Mini Review

Augmented renal clearance in the intensive care units: concepts to considerate in drug dosing

Abstract

Augmented renal clearance (ARC) is a manifestation of renal function that can be seen in patients admitted to the Intensive Care Unit. Its exact prevalence is unknown and it is detected by way of an urinary measurement of creatine. ARC is defined as a creatinine clearance greater than 130 ml / min / 1.72 m2. Pathological mechanisms are not clearly defined and are probably multifactorial. For patients with confirmed ARC, dosing modifications of all renally purified medicinal products should be taken into account. The use of conventional doses can lead to the failure of the therapy with worse results for the patient and a higher economic cost for the healthcare system. Future research will determine dosages in ARC cases and the use of drug plasma concentration measurements will help us to individualize treatments.

Keywords: augmented renal clearance; critically; enhanced kidney function; intensive care

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Introduction

Renal function has a very important influence on the pharmacokinetics of many drugs used in intensive care units (ICU). Dose adjustment of renal elimination drugs is guided by the varying degrees of glomerular function that constitute the spectrum of acute renal failure. But do we know how to administer doses of drugs for increased renal clearance (ARC)? Do we routinely measure renal function in patients with normal creatinine?

ARC has been observed in critically ill patients.[1,2] It had not been studied until less than 20 years ago. Nevertheless, little attention is currently paid to this phenomenon. Either as a result of a general lack of research or solid evidence, little have questions concerning the dosage adjustment in this clinical situation been addressed. Increased renal drug clearance can have significant consequences for clinical outcomes. Therapy failures compromise the lives of critical patients (e.g. with suboptimate antimicrobial dosages). Studying the pharmacological aspects in the context of ARC should be a priority for future research. The purpose of this brief review is to provide an up-to-date summary of available evidence regarding ARC in the Intensive Care Unit (ICU). As such, a primary search was carried out on pubmed and additional bibliographical references were revised when deemed relevant.

Prevalence of arc and risk factors

Daily monitoring of renal function in the critical patient is a common practice. Therefore, identifying kidney damage or ARC is easier than in other care contexts. The ARC identification method is complicated because having access to a good glomerular function lab r marking outside the research environment is a challenge. To diagnose ARC we need an accurate determination of the glomerular filtration rate (GFR). Urinary measurement of creatinine clearance (8 to 24 h of urine collection) is the most common practice for guiding GFR outside the scope of clinical studies.[3] ARC has been defined using creatinine clearance but the cut-off point varies between published studies, preventing accurate identification of prevalence in the ICU. It has been reported that the prevalence of ARC in the ICU is around 14 to 80%, so we can say that it is a common phenomenon and that its implications may be clinically relevant for drug treatments.[4] In addition, within this definition there are nuances: it is not clear in the studies whether more requirements are needed than the single cut-off point of 130 ml/min/1.73m^2. Perhaps considering the stability of these measurements over time and through repeated treatments might be relevant.

Furthermore, one could relate the degree and stage of ARC in parallel with the categories used to describe renal failure as mild, moderate and severe. This taxonomy may shed light on other, as of yet un considered variables in the research. The true onset and duration of ARC is unknown. Its appearance consistently coincides with acute aggression to the body either by infection, trauma or surgical intervention. We find factors that are associated with ARC such as young age (<50 years), males, with antecedent trauma and low values on the severity scales at admission such as the sequential assessment score of organic insufficiency (SOFA),[6] Simplified Acute Physiology Score (SAPS) II[5] or Acute Physiology and Chronic Health Assessment (APACHE II). Age is the only risk factor repeated in several epidemiological studies. In studies in the paediatric patient, febrile neutropenia was identified as an independent risk factor of ARC in this critical patient subpopulation.[7]

From research in ICU, interesting scales have been proposed that try to predict whether or not patients will develop ARC. The ARC scoring system.[6] uses age, SOFA scales, and the presence of trauma to identify arc probability. Subsequently, based on these studies, Barletta et al. developed ARCTIC[8] focused on patients admitted to ICU following severe trauma (Table 1).

Pathophysiologyof ARC

ARC has been reported to affect many components of nephron physiology when studied using endogenous markers; glomerular hyperfiltration, renal tubular anion secretion and tubular reabsorption.[9] A hyperdynamic response to an aggression of the body, with the effects of inflammatory mediators secreted acutely and in large quantities, are involved in the appearance of the ARC phenomenon. Some authors even proposed a hyperdynamic state model[10] that would explain how from a number of factors resulting from critical disease are combined. Systemic inflammatory response syndrome (SIRS) results in an

increase in inflammatory mediators that generate increased cardiac output and decreased peripheral vascular resistance. Both combine to produce a hyperdynamic state that results in increased renal blood flow, which by glomerular changes is followed by glomerular hyperfiltration that manifests itself as ARC.

Not only do these factors alone explain the physiopathology of ARC. In the ICU, patients receive aggressive fluid therapy, transfusion of blood products, vasoactive drugs... Clinical situations that contribute to increased cardiac output by generating hyperdynamic status.

Although these studies propose valid circumstances to explain pathophyology, the exact mechanism that leads to ARC remains uncertain and only by having more evidence can we clarify why it does not manifest itself in all patients, and why it develops to varying degrees.

Table 1 ARC risk scoring systems (6.8). Abbreviations: ARC - increased renal clearance; ARCTIC - increased renal clearance in intensive trauma care (ARCTIC); SOFA, sequential evaluation score for organic insufficiency; SCr, serum creatinine concentration; pt s dot; sts dots

	Criteria	Interpretation	
ARC Scoring System	Age 50 or younger x 6 sts	7–10 points: high ARC risk	Sensitivity 100%
	Trauma s 3 sts		Specificity 71%
	SOFA score ≤4 x 1 st		
ARCTIC Scoring System	SCr< 62 µmol/L s 3 sts	>6 points: high ARC risk	Sensitivity 84%
	Male sex s 2 sts		Specificity 68%
	Age <56 years ? 4 sts		
	Age: 56–75 years x 3 sts		

Pharmacokinetics and ARC

Knowledge of pharmacokinetics is of great importance when administering pharmacological guidelines. Critical patients have an altered and often very changing pharmacokinetics even in less than 24 hours of disease,[11] so actively evaluating the optimal dose should be a daily task.

The clinical implications of ARC are more obviously related to conventional dose under dosing. Standard doses of medicinal products that are eliminated renally are not considered valid and only adjustments guided by plasma concentration monitoring will be as indicated.

The implications of under dosing an ICU patient can be very important for your clinical outcomes. Renally clarified drugs have a direct correlation between renal clearance and creatinine clearance. Improved drug clearance will result in shorter drug half-life, lower maximum drug concentration, and lower concentration curved area (AUC).

For example, antibiotics such as aminoglycosides, vancomycin and beta-lalactamics require dose adjustment. Also levetiracetam, widely used to treat or prevent comic seizures in patients with head trauma is eliminated by 95% renally.

In a survey of physicians questioning their attitudes towards antibiotic prescribing and renal function assessment in ICU septic patients, only 15% responded that they would consider modifying the antimicrobial dosing regimen in patients with ARC.[12]

To optimize our proper treatment in the critical patient it is necessary to insist on the individualization of treatments and the close monitoring of plasma concentrations, both to avoid toxicities and to ensure effectiveness.

Conclusion

ARC is a phenomenon present in the ICU and causes a significant impact on clinical outcomes and its consequence is underdosing. Knowledge of critical patient-dependent risk factors and the use of prediction tools such as proposed scales can help doctors make dose adjustment decisions and more actively monitor kidney function. More research is needed to be able to establish robust dosing adjustment recommendations in arc patients and with varying grades of ARC. Therapeutic monitoring of serum concentrations of the drug is recommended whenever available.

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