Commentary

Epinephrine kinetics in septic shock - a means to understand variable catecholamine efficiency?

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Published: 13 August 2009
This article is online at http://ccforum.com/content/13/4/177

Critical Care 2009, **13:**177 (doi:10.1186/cc7987)

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Abstract

It is well-established that the hemodynamic response to infusing catecholamines, the most frequently applied drugs for circulatory support during shock states, may vary markedly within and between individuals. In this context it is striking that only scarce data are available on the pharmacokinetics of catecholamines in critically ill patients. Furthermore, the existing literature comprises fairly equivocal observations. Abboud and colleagues now report that, in patients with septic shock, epinephrine kinetics are linear and its clearance directly depends on body weight and is inversely related to the severity of the disease. The authors conclude that the endogenous adrenal axis hormones do not assume any additional importance.

Catecholamines still represent the drugs of choice for hemodynamic support during circulatory shock. It is well known that the responsiveness to catecholamines shows pronounced inter- and even intra-individual variability. This variable efficiency might theoretically result from differences in catecholamine pharmacokinetics, but the available literature on this subject is surprisingly rare. In this issue of *Critical Care*, Abboud and colleagues describe the determinants of epinephrine kinetics in patients with septic shock [1]. According to the authors' local practice, epinephrine was started as the first-line vasopressor (0.15 μg/kg/minute) and titrated thereafter to obtain a mean arterial pressure of 65 to 75 mmHg. Blood samples for measurement of epinephrine levels were taken before and after infusion of an arbitrarily chosen cumulative dose of 0.15 mg/kg during steady state conditions of hemodynamics and fluid loading. The volume of distribution and the plasma clearance of epinephrine were calculated thereafter assuming a one-compartment model with first-order elimination. Simultaneously, the authors also determined the plasma levels of norepinephrine, renin, aldosterone, and cortisol. The major findings were that the plasma epinephrine kinetics were linear without any ceiling effect, even at high infusion rates, and were directly related to the body weight and inversely related to the severity of the disease (according to the new Simplified Acute Physiologic Score (SAPS II)); however, neurohormonal status had no impact on them.

How does Abboud and colleagues' study compare with the existing literature? As could be expected from the extremely variable pharmacodynamics of catecholamines in patients with circulatory shock, Abboud and colleagues report a nearly 70-fold difference between the lowest and highest infusion rates required to achieve the hemodynamic targets. According to the linear pharmacokinetics, this range of infusion rates coincided with a comparably large span of plasma epinephrine concentrations (0.8 to 99 μg/L). In this respect, the authors' findings are in good agreement with previous data on the direct relationship between epinephrine infusion rates and the corresponding blood concentrations in both healthy volunteers [2-4] and critically ill children [5]. The available data on epinephrine clearance, however, are far less clear. Depending on the infusion rate, in healthy volunteers a wide range of epinephrine clearance has been reported (250 to 360 L/h) [2,3], and these values are two- to three-fold higher than in the present study (115 to 140 L/h, corresponding to a half-life of 3.5 minutes) and several-fold higher than in critically ill children (10 to 50 L/h) [5]. Clearly, the results of Abboud and colleagues are comparable with recent data by Beloeil and colleagues [6], who found a norepinephrine half-life of 2.0 to 6.8 minutes in patients after trauma or with septic shock, and Johnston and colleagues [7], who reported a norepinephrine clearance of 60 to 180 L/h in head-injured patients. In good agreement with the present investigation, Beloeil and colleagues also showed that the catecholamine clearance was inversely related to the SAPS II score. By contrast, these authors did not find any

SAPS II = new Simplified Acute Physiologic Score.

impact of body weight on norepinephrine clearance, whereas Abboud and colleagues showed a direct relationship between body mass and epinephrine clearance. It is an open question whether this discrepancy is due to a difference between the pharmacokinetics of norepinephrine and epinephrine *per se* and/or to an interaction between these two catecholamines. It should be noted, however, that in the present investigation epinephrine infusion was associated with a fall in plasma norepinephrine blood levels. Moreover, at least in healthy subjects, norepinephrine clearance (120 to 220 L/h) [8] is somewhat lower than that of epinephrine (see above), and, finally, epinephrine and norepinephrine blood levels followed different decay patterns in patients that had undergone successful treatment of out-of-hospital cardiac arrest [9].

At first glance, the study by Abboud and colleagues confirms the few existing reports on catecholamine kinetics in critically ill patients with variable underlying pathology. Nevertheless, some intriguing aspects prevail. Abboud and colleagues demonstrated that epinephrine kinetics were linear over the whole range of infusion rates and blood levels without any saturation effect even at the highest infusion rates. Such a saturation of epinephrine metabolism, which would consequently result in non-linear pharmacokinetics, is conceivable in patients with gut and/or liver dysfunction. Chu and colleagues showed that approximately 30% of the circulating catecholamines are cleared in the hepato-splanchnic system [10], occurring in particular as a result of vanillylmandelic acid formation in the liver [11]. Consequently, it could be argued that lower epinephrine clearance values than those reported in healthy volunteers might be expected. In fact, since age increases the SAPS II score, Abboud and colleagues argue that their findings are well in line with the data by Wilkie and colleagues [3], although it must be underscored that the latter found an increased rather than a reduced plasma epinephrine clearance in older and slightly lighter subjects. In addition, other authors have emphasized that the sepsis-related enhanced formation of nitric oxide and the superoxide radical O_2^- accelerates catecholamine deactivation due to formation of nitro- [12,13] and quinone derivatives [14] and adrenochromes [15,16]. Can we reconcile these controversial findings? The most severe patients studied by Abboud and colleagues most likely also presented with impaired liver function and, consequently, increased bilirubin blood levels. Bilirubin in turn is well-established as an important endogenous antioxidant and thus contributes to the total antioxidant capacity [17]. Unfortunately, Abboud and colleagues did not report any of these measurements, and thus the impact of oxidative or nitrosative stress on the catecholamine clearance remains mere speculation.

In conclusion, Abboud and colleagues confirm previous findings that catecholamines obey the (relatively simple) rules of linear kinetics with first-order elimination without ceiling effects even at very high infusion rates. Catecholamine clearance seems to be particularly compromised in the most severely diseased patients. Hence, the reason(s) for the well-known extreme variability in catecholamine pharmacodynamics remain to be elucidated.

Competing interests

The authors declare that they have no competing interests.

Acknowledgements

Supported by the Deutsche Forschungsgemeinschaft (Klinische Forschergruppe KFO 200 "Die Entzündungsantwort nach Muskulo-Skeletalem Trauma")

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