Outcome of Continuous versus Intermittent Application of Meropenem In Critically Ill Patients with Septic Shock.

Thesis

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Karim Mohamed Megahed

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List of Abbreviations

ABG	:	Arterial blood gases
ACCP	:	American college of chest physicians
ACTH	:	Adrenocorticotropic hormone
APACHE II	:	Acute Physiologic and Chronic Health Evaluation II
aPTT	:	Activated partial thromboplastin time
ARDS	:	Acute respiratory distress syndrome
CBC	:	Complete blood count
CDAD	:	Clostridium difficile associated diarrhea
CI	:	Continuous infusion
CRP	:	C- Reactive protein
C/S	:	Culture and sensitivity
CT	:	Computed tomography
CVP	:	Central venous pressure
ECG	:	Electrocardiogram
ESBL	:	Extend Spectrum B-Lactamase
ESICM	:	European Society of Intensive Care Medicine
Fio2	:	Fraction of inspired oxygen
GCS	:	Glasgow coma scale
GI	:	Gastrointestinal
HAP	:	Hospital acquired pneumonia
HBF	:	Hepatic blood flow
HCPs	:	Health care professionals
IB	:	Intermittent bolus
ICUs	:	Intensive care units
INR	:	International normalized ratio
MAP	:	Mean arterial pressure
MIC	:	Minimum inhibitory concentration of pathogen
MODS	:	Multiple organ dysfunction syndrome

List of Abbreviations (Cont.)

NE	:	Norepinephrine
NIV	:	Non invasive mask ventilation
NMBs	:	Neuromuscular blocking agent
Paco2	:	Arterial carbon dioxide tension
Pao2	:	Arterial oxygen tension
PD	:	Pharmocodynamic
PEEP	:	Positive end expiratory pressure
PK	:	Pharmocokinetic
rhAPC	:	Recombinant human activated protein C
SBP	:	Systolic blood pressure
SCCM	:	Society of critical care medicine
SCVO2	:	Central venous oxygen saturation
SIRS	:	Systemic inflammatory response syndrome
SIS	:	Surgical infection society
SOFA	:	Sepsis-related Organ Failure Assessment
SSC	:	Surviving Sepsis Campaign
VAP	:	Ventilator associated pneumonia
WBC	:	White blood cell count
DIC	:	Disseminated intravascular coagulopathy
TNF	:	Tumor necrosis factor
HAP	:	Hospital acquired pneumonia
RR	:	Risk ratio
PD	:	Pharmacodynamic
FT%	:	Free drug concentration time percentage
NO	:	Nitric oxide

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Introduction

Severe infections in critically ill patients and increasing antibiotic resistance are major healthcare problems affecting morbidity and mortality in the intensive care unit. Antibacterial drug discovery and development have slowed considerably in recent years **(Devasahayam et al., 2010) (Livermore et al., 2011)** .

The effort to maximize antibiotic activity has led in recent years to the interest for optimal dosing based on pharmacodynamic and pharmacokinetic properties of antibiotics **(Roberts et al., 2008)** .

Meropenem is an ultra-broad spectrum injectable antibiotic used to treat a wide variety of infections. It is abeta-lactam and belongs to the subgroup of carbapenem similar to imipenem and ertapenem. It penetrates well into many tissues and body fluids including the cerebrospinal fluids, biles, heart valves, lung, and peritoneal fluid. **(Edwards et al., 1989)** . It is bactericidal except against listeria monocytogenes where it is bacteriostatic. It inhibits bacterial wall synthesis like other beta-lactam antibiotics. In contrast to other beta-lactams, it is highly resistant to degradation by beta-lactamases or cephalosporinases. It is metabolized in the liver to open beta-lactam form (inactive). Approximately 70% of the intravenously administered dose is recovered as unchanged meropenem in the urine over 12 hours, after which little further urinary excretion is detectable**(Yeung et al.,2012)**.

Meropenem have broad spectrum activity against Gram-negative (including Pseudomonas) and Gram -positive

organisms and anaerobic bacteria, it remains a suitable choice for treatment of severe infections in critically ill patients. It is currently established that meropenem, like other β-lactam antibiotics, displays time-dependent bactericidal activity and the percentage of the dosing interval that free drug concentrations remain above the minimum inhibitory concentration of pathogen (%fT> MIC) is the most important parameter for predicting their antibacterial efficacy**(Craig et al., 2003)(Drusano et al.,2003)**.

Meropenem concentrations must be maintained above the minimum inhibitory concentration for the set percent of a dosing interval. However, the pharmacokinetics of meropenem seem to differ in critically ill patients compared with healthy**(Drusano et al.,2003)(Turnidge et al.,1998).** The maximum killing effect of β-lactams is reached at four to five times the MIC with higher concentration not contributing further to increasing the antimicrobial effect**(McKinnon et al.,2008).**It can be presumed that intermittent infusion recommended by pharmaceutical companies results in high peak concentration and low through concentration and can cause reduced efficacy. Furthermore, pathophysiological changes that occur in seriously ill patients with sepsis often affect volume of distribution, drug clearance and altered pharmacokinetic parameters making these recommendations potentially inappropriate **(Roberts et al.,2008)(Novelli et al.,2005).** The use of continuous administration of β-lactams was studied in some trials, but strong evidence of clinical efficacy of this alternative is lacking **(Jaruratanasirikul et al.,2005) (Roberts et al., 2007)** .

Aim of The Work

This work aimed to:

Study the outcome of continuous versus intermittent application of meropenem in critically ill patients with septic shock.

Definition of sepsis :

Sepsis is a clinical syndrome that complicates severe infection. It is characterized by systemic inflammation and widespread tissue injury. In this syndrome, tissues remote from the original insult display the cardinal signs of inflammation including vasodilatation, increased microvascular permeability and leukocytes accumulation. Although inflammation is an essential host response, current beliefs regarding the onset and progression of sepsis center upon a "dysregulation" of the normal response with a massive and uncontrolled release of proinflammatory mediators creating a chain of events that leads to widespread tissue injury**(Neviere, 2013).**

Systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis and septic shock were initially defined in 1991 by a consensus panel convened by the American College of Chest Physicians (ACCP) and Society of Critical Care Medicine (SCCM) **(Arise, 2007).**These definitions were reconsidered in 2001 during an International Sepsis Definitions Conference that included representatives from the ACCP, SCCM, American Thoracic Society, European Society of Intensive Care Medicine and Surgical Infection Society (SIS) and again in 2012 by the SCCM and ESICM**(Levy et al., 2003)(Dellinger et al., 2012).**A practical modification of the definitions has been published, which provides exact hemodynamic definitions for sepsis and septic shock. The definitions provided below are based upon these resources and represent a continuum of SIRS through

multiple organ dysfunction syndrome (MODS)**(Annane et al., 2005)**.

Systemic inflammatory response syndrome: is a widespread inflammatory response that may or may not be associated with infection. The presence of two or more of the following criteria (one of which must be abnormal temperature or leukocyte count) defines SIRS**(Goldstein et al., 2005)**:

a) Core temperature (measured by rectal, bladder, oral, or central probe) of >38.5ºC or <36ºC.

b) Tachycardia, defined as a mean heart rate more than two standard deviations above normal for age, or for children younger than one year of age, bradycardia defined as a mean heart rate <10th percentile for age.

c) Mean respiratory rate more than two standard deviations above normal for age or mechanical ventilation for an acute pulmonary process.

d) Leukocyte count elevated or depressed for age, or >10 percent immature neutrophils.

Infection: Infection is a microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms.

Bacteremia: Bacteremia is the presence of viable bacteria in the blood.

Sepsis: is the clinical syndrome that results from a dysregulated inflammatory response to an infection**(Dellinger et al., 2012).**

Diagnostic criteria for sepsis includethe following:

General variables

- Temperature >38.3 or <36ºC.
- Heart rate >90 beats/min or more than two standard deviations above the normal value for age.
- Tachypnea, respiratory rate >20 breaths/min.
- Altered mental status.
- Significant edema or positive fluid balance (>20 mL/kg over 24 hours).
- Hyperglycemia (plasma glucose >140 mg/dL or 7.7 mmol/L) in the absence of diabetes.

Inflammatory variables

- Leukocytosis (WBC count >12, 000 cells/mm3) or leukopenia (WBC count <4000 cells/mm3).
- Normal WBC count with greater than 10 percent immature forms.
- Plasma C-reactive protein more than two standard deviations above the normal value.
- Plasma procalcitonin more than two standard deviations above the normal value.

Hemodynamic variables

- Arterial hypotension (systolic blood pressure SBP <90 mmHg, MAP <70 mmHg, or an SBP decrease >40 mmHg in adults or less than two standard deviations below normal for age).

Organ dysfunction variables

- Arterial hypoxemia (arterial oxygen tension [PaO_2]/fraction of inspired oxygen [FiO_2] <300).
- Acute oliguria (urine output <0.5 mL/kg/hr for at least two hours despite adequate fluid resuscitation).
- Creatinine increase >0.5 mg/dL or 44.2 micromol/L.
- Coagulation abnormalities (international normalized ratio [INR] >1.5 or activated partial thromboplastin time [aPTT] >60 seconds).
- Ileus (absent bowel sounds).
- Thrombocytopenia (platelet count <100, 000 micro/L^{-1}).
- Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 micromol/L).

Tissue perfusion variables

- Hyperlactatemia (>1 mmol/L).
- Decreased capillary refill or mottling.
- oliguria

Severe sepsis: Severe sepsis refers to sepsis-induced tissue hypoperfusion or organ dysfunction with any of the following thought to be due to the infection**(Dellinger et al., 2012)**:

- Sepsis-induced hypotension.
- Lactate above upper limits of laboratory normal.
- Urine output <0.5 mL/kg/hr for more than two hours despite adequate fluid resuscitation.
- Acute lung injury with PaO_2/FIO_2 <250 in the absence of pneumonia as infection source.

- Acute lung injury with PaO_2/FIO_2 <200 in the presence of pneumonia as infection source.
- Creatinine >2 mg/dL (176.8 micromol/L).
- Bilirubin >2 mg/dL (34.2 micromol/L).
- Platelet count <100, 000 $microL^{-1}$.
- Coagulopathy (INR >1.5)..

Septic shock: Septic shock is defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation, which may be defined as infusion of 30 mL/kg of crystalloids. Septic shock is a type of vasodilatory or distributive shock. In other words, it results from a marked reduction in systemic vascular resistance, often associated with an increase in cardiac output **(Dellinger et al., 2012).**

Multiple organ dysfunction syndrome (MODS): refers to the presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention. The MODS is classified as either primary or secondary **(Bone et al., 1992) .**

- **Primary MODS:** is the result of a well-defined insult in which organ dysfunction occurs early and can be directly attributable to the insult itself (e.g., renal failure due to rhabdomyolysis).
- **Secondary MODS:** is organ failure not in direct response to the insult itself, but as a consequence of a host response.