CORRESPONDENCE

Anesthesiology
78:1187, 1993

Concentration Ranges in Dose–Response Determinations for Propofol and Thiopental *In Vitro*

To the Editor:—Recently, Park *et al.* noted the absence of contractile response by rat aortic and pulmonary arterial rings exposed to concentrations of propofol ranging from 30 to 300 μM.[1] Their work revealed a statistically significant concentration-dependent relaxation response. Introna *et al.* have reported that lower propofol concentrations cause an endothelium-independent constriction of canine coronary artery rings across a range of 10^{-8} M (10 nM) to 10^{-5} M (10 μM),[2] the latter concentration approaching the initial concentration used by Park *et al.* to establish a propofol dose-response curve.

In addition, Park *et al.* did not observe significant effects of thiopental upon aortic tissues within a concentration range of 10–100 μM. We have noted a biphasic response to thiopental in endothelium-denuded canine coronary artery rings, both untreated (Bridges *et al.*)* and pretreated with serotonin.[3] Thiopental concentrations of 100 nM–100 μM caused ring contraction, and ring relaxation was seen at higher concentrations. Our observations were similar to those of Hatano and colleagues, who demonstrated increased contractile responses in a variety of canine arteries using thiopental concentrations ranging from 10 μM to 1 mM.[4]

Multiple variables affect the *in vivo* milieu, including physiochemical properties such as protein binding, lipid solubility, and pKa, as well as the pharmacokinetic profile of the drug. This makes it difficult to correlate *in vivo* with *in vitro* studies, as well as to infer specific tissue drug levels across a relatively narrow concentration range. Clinically relevant concentrations of thiopental have been estimated at 40–350 μM,[5] and those of propofol at 16–22 μM (maintenance infusion) and >35 μM (bolus).[6] The study by Park *et al.* approximated this range (10–100 μM thiopental and 30–300 μM propofol).[1] However, we have observed a biphasic response in coronary rings across a wider concentration range of thiopental (100 nM–1 mM),[3] and Introna and colleagues have demonstrated a contractile response at propofol levels of 10 nM up to 10 μM, with relaxation at higher doses.[3] It is possible that vasodilation might follow a bolus dose of propofol, with vasoconstriction occurring at lower concentrations (*i.e.*, maintenance blood levels).

These studies contain differences in animal species, vascular tissue type, and experimental technique. Still, we maintain that important effects of these two drugs, such as the biphasic contraction/relaxation response we have observed, may be overlooked if one is limited to a relatively narrow concentration range. It would seem prudent to expand the dose range to include both higher and lower concentrations, considering the difficulty of extrapolating from *in vitro* to *in vivo* and from animal to human tissue and considering the pharmacokinetic and physiochemical complexities involved.

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* Bridges MT, Introna RPS, Pruett JK: Direct effects of thiopental on endothelium-denuded canine coronary artery rings. Unpublished data.

(Accepted for publication March 2, 1993.)