Racial Difference: Impact on Morphine Clearance and Perioperative Pain in Children

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Abstract

- **Background:** Inter-individual variability in analgesia response and adverse effects is a major perioperative problem, especially with narrow therapeutic drugs such as opioid. We previously observed that African-American (AA) children experienced more postoperative pain and Caucasian children had more morphine related side effects.
- **Objectives:** To address underlying pharmacokinetic and pharmacogenetics mechanistic factors contributing to the racial differences in perioperative pain and morphine related adverse effects
- **Methods:** In this prospective genotype-blinded observational study, we evaluated pharmacokinetics, pharmacogenetics and pharmacodynamics of intravenous morphine in 150 Caucasian and African-American children undergoing tonsillectomy and adenoidectomy. We measured morphine, morphine metabolites and common UGT2B7 genotypes.
- **Results:** African-American children have significantly higher morphine clearance, 23% more than Caucasian childrenn. The wild type of the UGT2B7 isozyme is more prevalent in the AA patients. The common UGT2B7 genetic variations (-161C>T and 802C>T) were not associated with observed racial differences in morphine clearance
- **Conclusion:** Race of the child is an important factor in perioperative morphine clearance and its potential role in personalizing analgesia with morphine needs further investigation.

Objective:

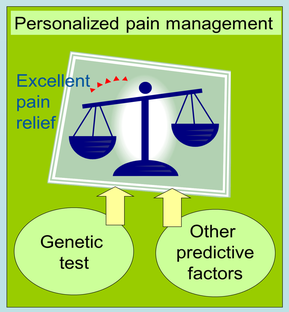
- To address underlying pharmacokinetic and pharmacogenetics mechanistic factors contributing to the racial differences in perioperative pain and morphine related adverse effects.

Methods:

- Prospective genotype-blinded observational clinical study
- We evaluated pharmacokinetics, pharmacogenetics and pharmacodynamics of intravenous morphine during tonsillectomy and adenoidectomy (T&A), among 150 Caucasian and African-American children aged 6 to 18 years.
- All participants received standard perioperative care with an intraoperative dose of 0.2 mg/kg morphine. (children with obstructive sleep apnea received 0.1 mg/kg of morphine).
- Serial blood samples (3 or 4 blood samples per patient) were obtained for morphine, morphine-3-glucuronide and morphine-6-glucuronide levels and for pharmacogenetics testing.
- UGT2B7, the major Uridine Glucuronyl Transferase isoform responsible for 3- and 6-glucoronidation of morphine was tested for genotype

Background :

- Inter-individual variability in analgesic response and adverse effects and narrow therapeutic indices of opioids is a major problem in perioperative practice.
- Morphine is a commonly used perioperative opioid in children.
- We observed high between subjects variability in the analgesic response to morphine.
- African-American children experienced more postoperative pain and Caucasian children had more morphine related adverse effects (1).



Results:

- Of the 146 children evaluable for analysis, 29 were African-American and 113 were Caucasian (Table1).
- African-American children have lower morphine/M3G ratio, similar morphine/M6G ratios and higher M3G/M6G ratios than Caucasian children (Figure 1).
- African-American children have significantly higher morphine clearance, 23% more than Caucasian patients (Figure 2).
- Although the wild type of the UGT2B7 isozyme is more prevalent in the African-American patients, common UGT2B7 genetic variations (-161C>T and 802C>T) were not associated with observed racial differences in morphine clearance.

Table 1: Covariate distribution stratified by race. WT = Wild type (-161C/C and 802C/C), hetero = heterozygous mutation carrier (-161C/T and 802C/T), homo = homozygous carrier (-161T/T and 802T/T), OSA = obstructive sleep apnea

	Bodyweight (kg) (range)	Age (yr) (range)	Sex (M/F)	Genotype (WT/ hetero / homo)	OSA	Additional Analgesics
Caucasians (n=113)	38 (17.9 – 79.5)	8.47 (6.0 – 15.87)	46 / 67 41% / 59%	33 / 47 / 33 29% / 42% / 29 %	52 (46%)	48 (42%)
African Americans (n=29)	37.3 (21.5 – 75.5)	8.81 (6.36 – 14.75)	12/17 41% / 59%	13 / 14 / 2 45% / 48% / 7%	21 (72%)	18 (62%)
Other races (n=4)	28.95 (20.7 – 41.2)	8.57 (7.03 – 10.36)	2/2 50% / 50%	1 / 2 / 1 25% / 50% / 25%	3 (75%)	4 (100%)
Total (n= 146)	*37.25 (17.9 – 79.5)*	*8.77 (6.0 – 15.87)*	*60/86 41% / 59%*	*47 / 63 / 36 32% / 43% / 25%*	*76 (52%)*	*70(48%)*

Figure 1: The morphine and metabolite ratios *vs* time. ▲ Indicating Caucasian patients, ∗ Indicating Aferican-American patients

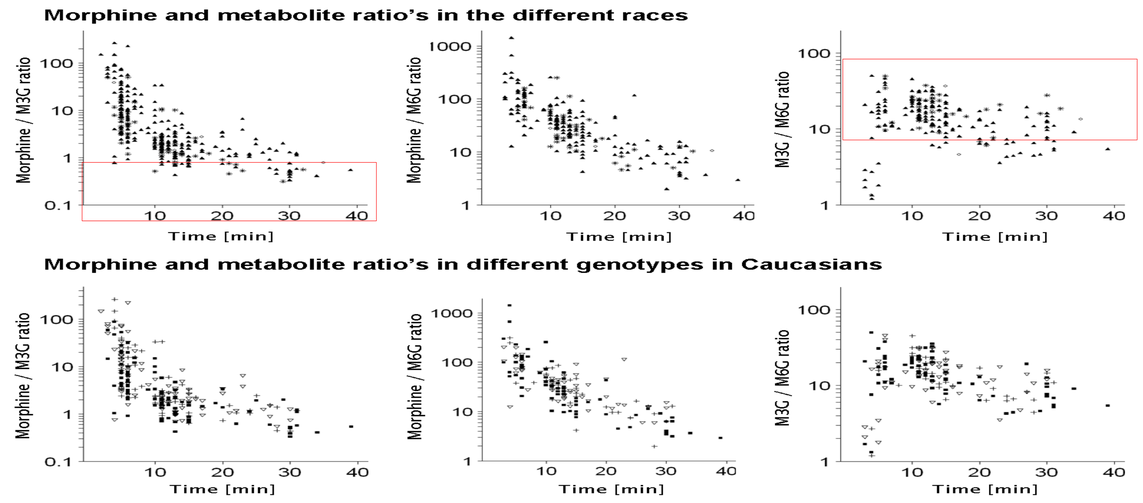
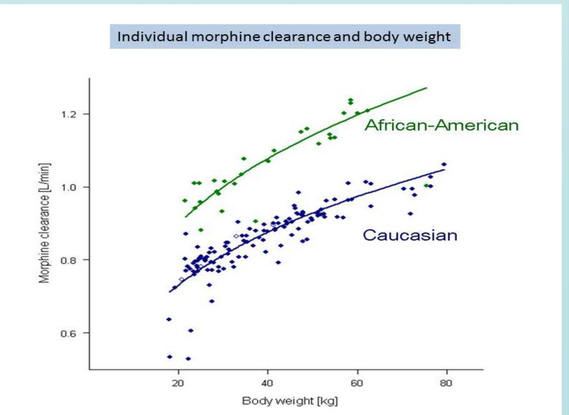


Figure 2: The change in population morphine clearance *vs* body weight



Conclusion:

- Race of the child is an importance factor in perioperative intravenous morphine clearance.
- This can partly explain an unequal burden of increased perioperative pain in African-American children and increased opioid adverse effects in Caucasian children.
- Its role in personalizing analgesia with morphine needs further investigation.

Reference:

1. Sadhasivam et al. Pediatrics 2012 (in Press)