Pharmacokinetics of epinephrine in patients with septic shock: modelization and interaction with endogenous neurohormonal status

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Résumé en anglais	Introduction In septic patients, an unpredictable response to epinephrine may be due to pharmacodynamic factors or to non-linear pharmacokinetics. The purpose of this study was to investigate the pharmacokinetics of epinephrine and its determinants in patients with septic shock. Methods Thirty-eight consecutive adult patients with septic shock were prospectively recruited immediately before epinephrine infusion. A baseline blood sample (C0) was taken to assess endogenous epinephrine, norepinephrine, renin, aldosterone, and plasma cortisol levels before epinephrine infusion. At a fixed cumulative epinephrine dose adjusted to body weight and under steady-state infusion, a second blood sample (C1) was taken to assess epinephrine and norepinephrine concentrations. Data were analyzed using the nonlinear mixed effect modeling software program NONMEM. Results Plasma epinephrine concentrations ranged from 4.4 to 540 nmol/L at steady-state infusion (range 0.1 to 7 mg/hr; 0.026 to 1.67 μg/kg/min). A one-compartment model adequately described the data. Only body weight (BW) and New Simplified Acute Physiologic Score (SAPSII) at intensive care unit admission significantly influenced epinephrine clearance: CL (L/hr) = 127 × (BW/70)0.60 × (SAPS II/50)-0.67. The corresponding half-life was 3.5 minutes. Endogenous norepinephrine plasma concentration significantly decreased during epinephrine infusion (median (range) 8.8 (1 – 56.7) at C0 vs. 4.5 (0.3 – 38.9) nmol/L at C1, $P < 0.001$). Conclusions Epinephrine pharmacokinetics is linear in septic shock patients, without any saturation at high doses. Basal neurohormonal status does not influence epinephrine pharmacokinetics. Exogenous epinephrine may alter the endogenous norepinephrine metabolism in septic patients.

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