CORRESPONDENCE

Psychological characteristics and patient-controlled analgesia

Sir,—Dr McConaghy writes [1] requesting clarification of some aspects of our study of psychological characteristics and patient-controlled analgesia [2]. We are grateful to Dr McConaghy for his appreciation of the importance of our findings for anaesthetists involved in the management of acute postoperative pain. He suggests that the anaesthetic technique may have been insufficiently standardized because “the analgesic component consisted of either fentanyl or papaveretum, together with an opioid premedicant (either pethidine or papaveretum)” and that the timing of intraoperative opioid may have affected consumption of postoperative analgesics. Further, he suggests that we chose to compare an inefficient i.m. regimen when an hourly “as required” regimen has been shown to be safe and effective [3]. With regard to premedication, as stated in the article, the majority (90 of 110) of patients received temazepam and some of the remainder received lorazepam; the few patients who received opioid premedication were approximately equally distributed between the groups, and therefore it is unlikely that this had any significant effect in this fairly large study. They received opioids because of occasional preoperative assessment by trainee anaesthetists who had been taught to use opioids during their previous appointments.

The other concerns are appropriate but must be viewed in the context of when and where this study was performed. It was for this reason that we gave the dates (1988–90) of the study. In planning the study it was necessary to obtain the co-operation of the career anaesthetists who regularly anaesthetized such patients. In a district hospital without a major research programme, individual clinicians were accustomed to modifying their clinical techniques in the interests of research. Two consultants were unable to agree: one because the study required that patients would not know before operation what pain relief regimen they would be prescribed, the other because it was his practice to use trichlorethylene for intraoperative analgesia–anaesthesia and he would not know before operation what pain relief regimen they would be prescribed, the other because it was his practice to use trichlorethylene for intraoperative analgesia–anaesthesia and he was not prepared to change to either fentanyl or papaveretum. The other anaesthetists normally used either fentanyl or papaveretum as a bolus dose immediately after induction of anaesthesia, with occasional increments if indicated clinically during the procedure. We felt that these techniques were sufficiently alike, together with randomization of patients, to ensure the absence of bias.

The problem of the effectiveness of the standard 4-hourly i.m. regimen is somewhat similar. For many years one of us has had been taught to use opioids during their previous appointments.

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Ulnar and common peroneal nerve block revisited

Sir,—There has been much recent discussion in this journal on the incidence and mechanisms of nerve injury after local anaesthetic block [1,2]. However, little attention has focused on particular blocks. After discussions of the advantages and disadvantages of ulnar nerve block at the elbow and common peroneal nerve block at the head of the fibula, we decided to investigate the evidence for and against these two nerve blocks.

It is commonly taught that the ulnar nerve should not be blocked at the elbow. The nerve is palpable as it runs around the medial epicondyle and is easily accessible at this point. However, it is said to be protected by a thick fibrous epineurium and therefore intraneural injection may be required to allow adequate axonal block, risking neuritis. Some standard texts reinforce this view. Bridenbaugh states: “block of the ulnar nerve at the elbow is often said to lead to residual neuritis” [3]. This is similarly described by Löfström [4]. Likewise, the common peroneal nerve is easily palpable at the head of the fibula and for similar reasons it is stated that block at this landmark carries a “considerable risk of post-anaesthetic neuritis” [5]. However, elsewhere these risks are not mentioned and the blocks described at these sites [6].

This variation in advice prompted us to carry out a comprehensive literature search to identify case reports of nerve damage after the two blocks. A Medline search back to 1966 revealed no case reports of ulnar or common peroneal nerve pathology after block at the elbow or head of fibula. We then searched through textbooks on regional anaesthesia dating back to 1922 and could find no reports of such neuropathies. In fact the earlier texts described how to perform these blocks [7]. Furthermore, neuropathies are rare after common peroneal nerve block at the head of the fibula and have been reviewed extensively, providing information on their aetiology. Ulnar neuropathy is the most common mono-neuropathy in this situation and a study of closed malpractice claims by the American Society of Anesthesiologists found 77 cases of ulnar neuropathy from a total of 227 cases of nerve damage [8]. In the majority of cases the causative mechanism was unknown. Regional anaesthesia was uncommon but tended to be central or plexus block, and there was no mention of ulnar nerve block at the elbow. Another retrospective study reviewed the postoperative courses of 1 129 692 surgical patients undergoing non-cardiac surgery and found 414 cases of ulnar neuropathy [9]. This was associated with male gender, abnormally high or low body mass index and prolonged hospital stay. It was not associated with regional anaesthesia in general or ulnar nerve block in particular.

It would be wise to perform these blocks meticulously and only in awake patients to minimize the risk of intraneural injection. However, in this era of evidence-based medicine, there is nothing to support the contention that these nerve blocks are associated with neuritis. Should we therefore disallow ourselves the advantages presented by the convenient anatomy of these nerves?

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Nebulized lignocaine before gaseous induction with desflurane

Sir,—I read with interest the recent study by Bunting, Kelly and Milligan [1] illustrating the failure of nebulized lignocaine to suppress airway irritation during gaseous induction with desflurane. The results of this study are alarming, and provide further evidence against the use of desflurane as an induction agent. However, I am concerned that the authors have failed to document the duration of administration of the nebulized solution (4 % lignocaine or 0.9 % saline), nor formally tested the airway for the absence of reflexes (e.g. gag reflex) before administration of desflurane. It is therefore possible that insufficient time was allowed for the onset of action in those given lignocaine.

While the use of lignocaine in providing topical anaesthesia to the airway has been studied widely, the onset time of nebulized lignocaine is poorly documented. The information available in standard texts suggests an onset time of 5 min or less [2, 3]. However, Vuckovic and colleagues [4] administered 4 % lignocaine via a nebulizer (4–6 ml in total) for up to 7 min and found that 10 % of patients required additional nebulized lignocaine after formal testing of upper airway reflexes. These findings suggest a variable onset of action which can only be proved by the absence of upper airway reflexes.

The “blinded” nature of the authors’ study has precluded formal testing of the airway, making any assumption of the efficacy of nebulized lignocaine in decreasing respiratory responses during gaseous induction with desflurane misleading. Allowing sufficient time for verifiable onset of action may yet show this technique to be a useful adjunct to gaseous induction with desflurane.

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Factors governing onset of neuromuscular block

Sir,—Audibert and Donati’s article [1] demonstrated the phenomenon first reported by Hood, Campkin and Feldman [2], Campkin and Hood [3], and Feldman [4] that an increase in non-depolarizing block occurs despite cessation of drug delivery from the circulation. Hood, Campkin and Feldman [2] used a 0.1 × ED95 drug dose injected into the isolated forearm of conscious volunteers and released the tourniquet during onset at 50 % block. We found that the non-depolarizing blocks progressed to a much greater degree, and over a much longer time scale, than that of decamethonium; the results are shown in figure 1.

The isolated forearm is akin to a Bier’s block: drug is flushed from the arm after tourniquet release. Mean time courses of the increase in block after tourniquet release were 3.26 (SD 0.24) min for vecuronium, 2.6 (0.43) min for atracurium and less than 4 (4) s for decamethonium.

The isolated forearm is akin to a Bier’s block: drug is flushed from the arm after tourniquet release, and recirculation of drug is not the cause of any subsequent increase in block [5]. Audibert and Donati’s technique of inflating a tourniquet during onset of systemic block would presumably trap drug-containing blood in the arm. We suggest that transfer of drug from this reservoir would account for some of the subsequent increase in block thereafter and, in particular, that of suxamethonium over approximately 3 min, because intra-arterial administration of agonists reveals little delay in onset of block. While Bartowski and colleagues [6] observed that small doses of intra-articular vecuronium took 1.39 min to achieve 90 % of maximum effect, Baoq and

Figure 1 Isolated forearm blocks after decamethonium 0.15 mg, atracurium 2 mg and vecuronium 0.3 mg. These doses produced similar rates of onset before tourniquet release. Mean time courses of the increase in block after tourniquet release were 3.26 (SD 0.24) min for vecuronium, 2.6 (0.43) min for atracurium and less than 4 (4) s for decamethonium.
Brown [7] found that acetylcholine achieved maximal block in 10 s. We believe the sum of this previous work contradicts Audibert and Donati’s explanation of their results. The suggestion that their observed increase in both suxamethonium and vecuronium block was caused by a common mechanism (drug transfer from the extracellular fluid to the junction) would appear unlikely unless some other differential existed. The likelihood that the two classes of drug achieve effect at very different receptor occupancies does not provide that differential, in our opinion.

The relationship between receptor occupancy and biophase drug concentration is described by a rectangular hyperbola. Non-depolarizing drugs, effective at 80% occupancy, are on the flat part of the curve, while suxamethonium, perhaps effective at less than 10% occupancy, is on the steep part. For equal percentage increases in biophase concentration, the latter has a much greater increase in percentage receptor occupancy than the former. Yet Audibert and Donati found a smaller increase in depolarizing block than non-depolarizing block after cessation of the blood supply to the arm, and we found a more marked difference between the two classes of drug (fig. 1). Some mechanism would appear to exist which produces the difference between the two classes of drug.

Buffered diffusion has been suggested by the authors as the mechanism causing the delay in onset of non-depolarizing drugs. However, it is not clear why depolarizing drugs should not also be subject to this process and so buffered diffusion alone would not appear to explain their shorter onset time occurring from intra-arterial or isolated forearm delivery.

We suggest that non-depolarizing drugs undergo extensive binding in the junction with non-specific biophase binding sites. These provide a reservoir which limits ingress [8] and egress [9, 10] from the junction at a specific rate for each drug. The studied depolarizing drugs do not act in the same way [11] which allows recovery from block with these agents to be affected by blood flow [12].

The authors’ important conclusion is that redistribution of drug within the muscle may place intrinsic limits on the speed of onset of action of non-depolarizing drugs. Whatever the cause of this delay in transfer of drug between blood and biophase (suggested 25 yr ago [11]) its elucidation will aid the development of a safe non-depolarizing equivalent of suxamethonium.

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Sir,—We thank you for the opportunity to respond to the letter of Feldman and Hood. In our view, there is no contradiction between the results of the isolated arm experiments [1–3], the delay observed after intra-arterial injection of drug [4] and our results [5]. A single explanation can account for all observations. In our article [5], we suggested diffusion of molecules from extrajunctional to junctional sites. Feldman and Hood prefer to talk about a reservoir. Both concepts are essentially the same.

They provide for transfer of drug to the neuromuscular junction in spite of interruption of blood circulation. The only assumption that has to be made is that the affinity for this extrajunctional site or for the reservoir is less than the affinity for the neuromuscular junction. As a result, the concentration of the drug increases more rapidly in the extrajunctional sites or reservoir during onset.

In the isolated arm experiments, drug is injected i.v., distal to a cuff inflated above arterial pressure. Diffusion to high affinity sites (the neuromuscular junction) takes longer compared with other sites. If the cuff is released during onset, the concentration of drug at extrajunctional sites (the majority of the tissue) is greater than at the junction. Thus, on release of the tourniquet, transfer of drug from a high concentration area to a low concentration area (the junction) is possible, and neuromuscular block increases. In the intra-arterial injection experiments, drug concentration in plasma is presumed to be zero at all times, except for a large increase during injection. This has access to the junctional sites and is released more rapidly in the latter. When the tourniquet was inflated, drug concentration in plasma is presumed to be zero at all times, except for a large increase during injection. Thus, drug is free to move along its concentration gradient, allowing block to increase after injection is finished. In our experiments, where the tourniquet was inflated during onset, the situation was the same. Drug had access, via arterial blood, to both junctional and extrajunctional tissue. At the end of injection, its concentration is less at the junction because the affinity for junctional tissue is greater. Thus, drug is free to move along its concentration gradient, allowing block to increase after injection is finished.

According to the same logic, the concentration of drug increased more rapidly in the latter. When the tourniquet was inflated, drug transfer occurred between extrajunctional areas and junctional areas, thus increasing neuromuscular block.

The reasons for the different affinities for both sites cannot be elucidated from these experiments, but there are data which give a few hints. Feldman, Xu and England [3] reported that decamethonium, atracurium and vecuronium behaved differently when the tourniquet used in the isolated arm experiments was deflated prematurely. Onset continued for the non-depolarizing drugs, but not for the depolarizing drug. We found the same, using a different mode of drug delivery, and interrupting delivery in a different way. Based on the above explanation, one has to conclude that the affinity of depolarizing drugs for junctional and extrajunctional tissue is approximately the same, while the affinity of atracurium and vecuronium for both types of tissue is different.

Feldman and Hood suggested that non-depolarizing drugs undergo extensive binding in the junction with non-specific biophase binding sites. We suggest that these sites need not be non-specific and may be the junctional receptors themselves. Binding of depolarizing drugs would be much less extensive, if they are effective at a lower proportion of receptor occupancy. Also, our hypothesis suggests that, for non-depolarizing drugs, the extent of binding depends directly on potency. This hypothesis was tested in another set of experiments which showed that for rocuronium, a less potent drug than vecuronium or atracurium, block is affected in much the same way as suxamethonium by tourniquet inflation. This result is also explained by the mechanism of buffered diffusion, which predicts that high affinity drugs (potency is a measure of affinity) have a slower onset [6].

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**Effects of propofol and isoflurane on right ventricular function**

Sir,—We read with interest the article by Kellow and colleagues [1]. It would appear that they have not noticed our article [2] published over a year ago, which also studied the effects of propofol and isoflurane on right ventricular function. Interestingly we came to the opposite conclusion. Using a within-patient crossover design, we found that cardiac index and right ventricular ejection fraction were significantly higher when propofol was given for maintenance of anaesthesia compared with isoflurane.

We found no differences in end-systolic volume index between the two agents, but agree with Kellow’s study that end-diastolic volume was significantly higher than propofol. The differences in results probably reflect differences in the experimental design, although it is not possible to exclude differences in the populations studied.

In all studies comparing the effects of two anaesthetic agents on the function of a specific organ it is vital that equipotent or equivalent anaesthetic doses of the two agents are used for the comparison. Furthermore, comparisons must only be made when steady state anaesthesia with these equipotent doses has been achieved. Kellow and colleagues seem to have compared two “…generally accepted techniques…”, whereas we took considerable care to compare similar anaesthetic doses of propofol and isoflurane, by using the same numerical values of minimal infusion rate for propofol and minimal alveolar concentration for isoflurane for each patient [3].

It is particularly important that observations on cardiac function are made during periods of steady state anaesthesia. It is likely that plasma concentrations of isoflurane and propofol were not constant for the measurement times in the current study. It is known that the inspired concentration of a volatile agent does not have a relationship to blood or brain concentrations, without taking into account other factors, particularly time. It appears from the study design that a constant inspired concentration of isoflurane was given throughout. This is likely to have resulted in greater brain concentrations of isoflurane at the end of operation than at the first datum point 20 min after starting isoflurane, implying that isoflurane concentrations and anaesthetic depth were not constant in the isoflurane group throughout the study. Similarly, kinetic models for plasma concentrations of propofol related to infusion rate take into account the age and weight of the subject [4]. In Kellow’s study it appears that the age of the patient was not considered in controlling the propofol infusion rate, and no attempt was made to estimate plasma concentrations which continue to increase if a constant infusion rate is used. Consideration of both of these effects are accepted techniques for propofol infusion regimens [4].

Finally, and perhaps most importantly, in any study considering right ventricular function, it is vital that venous preload is standardized, and the same, in both groups, and that these filling pressures are maintained throughout the study. It is generally accepted practice to use right atrial pressure as a measure of preload. The authors did have this information available, as they were using a REIF-1 pulmonary artery catheter, but they have not presented the data. Interestingly they gave only the changes in end-diastolic volume. In our study we have shown this to change, despite constant filling pressure, as compliance changed in response to propofol. Using end-diastolic volume, although there were no differences within each group over time, there were significant differences between the groups. Therefore, comparisons of cardiac function between the groups may not be appropriate.

We agree that it is difficult to compare two anaesthetic agents, particularly when they are given by different routes. Kellow’s study showed that with the procedure used, propofol and isoflurane have different effects on right ventricular function. However, the experimental conditions may not have been equivalent for each agent, because of the difficulty in comparing the anaesthetics, and lack of standardization of anaesthetic administration over time and right ventricular filling pressures. We suggest that their study regimen may have not have been appropriate to compare these two anaesthetic agents.

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**ERRATUM**

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p. 279. In the paragraph headed “Patient-related factors”, the sentence beginning “However, we did not investigate the possible interference of other factors, such as the dose of local anaesthetic .......... block, should read “However, the authors [10] did not investigate the possible interference of other factors, such as the dose of local anaesthetic .......... block.

We apologize to the authors for this confusion which arose during the editorial process.