Anaesthesia after exhaustive exercise

Sir,—There are no reports on the effect of preceding exhaustive exercise, such as marathon running, on the course of anaesthesia. We report an extreme case. A healthy 21-yr old (65 kg,173 cm) active jogger (40–60 km/week) presented for day-case tonsillectomy under general anaesthesia. Three days earlier he had run his first marathon and told the anaesthetist that his legs were painful. He had difficulty in getting down on the operating table. After operation, he told us that after 30 km of the marathon he had become so exhausted that he could remember little of the rest of the race.

An i.v. anaesthetic was used, supplemented with 70% nitrous oxide in oxygen. The drugs given and their total doses were as follows: glycopyrrolate 0.2 mg, propofol 280 mg, fentanyl 300 µg and rocuronium 50 mg. Residual neuromuscular block was antagonized at the end of operation with neostigmine 2.5 mg and glycopyrrolate 0.5 mg. During surgery, 2500 ml of crystalloid i.v. solutions were given. Postoperative analgesia was achieved with ketoprofen.

After operation the patient was able to breathe satisfactorily but despite normal responses to peripheral nerve stimulation he appeared extremely weak, that is he was unable to lift his head or even his hand. Because his condition had not improved after 6 h, he was moved to the local university hospital. Thirteen hours after operation the patient had to be escorted to the toilet by two people. Next morning he was able to walk but still complained of muscle pain, especially in his legs. The muscle pain disappeared gradually over the next 3 days.

Eight hours after operation total blood count, C-reactive protein concentrations, serum concentrations of creatinine, sodium, potassium and chloride, and blood-gas analysis, serum lactate, ammonium ion and insulin concentrations were normal. The only abnormal value was serum creatine kinase (1572 u. litre⁻¹, normal value <285 u. litre⁻¹), which was still high 2 days after operation (5 days after the operation it was 338 u. litre⁻¹), but was within normal limits by 10 days after operation (114 u. litre⁻¹). The patient underwent 31P-magnetic resonance spectroscopy (MRS) 33 h after the beginning of anaesthesia to assess the status of skeletal muscle energy metabolism.12 He was re-examined 5 months later for comparison. The patient resumed his usual training schedule 1 month after surgery.

From the MRS studies we found no evidence of altered energy metabolism of striated muscle to anaesthesia after exhaustive exercise. Variables assessing the main energy producing pathways (phosphocreatine hydrolysis, glycolysis or aerobic oxidative phosphorylation) were similar immediately after the incident compared with 5 months later. In contrast, resting concentrations of phosphodiesters were substantially higher immediately after the incident (4.5 compared with 2.7 mmol litre⁻¹). Phosphodiesters are hypothesized to be indicators of release of membrane molecules in muscle cell damage.5 But muscle overuse is associated with damage to the muscle contractile elements.6 This damage to the contractile elements could also be an explanation for our phosphodiester results.

After exhaustive exercise, a general anaesthetic could cause some type of interaction between the exhausted muscles and anaesthetic agents. Importantly, significant rhabdomyolysis may occur if succinylcholine is used.

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Pain after laparoscopic cholecystectomy

Sir,—We were interested in the review article by Alexander1 and wish to comment specifically regarding local anaesthesia for pain after laparoscopic cholecystectomy.

First, Alexander1 pointed out that analgesia tended to be given more readily during studies of pain or analgesics and that nearly all patients had received some form of intraoperative analgesia. We strongly support this view. It is difficult to compare postoperative pain when patients received various amounts of analgesics in the perioperative period. For this reason in our published study2 no opioid or non-opioid analgesics were used for premedication or during the perioperative period. Patients received only halothane and pancuronium during anaesthesia. For postoperative analgesia, patients received metamizol on request, as was usual in our hospital, by nurses who were blinded to the treatment. Postoperative pain was measured using a VAS score. The VAS score was not used as a threshold for administering metamizol.

Second, the timing of i.p. local anaesthetic (IPLA) is crucial, as it is for an NSAID. In the studies quoted in the review1 and in our study,2 IPLA was used after surgery, but in our study, in addition to that of Pasqualucci and colleagues,3 IPLA was given before and after surgery. Administration before surgery is important for pre-emptive analgesia. Third, the site of administration is important. The quoted studies reported that IPLA was ineffective when given only into the subdiaphragmatic space. In contrast, IPLA was effective for pain relief when given onto the gallbladder bed4 or into the subdiaphragmatic space and on the operative area.2,3

Fourth, the local anaesthetic concentration should be important. The quoted studies reported that IPLA was not effective when a low concentration of IPLA (0.15–0.25% bupivacaine) was given in contrast with those5–7 in which IPLA was effective for pain relief when given in high concentrations (0.5% bupivacaine).

Finally, Alexander1 concluded that local anaesthetic techniques appear to be more successful for pelvic laparoscopy than for laparoscopic cholecystectomy. We disagree. When IPLA is given at the correct time, on the right site and at the right concentration, it is also effective for pain relief after laparoscopic cholecystectomy. No side effects from IPLA have been reported. Therefore, we recommend routine administration of 0.5% plain bupivacaine 15 ml² or 0.5% bupivacaine 20 ml with epinephrine1 into the subdiaphragmatic space and on the operative area before and after surgery.

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SIR,—Thank you for the opportunity to reply to Mraovic and Majeríc-Kogler, and to acknowledge a material addition to the evidence. In an adequate double-blind, randomized, controlled study, they demonstrated the lesser need for additional analgesics and lower pain scores in those who had bupivacaine injected between the liver and diaphragm and above the hepato-duodenal ligament. Their study was not reviewed because the article was published at the same time as the review\(^2\) was submitted.

Their method was similar to that described in an earlier article by Pasqualucci and colleagues.\(^1\) This was primarily a study of preemptive analgesia and either bupivacaine or saline was sprayed above the liver and on the right subphrenic surface either before or after removal of the gallbladder, or both. Distension of the peritoneum occurred before application of local anaesthetic or saline. In those in whom bupivacaine was used at the end of infra-abdominal surgery, pain scores and ratings were lower than those in the placebo group at the end of surgery and 8 h after operation, but similar to those in the placebo group at 4 h (the time at which pain is most intense).\(^1\) Intraperitoneal i.v. fentanyl was used in a dose which was stated to be 15 mg kg\(^{-1}\).\(^1\)

Whether or not effective local anaesthesia or systemic analgesia provides pre-emptive analgesia during continuing nociception, as distinct from requirements for effective analgesia at the time of nociception, still appears to be in dispute.

Mraovic and Majeríc-Kogler disagree only with my statement\(^2\) that “local anaesthetic techniques appear more successful for pelvirectal laparoscopy than for, say, laparoscopic cholecystectomy.” However, as they pointed out in their discussion, “six studies compared intraperitoneal bupivacaine for pain relief after laparoscopic cholecystectomy, four of which suggested that intraperitoneal bupivacaine does not reduce pain and two of which suggested that it does.”

Nevertheless, the studies of Chundrigar and colleagues,\(^5\) Mraovic and colleagues\(^1\) and Pasqualucci and colleagues\(^1\) suggest with increasing evidence that to which I merely alluded: that local anaesthetic techniques are more likely to be effective when the local anaesthetic is placed accurately at the site of origin of nociception, rather than relying on movement or diffusion of local anaesthetic to the target area from a convenient site in the peritoneal cavity, especially when such movement is against gravity in a cavity partly filled with gas.

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**Ondansetron compared with metoclopramide in the treatment of PONV**

SIR,—We wish to comment on the study on postoperative nausea and vomiting (PONV) by Diemunsch and colleagues.\(^1\) This is the largest study to date comparing ondansetron with a commonly used antiemetic in the treatment of established PONV, and showed improved outcome for patients treated with the 5-HT\(_3\) antagonist. However, we were struck by the fact that even this drug, the non-dopaminergic most highly promoted antiemetic in the pharmacopoeia, still failed to show a benefit in 56% of patients who were vomiting in 41% of patients.

A recent review in the *BMJ* by Tramer and colleagues\(^2\) concluded that there is little information in relation to the effectiveness of intervention in established PONV, and that a 25% success rate is perhaps the best that can be achieved. The study of Diemunsch and colleagues goes someway to addressing this insufficiency in the literature and, in addition, had a greater success rate than Tramer and colleagues felt may be the best possible.

However, we feel that the study poses several questions: (1) Can we identify a group at high risk of PONV, and should we make more of an effort to do so using scoring systems such as that devised by Koivuranta and colleagues?\(^3\) (2) If we can identify these patients, is prophylaxis effective? (3) Are there non-drug interventions that can help, such as reducing the length of the preoperative fast,\(^4\) or the use of pre- or intraoperative i.v. fluids?\(^2\) If this study shows the best that can be achieved with single agent therapy, should future research be conducted on double or even triple agent regimens compared with other active comparators?

In a recent audit of PONV and pain in 198 patients in our day-case unit in 1996 it was submitted that, say, laparoscopic cholecystectomy. "Nevertheless, the studies of Chundrigar and colleagues,\(^5\) Mraovic and colleagues\(^1\) and Pasqualucci and colleagues\(^1\) suggest with increasing evidence that to which I merely alluded: that local anaesthetic techniques are more likely to be effective when the local anaesthetic is placed accurately at the site of origin of nociception, rather than relying on movement or diffusion of local anaesthetic to the target area from a convenient site in the peritoneal cavity, especially when such movement is against gravity in a cavity partly filled with gas. (b) The adjusted odds ratio associated with sex and vomiting:\(^2\) female sex, previous history of PONV, use of postoperative opioids and previous history of motion sickness. In our study, we identified the prognostic factors for the absence of emetic episodes after administration of the study drug. Sex appeared to influence the antiemetic response, as 72% of male patients experienced no emetic episodes between 15 min and 24 h after drug administration compared with 48% of female patients. Other factors influencing the antiemetic response include: history of PONV (55% of patients with a history of PONV experienced at least one emetic episode compared with 47% with no history); postoperative opioid analgesia (55% of patients who received opioid postoperative analgesics experienced at least one emetic episode compared with 45% who did not); and benzodiazepine premedication (54% of patients who received a benzodiazepine premedicant experienced at least one emetic episode compared with 40% who did not). Induction of anaesthesia with propofol had no influence on the antiemetic response, as 49% of patients who received propofol experienced at least one emetic episode compared with 50% of patients who did not.

The logistic regression analysis carried out for the absence of an emetic episode between 15 min and 24 h after drug administration showed that: (a) significant prognostic factors, adjusted for treatment, were sex, history of PONV, benzodiazepine premedication and postoperative opioid analgesia. The 95% confidence intervals (98% confidence intervals) for the absence of an emetic episode in the ondansetron group compared with the metoclopramide group was 2.12 (1.57–2.87), adjusted for the above mentioned prognostic factors (*P*=0.0001). (b) The adjusted odds ratio associated with sex indicated that males were 2.76 times more likely to experience no emetic episode than females (*P*=0.0006). Patients having one of

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Sir,—Harper and Barker ask the question: (1) Can we identify a group at high risk of postoperative nausea and vomiting (PONV), and should we make an effort to do so using scoring systems such as that devised by Koivuranta and colleagues?\(^3\) (b) The adjusted odds ratio associated with sex and vomiting: female sex, previous history of PONV, use of postoperative opioids and previous history of motion sickness. In our study, we identified the prognostic factors for the absence of emetic episodes after administration of the study drug. Sex appeared to influence the antiemetic response, as 72% of male patients experienced no emetic episodes between 15 min and 24 h after drug administration compared with 48% of female patients. Other factors influencing the antiemetic response include: history of PONV (55% of patients with a history of PONV experienced at least one emetic episode compared with 47% with no history); postoperative opioid analgesia (55% of patients who received opioid postoperative analgesics experienced at least one emetic episode compared with 45% who did not); and benzodiazepine premedication (54% of patients who received a benzodiazepine premedicant experienced at least one emetic episode compared with 40% who did not). Induction of anaesthesia with propofol had no influence on the antiemetic response, as 49% of patients who received propofol experienced at least one emetic episode compared with 50% of patients who did not.

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the following prognostic factors experienced more frequent emetic episodes: previous history of PONV (odds ratio = 0.70; P = 0.0237), benzodiazepine premedication (odds ratio = 0.56; P = 0.0008), postoperative opioid analgesia (odds ratio = 0.64; P = 0.0040). No significant effect from treatment of the prognostic factors was found.

(2) If we can identify these patients, is prophylaxis effective? Yes, clinical studies confirmed that ondansetron was effective in both the prophylaxis and treatment of PONV. Moreover, there are also other benefits from reducing PONV, such as patient global satisfaction, quality of recovery and prevention of delayed recovery.

(3) Are there non-drug interventions that can help, such as reducing the length of the postoperative fast, or the use of IV fluids before or after operation? Apart from drugs which are known to have antiemetic properties, such as lorazepam, hydroxyzine and propofol, other factors could enhance the incidence of PONV, such as postoperative pain or movement.

(4) If this study shows the best that can be achieved with simple agent therapy, should future research be conducted on double or even triple agent regimens compared with other active comparators? The incidence of PONV is approximately 60% in both the prevention and treatment studies. The number of complete responders in our treatment study does not reflect the real benefits to the patient. The non-surrogate criteria (for example, global satisfaction of the patient) reflect other benefits which are not sufficiently taken into account. These results could probably be improved with the additional use of drugs such as corticosteroids, as was demonstrated in clinical studies in chemotherapy.

1. Palazzo M, Evans R. Logistic regression analysis of fixed hydroxyzine and propofol, others factors could enhance the satisfaction, quality of recovery and prevention of delayed chemotherapy.


Sevoflurane for difficult intubation in children

Sir,—We read with interest the case reports by Mostafa and Atherton in which sevoflurane was used to induce anaesthesia in three adult patients in whom difficult tracheal intubation was anticipated. We wish to report two paediatric patients with a difficult airway where sevoflurane was used as the induction agent.

The first patient was a 6-yr-old boy with neurofibromatosis who presented for tracheotomy and debulking of a large intraoral tumour. The patient was a 6-yr-old boy who presented for tracheotomy and debulking of a large intraoral tumour (fig. 1). He also had a 6-month history of progressive difficulty in breathing and stridor. Inhalation induction was planned because of airway obstruction. EMLA cream was applied to both hands 1 h before induction. I.V. access was established. Anaesthesia was induced with sevoflurane in oxygen. The concentration of sevoflurane was increased gradually until an end-tidal concentration of 5.5% was achieved. Direct laryngoscopy was performed and revealed a grade III larynx which was grossly deviated to the left. The larynx was intubated uneventfully with a 5.0-mm plain Portex tube orally. Oxygen saturation was maintained at 99% throughout induction.

The second patient was a 11-yr-old girl with a fixed right temporomandibular joint and a very receded mandible. Her inter-incisor distance was only 1 cm at full mouth opening. Fibreoptic intubation under inhalation induction was planned. I.V. access was established before induction. Anaesthesia was induced with incremental concentrations of sevoflurane in oxygen. A nasal airway was inserted via the left nostril and attached to a T-piece. When the end-tidal sevoflurane concentration reached 5.5%, the trachea was intubated with a 5.5-mm plain Portex tube nasally via the flexible fiberoptic laryngoscope. Both surgery and anaesthesia were uneventful.

A difficult airway in paediatric patients presents a challenge to anaesthetists. Inhalation induction is the technique of choice because it is often difficult to perform awake fibreoptic intubation of tracheotomy under local anaesthesia in children. We agree with Mostafa and Atherton that sevoflurane has many advantages compared with halothane in the management of the difficult airway in both children and adults. The low blood:gas solubility of sevoflurane and consequent rapid induction and rapid recovery are reassuring features in the management of difficult intubation.

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Caudal tramadol for postoperative analgesia in hypospadias surgery

Sir,—Prolongation of caudal anaesthesia is indeed a laudable aim. However, I have some concern with the recent article describing the use of tramadol in this role. The evidence that tramadol may be effective in this regard is scanty. There is little evidence that it is safe or effective by the extradural route in adults.
We do not know the incidence of neurological damage that may be caused by this drug, and just one child with a painful or disabling neuropathy would be disastrous. Until evidence emerges of its safety and efficacy in adults, I do not believe that studies of this nature should be carried out in children.

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Sir,—Thank you for the opportunity to respond to Dr Russell about our caudal tramadol study.1

Although we agree in principle that studies should not involve children if the relevant data can be obtained from adults, this is rarely possible. In this instance, the significant age-related differences in opioid pharmacokinetics and pharmacodynamics,2 and vascularity, fat content and volume of the extradural space3 make extrapolation of clinical data from adults to young children rather suspect. Although some initial data may be gleaned from studies of drugs injected into the lumbar extradural space in adults, our results supported the concept that data achieved in this way cannot be used to predict accurately drug pharmacodynamics after caudal injection in children. All but one of the adult studies and the one paediatric study published in the past decade that have examined the effects of tramadol after extradural administration have recorded encouraging results. Our findings would not have been anticipated from meta-analysis of these studies. Furthermore, for various well recognized reasons, administration of drugs into the caudal extradural space is much less common in adults than in the very young. If studies examining caudal administration of drugs in adults were required before paediatric studies could proceed, we would often have to rely solely on data from non-randomized, unblinded, uncontrolled studies carried out in developing countries.

The second point about drug safety is a thorny issue but one that is always raised at Paediatric Ethics Committee meetings when a study of a “new” drug is being reviewed. To prove the safety of any drug is almost impossible, but a thorough examination of all published (and any available unpublished) clinical and experimental evidence offers the best possible compromise between ensuring optimal safe care for our patients and advancement of our knowledge base. In this instance we were able to point out that tramadol, which has been widely available in all of Europe for more than 20 yr, has an exceptional safety record; to the best of our knowledge no long-term adverse side effects attributable to its use have been reported. Finally, we did not perform this study because it was possible or because we wished to write another article; we believed that there was a problem (postoperative pain in children undergoing day-case hypospadias surgery) that could be prevented or alleviated. On the basis of previously published clinical work, we hypothesized that the analgesic effect produced by bupivacaine could be usefully prolonged by the addition of tramadol. Similar studies using more conventional opioids have shown that delayed respiratory depression may, occasionally, be a problem.6,7 Tramadol has the important and significant advantage over other commonly used opioids of having a marked lack of respiratory depressant effects.8,9 If we had found tramadol to be clinically useful in inpatients, then we would have extended our study to day-case patients. In the light of our initial findings, we did not believe that a study extension was justifiable. Many of these same arguments were presented and examined carefully by our Paediatric Ethics Committee before commencement of this study. One of the guiding principles used by this Committee in determining whether or not a study should be allowed to proceed is: “Children are not small adults and research should only be done in this group of patients if comparable research on adults cannot answer the same questions”. We believe, as did the Ethics Committee, that this principle was strictly adhered to in the conduct of this study.

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2. Fujii Y, Toyooka H, Tanaka H. Granisetron reduces the incidence of postoperative nausea and vomiting (PONV) in middle ear surgery.1 First, when established treatments are available, research must be compared with existing treatments, not with placebo. I wish to know if granisetron is more or less effective than other antiemetics on offer. Second, the same authors had already proved the effectiveness of granisetron in PONV in gynaecological patients (including a placebo group).2 Third, by withholding antiemetic therapy in the placebo group until significant morbidity from PONV had occurred represents sub-standard medical care.

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Sir,—We have already studied the efficacy of granisetron, a selective 5-hydroxytryptamine type-3 receptor antagonist, in preventing postoperative nausea and vomiting (PONV) after gynaecologi-


Sir,—In common with Sigston and colleagues, we have found induction in 8% sevoflurane to be rapid and well tolerated in young children. However, the development of profound bradycardia in four children has caused us to reflect on its use. These were healthy children, aged 6 months to 2 yr, undergoing minor surgery. None was premedicated and induction was by inhalation of 8% sevoflurane and 66% nitrous oxide in oxygen, using a standard technique. In all cases the onset of bradycardia occurred during induction with no loss of airway or ventilation. One infant required treatment with atropine because of clinical evidence of a decrease in cardiac output. In the other children heart rate recovered spontaneously when the concentration of sevoflurane was reduced or we changed to using isoflurane.

In the study of Sigston and colleagues, bradycardia occurred in one child who received halothane (age unknown) but not in the sevoflurane group. It is noteworthy that all of their patients received atropine premedication. Baum, Yemmen and Baum reported no arrhythmias when comparing 8% sevoflurane with incremental sevoflurane in unpremedicated children. Johannesson, Floren and Lindahl found an incidence of cardiac arrhythmias of 5% while using incremental sevoflurane in premedicated patients. Otherwise, incremental induction with sevoflurane in children seems to show an increase or have little effect on heart rate.

Those familiar with halothane induction in infants may admonish us for not routinely prescribing atropine where an inhalation induction is planned, if not to dry secretions and thus reduce airway complications, then to offset the myocardial depression which can accompany high concentrations of a volatile agent. The cardiovascular depression produced by sevoflurane is much less than that with halothane, but not absent. The single-handed anaesthetist, anticipating difficult i.v. cannulation, would be well advised to consider atropine premedication when planning induction with high concentrations of sevoflurane in infants.

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