CORRESPONDENCE

POSTOPERATIVE PAIN THRESHOLDS
Sir,—Dahl and colleagues have demonstrated a decrease in the pain threshold and an increase in subjective assessment of pain in postoperative female patients recovering from gynaecological operations [1], in contrast to a lack of alteration in a control group. The degree of hyperalgesia showed a significant inverse correlation with time after surgery. The patients had received morphine and paracetamol after operation, but not for 12 h before testing. Of relevance, however, is the fact that in all patients anaesthesia was induced with thiopentone 4–5 mg kg⁻¹ i.v. Thiopentone has long been known to have antianalgesic properties in small doses [2].

Kissin and colleagues have demonstrated that barbiturates inhibit stress-induced analgesia in Sprague-Dawley rats [3]. In this study, a motor reaction threshold to noxious pressure on the tail was measured. Stressing the animal by placing a clamping on the hind paw produced an increase in reaction threshold. Pento-barbitone in subanaesthetic doses largely abolished the stress-induced increase in motor reaction threshold. Stressing the rats on recovery from thiopentone anaesthesia failed to increase the motor reaction threshold from that in the unstimulated rat. This parallels the situation in Dahl’s study. Wilder-Smith and Borgeat also have demonstrated a hyperalgesic response to small doses of thiopentone in unstimulated patients [4]. Their study showed similar results with low-dose propofol, but neither hyperalgesia nor analgesia with etomidate.

In Dahl’s study, testing was performed 40–80 h after anaesthesia. At this time, a small proportion of the anaesthetic agent remains within the circulation. This may or may not be sufficient to produce an antianalgesic effect (whether or not the antianalgesic effect is related to plasma concentration is not clear from Kissin’s work). The decrease in pain threshold diminishes with time, consistent with a decrease in circulating barbiturate.

The quoted studies do not refute Dahl’s findings, but it may be that the increase in postoperative pain perception and decrease in pain threshold are not caused solely by central neuronal sensitization, but that a contribution is made by residual thiopentone. It would be interesting if Dahl’s findings were repeated with different anaesthetic induction agents.

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PHARMACOKINETIC/PHARMACODYNAMIC MODELLING OF ATRACURIUM
Sir,—The multiple elimination pathways of atracurium from both the central and tissue compartments confound its pharmacokinetic/pharmacodynamic analysis and necessitate the use of innovative models. Three recent articles [1–3] proposed models that differ from ours [4]. I contend that each of these new proposed models is flawed.

Beemer, Bjorksten and Crankshaw [1] infused atracurium using a computer-controlled infusion regimen to estimate volume of distribution at steady-state ($V^e$) as the ratio of the amount of drug in the body at steady-state ($X^e$) divided by the steady-state atracurium concentration. $X^e$ was estimated as the quantity of atracurium infused minus that eliminated. However, their estimate of the quantity eliminated (the product of plasma clearance and area under the plasma concentration–time curve (0–1 h)) is flawed—it does not account completely for drug eliminated from tissue rather than plasma. Because atracurium is eliminated from both plasma and tissue, Beemer’s group underestimated $V^e$. The authors’ retort that they used a non-parametric approach to avoid this problem is invalid—these non-parametric techniques require that elimination be from the central compartment only [5].

Parker and Hunter’s interesting approach to relating the recovery of atracurium to its pharmacokinetics used “standard formulae” to estimate $V^e$ [2]. Yet, in their letter to the editor criticizing the manuscript by Beemer, Bjorksten and Crankshaw, they stated that for atracurium, “standard formulae...[do not] allow calculation of the...steady-state volume of distribution as usually defined” [6]. Their letter is correct, their manuscript in error—standard formulae require the assumption, invalid for atracurium, that clearance occurs only in the central compartment. As with Beemer’s group, Parker and Hunter underestimate $V^e$.

Parker and Hunter also propose a new pharmacodynamic model for atracurium in which a threshold concentration is necessary at the neuromuscular junction to produce paralysis [3]. The systematic error they observed fitting the traditional link models (leading them to reject that model) may arise from their obtaining venous rather than arterial blood samples—for atracurium (as other drugs), venous concentrations obtained early during an infusion underestimate arterial and effect site concentrations [7]. Alternatively, a more complicated link model may be necessary to explain the relationship between concentrations in the plasma and those at the neuromuscular junction. However, in the absence of actual measurements of effect site concentrations, all pharmacokinetic/pharmacodynamic models describe “black boxes”; therefore, no single model can be demonstrated to be valid or invalid. Parker and Hunter claim that their model provides “explicit demonstration of a margin of safety of neuromuscular transmission in the human”. Yet, the margin of safety associated with their model ($C_{	ext{target}} = 159$) differs little from a concentration (120 ng ml⁻¹) that I calculate produces minimal (1%) twitch depression with the traditional model. Perhaps these investigators should evaluate their model using a more appropriate data set (arterial plasma concentrations) before rejecting a well accepted (and parsimonious) model.

Our model for atracurium [4] is the only one to incorporate Dr Hull’s editorial suggestion that atracurium’s pharmacokinetics can only be determined if the rate of elimination from the peripheral compartment is estimated [8]. Although our model may be flawed, to date no one has presented a cogent argument regarding any errors. I am delighted that this topic has elicited so much interest in the anaesthesia research community, but I believe that errors by these other investigators should be corrected.

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