presented will assist practitioners in the thoughtful interpretation of the information this monitor provides.

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(Accepted for publication February 26, 2010.)

The Dose of Epinephrine to Treat Anaphylaxis

To the Editor:

The article reviewing anaphylaxis and anesthesia[1] is a useful timely reminder of a serious problem that may arise with any of us during anesthesia. I agree that the basic treatment should focus on intravenous (IV) epinephrine and expansion of intravascular volume. However, there is one aspect of this treatment that is misleading. The early administration of epinephrine is emphasized and the dose adjusted to the hemodynamic response, but for severe reactions a single IV bolus and infusion is suboptimal, because it may be slow to achieve the desired effect. Basic pharmacology teaches that the dose–effect relationship of a drug is log-linear and so the titration should be done in a logarithmic fashion. This is most easily done by doubling the amount of epinephrine in each progressive dose until the desired effect is achieved. Commencing with 100 μg IV epinephrine and administering a dose every 2 min as suggested, if the doubling is used, a 3-mg dose of epinephrine, if required, is reached in 8 min. If a 3 mg IV dose is required, the 200 μg epinephrine bolus and 4 μg/min infusion would take over 10 h! When an anaphylaxis occurs, it is not always obvious whether it is a grade III or IV reaction. Early progressive titration of the IV epinephrine will achieve an optimal dosing in the shortest time.

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(Accepted for publication February 26, 2010.)

In Reply:

We thank Dr. Russell for his careful reading of our article.[1] As highlighted by Russell, perioperative anaphylaxis remains a clinical diagnosis that is not always obvious. The Ring and Messmer four-step grading scale adapted for perioperative immediate reactions helps to stratify the severity and guides therapy for the ongoing clinical reaction.[1] Common key points are highlighted in the various current clinical guidelines that recommend careful titration of epinephrine boluses according to the hemodynamic response during cardiovascular collapse (grade III reactions).[2–6] Recommendations in the United States propose an initial dose of 100–300 μg intravenously, advise close monitoring because fatal overdoses of epinephrine have been reported, and suggest that an intravenous infusion of epinephrine (1–4 μg/min) may prevent the need to repeat epinephrine bolus administration.[3,4] French guidelines recommend a 100–200 μg intravenous epinephrine bolus and state that intravenous infusion at a dose (0.05–0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) might be used in place of repeated bolus administration.[2] Scandinavian recommendations state that a continuous infusion (0.05–0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) is advantageous in patients in need of repetitive doses of epinephrine (initial intravenous doses 100 μg), whereas British guidelines also state that an intravenous infusion should be considered in patients requiring repeated bolus dosing (initial intravenous boluses of 50 μg).[5,6]

Plotting the logarithm of the dose that fits a dose–response curve is a mathematical description of the receptor-occupancy theory that allows us to study the competition of a ligand (such as epinephrine) for receptor binding and allows the comparison of receptor agonists in terms of efficiency (E_{max}) and potency (EC_{50}). The shape of the dose–response curve corresponds to drug binding to its receptor, and the slope of the curve identifies the range of doses useful for achieving a clinical effect. With such a design, we previously provided dose (epinephrine)–response (mean arterial pressure) relationships and showed that the EC_{50} of epinephrine in a rat model of anaphylactic shock was 10 μg/kg.[7] Pulmonary edema and episodes of ventricular arrhythmia occurred at the highest doses of epinephrine in this rat model. However, most importantly, the magnitude of a pharmacologic drug response and the clinical use of a drug should be distinguished. Epinephrine has a relatively narrow therapeutic index,[8] with pulmonary edema, ventricular dysrythmias, and poor outcomes, including myocardial and cerebral infarctions or deaths (and in recent years *Tako-Tsubo* cardiomyopathy), associated with its use after excessive dosing during anaphylaxis.[9,10] Finally, none of the current clinical guidelines recommend that "the titration of epinephrine should be per-

formed in a logarithmic fashion" or "by doubling the amount of epinephrine in each progressive dose."[2–6] Conversely, the need for careful epinephrine titration according to the hemodynamic response is strongly recommended.[2–5]

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(Accepted for publication February 26, 2010.)