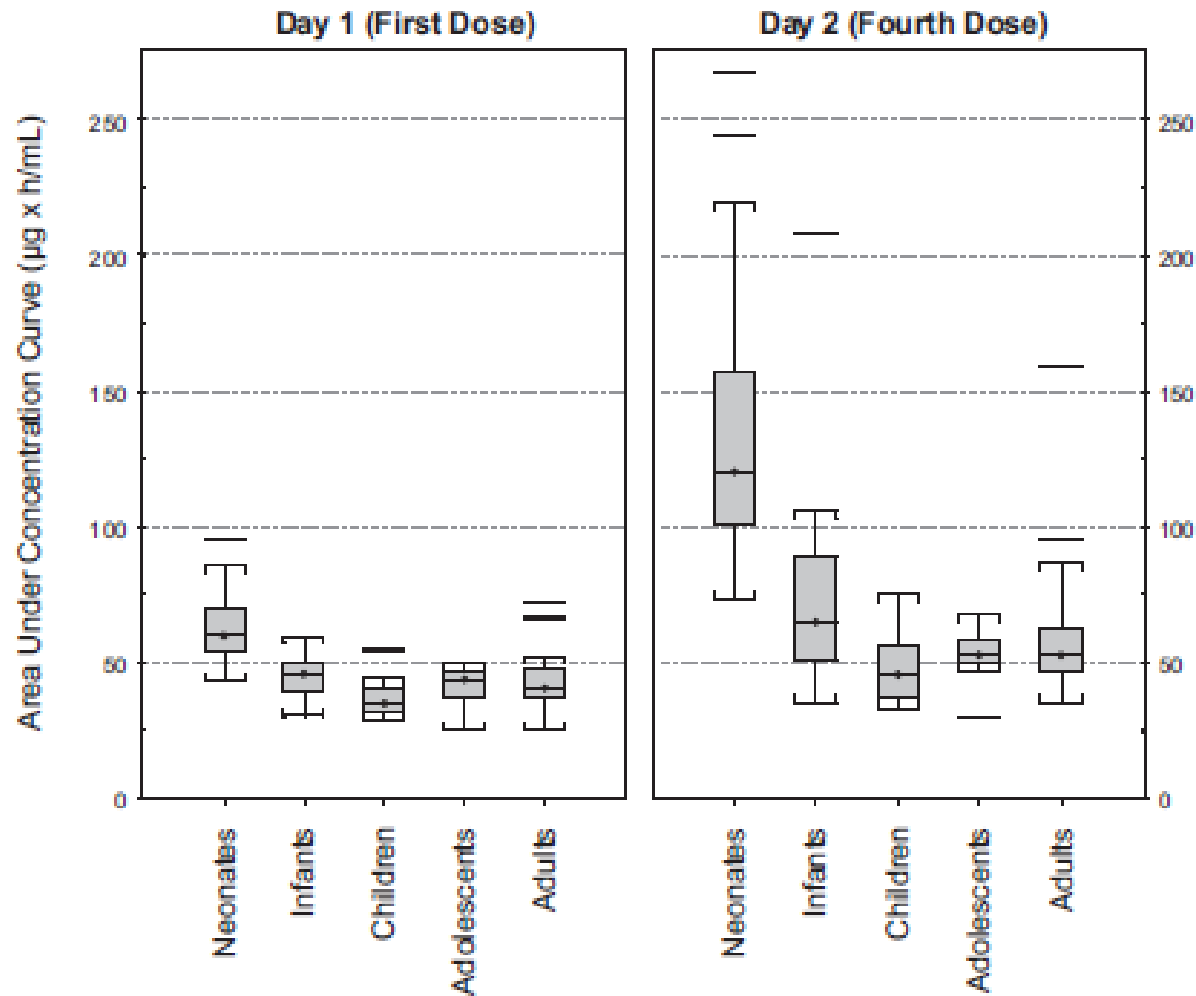
Maturation of Clearance Versus Post-natal Age



APAP clearance increases with postnatal age (propacetamol)



Neonates had rising APAP levels with q6 dosing

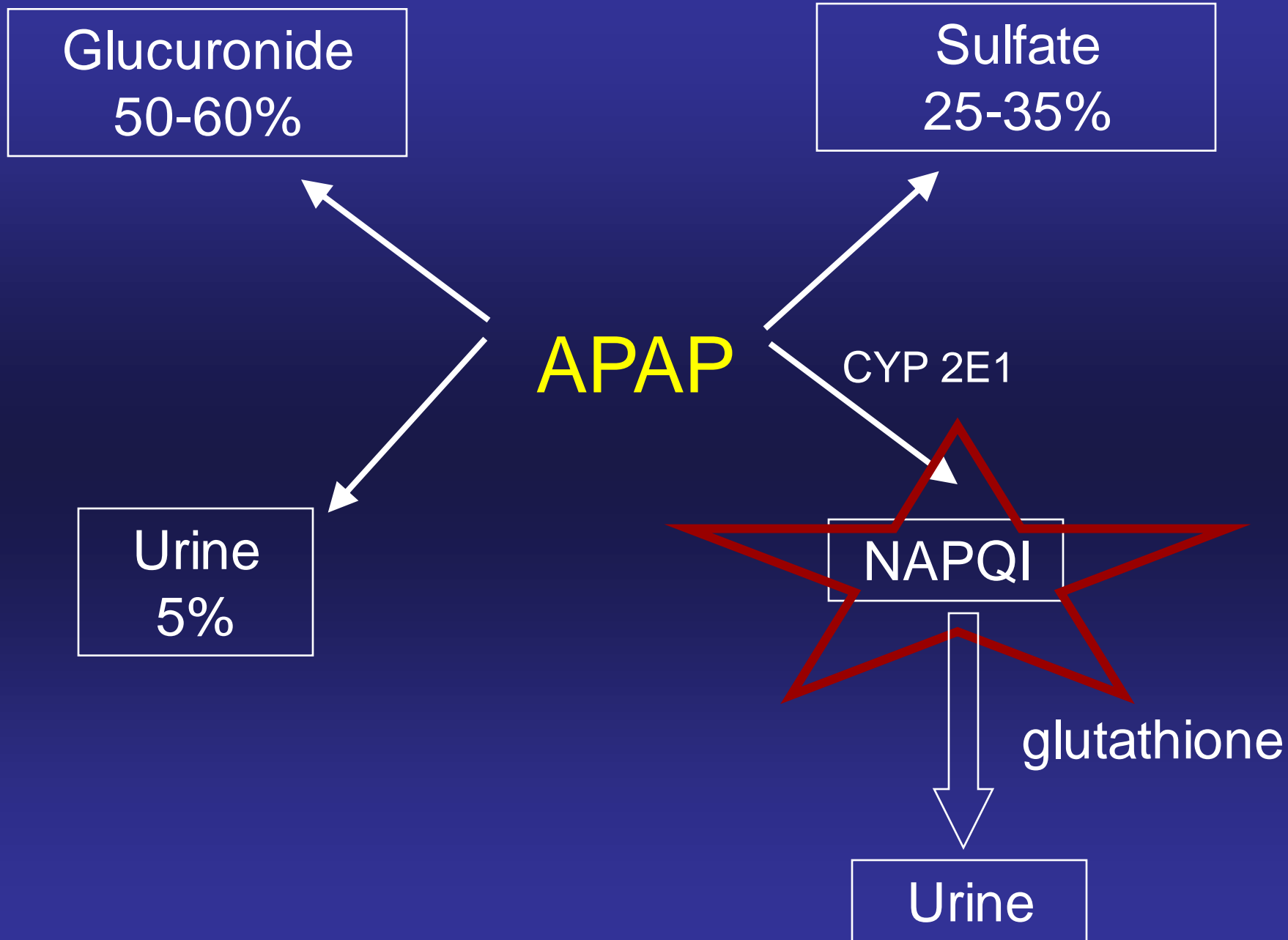


Conclusions CPI-APA-102

- Intravenous acetaminophen was well tolerated
- The mean CL and Vd values of acetaminophen derived with the final Population PK Model were consistent with previously reported values
- There was no trend between
 - individual AUC / Cmax and percent change from baseline in LFTs
 - between individual values for urinary excretion of glutathione adducts and LFT values

Acetaminophen: Toxicity

- Toxicity has been reported commonly in younger infants, increased risks with fever and dehydration.
- Controversial view: being younger is protective because of delayed biotransformation to toxic metabolite.



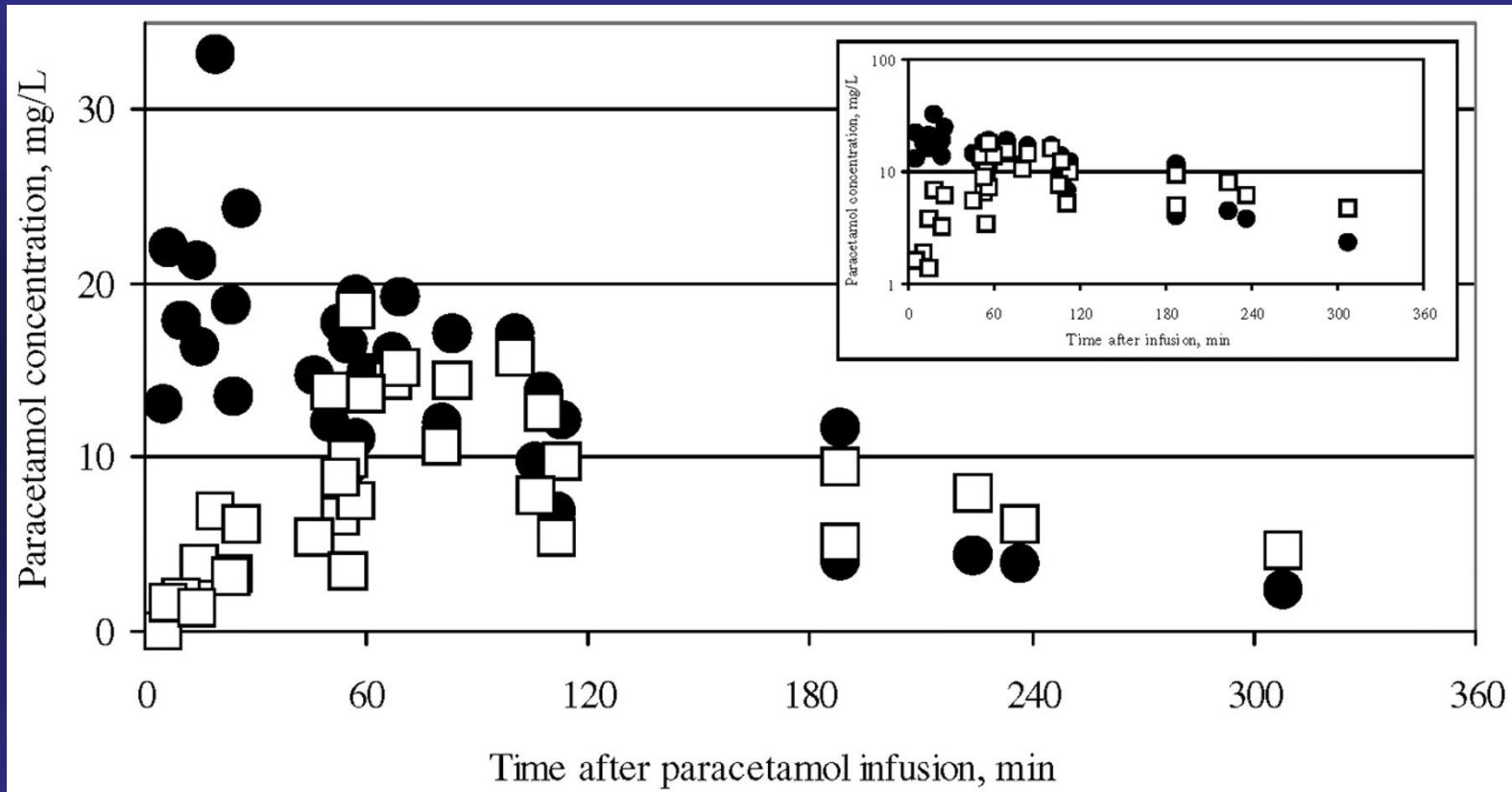
Acetaminophen: Toxicity

- Toxicity due to formation of NAPQI through metabolism by CYP2E1, 1A2, 3A4
- Neonates may be protected because of delayed biotransformation to toxic metabolite
 - Delayed maturation of CYP3A4 and 1A2
 - Decreased CYP2E1 in pretermatures
 - Decreased clearance of CYP2E1 substrates inhibiting 2E1 function
 - greater ability to synthesize and higher stores of glutathione
- Less exposure of liver to APAP with IV administration = less toxicity?

PK/PD of IV APAP in children

- Similar maturation of elimination half-life from neonates to children
- Narrower range of blood levels compared to enteral administration
- Faster appearance in CSF than enteral
- Less liver metabolism than with enteral
- ? Lower risk of toxicity

Rapid equilibration of APAP in CSF



Plasma● and CSF□ paracetamol concentrations after a single IV injection of paracetamol 15 mg/kg

IV Acetaminophen: Pediatric Safety Data

Study	n	Design	Result
Allegaert et al. (2008)	189	Open-label safety in neonates	Well tolerated up to 20days (73 with at least 3 days of exposure)
Kumpulainen et al. (2007)	32	Open-label, PK trial in 32 children (age 3 mo – 12 y) undergoing lower body surgery with a spinal anesthetic	IV acetaminophen 15 mg/kg is well tolerated; it appears in the CSF within 5 min post infusion and mean time for peak levels at 57 min
Wurthwein et al. (2005)	7	Open-label PK study in 7 children and adolescents 4 wks post chemo undergoing hepatic resection (5 with osteosarcoma and 2 with Ewing's sarcoma)	A single dose of IV acetaminophen was well tolerated.

IV APAP safety: hepatic

Pediatric Anesthesia 2008 18: 388–392

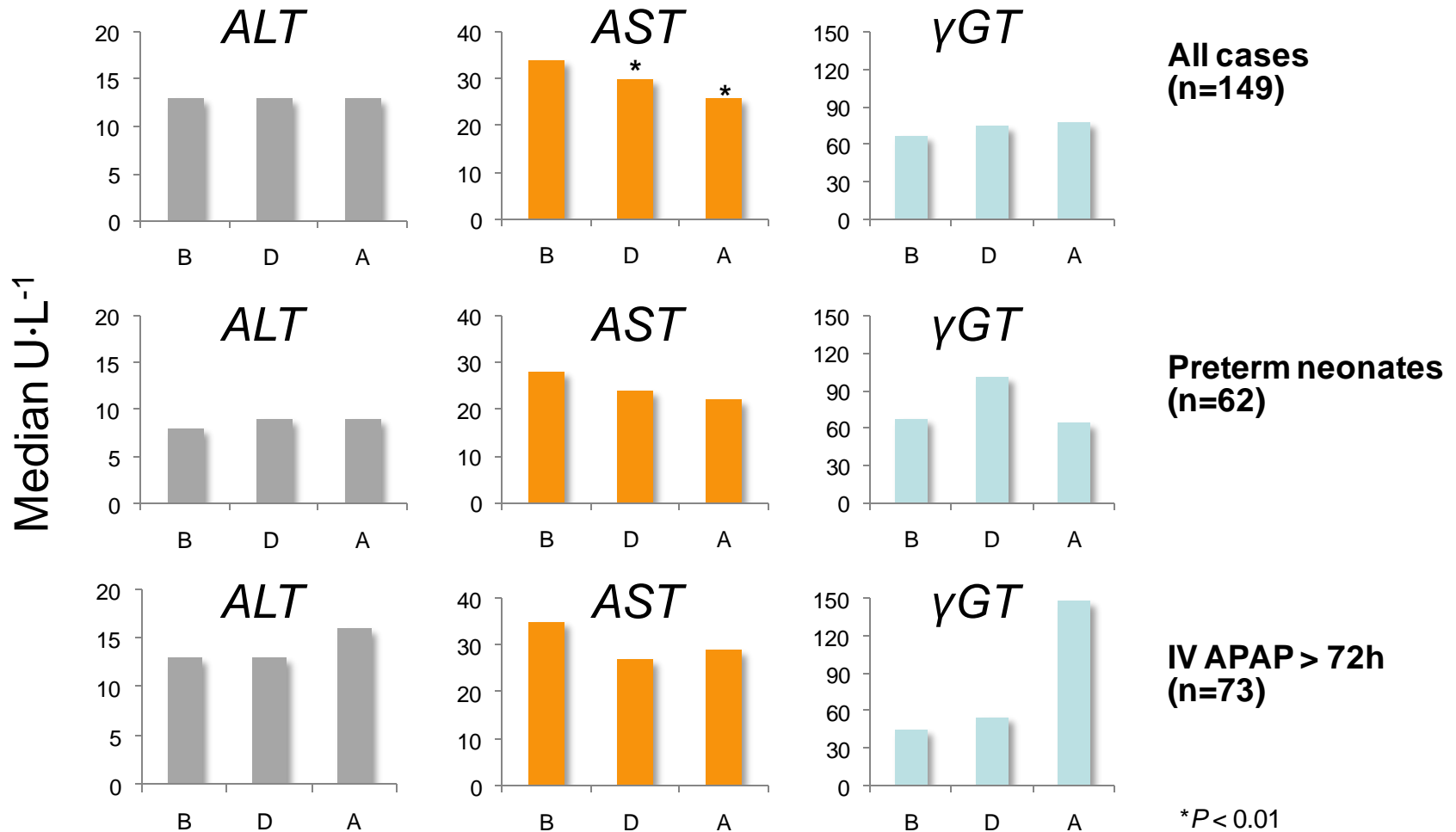
doi:10.1111/j.1460-9592.2008.0253

Hepatic tolerance of repeated intravenous paracetamol administration in neonates

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Hepatic Tolerance of Repeated Acetaminophen Injection Administration in Neonates (<182 days)



Liver enzymes > 72h administration: neonates

	n	Median (range) U·l ⁻¹
ALT		
Before	61	13 (4-228)
During	176	13 (5-216)
After	33	16 (4-117)
AST		
Before	62	35 (12-389)
During	178	27 (10-355)
After	34	29 (8-198)
γGT		
Before	19	45 (12-192)
During	43	55 (18-244)
After	9	148 (28-255)

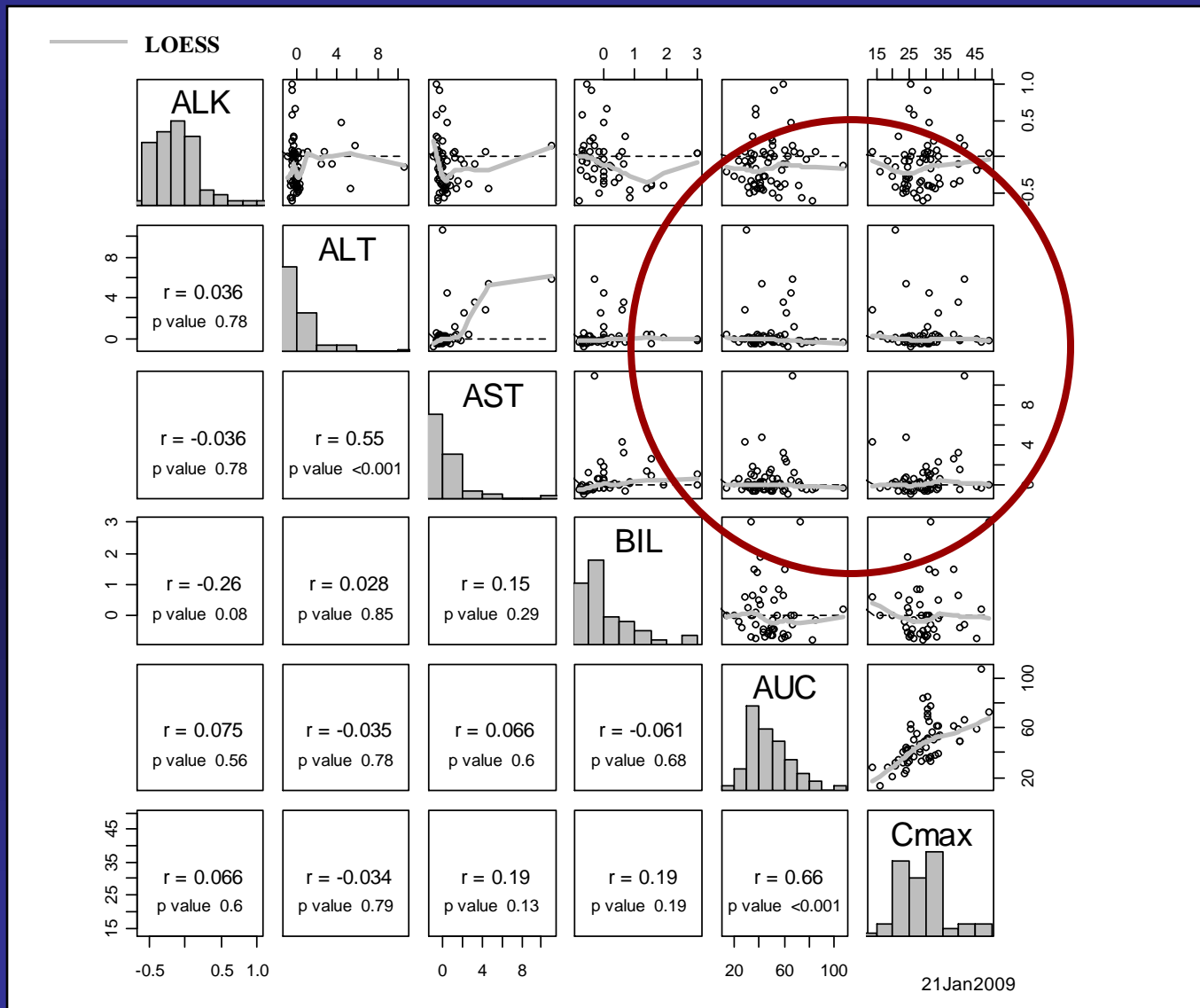
OBJECTIVES CPI-APA-352

- **Primary:** To assess the safety of IV APAP when used over five or more days for the treatment of acute pain or fever in pediatric inpatients who are NPO, require or would benefit from IV treatment, or are willing and able to stay on IV APAP therapy for 5 to 7 days
- **Secondary:** To assess the efficacy of IV APAP in an open-label, prospective fashion when used in a variety of clinical settings

Safety Assessments

- Most (93%) treatment-emergent adverse events (TEAEs) assessed to be mild or moderate in severity
- No clinically relevant differences between age or treatment groups in frequency of serious, severe, related, or overall TEAEs
- No serious TEAE related to study medication
- No deaths
- Only one hepatic TEAE (non-serious and mild)
 - adolescent male post extensive (C6 to T12) spinal fusion for scoliosis
 - isolated AST elevation (normal ALT, total bilirubin, and alkaline phosphatase)
 - likely due to underlying surgery-induced muscle injury

Exposure and Liver Function



Intravenous acetaminophen: adult efficacy data

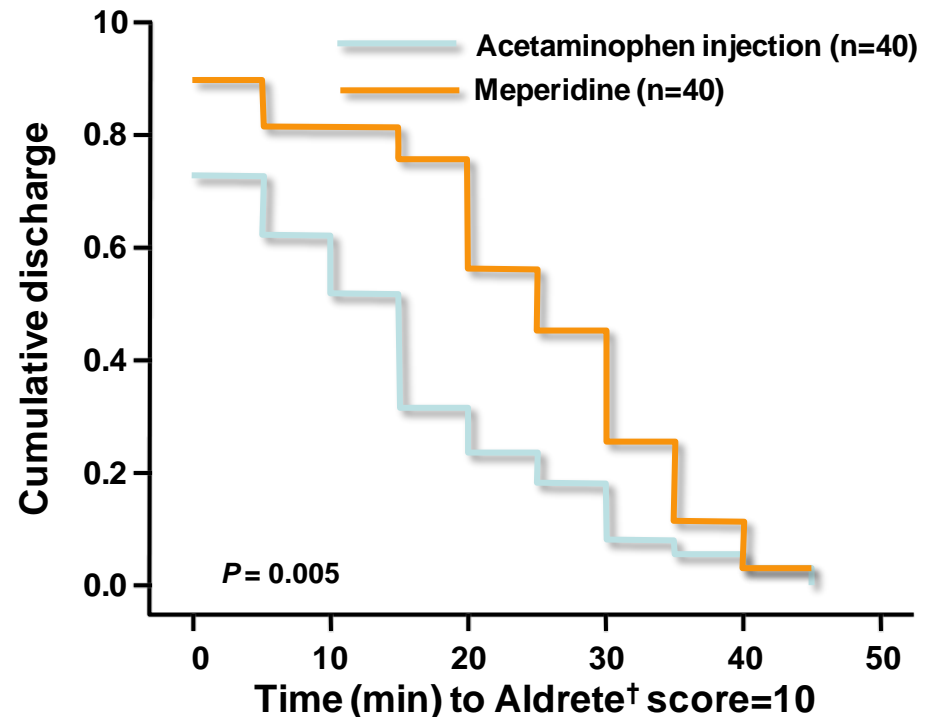
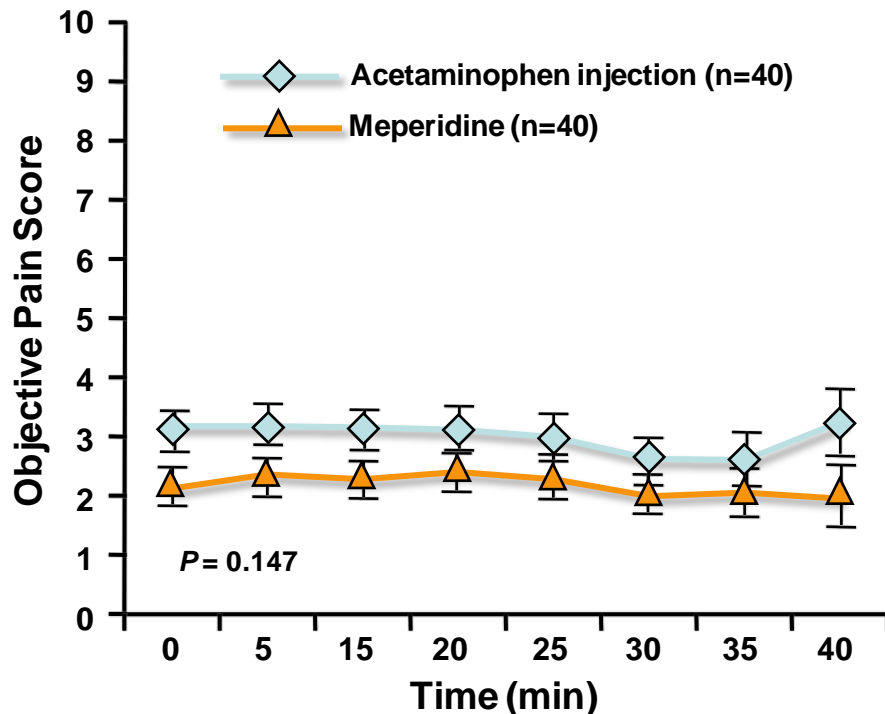
- **Demonstrated efficacy vs. placebo and in active comparator trials**
- **Rapid onset: 5-10 minute**
- **2 hour peak effect**
- **Peak CSF levels in <1 h compared with 3-4 h with PO or rectal**
- **Up to 4-6 hour duration**
- **30-50% opioid-sparing effect (moderate to severe pain)**
- **>50% opioid avoidance (mild to moderate pain)**
- **Studied in several thousand patients undergoing cardiac, dental, orthopedic, gynecologic, abdominal, and outpatient surgeries (adult and pediatric [Europe])**

IV Acetaminophen: Pediatric Efficacy Data

Study	n	Design	Result
Murat et al. (2005)	183	R, DB, active comparator pain (hernia repair) single dose (SD) trial in 183 children (age 1 - 12y)	IV acetaminophen 15 mg/kg is efficacious and equivalent to IV propacetamol 30 mg/kg. IV acetaminophen produced a 50% reduction in PI by 30 min
Duhamel et al. (2007)	67	R, DB, active comparator fever (infectious origin) SD trial in 67 children (age 1 - 12y)	IV acetaminophen 15 mg/kg is efficacious and equivalent to IV propacetamol 30 mg/kg. IV acetaminophen produced a mean of 0.6°C/h with 70% of patients below 38°C by 3h
Alhashemi et al. (2006)	80	R, DB, active comparator pain (tonsillectomy) SD trial in 80 children (age 3 – 15 y)	IV acetaminophen 15 mg/kg is efficacious and equivalent to IM meperidine 1 mg/kg but with less sedation
Capici et al. (2008)	50	R, DB, active comparator pain (tonsillectomy) SD trial in 50 children (age 2 – 5 y)	IV acetaminophen 15 mg/kg is efficacious and equivalent to a PR acetaminophen dose 2.7X larger (40 mg/kg). IV acetaminophen group mean time to rescue 7h

Acetaminophen Injection vs IM Meperidine After Pediatric Tonsillectomy

- Randomized double-blind study with 80 children undergoing tonsillectomy comparing the effects of acetaminophen injection 15 mg kg^{-1} and IM meperidine 1 mg kg^{-1} on pain and recovery room discharge

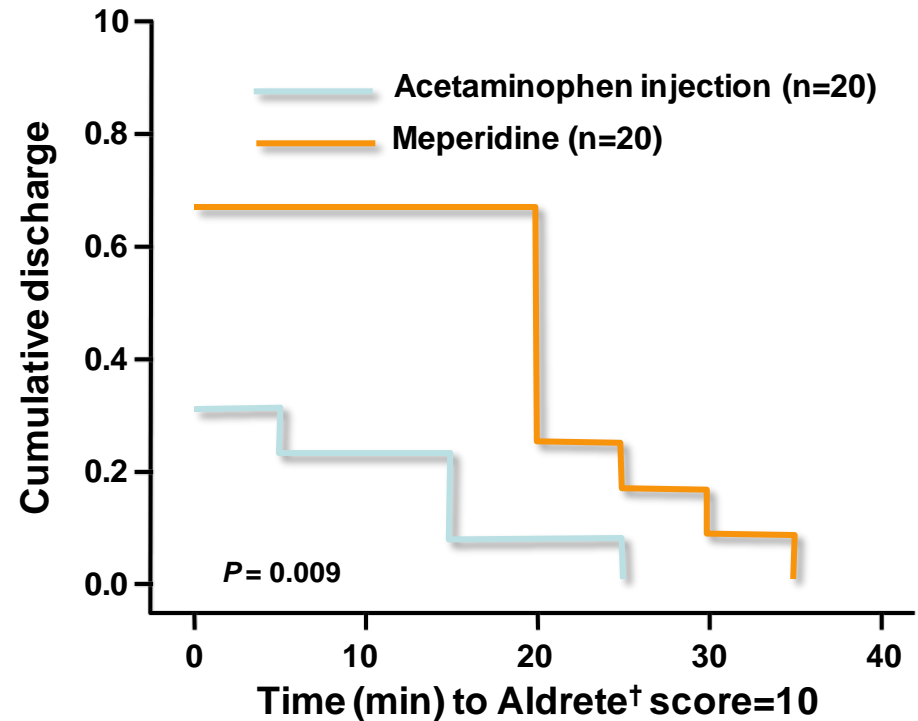
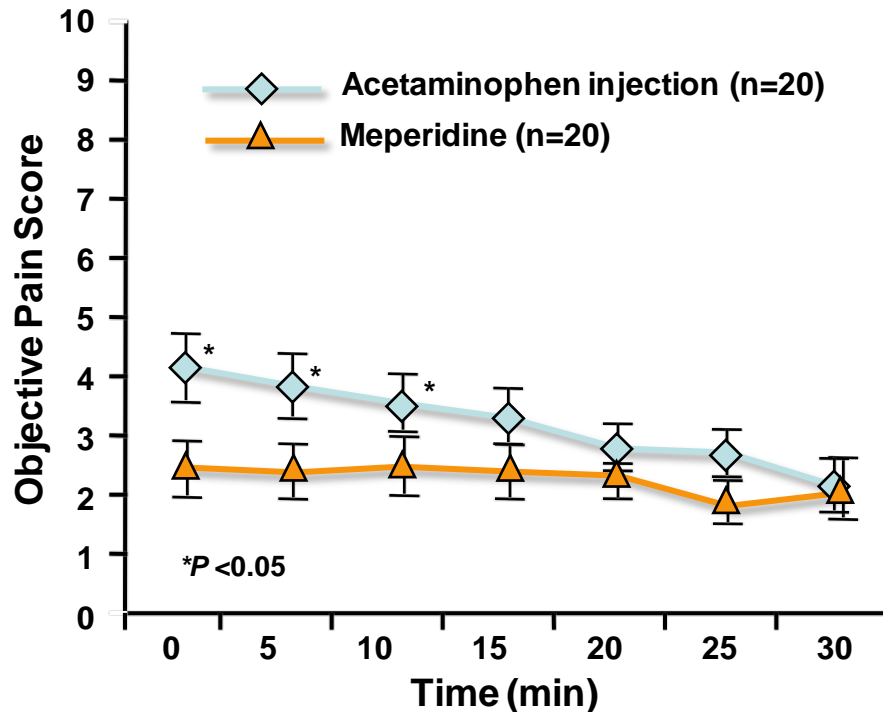


† Standardized post-anesthesia recovery score.

Alhashemi JA, et al. *Br J Anaesth.* 2006;96:790-795

Acetaminophen Injection vs IM Meperidine After Pediatric Dental Surgery

- Randomized double-blind study with 40 children undergoing dental surgery comparing the effects of Acetaminophen injection 15 mg kg^{-1} and IM meperidine 1 mg kg^{-1} on pain and recovery room discharge



†Standardized post-anesthesia recovery score.

Alhashemi JA, et al. *Eur J Anaesthesiol.* 2007;24:128-133.

IV APAP Safety Overview

- Overall safety profile comparable to oral APAP or to placebo
- No risk of postoperative bleeding as seen with NSAIDs (ketorolac)
- Local injection site adverse events comparable to placebo
- No dose adjustment required for mild to moderate chronic renal insufficiency; use with caution in cases of creatinine clearance < 30 mL/min
- Use with caution in patients with mild or moderate hepatic impairment; contraindicated in cases of severe hepatocellular insufficiency

Possible Dosing Guidelines

- 15 mg/kg (maximum 1 gm) q 6 hr
(maximum 4 g/day)
- Neonates 20 mg/kg 1st dose followed by
10 mg/kg Allegaert et al, Ped Anesth, 2008

> 36 weeks GA	q6h
31-36 weeks GA	q8h
< 31 weeks GA	q12h

Possible Dosing Guidelines

- Alternative neonatal dosing regimen (q6h)

28-32 weeks	10 mg/kg
32-36 weeks	12.5 mg/kg
> 36 weeks	15 mg/kg

Palmer GM et al, BJA, 2008

- Ultimate dose recommendations may be more conservative: many pharmacies require q8h dosing of APAP in infants < 3 months of age

Technical Considerations

- Supplied as 100 mL bottle, 10 mg/mL
- Must be drawn up at point of care because of degradation with exposure to air
- Administration by infusion over 15 minutes
- FDA approval pending

Summary

- Intravenous acetaminophen appears to be a safe and effective drug for postoperative analgesia
- Opioid sparing likely
- Pharmacokinetics comparable to enteral administration but with narrower range of blood levels and higher peak level
- Dosing different than oral (q6h rather than q4h)
- Dose recommendations likely to be lower for neonates
- Staff education required (dosing, infusion)
- Initial restrictions/audit of use?

Thank you for your attention



Questions?