235-T

SUBOPTIMAL AMINOGLYCOside DOSING IN CRITIcALLY ILL PATIENTS.
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Introduction: Maximal aminoglycoside (AG) killing requires peak serum concentrations (Cmax) exceed the pathogen MIC by 10 to 12 fold (Cmax/MIC). Achievement of this target with gentamicin or tobramycin (5 to 7 mg/kg) has been shown to hasten resolution of infection in the general patient population.

Hypothesis: We hypothesized that critically ill patients are underdosed since unconventionally high AG doses would be required to attain the Cmax/MIC target based on larger intravascular volumes. We sought to determine the Cmax/MIC target attainment rate in medical ICU patients and factors that may be used to predict target non-attainment.

Methods: A retrospective review was conducted for MICU patients who received at least one IV dose and serum concentration of either gentamicin or tobramycin from January, 2001 to January, 2004. Patients with cystic fibrosis, organ transplantation, receiving dialysis, or those receiving doses < 3 mg/kg were excluded. Demographics and amount and timing of aminoglycoside doses and levels were collected. Population pharmacokinetic parameter estimates (Cmax, Cl, Vd) were determined via a nonlinear mixed-one-compartment pharmacokinetic model (NONMEM V; Globomax; Hanover, MD). Cmax/MIC was determined based on our median Pseudomonas aeruginosa MIC of 2 mcg/mL.

Results: 174 unique patients with 399 AG concentrations were analyzed. Mean clearance was 2.3 ± 1.3 L/hr. The mean predicted Cmax was 8 ± 3.9, 9.8 ± 4.5, 15.4 ± 6.4 mcg/mL with doses of 3 to 4.9, 5 to 6.9 and ≥ 7 mg/kg, respectively. The average Vd was 44.8 ± 10.6 L or 0.56 L/kg. Mean dose was 4.9 ± 1.3 mg/kg. The target attainment rate was 1.3% achieved with five doses in three patients. Conclusions: The majority of MICU patients were sub-optimally dosed with AG. The Vd in MICU patients exceeded that reported in the literature for the general patient population. It may be postulated that based on an expanded volume, larger than conventional (5 to 7 mg/kg) AG doses may be required in critically ill patients for therapeutic optimization.

236-T

DOES ANTISECRETORY THERAPY INFLUENCE THE DEVELOPMENT OF YEAST IN COMPLICATED INTRA-ABDOMINAL INFECTION?
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Introduction: A possible relationship exists between gastric acid suppressive agents and bacterial peritoneal overgrowth associated with complicated intra-abdominal infection (IAI). Hypothesis: Chronic administration of proton pump inhibitor (PPI) or histamine antagonist (H2RA) therapy influences the presence of yeast in cases of complicated IAI. Methods: Case-control retrospective study of adult surgical intensive care unit (ICU) patients with complicated IAI per ICD-9 code and extensive chart review. Criteria included diagnosis of complicated IAI consistent with the recent guidelines (Solomon M, et al. Clin Infect Dis 2003;37). Patients were excluded if primary peritonitis was present, the IAI diagnosis was greater than 7.2 hr prior to hospital admission, or the ICU stay was less than 3 days. Patients were categorized into either the antiresecretory group (H2RA or PPI therapy prior to admission) or control group (no prior antiresecretory therapy).

Results: One hundred eighteen patients met inclusion criteria: chronic anti-secretory (n=41) and control (n=77) patients were similar except for median age (69.9 vs. 59.0 yrs, p=0.026) and antibiotic use prior to admission (36.6% vs. 15.6%, p=0.010). The overall extent of yeast recovered from peritoneal cultures was similar (39.3% vs. 32.1%, p=0.857) and included C. albicans, C. glabrata, and C. parapsilosis. However, a trend was detected in the rate of yeast recovered in patients diagnosed with community-acquired IAI and PPI use prior to hospital admission (p=0.066). Additionally, yeast was recovered more often in patients with a history of prior abdominal surgery receiving antiresecretory therapy compared to control (91.7% vs. 62.5%, p=0.066). Conclusions: No difference was found in the percent of yeast recovered from peritoneal cultures between the antiresecretory vs. control groups. However, patients with prior abdominal surgery or those with chronic PPI use in the community may be predisposed to developing Candida IAI and deserve further study.

237-T

ARGATROBAN THERAPY IN HEPARIN-INDUCED THROMBOCYTOPENIA WITH HEPATIC DYSFUNCTION.
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Introduction: We retrospectively evaluated the dosing requirements of argatroban, a heparinically metabolized direct thrombin inhibitor (DTI), in patients with heparin-induced thrombocytopenia (HIT) and hepatic dysfunction and compared clinical outcomes with argatroban versus historical control therapy in this population. Methods: Patients with a total serum bilirubin >1.5 mg/dL or ALT >200 U/L were identified from previous studies of HIT in which argatroban dosing data were extracted from study records. Results: 104 prospectively treated patients received argatroban, adjusted to maintain aPTT 24 h after argatroban initiation was 69±22 s. Doses were significantly lower with elevated vs normal bilirubin (0.840±0.6 vs 1.730±0.8 μg/kg/min; p=0.006) and with hepatic/renal vs hepatic dysfunction (1.2±1.1 vs 2.0±1.1 μg/kg/min; p=0.001). In 7 patients with hepatic/renal dysfunction, doses were 0.1-0.4 μg/kg/min. A 37-day composite endpoint of death, amputation, or new thrombosis occurred in 34 (41%) argatroban-treated patients and 17 (50%) controls (p=0.32). Argatroban significantly reduced new thrombosis (8.5% vs 26.5%; p=0.012). Major bleeding rates were similar (4.9% vs 2.9%, p=0.68). Conclusions: Hepatic dysfunction affects argatroban dosing, with reduced doses required in patients with elevated bilirubin and particularly with combined hepatic/hepatic dysfunction. Individual mean, aPTT-adjusted doses were typically ≥0.5 μg/kg/min, suggesting the recommendation of 0.5 μg/kg/min as a conservative initial dose for most patients with hepatic impairment. Argatroban, versus control, provides effective anticoagulant therapy in HIT and hepatic dysfunction, without increasing bleeding.

238-T

CEFEPIME CONTINUOUS INFUSION (CTI) VERSUS CONVENTIONAL DOSING (CVD) FOR VENTILATOR-ASSOCIATED ED PNEUMONIA (VAP).
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Introduction: Given the time-dependent bactericidal mechanism of beta lactam antibiotics, CTI may confer superior time above bacterial minimum inhibitory concentration (MIC) and efficacy in the treatment of VAP. Hypothesis: Cefepime CTI exhibits comparable pharmacokinetics (PK) and confers superior time above bacte- rial MIC compared to CVD. Methods: The study compared the effects of CTI and CVD on PK and time above the bacterial (MIC) for VAP through a randomized, prospective trial. Adult trauma patients treated with cefepime for VAP were eligible; creatinine clearance (CrCl) < 60 mL/min and body mass index > 30 were excluded. Seven patients were randomized to 3 cohorts: 1) < 2 gm Q12 h (CVD), or 4 gm CTI. Levels were drawn at 30 min, 6 h, and 12 h after dosing on days 1 and 3. CTI and CVD cohorts were compared relative to PK data and % time above the calculated (E test) and theoretical MIC of 4 and 8 mcg/mL. Results: Of 21 patients enrolled, two CVD patients died during study. Due to variability in day 3 drug levels, 6 of 12 CVD patients did not undergo PK or MIC evaluation. PK and MIC data for the remaining 14 patients (7 CTI, 7 CVD) are displayed in the Table. A higher percentage of patients in the CTI cohort had levels exceeding both the actual and theoretical MIC for the duration of the dosing interval. Conclusions: Cefepime administered by CTI for VAP results in PK values comparable to CVD. CTI results in concentrations above the MIC for the duration of administration more consistently than CVD. Given the time dependent bactericidal mechanism of beta lactams, CTI may confer superior efficacy compared to CVD.