Opioid-induced pruritus: repeated vs single dose ondansetron administration in preventing pruritus after intrathecal morphine

Editor—We read with interest the study of Kyriakides, Hussain and Hobbs concerning the possible role of 5-HT3 antagonists in the management of opioid-induced pruritus. They used a ‘human model’ and probably the aim of their study was prevention and not management of pruritus, as patients were given the study drug before the i.v. opioid. Additionally, the authors noted that ondansetron may have efficacy in treating pruritus after intrathecal administration of morphine without presenting any data to substantiate this. We would like to convey our experience concerning repeated vs single dose administration of ondansetron in preventing pruritus after intrathecal administration of morphine.

In a double-blind, randomized study, we compared the efficacy of different regimens of ondansetron with placebo for prevention of pruritus after orthopaedic surgery using intrathecal morphine. After obtaining approval from our institute and written consent, we studied 130 patients (60 males), ASA I–III, aged 35–75 yr. All patients were given subarachnoid injection of 0.5% plain bupivacaine with morphine 0.3 mg for surgical and postoperative analgesia. Patients were allocated randomly to one of three groups. In group 1 (n=44), patients received saline 2 ml i.v., 20 min before the spinal and 12, 24, 36 and 48 h after surgery. In group 2 (n=43), patients received ondansetron 4 mg i.v., 20 min before the spinal and saline 2 ml at 12, 24, 36 and 48 h after surgery. In group 3 (n=43), ondansetron 4 mg was given 20 min before the spinal and at 12, 24, 36 and 48 h after surgery. In the postoperative period, the pruritus score was recorded using a three-point scale (0 = nil, 1 = mild, 2 = moderate and 3 = severe) every 4 h for 48 h. The incidence of pruritus was analysed using Fisher’s exact test and the chi-square test with Yates’ correction. Differences in continuous variables were assessed using the Student’s t test. P<0.05 was considered statistically significant.

Randomization was successful in balancing the study groups with respect to age, weight, sex and ASA status. Postoperative pain relief was excellent in all groups. The overall incidences of pruritus were 32 of 44 patients (72.7%) in group 1, 27 of 43 (62.8%) in group 2 and 21 of 43 (48.8%) in group 3. Statistical analysis showed that group 3 had significantly less pruritus compared with group 1 (Fisher’s exact test: two-tailed P value=0.03), whereas all other paired comparisons between groups (1 vs 2 and 2 vs 3) were not significant. Table 1 shows the analytical distribution of frequencies of pruritus scores among the groups.

Pruritus is a common side effect of opioid administration and is usually localized to the face, neck or upper thorax. The incidence varies widely (0–90%), reflecting the difficulty in investigating this symptom. Epidural and intrathecal administration of opioids appear to be more pruritogenic than the i.v. or i.m. route. Our results suggest that repeated i.v. administration of ondansetron is useful in preventing opioid-induced pruritus after intrathecal administration of morphine, as it seems to diminish the incidence and severity of this common and distressing symptom.

V. Dimitriou
G. S. Voyagis
Department of Anaesthesiology
Gennimatas and Sotiria Hospitals
Athens, Greece

Table 1 Analytical distribution of frequencies of pruritus scores (number (%)). There was a significant difference between groups (P<0.02) (chi-square test).

<table>
<thead>
<tr>
<th>Pruritus score</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>12 (27.3)</td>
<td>16 (37.2)</td>
<td>22 (51.2)</td>
</tr>
<tr>
<td>1</td>
<td>13 (29.5)</td>
<td>14 (32.6)</td>
<td>15 (34.9)</td>
</tr>
<tr>
<td>2</td>
<td>10 (22.7)</td>
<td>11 (25.6)</td>
<td>5 (11.6)</td>
</tr>
<tr>
<td>3</td>
<td>9 (20.5)</td>
<td>2 (4.6)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>44 (100)</strong></td>
<td><strong>43 (100)</strong></td>
<td><strong>43 (100)</strong></td>
</tr>
</tbody>
</table>

Editor—We thank Dimitriou and Voyagis for their comments on our article. They imply that prevention of opioid-induced pruritus does not form part of the overall management of this clinical problem. We believe that prevention of this common and potentially distressing symptom is as important and integral a part of management as its actual treatment.

Our data suggesting that ondansetron may have efficacy in treating opioid-induced pruritus after intrathecal administration of morphine were acquired from studying a
limited number of patients who complained of this symptom after intrathecal administration of 0.5% heavy bupivacaine with morphine 0.1 mg for elective Caesarean section (the standard regimen used in our institution). Results obtained from treating such patients with ondansetron suggested that 5-HT₃ antagonists may have a role in the treatment of established opioid-induced pruritus (unpublished data). However, the relatively low incidence of troublesome opioid-induced pruritus after intrathecal administration of morphine 0.1 mg coupled with the fact that ondansetron is not licensed for administration in lactating women, made it impossible for us to recruit enough patients to enable us to carry out a randomized, placebo-controlled, double-blind study.

In the study of Dimitriou and Voyagis on prevention of opioid-induced pruritus with ondansetron, patients underwent orthopaedic surgery under a spinal technique using 0.5% bupivacaine with morphine 0.3 mg. At our institution, patients who receive intrathecal–epidural by Dr Chiu. While we are assured that tracheal intubation morphine as part of their anaesthetic are observed after operation in the intensive care unit (ITU) because of the risk of delayed opioid-induced complications such as respiratory depression. The lack of a surgical high dependency unit in our institution together with a high demand for the limited number of ITU beds impose severe limitations on the use of this technique.

The results of Dimitriou and Voyagis’ study support our findings that ondansetron has a role in the prevention of opioid-induced pruritus. This was reflected in their findings of a statistically significant difference in the incidence of pruritus between study groups 1 and 3. Although paired comparisons between the other groups (1 vs 2 and 2 vs 3) failed to reach statistical significance, probably because of a type II error, their results suggest that the efficacy of ondansetron in the prevention of opioid-induced pruritus may be dose-related. Indeed, data already available show that this is so in the case of the management of postoperative nausea and vomiting.¹

Finally, when a drug is given regularly it is difficult to delineate between the prevention and treatment components of such an intervention. Nevertheless, the results of Dimitriou and Voyagis’ study suggest that ondansetron may also have a role in the actual treatment of opioid-induced pruritus, as reflected in the clinically, but not statistically, significant difference of pruritus severity scores between the three groups.

K. Kyriakides

University Department of Anaesthesia
Queen’s Medical Centre
Nottingham, UK


Effect of rocuronium compared with succinylcholine on IOP

Editor—Chiu, Jaais and Wang are to be congratulated on their careful investigation of the effects of rocuronium and succinylcholine on intraocular pressure (IOP) during rapid sequence induction of anaesthesia.¹ Research which casts light on practical, controversial anaesthetic problems (in this case the management of an inadequately fasted patient with a penetrating eye injury) is always welcome. However, we wish to raise three points regarding their study.

First, although the investigators took care to blind the anaesthetists involved to the drugs used, no details are given as to how patients were randomized into the two groups. As the method of allocation concealment is one of the more important determinants of the validity of a controlled study,² it would be useful to know how this was achieved.

Second, we note that all IOP measurements were made by Dr Chiu. While we are assured that tracheal intubation was performed by experienced practitioners, we are given no information on the accuracy and precision of the IOP measurements. We would be interested to know if the authors feel that the study might have been strengthened by having an ophthalmologist, rather than an anaesthetist, perform the IOP measurements.

Lastly, the assumption on which the investigation is predicated is that succinylcholine increases IOP, as this study demonstrated once again. However, as the study was designed to investigate rapid sequence induction of anaesthesia, it is pertinent to examine this in detail. We were always taught that pure rapid sequence induction consists of a pre-determined ‘expected sleep dose’ of thiopental and succinylcholine given rapidly (albeit in an unpremedicated patient, followed immediately by succinylcholine 1–1.5 mg kg⁻¹). Thus prompt return to consciousness and muscle activity can be assured should tracheal intubation prove difficult. We recognize that there are many variations on this theme. Nevertheless, addition of fentanyl 2 µg kg⁻¹ and the relatively slow injection of propofol may have influenced the absolute increases in IOP in both groups (although one would still expect the increase to be less after rocuronium). The timing of drugs is likely to be of crucial importance.

In 1988, Edmondson and colleagues³ studied the effects of thiopental and succinylcholine given rapidly (albeit in patients premedicated with papaveretum and hyoscine). The mean increase in IOP after tracheal intubation was only 0.93 mm Hg (95% confidence intervals –1.5 to 3.4 mm Hg). The authors suggested that the opposing effects of thiopental and succinylcholine on IOP tended to cancel each other out when given almost simultaneously. While it remains true that succinylcholine increases IOP, the increase does not appear to be as great when the ‘unmodified’ rapid sequence injection of thiopental and succinylcholine is used. These findings shift the ‘balance of risks’ when choosing a neuromuscular blocking agent in this clinical situation.
One failing of both Chiu’s and Edmondson’s work is that cricoid pressure was not applied, as this is the other essential feature of emergency tracheal intubation. We agree with Chiu, Jaais and Wang that a further study is needed of the effect of cricoid pressure on IOP and look forward to the results.

K. Lim
A. F. Smith
Royal Lancaster Infirmary
Lancaster, UK

Editor—While we do not dispute the quality of research by Chiu, Jaais and Wang, their study nevertheless causes us some concern. First, evidence would appear to be lacking for the objection to the use of succinylcholine in the patient with an open eye injury, and second, we would question the acceptance of rocuronium as an alternative agent for use in rapid sequence induction of anaesthesia.

A literature search revealed only one case report in the past 40 yr of extrusion of intraocular contents after halothane anaesthesia.56 even though Libonati, Leahy and Ellison7 advocated cricoid pressure was not applied, as this is the other essential feature of emergency tracheal intubation. We agree with Chiu, Jaais and Wang that a further study is needed of the effect of cricoid pressure on IOP and look forward to the results.


Editor—We thank Drs Lim and Smith and Drs Cadamy and Booth for their interest in our article.1 Drs Cadamy and Booth are correct in highlighting an area of continuing controversy regarding the use of succinylcholine in eye injuries. It is well documented that succinylcholine causes an increase in intraocular pressure (IOP) and its use in patients with penetrating eye injuries remains controversial.4 But there is certainly more than one case of expulsion of intraocular contents after succinylcholine over the past 40 yr,5,6 even though Libonati, Leahy and Ellison7 advocated that it was safe to use in patients with perforated eye injuries. However, this report7 has been criticized as a retrospective analysis without a control group and for having as its only end-point whether the surgeon complained of extrusion of eye contents. No mention was made, for example, of difficulty with uveal prolapse, bleeding or reformation of the globe.8 They could not have known if avoiding succinylcholine would have resulted in better functional results. No doubt the findings of Moreno, Kloess and Carlsson were significant, but this study was performed in an animal model and cannot be extrapolated directly to clinical practice.

7 Vaughan RS. ‘The only man to have all his work done by Friday was Robinson Crusoe’. Br J Anaesth 1999; 82: 663–5

824
patients with penetrating eye injuries who are the group most at risk from increased IOP.

We agree with Cadamy and Booth that there is a low risk of 1 in 2230 in non-patients of an ‘unanticipated difficult airway’ and its consequences. Therefore, one should consider the risk vs the benefit to patients with penetrating eye injuries of the use of succinylcholine.

In response to the three points raised by Lim and Smith, first, regarding the method of randomization, we used a randomized block design with 15 patients in each group. Second, they were concerned that the IOP measurements were not performed by an ophthalmologist and also about the accuracy of the IOP measurements. The Keeler Pulsair air impulse tonometer is a hand-held, non-contact tonometer which is suitable for use by those who are not ophthalmologists for rapid measurement of changes in IOP during anaesthesia. The instrument is simple to use after a minimal period of familiarization. The Pulsair measures automatically when positioning is achieved: no reading can be obtained unless alignment with and distance from the cornea are correct. To that extent the tonometer is operator-independent; there is no interpretative element to the reading. The accuracy of the Pulsair compares well with the Goldmann applanation tonometer, traditionally regarded as the gold standard for IOP measurements.

Lim and Smith raised an interesting point as to whether the rate of propofol injection could have influenced the absolute increases in IOP in both groups in our study. We are unable to comment as this was not the aim of our study. However, Zimmerman, Funk and Tidwell studied 60 patients allocated randomly to receive either thiopentol 5 mg kg\(^{-1}\) and succinylcholine 1.5 mg kg\(^{-1}\) (group I), propofol 2 mg kg\(^{-1}\) and succinylcholine 1.5 mg kg\(^{-1}\) (group II) or propofol 2 mg kg\(^{-1}\), alfentanil 40 µg kg\(^{-1}\) and succinylcholine 1.5 mg kg\(^{-1}\) (group III) in a rapid sequence induction. Despite injecting the drugs in 30 s, which is faster than the rate of propofol injection in our study, the results showed that IOP values after intubation in groups I and II were significantly higher than baseline. In our study, propofol was given at a rate of 200 mg min\(^{-1}\) because this is almost the maximum rate recommended. Lim and Smith quoted the study of Edmondson and colleagues, which demonstrated that there was no significant increase in IOP after tracheal intubation when thiopentol and succinylcholine were used as part of a rapid induction. In this study, the drugs compared were succinylcholine and atracurium, but they did not compare the rate of injection of thiopentol between groups. Therefore, a further study is needed to investigate if varying the rate of injection could have produced different changes in IOP.

C. Y. Wang
C. L. Chiu
Department of Anaesthesia
University of Malaya
Kuala Lumpur, Malaysia

Intraoperative therapeutic suggestions

Editor,—Lebovits, Twersky and McEwan suggest that benefit may result from intraoperative therapeutic suggestions. They argue such suggestions can decrease nausea–vomiting (see Fig. 2 and associated text). However, they combined their findings for 30, 60 and 90 min to reach this conclusion. Doing so, they found that five and five and six (total 16) patients in the control group had nausea–vomiting whereas one and one and two (total four) in the treatment group had nausea–vomiting (P<0.02). However, the results at 30, 60 and 90 min are not necessarily independent. That is, a patient nauseated at 30 min might also be nauseated at 60 and 90 min, and thus be counted three times. At no individual assessment time was there a difference between groups.

Further, Lebovits, Twersky and McEwan also found no significant differences in patient characteristics between the treatment and control groups. However, the control group included nine females and the treatment group only four.

10 Samsoom GLT, Young JRB. Difficult tracheal intubation: a retrospective study. Anaesthesia 43: 487–90
11 Bricker SRW, McGalliard JN, Mostafa SM. The Keeler Pulsair air impulse tonometer. Anaesthesia 1990; 45: 36–9
On average, these were premenopausal patients. As such, the control group had a higher proportion of patients at greater risk of nausea–vomiting. At any given time, the control group never had greater than four more patients than the treatment group who displayed nausea–vomiting. If the analysis of nausea–vomiting (and perhaps other variables) is confined to the male subset, do the average difference and statistical significance disappear?

E. I. Eger
University of California, San Francisco
San Francisco, CA, USA

1 Lebovits AH, Twersky R, McEwan B. Intraoperative therapeutic suggestions in day-case surgery: are there benefits for postoperative outcome? Br J Anaesth 1999; 82: 861–6

Editor—Thank you for the opportunity to respond to Dr Eger’s very careful analysis of our data. We stated clearly in our article that there were no group differences in nausea–vomiting at each time, rather that the number of times nausea–vomiting was experienced over the first 90 min was statistically significant. The point regarding the lack of independent observations is well taken, however, this issue remains the same for both groups and we were examining between-group differences.

We recognize that female sex is a risk factor for postoperative nausea–vomiting. However, we are unaware from reviewing the literature that premenopausal women per se are at higher risk of nausea–vomiting. Although there were more women in the comparison group than in the treatment group, the difference was not statistically significant. In any case, women in our study did not appear to be ‘premenopausal’ (mean age of the 13 women in the study was 41 yr, and the mean age of the nine women in the comparison tape group was 38 yr compared with 47 yr for the four women in the therapeutic tape group, a difference that was not statistically significant). Data from other studies suggest that women in the earlier phases of the menstrual cycle are more at risk of postoperative nausea–vomiting. We did not evaluate this.

Regarding the comment about there being a difference of only four patients between the groups who displayed nausea–vomiting, it must be remembered that only 27% of all patients experienced nausea–vomiting at any time after operation and hence it did not occur frequently at each assessment time. Nevertheless, statistical differences between groups were obtained by combining assessment times. The infrequent occurrence of nausea–vomiting would also preclude Dr Eger’s suggestion of limiting the analyses to the male subset. Sex differences in rate of nausea–vomiting could perhaps be explored more effectively with larger sample sizes.

A. H. Lebovits
Departments of Anesthesiology and Psychiatry
New York University Medical Center
New York, NY, USA

R. S. Twersky
Department of Anesthesiology
SUNY Health Science Center at Brooklyn
Brooklyn, NY, USA

The Oxford Textbook of Critical Care, released in 1999, weighs some 4 kilos and is almost 1400 pages long. This makes it ideal for purchase for intensive care units or other areas where smaller books would ‘wander’. We have previously purchased copies for this purpose in our institution.

Although the name would suggest that this is a British textbook originating in Oxford, this is not the case. The broad spread of editors and authors (more than 400) means that it is an international text. The book is divided into 18 major sections which include: resuscitation; applied physiology and pathophysiology of different body systems; physical injury; perioperative care; and descriptions of the various interventions that constitute the specialty of intensive care medicine. Each of these sections is subdivided into more than 450 short monographs on individual topics. Each monograph is limited to 2000–3000 words and has five key references for further reading. This makes for a very easy, accessible and readable format. It has also been designed to fit easily on CD ROM format, which is to be released soon. The breadth of coverage is very wide and there are many unexpected interesting sections, for example on sleep deprivation, ballistics and noise in the ICU.

Overall, I think the editors, authors and publishers should be congratulated for producing an excellent book. I found little to criticize and few errors on delving into the book on a regular basis over a few weeks. The book best serves as a reference text for a vast range of topics in relation to intensive care medicine. It is not a ‘how to do it’ practical procedures book, but more a theoretical text exploring normal and abnormal physiology and the pathophysiology of the large number of conditions that make up the case mix of adult general intensive care. In addition, there is much information on other matters related to general patient care in the ICU, including ethics, medico-legal issues, organizational issues, transport, ICU design, applied pharmacology, imaging and monitoring.

The sections on practical procedures are generally short with few illustrations and would be usefully supplemented by reference to more practical based texts, which already exist. Other minor criticisms relate to some of the figures, particularly in relation to imaging, which are too small to be of any value. At times I was surprised by the depth of coverage of some more unusual conditions compared with more common ones. For example, aortic dissection is covered in three separate sections totalling six pages while aortic aneurysm is mentioned briefly in half a page.

At £165, this book is likely to be bought by institutions rather than individuals. The price is a major disadvantage; if more competitively priced, I think it would be purchased widely by individual clinicians and also would be very attractive to them in CD ROM format. It will have wide appeal to anyone involved in intensive care. It is likely to become a standard reference text for trainees; the short sections are ideal for revision purposes and background reading. I have received very favourable comments about the book from candidates sitting the new UK diploma in intensive care medicine. The level of detail is well suited to this examination. My complimentary copy will be joining the already well-thumbed copy on the general ICU for nurses, physiotherapists and medical staff to use on a daily basis.

A. Bodenham