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 antinociceptive 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 clamp on the hind paw produced an increase in reaction threshold. Pentobarbitone 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. It would be interesting if Dahl’s findings were consistent with a decrease in circulating barbiturate. As with Beemer’s group, Parker and Hunter underestimate 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 antinociceptive effect (whether or not the antinociceptive 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 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.

T. M. Cook
Royal Cornwall Hospital
Treliske, Truro


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 Cranckshaw [1] infused atracurium using a computer-controlled infusion regimen to estimate volume of distribution at steady-state ($V_{ss}$) as the ratio of the amount of drug in the body at steady-state ($X_{ss}$) divided by the steady-state atracurium concentration. $X_{ss}$ 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 $V_{ss}$. The authors’ report 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 $V_{ss}$ [2]. Yet, in their letter to the editor criticizing the manuscript by Beemer, Bjorksten and Cranckshaw, 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 $V_{ss}$.

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 model (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 ($C_{min}$ = 120ng 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.

D. M. Fishcr
University of California
San Francisco, California

Sir,—The criticism by Dr Fisher of our method to calculate the $V^\text{m}$ of atracurium is the same as that previously raised by Parker and Hunter [1,2]. We agree that our method does underestimate the true $V^\text{m}$. However, the $V^\text{m}$ we derived, which perhaps can best be termed the “apparent” or “functional” $V^\text{m}$, is that which is required in conjunction with our estimate of the total clearance of atracurium at steady-state, for design of a bolus-infusion regimen [3]. We contend that derivation of parameters which predict dosing requirements is the primary goal of pharmacokinetic research. The true $V^\text{m}$ has no clinical use, as the time-dependent changes in the clearance of atracurium cannot be measured directly, and any hypothesized estimate may be the result of a significant modeling error.

The pharmacokinetic parameter estimates derived from the model proposed for atracurium by Fisher and colleagues are erroneous [4]. The slow sampling rates were insufficient to allow the model to take into account the contribution of the rapidly degraded isomers of atracurium [5]. Our own unpublished observations are consistent with those reported in the latter paper and suggest that 22.5% of the total dose of atracurium, components of the cis-trans and trans-trans isomers, undergo rapid degradation in blood. The errors caused by the slow sampling rate were compounded by Fisher and colleagues using only samples obtained 25 min after the addition of atracurium in the analysis of their $V^\text{m}$ data. The contribution from these rapidly degraded isomers to the in vitro degradation of atracurium was totally neglected.

G. H. BEEMER
A. R. BJORKSTEN
D. P. CRANKSHAW
The Royal Melbourne Hospital,
Melbourne, Victoria 3050


We agree with Fisher that our estimates of $V^\text{m}$, in common with those of Beemer, Bjorksten and Crankshaw [4], are subject to error on this account, and it was for this reason that we stated exactly how we obtained the values of $V^\text{m}$, and that these are estimates [2] “Data analysis...”, paragraph 3). We do not feel that this seriously calls into question the utility of the results in the context of that paper, for the standard formula allows standardized comparison of the data in volume terms. The purpose of the paper was to demonstrate, across a range of individuals, that drug effect is dependent on disposition. This is almost routinely assumed to be the case for the non-depolarizing nonneuromuscular blocking drugs and, of course, is implicit in the attempt to formulate a pharmacodynamic model. Direct evidence on this point is, as we pointed out in the introduction to the paper, rather scant, and the demonstration which is given in our paper of the correlation between the pharmacokinetic and pharmacodynamic data sets materially adds to the evidence which is available in this paradigm.

The second area of interest is the threshold term of the pharmacodynamic model, concerning which Dr Fisher raises several points:

1. We agree that it would have been preferable to have used arterial rather than venous blood samples. We did not do so because the patients we studied were healthy, and were not about to undergo very major surgery. However, we must correct the suggestion that the systematic error in fitting the standard model is an artefact arising from the use of venous samples. On the contrary, venous samples underestimate the arterial plasma concentration to which the site of action is exposed during onset, for two reasons: first, because they are “downstream” at a time of increasing plasma drug concentration; second, because extraction of drug by the tissues ensures that venous concentrations are smaller than arterial during onset of block. If anything, the site of action was exposed to a greater drug concentration than that which we measured, during the period of the “residual discrepancy”. Any systematic error arising from the use of venous samples thus militated against the discovery of a threshold, and we would have perhaps found a stronger case for postulation of a threshold, and greater values of $C_{\text{th}}$, had we used arterial samples.

2. ( Perhaps the most important point concerns the calculation which Dr Fisher presents of the effect of the drug at a concentration close to our estimate of $C_{\text{th}}$. We agree that a concentration of 120 ng ml$^{-1}$ produces light twitch depression, and this is predicted by the standard model, if one assumes a value of gamma of 4. For example, if one applies a concentration of 120 ng ml$^{-1}$, mentioned by Dr Fisher, to the standard logistic equation, with a $C_{50}$ of 360 ng ml$^{-1}$, and gamma of 4, then:

$$\text{Effect} = \frac{120}{120 + 360} \times 100 \approx 1.2\%.$$

The value of gamma which Dr Fisher must have used in this calculation is close to what one obtains if one fits the standard model. Unfortunately, to fit an inappropriate model may lead to inappropriate parameter values, and it is precisely gamma which decreases in value when one restructures the standard model to include a threshold. The greater values of gamma which are obtained with the standard model are the means by which the standard model obtains a small value of effect when effect site concentrations are relatively great. We can see no other reason for proposing or holding onto such a value of gamma, whilst we can see good reasons for the calculation of a threshold.

3. ( Whilst effect site concentrations are hypothetical, and pharmacokinetic and pharmacodynamic models may represent “black boxes”, we do not agree that they are black boxes of an entirely arbitrary structure. In our view, structural and statistical aspects of model building should go hand in hand. To accept the nihilistic suggestion that no single model can be valid or invalid implies that we should abandon the structural aspects of model building altogether and simply fit, say, a polynomial to our data set. This would, however, fail to advance our understanding of what factors are quantitatively responsible for drug actions, and we do not feel that Dr Fisher would seriously entertain this logical conclusion of his proposition.

4. Dr Fisher makes the interesting suggestion that a more complicated link model might be necessary to explain the