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Interethnic Differences in β-2 Agonist Treatment of Acute Asthma on Electrolyte/Glucose Concentrations

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Objective

- Is there an ethnic disparity regarding the effect of plasma albuterol on:
  - Potassium
  - Magnesium
  - Bicarbonate
  - Phosphate
  - Glucose

β2-Agonists and Electrolyte Abnormalities

- Potassium
  - Hypokalemia through increased cellular uptake
- Glucose
  - Gluconeogenesis
- Phosphate
  - Hypophosphatemia may be associated with ventilatory failure
- Bicarbonate
  - Increase in lactic acidosis (Type B) in asthma

Ethnic Differences in Asthma

- Higher morbidity and mortality in African Americans compared to Caucasians with asthma
- Higher rates of ED visits (350%) and hospitalizations (240%)
- Reports of interethnic differences in β2 treatment for acute asthma
  - SABA overuse and tolerance mechanism
  - Genetic differences at β2-receptor

Study Methods

MN-221 Trial

- Sub-group analysis of large, multi-center RCT evaluating a novel IV β2-agonist for acute asthma exacerbation

Select Exclusion Criteria

- <18 and >55 years old
- At risk for increased β1 response
- Significant smoking history
- COPD, or other chronic lung disease or respiratory dysfunction

Methods Continued

Subject Inclusion

- Serum Mg, K, bicarbonate, and glucose were measured at "baseline" and "1.25hrs post-baseline"
- 70 placebo subjects with plasma albuterol (R- and S-) data

Analysis

- Percent of lab values outside normal range
- Pearson correlations for albuterol to electrolyte/glucose concentration

Results

- 43 African-Americans and 27 Caucasians
- Significant correlations observed in 4/5 measures, all ethnic specific
  - Largest effect size with potassium and bicarbonate
  - Smaller effect size with magnesium and glucose
  - No effect with Phosphate, however large % low values

Correlation Results

Pearson r [95% CI] p value, R^2	**Total albuterol: Caucasians**	**Total albuterol: African-Americans**
Magnesium (mEq/L)	-0.15 [-0.43, -0.15]	0.36 [0.13, 0.56]
	p= 0.32	p<0.01*, 0.13
Potassium (mmol/L)	-0.55 [-0.7, -0.31]	-0.08 [-0.31, -0.14]
	p< 0.01*, 0.31	p=0.44
Glucose (mg/dL)	0.34 [0.07, 0.56]	0.10 [-0.11, 0.32]
	p=0.015*, 0.11	p=0.33
Phosphate (mg/dL)	-0.07 [-0.35, 0.21]	0.15 [-0.07, 0.36]
	p= 0.62	p= 0.17
Bicarbonate (mmol/L	-0.55 [-0.72, -0.32]	-0.15 [-0.35, 0.07]
	p<0.01*, 0.30	p= 0.18

Metabolic Abnormalities

Value [Lab Cut-Off]	Median [IQR]	N (%) AA ONR	N (%) CA ONR
Potassium [<3.6] mmol/L	3.8 [3.5-4.1]	14 (32.5%)	11 (46%)
Magnesium [>2.1] mEq/L	1.7 [1.5-1.8]	3 (8.8%)	0 (0%)
Phosphate [<2.4] mg/dL	2.7 [2.3-3.2]	17 (40.5%)	10 (40%)
Bicarbonate [<20] mEq/L	22 [20-24]	10 (23%)	9 (36%)
Glucose [>140] mg/dL	120 [107-152]	22 (51%)	11 (42%)

Conclusions

- Ethnic-specific correlations between plasma albuterol and serum K, Bicarb, Mg, and Glu.
- Specific to Caucasian population:
  - Sig negative correlation with K and Bicarb
  - Sig positive correlation with Glucose
- Specific to African American population:
  - Sig positive correlation with Mg
- High % hypophosphatemia observed for both populations

Potential Clinical Implications

- When repeated β2-agonist treatments given for acute asthma, closer ED monitoring may be required for:
  - Low K, low Bicarb and high Glucose in Caucasians
  - High magnesium in African Americans
- Future research implications
  - These data suggest that combining ethnic groups may mask true effect size in one group

Limitations

- Clinical relevance depends on magnitude of change—generally small effect size observed
- Relatively small sample size due to sub-group analysis

Questions?

Exclusion Criteria

- Administration of parenteral (intravenous or subcutaneous) beta agonist within 6 hours prior to randomization.
- A current or prior diagnosis or suspected diagnosis of COPD or other chronic lung disease other than asthma, the presence of pneumonia, or presence of significant other respiratory dysfunction such as pneumothorax, pneumomediastinum, or pulmonary edema.
- Known or suspected vocal cord dysfunction syndrome or the presence of aspirated foreign body (known or suspected).
- History of any current clinical evidence suggesting cardiomyopathy or congestive heart failure, history or presence of tachyarrhythmia, with the exception of sinus tachycardia, or a heart rate ≥ 140 bpm.
- Hypokalemia, defined as potassium level ≤ 2.8 mEq/L obtained at Screening.
- Significant cardiac, renal, hepatic, endocrine, metabolic, neurologic or other systemic disease.
- Self-reported history of greater than 15 packer year smoking history.
- Fever ≥ 102.0 ˚F (38.9˚C).
- Uncontrolled hypertension defined as blood pressure ≥ 170/100 mm Hg.
- Need for immediate intubation, mechanical ventilation, or non-invasive positive pressure ventilation as determined by the Investigator.
- Pregnant or lactating females.
- Participating in another clinical study with an investigational drug within 30 days of randomization.
- Positive urine drug screen for cocaine, methamphetamine or PCP.
- Any subject with a known allergy components of the MN-221 drug product or other beta agonists.
- Previous exposure to MN-221
- Use of theophylline, beta blockers, diuretics, digoxin, MAO inhibitors, or tricyclic antidepressants, within 2 weeks prior to randomization.

Plasma/ Nebulized Albuterol Correlation

Plasma Albuterol	Mean	Nebulized Dose (mg)
Total (R+S)	7.0 ng/mL	12.1 mg