Serotonin toxicity and malignant hyperthermia: role of 5-HT2 receptors

Editor—We congratulate the authors on an excellent review of aspects of the pathophysiology of malignant hyperthermia (MH). They have explained the postulated role of serotonin in MH, in particular the role of peripheral 5-HT2 receptors, based on in vitro and in vivo animal work. There are important parallels between serotonin toxicity and MH, and this review adds to our understanding of the role of 5-HT2 receptors, peripheral and central, in both serotonin toxicity and MH. There is recent animal work that has defined the role of 5-HT2a receptors in serotonin toxicity, and reports of the use of 5-HT2 antagonists in the treatment that should make us rethink the conventional descriptions of serotonin toxicity, which were restated by Wappler and colleagues.

Serotonin syndrome, better described as a spectrum of toxicity than a distinct syndrome, is characterised by:

(i) neuromuscular hyperactivity—hyperreflexia, clonus, myoclonus, tremor and rigidity;
(ii) autonomic hyperactivity—hyperpyrexia, tachycardia and diaphoresis; and
(iii) altered mental status—agitation, anxiety, hypomania and confusion.

While there are some similarities with neuroleptic malignant syndrome, the time course, neuromuscular features and autonomic features are usually quite distinct. Malignant hyperthermia is also a distinctly different condition, but some of the peripheral and autonomic features that occur with severe serotonin toxicity more closely resemble MH. This raises the possibility that peripheral 5-HT2 receptors are involved in both conditions.

Recent studies implicate 5-HT2a receptors in the pathophysiology of serotonin toxicity, not the 5-HT1a receptor which was initially thought to be involved. These studies have used an animal model of serotonin toxicity where rats were administered clorgyline, a monoamine oxidase inhibitor (MAOI), and 5-hydroxy-L-tryptophan (5-HTP). In the control group, the temperature increased to more than 40°C, and the rats exhibited behavioural changes including tremor, and died within 75 min. Animals pretreated with the potent 5-HT2a antagonist, ritanserin, and the atypical antipsychotic risperidone which has strong 5-HT2a blocking action, had no rise in temperature, no behavioural changes and all survived. Animals pretreated with high dose chlorpromazine and cyproheptadine, both 5-HT2 antagonists, all survived and had a suppression of the temperature rise. However, pretreatment with propranolol, 5-HT1a receptor antagonist (as well as a beta blocker), dantrolene and haloperidol did not prevent death in any of the animals, although the first two drugs did suppress the rise in temperature to some extent.

The lack of effect of dantrolene in these two studies suggests that peripheral muscle effects play a lesser role in serotonin toxicity compared to MH, where dantrolene is more effective. The studies also do not support the use of propranolol or haloperidol in the treatment of serotonin toxicity. Clinical studies do, however, support the use of 5-HT1a antagonists, such as cyproheptadine, in the treatment of serotonin toxicity.

The animal studies described by Wappler and colleagues also raise the possibility that peripheral 5-HT2 receptors may be involved in serotonin toxicity. In our experience, the main features of mild to moderate serotonin toxicity are hyperreflexia, clonus, tremor and autonomic features, with rarely any mental state changes. These neuromuscular features are similar to those described in the animal studies quoted by Wappler and colleagues, which were elegantly demonstrated to be due to peripheral 5-HT2 receptor effects. Thus, neuromuscular features are an intrinsic part of serotonin toxicity, although whether this is mediated only via central 5-HT2a receptors or peripheral 5-HT2 receptors is unclear.

In severe serotonin toxicity, which occurs almost exclusively when MAOIs (including reversible inhibitors of monoamine oxidase) or serotonin-releasing agents (e.g. MDMA or ecstasy) are combined with a selective serotonin reuptake inhibitor (SSRI), the condition is even more like MH with severe hyperpyrexia, rigidity and hypercapnia, requiring paralysis and sedation for effective management. Rhabdomyolysis and increased creatine kinase can also occur. Peripheral 5-HT2a receptors in skeletal muscle may be involved in these severe cases, resulting in a picture similar to MH.

Serotonin toxicity is becoming increasingly common in many situations in medicine. It commonly occurs in overdoses of serotonergic agents, and drug interactions continue to be a problem. This can be a problem in perioperative patients, where a number of analgesics can induce serotonin toxicity in patients already taking SSRIs. The most important is pethidine, which is well reported as causing serotonin toxicity in patients on SSRIs. Tramadol may also be a problem, particularly in patients requiring longer term pain management. Thus, in the postoperative period, there is the possibility of both serotonin toxicity and MH occurring. Careful clinical assessment is needed to distinguish between these possibilities and allow appropriate treatment to be given.

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Editor—We wish to thank Isbister and Whyte for their interest in our review and their contribution to this debate. The main problem in interpreting the results from animal studies using the established MH pig model is whether MH-like episodes, following administration of 5-HT2A receptor agonists, are ‘true’ MH or are due to other mechanisms like the serotonin syndrome.
Three underlying pathways might be responsible for the MH-like signs and symptoms after administration of 5-HT$_{2A}$ agonists in conscious pigs. First, substance-specific direct effects at peripheral sites (i.e., an activation of the skeletal muscle cell via 5-HT$_{2A}$ receptors resulting in a MH crisis) could be responsible for the clinical presentation. This hypothesis has been proved using the in vitro contracture test model. The in vitro results demonstrated that the 5-HT$_{2A}$ receptor agonist, DOI, induced contractures in skeletal muscle specimens from both MH susceptible (MHS) and normal (MHN) patients, indicating a direct serotonegenic effect on skeletal muscles. Furthermore, the onset of contracture development was significantly faster and more intense in MHS compared to MHN sample. Pretreatment with DOI led to an accelerated and increased contracture development following halothane administration in specimens from MHS but not MHN patients. The in vitro effects of 5-HT$_{2A}$ receptor agonists on muscle specimens from MHS patients could be reduced or completely counteracted by dantrolene, as well as with the 5-HT$_{3}$ receptor antagonist, ritanserin. In subsequent experiments, ritanserin was shown to inhibit halothane-induced contractures in MHS muscles in a concentration-dependent manner. However, compared to the established triggering agents, halothane, ryanodine and 4-chloro-m-cresol, the contracture development in MHS preparations after DOI was prolonged and of only moderate intensity.

Second, a porcine stress syndrome might be induced after administration of 5-HT$_{2A}$ agonists in susceptible pigs. This syndrome describes MH susceptible animals which are adversely affected by stress induced by isolation, trucking, weaning, fighting, coitus and crowding. Clinical signs and symptoms are exactly comparable with a MH crisis induced by anaesthetic agents, and therefore the porcine stress syndrome is interpreted as a stress-induced MH. But hallucinogen-induced psychosis in conscious pigs might lead to a central stress situation, which secondarily results in the MH-typical pathomechanisms in skeletal muscles.

The third theory focuses on a 5-HT$_{2A}$ specific central agonism, which was recently described as serotonin syndrome. It is caused by excessive 5-HT availability in the central nervous system at the 5-HT$_{1A}$ receptor, distinct from possible interactions with 5-HT$_{2}$ and dopamine receptors. This syndrome can be initiated by serotomimetic medication in combination with 5-HT, or by an increase in dosage of serotomimetic drugs, leading to excessive elevation of intrasynaptic 5-HT levels. Clinical signs and symptoms include rapid onset of cognitive-behavioural alterations (agitation, confusion and disorientation), neuromuscular abnormalities (rigidity, tremor and myclonus), and dysfunction of the autonomic nervous system (fever, tachypnoea and altered blood pressure). Although the clinical presentations are similar, there is a differing severity between classic MH and serotonin syndrome.

Although the results from recent studies are interesting, a clear differentiation between MH and the serotonin syndrome cannot be drawn from these experiments. First, the authors used rats in their model and a MH disposition has not been demonstrated in these animals. Second, Löschner and colleagues investigated conscious pigs in their studies. This study design enabled the induction of MH by psychomimetics but, as mentioned above, this might be due to porcine stress syndrome.

It would, therefore, be worthwhile to investigate the in vivo effects of 5-HT$_{2A}$ receptor agonists on anaesthetized MHS and MHN swine. In such an experimental setting, a hallucinogen-induced stress reaction would be excluded and a differentiation between MH and serotonin syndrome would be possible. Furthermore, we agree with the suggestions made by Isbister and Whyte that beside experimental settings, careful clinical assessment of mechanisms leading to a serotonin syndrome and/or MH are needed in order to allow appropriate treatment in such cases.

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Anaphylaxis during anaesthesia

Editor—We read with interest the article by Laxenaire and colleagues concerning the French survey of anaphylaxis during anaesthesia. In this retrospective study, most of the reactions were attributed to neuromuscular blocking drugs or latex, and the authors claim that succinylcholine and rocuronium are responsible for more accidents than expected. There are several reasons to be cautious about the interpretation of this data.

(i) The present survey, like others, is based on case reports. According to guidelines for grading the quality of evidence, case reports, even numerous (n=477 in the present survey), have the lowest level of scientific relevance (grade V). In epidemiology, an association between an event (i.e. anaphylaxis) and a battery of tests (i.e. skin and blood tests) is demonstrated through case–control studies. Thus it is necessary to include a control group made up of patients exposed to the products incriminated but who did not develop any anaphylactic reaction and who also underwent blood and skin tests. The authors of the present article do not mention any data on the specificity of these tests.

(ii) To determine the incidence of an event, one requires a numerator and a denominator. The denominator (i.e. the number of patients exposed to muscle relaxants during anaesthesia in France) can be estimated from a 1996 survey of anaesthesia in that country. According to that study, five million patients received muscle relaxants during a 2-yr period. The value of the numerator is more difficult to obtain. Only patients having clinical features of anaphylaxis confirmed by true positive tests should be counted. However, the authors of this study do not provide any information about the number of true and false positives. Assuming that all cases reported are true positives, the incidence can be estimated to be 336 per 5 000 000 patients exposed to muscle relaxants (approximately 1:15 000), or 1:312 000 when taking account of only severe, grade IV (4.9%) reactions.
(iii) Ninety-eight patients were suspected of developing an anaphylactic reaction to rocuronium, but only 77 skin tests were performed. Six of these tests were done using a 10^−3 dilution, which can yield non-specific responses according to the results of Levy and colleagues. Thus one can assume that 10% of patients receiving rocuronium and developing clinical signs of an anaphylactic reaction had false positive skin tests, suggesting that the incidence of a rocuronium-induced anaphylactic reaction is overestimated in the present study.

(iv) The clinical manifestations of an anaphylactic reaction (cutaneous signs, hypotension, tachycardia, and/or bronchospasm) are non-specific, so reporting might be modulated by the clinician’s perceived likelihood that a drug might produce such reactions. Thus data on the sensitivity and specificity of the tests are required.

(v) To determine a relative risk of anaphylaxis based on estimated sales of muscle relaxants and to apply a statistical analysis to the results is very hazardous at best. Some patients receive more than one vial, muscle relaxants are also used outside the operating room (e.g. intensive care unit, emergency unit), some vials are not used (e.g. broken, lost, expired), and the contents of multidose vials might be given to different patients. This kind of calculation might lead to completely erroneous numbers. For example, Rose and colleagues conclude that rocuronium is not associated with an increased risk anaphylaxis, contrary to what is suggested by Laxenaire and colleagues.

(vi) For this type of investigation, it is essential to distinguish between the individual and the population. For a patient who has had a positive reaction to a certain agent, it is prudent to avoid the drug in a future anaesthetic. However, even if the tests are positive, this does not constitute proof that the suspected drug is responsible for the observed symptoms, especially if they are not specific. In a given population, a high incidence of a positive test concerning a drug does not mean that the agent will trigger symptoms in these patients.

(vii) Paradoxically, atracurium and mivacurium, which are known to produce dose-dependent histamine release, were not incriminated often. As the manifestations of anaphylactoid and true anaphylactic reactions are similar, it is possible that cases involving these agents were under-reported, as the symptoms were likely to be interpreted as an expected side-effect.

In conclusion, there is no evidence to support the belief that anaphylactic reactions with succinylcholine and rocuronium are more frequent in France than in other countries, and these events are very rare. Moreover, in the absence of a personal history, it would be ill advised to choose one muscle relaxant over another or to avoid muscle relaxants altogether solely on the basis of their alleged allergic potential.

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1 Laxenaire MC, Mertes PM. Anaphylaxis during anaesthesia. Results of a two-year survey in France. Br J Anaesth 2001; 87: 549–58

Editor—Thank you for the opportunity to respond to the remarks of Plaud and colleagues concerning our article.

Our study concerns a collection of cases of anaphylaxis occurring during anaesthesia, recorded consecutively over a 2-yr period by the GERAP, a nation-wide network of 38 French allergo-anaesthesia outpatient clinics. As in many countries, these data are based on a system of reporting by practitioners who observed anaphylactoid reactions during anaesthesia and then referred the patients for allergy investigations. In the case of rare, random, independent adverse reactions, such as immune-mediated anaphylactic reactions, epidemiological surveys do not usually involve a control group. However, the sample size of such observational studies is of crucial importance. Pharmacovigilance reports, as in this study, should not be considered as a simple collection of individually published case reports with the lowest level of scientific evidence (grade V). These pharmacovigilance reports are more likely to be considered as large series of well-defined patients undergoing standardized investigations. Such series, which have not been defined in the classification established by Cook, are considered as studies of grade III level of scientific evidence by the French Society of Anaesthesiology.

The sensitivity of skin tests to neuromuscular blocking agents is estimated at 94%. Their specificity must be considered relative to the dilutions used and has been evaluated at 97%. The sensitivity and specificity of specific IgE assay against muscle relaxants have been shown to vary from 88 to 97% and 97 to 100%, respectively.

However, the positive predictive value of these tests will be very different in groups with a highly different prevalence of anaphylaxis. It has been estimated at 71% for a specific IgE assay against muscle relaxants in a selected population of patients who have experienced an anaphylactoid reaction during anaesthesia, but will only be 0.11% in control subjects. Similarly, the positive predictive value of skin tests in normal subjects could be estimated at 0.3%. For these reasons, the use of such tests for muscle relaxant sensitivity screening, prior to surgery, is not advisable.

As stated by Plaud and colleagues, the incidence of anaphylaxis remains difficult to determine. Among the many potential problems of the surveillance of adverse reactions, they emphasize the necessity to avoid false positives. However, one should keep in mind that one of the major problems encountered is under-reporting of adverse drug reactions, which has been evaluated at 40% in France. For these reasons, we did not perform any estimation of the incidence of anaphylaxis in our report. Moreover, to estimate the incidence of severe anaphylaxis, they take into account only grade IV reactions (cardiac arrest, 4.9% of our cases). However, grade III reactions (67.1% of our cases), must also be considered.

Concerning the 98 patients allergic to rocuronium, skin tests were found to be positive in all subjects; prick tests in 21 patients, and intradermal tests in 77 patients. A prick test, carried out with undiluted drug is considered to correspond with an intradermal test using a 10^−3 dilution. Notwithstanding the results reported by Levy and colleagues in healthy volunteers, in our six cases where positivity of the intradermal test was observed at a 10^−1
dilution, specific IgE assay against rocuronium was positive. These results confirm the responsibility of this agent for the adverse reaction observed.

As mentioned in our report, we agree that the number of patients exposed to the various neuromuscular blocking agents was based on the estimation of the market share of these agents and should therefore be considered with circumspection. Nevertheless, as specified in the method section, this estimation concerns the consumption of each neuromuscular blocking agent effectively used during anaesthesia and not the vials used in intensive care units or in emergency settings (data obtained from Le Panel Hospitalier, MAPI, Lyon, Edition Domaine Médical, 1998). In addition, a correction factor, which took into account the agent used during a standard anaesthetic procedure, was applied. This correction factor was established in accordance with Glaxo Wellcome and Organon Teknika for the products they sold.

Finally, the number of vials not used (e.g. broken, lost, expired) will not be different for the various muscle relaxants, and the use of multidose vials for different patients is not authorized in France.

Plaud and colleagues stated that there is no evidence to support the belief that anaphylactic reactions to suxamethonium and rocuronium are more frequent in France than in other countries, and that these events are very rare. We completely agree with this statement. Indeed, in previous reports from our group and others the estimated incidence of anaphylaxis was 1 in 10 000 to 1 in 20 000 in Australia in 1993,12 and 1 in 13 000 in France in 1996.9 In the series of 24 cases recently published by Rose and Fisher13 from Australia, the incidence of rocuronium allergy increased in parallel with national sales. However, one third of the cases of anaphylaxis to rocuronium (n=10), which fulfilled all the criteria, were not included in the estimation of this incidence, because they were investigated in another centre. Thus, the Australian report concerns results from a single centre (Sidney), whereas our data are obtained from a nationwide network of allergo-anaesthesia outpatient clinics. In addition, based on data from intradermal testing, as in our report, some unexplained differences between drugs were observed by Rose and Fisher. These unexpected differences, led these authors to consider rocuronium as a neuromuscular blocking agent at intermediate risk of sensitization, when compared with low-risk agents (e.g. pancuronium, vecuronium) and high-risk agents (e.g. succinylcholine, alcuronium).

We agree that a positive skin test for a drug does not mean that the agent will trigger symptoms in a patient. The only way to definitely establish the responsibility of the suspected drug will be to reintroduce it, but this is not ethically possible.

Finally, Plaud and colleagues raise the problem of possible under-reporting or bias-reporting of adverse reactions, especially concerning known histamine-releasing drugs. However, one should note that patients are referred to our centres by anaesthetists after an anaphylactoid reaction, independently of the anaesthetic protocol used and/or the severity of the reaction.

Above all, they want to know the mechanism of the reaction, and in the case of anaphylaxis, the incriminated agent (neuromuscular blocking agent, latex, antibiotics, colloids etc). This is illustrated by the high proportion of mild immune-mediated adverse reactions to atracurium reported in our study, as shown in Table 1.

Surveillance of adverse reactions represents a methodological problem and a statistical challenge. For these reasons, we never recommend one muscle relaxant over another, or avoiding muscle relaxants on the basis of their allergic potential. On the contrary, we advocate the need for post-marketing risk surveillance, investigation of adverse reactions, and training of anaesthetists in the diagnosis and treatment of potentially life-threatening anaphylactic reactions.

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Table 1 Clinical severity of anaphylaxis to neuromuscular blocking agents collected in France in 1997–8 (n=333)

<table>
<thead>
<tr>
<th>Neuromuscular blocking agents</th>
<th>Number of patients</th>
<th>Clinical grade of severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atracurium</td>
<td>71</td>
<td>I</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>98</td>
<td>I</td>
</tr>
<tr>
<td>Succinylcholine</td>
<td>78</td>
<td>I</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>59</td>
<td>I</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>18</td>
<td>I</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>9</td>
<td>I</td>
</tr>
</tbody>
</table>

Receptive site topology of the acetylcholine receptor

Editor—I read with interest the review article by Lee, which represents an important addition to the field of clinical neuromuscular pharmacology. I noted, however, that the acetylcholine receptor structure presented by Lee (both in Figure 2 and
in the text) represents the fetal form (containing a γ rather than an ε subunit).\textsuperscript{2,3} We now know that the nicotinic acetylcholine receptor (nAChR) of adult mammalian skeletal muscle is a pentameric complex of 2 α subunits in association with a single β, δ, and ε subunit. We also know that the fetal type nAChRs are resistant to nondepolarizing neuromuscular blockers are more sensitive to succinylcholine.\textsuperscript{4} In the future, there may be drugs that take advantage of the differing pharmacological sensitivities of the mature and immature receptors.

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1 Lee C. Structure, conformation, and action of neuromuscular blocking drugs. Br J Anaesth 2001; 87: 755–69

Editor—Indeed, the adult form of AchR has the αε instead of the αγ receptive site. However, the differences between the adult and fetal receptors are not known to qualitatively affect the structure activity relationships and the conformation activity relationships of the neuromuscular blocking agents discussed. For simplicity, I therefore used the generic nomenclature in the review, except that ‘(or ε)’ was inserted when αγβδ was first mentioned. The dimensions of the AchR were also generic. Different preference of neuromuscular blocking agents for either the αγ (or αε) or the αδ receptive site\textsuperscript{1} was also left out.

Being mindful of the need for greater precision, I have updated the topology of the receptive sites and fitted molecules of Ach into the picture with what appears to be the correct dimensions and orientation, as follows:

If 20 Å separates the receptive sites and each of the two Ach molecules that open the ionic channel occupies 6 Å with its methionum head, 8 Å remains in the lumen for the influx of the cations. This is just enough to prevent a bottleneck at the level of the receptive sites, considering that the trans–membrane tube portion of the channel also measures about 8 Å.\textsuperscript{2} Relative to the depolarizing cations and the channel, Ach is a large molecule.

Each subunit has a positive and a negative face, arranged so that the positive face of each subunit faces the negative face of its neighbour (Fig. 1). It is the negative face of the γ (or ε) subunit that faces the α subunit and attracts the positively charged methonium head of Ach to their interface.\textsuperscript{5} For Ach to be bound to the α subunit, and if its methionum head fits the interface, its acetyl portion has to point to the α subunit, not the other way around. Looking from the synaptic cleft down the receptor channel, this means that Ach sits clockwise from the carbonyl ω to the quaternary N. This is because the subunits are clockwise from the α to the γ (or ε).\textsuperscript{5}

Scientists may one day taylor the relaxant molecule to fit the specific receptive site; however, specific targeting of neuromuscular blocking agents to the adult or fetal type AchR seems a remote challenge.

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The alveolar lining

Editor—In their recent editorial, Dorrington and Young\textsuperscript{1} are to be commended for daring to question the culturally embedded concept that there is a continuous liquid (bubble) lining to the normal alveolus—a sacred cow of respiriologists and neonatologists long challenged by this ‘dissident’.\textsuperscript{2,3} Those authors together with Bangham\textsuperscript{4} in his letter, and even the original proponents\textsuperscript{5} of the ‘bubble’ model all point out that, for a series of interconnected bubbles to be stable, it is vital that there be no surface communication between them. Otherwise, surfactant monolayers could spread and equalize surface tension. Even if the surfaces are not connected via terminal bronchioles, they are surely connected via the abundant pores of Kohn which are large enough to allow direct passage of a macrophage from an alveolus to its immediate neighbours.\textsuperscript{5} In response to such criticisms, ‘the believers’\textsuperscript{6} have frozen lungs and claim to have demonstrated a liquid lining, but only after artefactually exsanguinating those lungs, thus removing micro-concavities caused by red cells bulging their way through capillaries underlying the very thin alveolar wall. Classical studies of non-exsanguinated frozen lungs display convex areas of alveolar epithelium apparently free of fluid, as reviewed.\textsuperscript{1}

Dorrington and Young must be challenged, however, when they boldly state that there are ‘two fundamental errors’ in my review.\textsuperscript{7} First, my discussion of the role of surfactant in alveolar fluid balance is hardly a ‘fundamental error’ if the normal homeostatic mechanisms are not mentioned until the next paragraph, when ion-
channel pumps are described—but admittedly described as ‘water pumps’ rather than ‘aquaporins’. However, this is an interesting point which they raise because, when adsorbed, surface-active phospholipid (SAPL) can impart semi-permeability which is vital before ion gradients can be maintained long enough to shift water.

Second, they are correct in stating that, to physicists, a non-spherical continuous liquid lining is inconceivable, but the areas over which asperities on the epithelial surface would breach that liquid lining would be negligible unless there were some degree of hydrophobicity of the alveolar wall. A hydrophilic lining would cause a meniscus of fluid to encroach until only a point or ridge of tissue were exposed to air, just as water rises up a hydrophilic glass plate to a height of many alveolar diameters, even when immersed vertically. It is a moot point as to how much of the alveolar surface needs to be fluid-free before the instability of interconnected bubbles no longer applies. An interesting example of the principle of dewatering surfaces by bound (adsorbed) surfactant, occurs on the ocular surface where adsorbed SAPL ruptures the tear film unless we blink every 20 s or so. This time-dependent aspect of wetting/dewetting must cast doubt upon our use of static models, especially when ‘bulging’ caused by red cells means that areas on the alveolar surface are ‘oil-canning’ at frequencies approaching that of the electric mains, viz. 50 Hz. At the microscopic level, the system is highly dynamic.

Dorrington and Young have taken a major step in expressing so clearly the shortcomings of the concept of a continuous liquid lining to the alveolus which I challenged 20 yr ago.7 Are they going to address the next sacred cow that surfactant3 occurs on the ocular surface where adsorbed SAPL peeled from a glass plate to a height of many alveolar diameters, even when immersed vertically. It is a moot point as to how much of the alveolar surface needs to be fluid-free before the instability of interconnected bubbles no longer applies. An interesting example of the principle of dewatering surfaces by bound (adsorbed) surfactant occurs on the ocular surface where adsorbed SAPL ruptures the tear film unless we blink every 20 s or so.9 This time-dependent aspect of wetting/dewetting must cast doubt upon our use of static models, especially when ‘bulging’ caused by red cells means that areas on the alveolar surface are ‘oil-canning’ at frequencies approaching that of the electric mains, viz. 50 Hz.10 At the microscopic level, the system is highly dynamic.

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2 Hills BA. What is the true role of surfactant in the lung? Thorax 1981; 36: 1–4
4 Bangham AD. Geodesic plates to facilitate the extension of alveolar liquid/air interfaces. Br J Anaesth 2001; 87: 519–20
7 Hills BA. An alternative view of the roles of surfactant and the alveolar model. J Appl Physiol 1999; 87: 1567–83

Editor—We thank Professor Hills for his constructive comments about our editorial.1 He calls us to account for our claim that he has made ‘two fundamental errors’ in his otherwise challenging critique of the established dogma that the pulmonary alveoli are lined in health with a continuous layer of liquid.

One of the points we made in our editorial was that Hills claims that passive forces alone account for the absorption of liquid from the corners of alveoli. This was the view he propounded using a diagram in his review published in this journal in 1990,2 and elsewhere, where it was hypothesized that liquid is induced by the hydrophobicity of the alveolar epithelium to sit in globules that present a convex surface to gas in the alveoli. The hydrostatic pressure within these globules would be higher than atmospheric pressure, to balance forces at the liquid–gas interface, and would act to encourage liquid to move from the globule into the pulmonary interstitium. A virtually identical diagram is used in the review by Hills to which we referred, published in 1999.3 In the legend to this diagram (Fig. 8), Hills writes that the surface tension in globules will ‘assist physiological water pumps’ in resolving oedema. The nearby text qualifies the term ‘physiological water pumps’ with the parenthetic expression ‘protein-oncotic and ion channel’.

We concede that these terms can be taken to refer to the process of active sodium transport from the alveoli, as elucidated by Basset and colleagues,4 and Mathay and colleagues.5 However, the terminology used by Hills, in both his review7 and his recent correspondence to which this letter is a reply, is unconventional. The term ‘pump’ is usually reserved in membrane physiology to refer to primary active transporters that utilize adenosine triphosphate (ATP) to move a molecule across a cell membrane against its electrochemical gradient. No pump, in this sense, has yet been found for water. The term ‘ion channel’ is usually reserved for a membrane channel that is to some extent selectively permeable to an ion that moves through the channel down its electrochemical gradient. The term ‘aquaporin’ designates a transmembrane channel that is at least partially selective for water. The component of water uptake from the alveoli associated with the utilization of ATP has been shown to require the sodium-potassium pump on the basolateral membrane of epithelial cells, sodium channels on the apical membrane of the cell, and, in some species at least, a sodium-glucose co-transporter, also on the apical membrane.6,7 The role of aquaporins in this process remains unclear.5

The other point made in our editorial that Hills appears to challenge is our claim that he relies upon the concept of a hydrophobic alveolar surface to account for why small amounts of liquid collect into pools or globules on the alveolar surface, rather than forming a thin film wetting the whole surface. Our claim appears to be confirmed by a statement in the same legend referred to above (reference 2, Fig. 8): ‘surfactant absorbs to . . . tissue surfaces, rendering tissue less wettable to explain the apparently fluid-free areas’. We set out to show in our editorial that, even if the alveolar surface were highly hydrophilic, liquid on the alveolar surface would cease to form a continuous coating of the surface when the volume of liquid in the alveolus was no longer sufficient to permit immersion of the whole alveolar surface below a spherical gas-liquid surface. The micrographs of Bachofen and colleagues illustrate this phenomenon.8 We believe that this statement addresses Hills’ comment in his letter that ‘it is a moot point as to how much of the alveolar surface needs to be fluid-free before the instability of interconnected bubbles no longer applies’.

We have described the limiting case of the minimum volume of liquid that could be sustained as a continuous lining by a highly hydrophilic surface. It appears likely that a less hydrophilic surface would lead to fragmentation of alveolar liquid at a larger volume of liquid, and that a highly hydrophobic surface might be able to maintain a substantial proportion of its area free of liquid,
even when a large volume of liquid is in the alveolus. The extent to which the alveolar surface may be regarded as either hydrophilic or hydrophobic appears to us to be unknown.

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J. D. Young
Oxford
UK

3 Hills BA. An alternative view of the role(s) of surfactant and the alveolar model. J Appl Physiol 1999; 87: 1567–83
5 Mathay, MA, Flori HR, Conner ER, Ware LB. Alveolar epithelial fluid transport: basic mechanisms and clinical relevance. Proc Assoc Am Physicians 1998; 110: 496–505

Transtracheal high frequency jet ventilation for endolaryngeal surgery

Editor—Bourgain and colleagues1 are to be congratulated on their excellent study of transtracheal high frequency jet ventilation for endolaryngeal surgery. The work helps to dispel the myths that the technique is difficult and dangerous. As with previous smaller studies, it is easily performed and taught, and provided it is carried out with care, it is also safe. The authors do not mention the extent to which the alveolar surface may be regarded as either hydrophilic or hydrophobic appears to us to be unknown.

K. L. Dorrington
J. D. Young
Oxford
UK

2 Russell WC, Jones GV, Maguire AM. Cricothyroidotomy and transtracheal high-frequency jet ventilation for elective laryngeal surgery. An audit of 90 cases. Anaesth Intens Care 2000; 28: 62–7

Avoiding airway obstruction

Editor—I read with interest the case report by Kurian and colleagues1 about an obstructed catheter mount. As stated, this has occurred previously.2

I disagree with their statement: ‘The equipment check even if it had been performed with the offending item in circuit would not have identified the obstruction’. The purpose of performing an equipment check is to be 100% certain that one can ventilate the patient’s lungs with 100% oxygen by a face mask. To do this, the breathing system being used must be checked in its entirety before the patient is anaesthetized. In our institution, the catheter mount, HME and face mask are connected to the breathing system from the start, and the patency of the system is checked by placing the face mask against one’s hand, creating an airtight seal, while squeezing the bag (with the oxygen flowmeter turned on). This manoeuvre, together with the use of an oxygen analyser, ensures that 100% oxygen can be administered under positive pressure via the mask.

When an LMA1 tubing is connected to the system, no other new items are inserted into the breathing system, thus simplifying the diagnostic pathway described by Kurian and colleagues3, should an obstruction occur. I suggest that, had they followed this procedure during their preoperative check, the incident could have been avoided.

D. Mayne
Gateshead
UK

2 Thomas R, Finch S. A blocked catheter mount. Anaesthesia 2001; 56: 88

Editor—Thank you for the opportunity to respond to Dr Mayne’s letter. The other similar case report occurred almost on the same day as ours, and one of the reasons for submission of our letter

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was the continued occurrence of similar incidents with disastrous outcomes.

We still stand by our statement to which Dr Mayne has taken objection. The manoeuvre which he has described, otherwise known as the ‘pressure leak test’, is mainly aimed at looking for leaks in the system and still would have missed a block in the catheter mount. The bag will inflate with the pressure-limiting valve turned shut, and deflate with opening of the valve, whether the patient end is occluded or not. This hypothesis was tested on 20 experienced anaesthetists in a single blinded fashion, and none could detect the obstruction, except those who routinely felt for the gas flow.

We would not be as bold as Dr Mayne and expect 100% certainly from any equipment check. This kind of thought process, we believe, will hinder early identification and correction of potentially life-threatening equipment malfunction.

J. Kurian
M. Renvick
Carshalton, Surrey
UK

Delayed diagnosis of cardiac tamponade

Editor—Dunsire and colleagues’ paper on delayed diagnosis of cardiac tamponade makes interesting reading, and deserves further comment.

The decision to proceed to emergency laparotomy in the first instance seems sensible, given the lack of imaging facilities at the receiving hospital. In the presence of congested hepatic veins and an engorged inferior vena cava, cardiac tamponade should have been seriously considered at that point. Furthermore, the lack of free blood in the abdomen should have alerted the surgeon to other causes of hypotension. The simple procedure of creating a subxiphoid pericardial window would have excluded a tamponade quickly and definitively, and is straightforward to perform at laparotomy.

The finding of blood on opening the pericardium should prompt extension of the incision into a median sternotomy, to allow inspection of the heart and repair of damaged structures. If the surgeon was not happy to proceed to sternotomy, the placement of a pericardial drain would likely have had a similar outcome to that described. Given the lack of a definitive diagnosis at laparotomy, the decision to return the patient to a non-intensive care setting, despite continuing haemodynamic instability, could also be called into question.

We agree that the lack of a chest radiograph hindered initial assessment. This is contrary to established advanced trauma life support principles. The finding of a fluid level in the hemithorax on an erect chest radiograph is diagnostic of haemothorax in the context of trauma, and should lead to prompt insertion of a chest drain. It is well known that the chest radiograph can be normal in acute cardiac tamponade, but the identification of a haemothorax before laparotomy would heighten suspicions of significant intrathoracic injury on discovering the lack of intra-abdominal haemorrhage.

Catheter drainage of the pericardium has been reported in the context of penetrating trauma, and would re-emphasize the need for very close supervision by specialist cardiothoracic surgeons with immediate access to the operating room if patients are to be treated in this way.

We would argue that pigtail catheter drainage is the initial treatment of choice for pericardial effusions and cardiac tamponade in the non-traumatic scenario; trauma patients who are suspected of cardiac tamponade require urgent evaluation by echocardiography (transthoracic or transoesophageal), or by creation of a subxiphoid pericardial window in the operating room.

We agree with Dunsire’s conclusion that cardiac tamponade must be high on the index of suspicion if the diagnosis is not to be delayed or missed.

C. A. Graham
G. M. Wares
Glasgow
UK

Editor—I thank Graham and Wares for their interest in my paper. I agree with their opening comments that a laparotomy was indicated given the lack of imaging. A lack of free blood in the peritoneal cavity combined with engorged hepatic veins and inferior vena cava should have alerted the surgeon to the possibility of cardiac tamponade. I would contend that the anaesthetist also should have been alert to other causes of hypotension. Had a central line been inserted at this stage, the finding of a high central venous pressure combined with hypotension would have indicated a cardiac problem and prompted further exploration. Creation of a subxiphoid pericardial window would have been appropriate, had the diagnosis of cardiac tamponade been considered at the time of surgery. After negative laparotomy, with ongoing haemodynamic instability, I agree that it would also have been appropriate to transfer the patient to an intensive care unit with imaging facilities.

The lack of a chest radiograph is contrary to established advanced trauma life support principles, and both surgeon and anaesthetist should have insisted on one being performed preoperatively. Had one been performed and a haemothorax noted, this would have indicated potentially serious intrathoracic injuries. However, given the mechanism of injury, lack of other imaging, and the clinical picture, there was still a high risk of serious intra-abdominal injury. The decision to proceed to laparotomy would have been correct, even in the presence of a documented haemothorax.

I note the comments concerning catheter drainage of the pericardium in penetrating trauma, and agree that if it is to be managed conservatively, cardiac surgeons and operating theatre space must be readily available. This is not standard treatment, as the vast majority of penetrating cardiac injuries require surgical intervention, whereas there is literature to support echocardiography and catheter drainage of pericardial tamponade in the non-traumatic scenario.

M. Dunsire
Bromley
UK

Unnecessary Caesarean section due to silent CTG

Editor—We read with interest the case report by Immer-Bansi and colleagues, describing an unnecessary emergency Caesarean section following an emergency thrombectomy. The need for Caesarean section arose due to loss of beat-to-beat variability on the cardiotocograph (CTG) whilst the 30-week primigravida was under general anaesthesia. We commend the authors on instituting continuous fetal monitoring during surgery. Their conclusion that anaesthesia alone is valid. But, the same CTG findings are seen during fetal sleep.2

There is no mention of whether left lateral tilt was employed during thrombectomy in this patient. We accept that there was no apparent aortocaval compression; and covert aortocaval compression is unlikely during general anaesthesia because of attenuation of baroreceptor reflexes. However, left lateral tilt of 15° has been recommended as a means of reducing aortocaval compression in women undergoing Caesarean section,3 and its use is commonly accepted for women undergoing non-obstetric surgery in the third trimester.

Despite this, the benefits of left lateral tilt for Caesarean section have been disputed in a randomized controlled trial4 where umbilical artery Po2 was significantly lower in the tilted group compared to the supine group. We are interested in whether the authors routinely use left lateral tilt when anaesthetizing women in their third trimester.

H. Hartley
J. Stone
Guildford
UK

Intrathecal ropivacaine or bupivacaine with fentanyl for labour

Editor—Hughes and colleagues1 have presented an interesting study comparing intrathecal ropivacaine or bupivacaine with fentanyl for labour. To our knowledge, this is the first study to have compared intrathecal ropivacaine/fentanyl with the standard bupivacaine/fentanyl mixture, which is the most commonly used combination for the intrathecal component of a combined spinal-epidural (CSE) in patients in labour in the UK.

We would suggest that the first step in assessing the value of ropivacaine as an intrathecal drug would be to assess its relative potency in comparison with bupivacaine. Previous work has demonstrated the lower potency of ropivacaine in the epidural space, and this might also be expected to apply when the drugs are administered intrathecally.2 3 It is, therefore, no surprise to find less motor block with ropivacaine than bupivacaine in this study. Interestingly, severe motor block, the main concern for safe maternal ambulation, was not found in either group.

It is also not a surprise to find no difference in analgesic efficacy between the two mixtures, despite the lower potency of ropivacaine. In early labour, fentanyl alone can produce near complete analgesia,2 so both mixtures probably exceed the minimum effective dose. Indeed, our view is that a CSE is most strongly indicated for the distressed woman in advanced labour. Unfortunately, this study does not tell us how the two mixtures will perform in this more relevant clinical situation.

Given these criticisms, we are grateful to Hughes and colleagues for this first assessment of ropivacaine in this role. An epidural study has shown a longer duration of action of ropivacaine than bupivacaine in this space.5 If an equipotent dose of intrathecal ropivacaine prolongs the duration of the spinal component of a CSE, this would be a most useful feature of the drug. Perhaps the authors would consider this as their next study.

A. J. Pinder
M. Dressner
Leeds
UK

Editor—Thank you for the opportunity to respond to the letter of Hartley and Stone, and for their interest in our case report. We agree that reduced beat-to-beat variability can also be seen during fetal sleep, and normal variability will return if the fetus is aroused by external stimulation. This was not clearly stated in our case report; however, a wake-up attempt was performed as can be seen in the Figure.

Concerning left lateral tilt, we routinely use a wedge under the right hip from the 20th week until term. This was also employed in the presented case. A left lateral tilt is recommended in the latest textbooks on obstetric anaesthesia although the hard evidence for using this manoeuvre is limited. We are aware of the paper by Matorras and co-workers (their reference 4), but those workers had a very high percentage of Caesarean sections performed under general anaesthesia (86%). More than 80% of our Caesarean sections are performed under regional anaesthesia. Latent aortocaval compression may become manifest during regional anaesthesia because sympathetic compensatory mechanisms will be attenuated or totally blocked.

A. Immer-Bansi
S. Petersen-Felix
Bern
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1 Hughes D, Hill D, Fee JPH. Intrathecal ropivacaine or bupivacaine with fentanyl for labour. Br J Anaesth 2001; 87: 733–7
Editor—Thank you for the opportunity to reply to Pinder and Dresner. They have raised many valuable points for discussion. As they correctly point out, research has shown ropivacaine to be less potent than bupivacaine when administered via the epidural route. This may also apply to intrathecal use, but as ours was the first comparative study in the UK of intrathecal ropivacaine and bupivacaine for labour analgesia, we felt it appropriate to start with a study employing equal doses of both local anaesthetics. If intrathecal ropivacaine is to have any place in clinical practice, it must compare favourably with the current bupivacaine regime used in most units, and this was the basis of our study.

The comments regarding motor blockade and safe ambulation are open to dispute. Women with even moderate motor weakness would, we suggest, be unlikely to mobilize safely unaided. The ability to walk independently and safely is perhaps the end-point we should concentrate on. In this respect, it has now been established that the absence of motor weakness is the major factor determining safe and normal ambulation. In this respect, the women receiving intrathecal ropivacaine were at a distinct advantage.

Intrathecal opioid alone can produce adequate analgesia for early labour. We have published work in this area demonstrating effective analgesia with intrathecal alfentanil. Although CSE analgesia may be particularly advantageous for women in advanced labour, it is difficult ethically and practically, to limit a CSE study such as ours to women in this category. Only with increased use of intrathecal ropivacaine, will sufficient experience be gained to assess performance in this group of women. Of note, a number of women in our study had effective analgesia with intrathecal ropivacaine at cervical dilatation of 5 or 6 cm.

Following on from this study, we have embarked on further research investigating varying doses of intrathecal ropivacaine and bupivacaine, again comparing efficacy, motor block and duration. This will hopefully enable us to address the outstanding issues raised.

D. A. Hughes
D. A. Hill
J. P. H. Fee
Belfast
UK

2 Hughes DA, Hill DA. Intrathecal alfentanil with and without bupivacaine for analgesia in labour. Anaesthesia 2000; 55: 1116–21

Combined epidural and general anaesthesia in a patient with a transplanted heart undergoing upper abdominal surgery

Editor—An early case report described a body surface operation under general anaesthesia in a patient with a transplanted heart. Though epidural anaesthesia was considered inappropriate for that particular operation, hypotension and infection in the central nervous system were cited as potential risk factors mitigating against its use. Sixteen years on, the combined use of general anaesthesia with epidural blockade, particularly in upper abdominal surgery, has become widely accepted as a means of achieving total postoperative pain control with less pulmonary morbidity, and other beneficial features lead to a swifter and smoother return to normal function.

We report a 47-yr-old male patient with a transplanted heart who had an 8 cm cyst in the tail of the pancreas secondary to steroid-induced pancreatitis. Splenectomy and resection of the distal pancreas was the definitive surgical cure but preservation of the spleen was considered essential in an immunocompromized patient; a Roux-en-y-cyst-jejunostomy was the preferred surgical option.

A transplanted heart has its own SA node as a pacemaker, though the recipient’s atrial remnant may still contain its own genetic SA node. This can give rise to two ‘p’ waves on the ECG. There is no normal anatomical continuity between the transplanted heart and the recipient’s autonomic nervous system. As a result, the cardiac component of the fight or flight response is delayed being dependent on direct action on myocardial cells of circulating catecholamines deriving from the adrenal medulla. The pressor response to stimuli (such as laryngoscopy) is delayed. Though the transplanted heart is often described as denervated, it is an inaccurate term because the transplant retains its own electrical conducting system but is devoid of functional autonomic innervation. There is some evidence that slow development of cardiac re-innervation may occur. The autonomic supply to the peripheral vasculature is, of course, preserved. The transplanted heart is unable to participate in the baroreceptor reflex and there is no chronotropic response to carotid massage or fluctuations in arterial pressure. There is, therefore, no reflex tachycardia in response to hypovolaemia or hypotension, and the importance of maintaining an adequate circulating preload to maintain stroke volume has been described. Also, it has been asserted that a transplanted heart tolerates hypertension better than hypotension.

Pharmacological responses are altered; drugs acting on the autonomic nervous system do not modulate the transplanted heart. Atropine does not produce a chronotropic effect and it has been suggested that the effect of neostigmine (if used) may not need to be modified with a vagolytic, although this is contentious. The accepted treatment for acute bradycardia in these patients is a direct-acting β1 agonist such as isoprenaline.

The article by Lyons and colleagues lists a number of potential non-cardiac surgical problems to which transplant patients may be prone, such as complications related to the transplant operation itself, complications of immunosuppressive and/or steroid therapy, extension of primary disease (atherosclerosis), and complications associated with anticoagulant therapy, if this is part of long-term therapy. Though subarachnoid anaesthesia has been described in these patients, we decided to use epidural combined with general anaesthesia, titrating local anaesthetic dosage to cardiovascular response in the usual way. Our patient was not on anticoagulant therapy.

The patient’s history included heart transplant 3 yr previously for cardiomyopathy and subsequent chronic renal impairment and hypertension; the renal dysfunction was secondary to long-term immunosuppressive therapy. The main symptoms from the pancreatic cyst were abdominal pain and nausea. Exercise tolerance was one flight of stairs, which would induce breathlessness and fatigue. Resting arterial pressure was 160/90 mm Hg and heart rate 90 min⁻¹, with no signs of heart failure. A routine cardiac biopsy 1 month previously had excluded evidence of graft rejection. Preoperative haemoglobin was 8.9 g dl⁻¹, unchanged from previous testing and low because of chronic renal impairment.

In a sterile manner, we sited a T9/10 epidural catheter under light sedation (midazolam and diamorphine), as well as peripheral venous access and a radial artery cannula for invasive pressure monitoring. Induction of anaesthesia was with propofol, followed by atracurium and tracheal intubation. Anaesthetic maintenance was with sevoflurane in oxygen and nitrous oxide. A left internal jugular catheter was inserted (taking sterile precautions), avoiding the right side which was scarred from multiple previous
procedures including regular cardiac biopsies. Antibiotic cover was with co-amoxiclav.

Before the start of surgery, we injected a loading dose of diamorphine 3 mg through the epidural catheter followed by 2 ml increments of 0.75% bupivacaine to a total of 8 ml. An infusion (8 ml h⁻¹) was then started using 0.1% bupivacaine with increments of 0.75% bupivacaine to a total of 8 ml. One litre each of normal saline and gelofusin were infused as a preload to maintain the CVP at 12–15 mm Hg. Reduction of arterial pressure following the epidural loading dose was corrected with increments of ephedrine (total 20 mg) followed by methoxamine (total 8 mg), to maintain a mean arterial pressure greater than 80 mm Hg. At this point, we decided to infuse norepinephrine continuously at a rate of 5–8 μg kg⁻¹ min⁻¹.

The operation was successful and the patient was discharged from the operating theatre to high dependency care for continued invasive monitoring and epidural infusion over the subsequent 4 days. The norepinephrine infusion was only required for 2 h postoperatively, after which it was discontinued and arterial pressure gradually returned to its former hypertensive level.

In summary, we used an epidural infusion effectively in a patient with a transplanted heart undergoing upper abdominal surgery. The risks of infection from invasive monitoring as well as those associated with extradural anaesthesia on the transplanted heart in an immunocompromised patient were considered and the decision was made to proceed. We agree with Shaw and colleagues, who described a patient who received epidural anaesthesia for postoperative pain control, and implied that the technique was justifiable. The outcome for our patient was favourable.

K. Grimsehl  
D. Levack  
Dundee  
UK

### Correspondence


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### Anaesthesia for cataract surgery

Editor—I would like to make three points on the interesting article by Allman and colleagues. The authors state that peribulbar block is the anaesthetic technique of choice for cataract surgery. They refer to work published in 1996. Maybe peribulbar block was the technique of choice in 1996, but now lens emulsification is more commonly performed under topical anaesthesia. Anaesthetic drop use is sufficient to control the discomfort as phacoemulsification of the lens is not painful. Consequently, it is inappropriate to compare the efficacy of two anaesthetic drugs in such procedures. It would be better to do such a study during posterior segment surgery, which is more painful. In addition, their patients were given alfentanil and midazolam. With this combination of drugs, it is not easy to assess pain.

We try to use purified anaesthetic drugs which do not contain preservatives and which are not extracted from animals. Procaine contains metasulphite which may produce allergic reactions. We would accept replacing the mixture we usually use (lidocaine and bupivacaine), if any new local anaesthetic drug to become available was purified.

In the discussion, the authors reported three cases of optic atrophy after the use of prilocaine with felypressin, and they have now stopped using prilocaine. Unfortunately, the references of these three cases are missing. Felypressin is as effective a vasoconstrictor as epinephrine. We think that these complications are probably due to felypressin and not to prilocaine.

E. Calenda  
Rouen  
France
Editor—Many thanks for the opportunity to comment on Dr Calenda’s letter. Although the use of topical anaesthesia for cataract surgery is certainly increasing, in our institution this still accounts for less than 5% of all cases. The main advantage of peribulbar block remains the degree of akinesia obtained and this (rather than analgesia) was our main outcome measure.

We used articaine with epinephrine (1 in 200 000) as we were initially uncertain if a plain solution would give sufficient duration of block for surgical extraction—it is not recommended for dental use. Metabisulphite is widely used in standard preparations of lidocaine anaesthetic solution. Contact Dermatitis 1989; 20: 124–6.

Widespread use of prilocaine 3% with felypressin for eye surgery was curtailed in January 2000 when the manufacturers (Astra Zeneca) issued a hazard notice describing three cases of optic atrophy. The precise cause remains unclear but prilocaine, the vasoressor and the technique could all be potentially implicated. As prilocaine 3% remains unlicensed for peribulbar use, it would seem imprudent to continue using it following such notification.

K. G. Allman
G. D. Sturrock
I. H. Wilson
Exeter
UK

Use of remifentanil in fast atrial fibrillation

Editor—We read the report by Kurdi and colleagues with interest. We would like to report a case of the use of remifentanil to slow the heart rate with benificial effects for the patient. A 90-yr-old female, weight 54 kg, presented acutely with a painful pelvic mass. She had a past medical history of stable angina and hypothyroidism. Her medications included thyroxine 500μg OD, frusemide 40 mg OD, and glyceryl trinitrate spray 300μg PRN. On examination, she was noted to have atrial fibrillation with a rate of 115 beats min⁻¹. Surgery was delayed to facilitate oral loading with digoxin, and to allow an ultrasound examination which confirmed the presence of a mass arising from the uterus. Following 3 days of digoxin therapy, the patient’s heart rate had fallen to 81 beats min⁻¹. Routine laboratory investigations revealed a full blood count within the normal range; urea and electrolytes: sodium 141 mmol litre⁻¹, potassium 4.6 mmol litre⁻¹, urea 7.4 mmol litre⁻¹, and creatinine 88 μmol litre⁻¹. The decision was made to proceed with surgery.

Following the placement of non-invasive monitoring and preoxygenation, anaesthesia was induced with thiopental 2.5 mg kg⁻¹ and atracurium 0.5 mg kg⁻¹, with oxygen and nitrous oxide in a 50:50 ratio. Immediately, the heart rate rose to 165 beats min⁻¹ with the ECG showing fast atrial fibrillation with concomitant ST-depression. The arterial pressure at this time was 156/84 mm Hg. A remifentanil infusion was commenced at a rate of 0.25 μg kg⁻¹ min⁻¹. The heart rate slowed to 95 beats min⁻¹ with an arterial pressure of 134/74 mm Hg; the ischaemic changes on the ECG also resolved. The heart rate remained stable at this level during subsequent laryngoscopy and intubation of the trachea. The patient received an infusion of magnesium sulphate 3 g intravenously. The remifentanil infusion was continued during the subsequent laparotomy with the rate adjusted according to the cardiovascular parameters. The patient remained in atrial fibrillation during the procedure and subsequent 24 h postoperatively in the HDU; however, there were no further episodes of fast atrial fibrillation.

The management of atrial fibrillation includes the use of drugs which slow A-V conduction, such as digoxin, verapamil and β-blockers. The A-V node is innervated by both the sympathetic and the parasympathetic systems, the latter predominantly derived from the left vagus nerve. Opioids lower the heart rate ablation of sympathetic tone and stimulation of the vagal nerve nucleus. The increasing number of reports of remifentanil causing bradycardia and asystole suggest that it is particularly efficacious in this regard. It is likely that the remifentanil used in this setting slowed A-V conduction, causing the ventricular rate to drop to a more acceptable level.

H. Williams
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Correspondence

6 Dooms-Goossens A, de Alam AG, Degreek H, Kochuyt A. Local anesthetic intolerance due to metabisulphite. Contact Dermatitis 1989; 20: 124–6