Pharmacy Friday

Brief pearls related to acute care pharmacology and evidence-based medicine
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Vitamin C, Thiamine, and Steroids in Sepsis

Introduction

1. Sepsis is a common and highly morbid condition with an estimated 1.7 million cases occurring in the United States each year, resulting in over 270,000 deaths.
2. Despite advances in critical care practices, sepsis remains the most common cause of death in non-cardiac ICUs.
3. There has been a widespread search for therapies that can assist decrease morbidity and mortality associated with sepsis
4. Individually, vitamin C (ascorbic acid), vitamin B1 (thiamine), and corticosteroids have been shown to have some utility in the management of sepsis.
5. Most recently, a study done by physician Paul Marik has popularized a combination of the mentioned agents, leading to a spur of clinical trials assessing the validity of using these agents in sepsis.
6. Vitamin C levels invariably fall during sepsis, sometimes dropping below the level of detection. Vitamin C deficiency correlates with multiorgan failure and death
7. Thiamine deficiency is common in sepsis, occurring in perhaps one-third of patients. This is associated with increased mortality

Pharmacology			
Properties	**Vitamin C (Ascorbic Acid)**	**Thiamine (Vitamin B1)**	**Hydrocortisone (Solu-Cortef)**
Dose	1500 mg q6h x 4 days	200 mg q12h x 4 days	50 mg q6h x 4 days
Administration	IVPB over	IVPB over 30 mins	IV-Push
Formulation	IV, IM, PO	IV, IM, PO	IV,PO
PK/PD	**Tmax:** IV- 30 minutes **Distribution:** Large concentrations are found in the liver, leukocytes, platelets, glandular tissues, and lens of the eye **Excretion**: Primarily excreted by the kidneys in large amounts	**Distribution:** Highest concentrations found in brain, heart, kidney, liver **Excretion**: Urine mostly as unchanged drug	**Distribution:** Highest concentrations found in brain, heart, kidney, liver **Excretion**: Less than 1% of hydrocortisone is excreted unchanged in the urine **Elimination Half Life:** 1 to 2 hours
Adverse Effects	Injection site pain Oxalate nephropathy Factitious hyperglycemia	Flushing, diaphoresis, infusion related reactions	Hyperglycemia, insomnia, fluid retention, adrenal suppression
Drug Interactions and warnings	Incompatible with ceftazidime, etomidate, nitroprusside, and phenytoin	No known significant drug interactions	Amiodarone, Cipro, Unasyn, dobutamine, Haldol, midazolam
Compatibility	Compatible with NS and D5W	Compatible with NS and D5W	Compatible with NS and D5W

Jlpruitt@gmh.edu

Overview of Evidence			
Author, year	Design/ sample size	Intervention & Comparison	Outcome – Intervention vs Comparator
VICTAS, 2020	RCT/ Estimated n= 2000	IV vitamin C 1.5 grams every 6 hr+ IV thiamine 100 mg every 6 hr+ IV hydrocortisone 50 mg every 6 hr vs Placebo	**Study completion expected October 2021** Primary: 30 day Vasopressor and ventilator-free days Secondary: Mortality at 30 days
ORANGES Trial,	RCT/ Estimated n= 140	IV vitamin C 1.5 grams every 6 hr+ IV thiamine 200 mg every 12 hr+ IV hydrocortisone 50 mg every 6 hr vs Placebo	**Study completion expected October 2021** Primary: 28-day mortality Secondary: Time to vasopressor independence, Procalcitonin clearance, change in SOFA score, ICU Mortality, ICU LOS, and ICU-Free Days
Woolum, 2018	Retrospective, cohort/ n=369	" IV thiamine within 24 hours" Vs Matched controls.	Thiamine was associated with an improved lactate clearance (HR, 1.307) and ↓ 28-day mortality (HR, 0.666)
Marik, 2017	Observational cohort/ n= 94	IV vitamin C 1.5 grams every 6 hr+ IV thiamine 200 mg every 12 hr+ IV hydrocortisone 50 mg every 6 hr vs Placebo	**Hospital mortality 8.5% vs 40.4%** • All in treatment group were weaned off vasopressors, a mean of **18.3 ± 9.8 h** • Propensity adjusted odds of mortality in the patients treated with the vitamin C protocol was **0.13 (95% CI, 0.04-0.48; P = .002)**
Donnino, 2016	RCT/ n=88	IV thiamine 200 mg every 12 hr vs Placebo	**No difference** in secondary outcomes including time to shock reversal, severity of illness and mortality In **thiamine deficient subgroup**, significantly ↓ **lactate levels and ↓ mortality (13% vs 46%)**
Zabet, 2016	RCT/ n=48	IV vitamin C 25/kg every 6 hr	**Vasopressor dose, duration, and mortality** were significantly reduced in patients receiving vitamin C

Conclusions

- There is a scientific rational and early evidence that the combination of vitamin C, thiamine, and hydrocortisone could be beneficial in the treatment of septic shock with mild adverse effects associated with each component of the regimen. However, providers must take into account that early therapies have shown early success in smaller and nonrandomized studies and there are currently 8-10 large studies on-going to help answer the question by 2020.

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Jlpruitt@gmh.edu