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The effect of pathophysiology on pharmacokinetics in the critically ill patient — Concepts appraised by the example of antimicrobial agents ☆

Stijn I. Blot [a,d,*], Federico Pea [b,c], Jeffrey Lipman [d,e]

[a] Dept. of Internal Medicine, Faculty of Medicine & Health Science, Ghent University, De Pintelaan 185, 9000 Ghent, Belgium
[b] Institute of Clinical Pharmacology, Azienda Ospedaliero-Universitaria Santa Maria della Misericordia, Italy
[c] Department of Experimental and Clinical Medical Sciences, University of Udine, Udine, Italy
[d] The Burns Trauma and Critical Care Research Centre, The University of Queensland, Brisbane, Australia
[e] Dept. of Intensive Care Medicine, Royal Brisbane and Women's Hospital, Butterfield St, Herston QLD 4006, Australia

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ABSTRACT

Critically ill patients are at high risk for development of life-threatening infection leading to sepsis and multiple organ failure. Adequate antimicrobial therapy is pivotal for optimizing the chances of survival. However, efficient dosing is problematic because pathophysiological changes associated with critical illness impact on pharmacokinetics of mainly hydrophilic antimicrobials. Concentrations of hydrophilic antimicrobials may be increased because of decreased renal clearance due to acute kidney injury. Alternatively, antimicrobial concentrations may be decreased because of increased volume of distribution and augmented renal clearance provoked by systemic inflammatory response syndrome, capillary leak, decreased protein binding and administration of intravenous fluids and inotropes. Often multiple conditions that may influence pharmacokinetics are present at the same time thereby excessively complicating the prediction of adequate concentrations. In general, conditions leading to underdosing are predominant. Yet, since prediction of serum concentrations remains difficult, therapeutic drug monitoring for individual fine-tuning of antimicrobial therapy seems the way forward.

Contents

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* Corresponding author at: Dept. of Internal Medicine, Faculty of Medicine & Health Science, Ghent University, De Pintelaan 185, 9000 Ghent, Belgium. Tel.: +32 9 332 6216.
E-mail addresses: stijn.blot@UGent.be (S.I. Blot), pea.federico@aoud.sanita.fvg.it (F. Pea), j.lipman@uq.edu.au (J. Lipman).

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1. Introduction

Dose–response relationships are indispensible to determine the therapeutic window of a drug and to define safe and deleterious concentrations and dosages. In general, these studies are conducted in healthy volunteers after which dosing is fine-tuned in mild-to-moderately ill patients. Results from these trials are frequently extrapolated for the use in critically ill patients. Such extrapolations presume comparable drug pharmacokinetics (PK) and pharmacodynamics (PD) in critically ill patients compared to patients with rather mild illness. Yet, critically ill patients may demonstrate multiple organ derangements inciting pathophysiological changes that can affect PK/PD properties of drugs. These changes can occur within an individual patient and may deviate according to the varying stages of illness. As such dosages being adequate at a given day may become inadequate some days later because of alterations in disease severity. In addition, critically ill patients usually receive a wide range of drugs thereby adding to the possibility of drug–drug interactions. Commonly prescribed drugs in intensive care units (ICUs) include sedatives and analgesics, anticoagulants, immunosuppressive and anticonvulsive agents, drugs with cardiovascular activity, and antimicrobials.

Basically the general principles of PK include absorption, distribution, metabolism, and elimination. Critical illness affects all of these processes thereby significantly influencing the PK of drugs [1]. Absorption refers to the process by which a drug leaves the site of administration (either by the enteral route, inhalation, topical, subcutaneously, intramuscular, or rectal) and concentrates in the circulation thereby representing the bioavailability. The amount of drug absorbed depends on drug characteristics (physicochemical properties, particle size, solubility, etc.) and properties of the organ/tissue of drug administration. For example, regarding enterally administered drugs, shock will reduce regional blood flow and motility, resulting in delayed gastric emptying and diminished absorption [2]. The use of vasopressors to restore arterial blood pressure will not per se normalize regional perfusion as these drugs have differing effects on organ vascular beds and notably on splanchnic blood flow. Alternatively, during shock or use of vasopressors skin perfusion will be reduced thereby decreasing absorption of subcutaneously administered drugs. Because of the issues of absorption intravenous drug administration is usually recommended during critical illness [3].

Volume of distribution (Vd) describes the relationship between dose and the resulting serum concentration. Critical illness and a plethora of associated interventions affect the distribution of drugs. Sepsis, shock, burn injury, pancreatitis, and alterations in plasma protein binding are just a few examples of disease entities influencing Vd. Alternatively fluid resuscitation, as frequently necessary in critically ill patients will also lead to increased Vd.

Drug metabolism occurs predominantly in the liver. The ability of the liver to clear drugs is proportionate to blood flow and/or the hepatic extraction ratio of the drug, mainly driven by the cytochrome P450 enzyme system [1]. Critical illness affects metabolic activity by alterations in plasma protein concentration, hepatic enzymatic activity and blood flow [4,5]. Additionally, many drugs used in critically ill patients may either induce or inhibit the activity of the various isoenzymes included in the cytochrome P450 complex.

Finally the elimination process can be disturbed during critical illness as renal clearance can be either enhanced or impaired. Augmented renal clearance can be driven by sepsis, burn injury, or use of inotropic agents [6]. On the other hand, acute kidney injury may complicate the ICU course [7,8]. Acute kidney injury may represent partial or complete loss of renal function. In the latter case renal replacement therapy will be necessary.

In the rest of this article we particularly focus on alterations in PK of antimicrobials in critically ill patients. In this regard antimicrobials are of extreme interest because (i) their PK is particularly vulnerable for the pathophysiological alteration during critical illness, (ii) dosing is not titrated to an immediately observed effect, and finally (iii) underdosing is associated with insufficient bacterial eradication and as such with bad outcome, while overdosing may provoke additional organ failure in a patient population already at increased risk for organ derangements. As such, the objective of this review is to summarize pathophysiological changes that may take place during critical illness, and their effect on pharmacokinetics of antimicrobials.

2. Infection and sepsis in the critically ill

Critically ill patients are at an increased risk for severe infection because of the extensive use of invasive devices for diagnoses and therapy, and because of their weakened physical condition [9]. Large point-prevalence studies indicated that 40% to 50% of critically patients experience infection during their intensive care unit (ICU) course [10,11].

Serious infections, such as bacteremia or pneumonia, incite a systemic inflammatory response syndrome (SIRS) indicating that the infectious process goes beyond local inflammation and affects the total organism. SIRS is part of the innate immune response and is, as per definition, characterized by the presence of at least two of the following conditions: fever or hypothermia, leukocytosis or leukopenia, tachycardia, tachypnoea, and hypotension [12]. Infections provoking SIRS produce the syndrome called sepsis. According to the level of severity a categorization is made between sepsis, severe sepsis and septic shock. Severe sepsis is associated with organ failure, while septic shock is accompanied by hypotension refractory to adequate fluid administration and necessitating vasopressor support.

The mortality rate associated with sepsis is approximately 20% to 30%, while mortality in patients with severe sepsis is about 30% to 50% [13,14]. An important proportion of this mortality rate is due to overall severity of acute illness and underlying disease [15,16]. The broad window of mortality can be explained by differences in source of infection [11], patients' age and underlying pathology (e.g. neutropenic patients) [17,18], microbial etiology and antimicrobial susceptibility patterns [19,20], associated organ failures [14,21], and adequacy of antimicrobial therapy. Prompt initiation of antimicrobial therapy limits the attributable mortality [22], but nevertheless outcomes often remain unacceptably grim and it has been hypothesized that the optimization of drug exposure might be the way forward in critically ill patients [23–25].

3. Defining adequate antimicrobial therapy

For antimicrobial therapy to be adequate, three requirements need to be fulfilled. First, the antimicrobial agent(s) should be initiated as soon as possible after the onset of sepsis [26,27]. In general this is before the causative pathogen is known. Second, as therapy is to be initiated empirically, the antimicrobial spectrum of the agent should be broad enough to cover the potential causative microorganisms [28,29]. Finally, appropriate antimicrobial dosing is required to maximize microbial killing, minimize the development of multidrug antimicrobial resistance, and avoid concentration-related adverse drug reactions [30–32].

While in the 1990s and the early 2000s there was a clear emphasis in the literature on the importance of empirically selecting the appropriate antimicrobial agent; in the recent years more attention has been given to the issue of adequate dosing. In mild-to-moderately ill patients target antimicrobial concentrations are achieved with standard dosages, as pharmacokinetics are relatively stable and foreseeable. As already mentioned however, in critically ill patients, PK is prone to a variety of pathophysiological alterations, thereby complicating optimal dosing.

4. Physicochemical properties of antimicrobial agents

The choice of appropriate antimicrobial dosing in critically ill patients is greatly affected by the intrinsic physicochemical properties of the drugs [33]. As a general rule, clinicians must be aware of the fact

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