**Maximum Tolerated Dose of Nalmefene in Patients Receiving Epidural Fentanyl and Dilute Bupivacaine for Postoperative Analgesia**

Thomas B. Dougherty, Ph.D., M.D., Vivian H. Porche, M.D., Peter F. Thall, Ph.D.

**Background:** This study investigated the ability of the modified continual reassessment method (MCRM) to determine the maximum tolerated dose of the opioid antagonist nalmefene, which does not reverse analgesia in an acceptable number of postoperative patients receiving epidural fentanyl in 0.075% bupivacaine.

**Methods:** In the postanesthetic care unit, patients received a single intravenous dose of 0.25, 0.50, 0.75, or 1.00 µg/kg nalmefene. Reversal of analgesia was defined as an increase in pain score of two or more integers above baseline on a visual analog scale from 0 through 10 after nalmefene administration. Patients were treated in cohorts of one, starting with the lowest dose. The maximum tolerated dose of nalmefene was defined as that dose, among the four studied, with a final mean probability of reversal of anesthesia \( P_{\text{ROA}} \) closest to 0.20 (i.e., a 20% chance of causing reversal). The modified continual reassessment method is an iterative Bayesian statistical procedure that, in this study, selected the dose for each successive cohort as that having a mean \( P_{\text{ROA}} \) closest to the preselected target \( P_{\text{ROA}} \) of 0.20.

**Results:** The modified continual reassessment method repeatedly updated the \( P_{\text{ROA}} \) of each dose level as successive patients were observed for presence or absence of ROA. After 25 patients, the maximum tolerated dose of nalmefene was selected as 0.50 µg/kg (final mean \( P_{\text{ROA}} = 0.18 \)). The 1.00-µg/kg dose was never tried because its projected \( P_{\text{ROA}} \) was far above 0.20.

**Conclusions:** The modified continual reassessment method facilitated determination of the maximum tolerated dose of nalmefene. Operating characteristics of the modified continual reassessment method suggest it may be an effective statistical tool for dose-finding in trials of selected analgesic or anesthetic agents. (Key words: Dose-finding trial designs; drug dose-response; opioid antagonists.)

NALMEFENE hydrochloride is a new intravenous, long-acting, pure opioid antagonist. Similar to naloxone, it may be effective in reversing the adverse effects of epidural opioids. To date, however, few studies have established a maximum tolerated dose (MTD) of nalmefene, which can be administered without reversing analgesia in an acceptable number of patients receiving postoperative epidural opioids.

The MTD of nalmefene could be determined by a traditional randomized, double-blind dose-response study, in which a preselected range of nalmefene doses are administered and reversal of analgesia (ROA) is the observed response. This approach tends to require a relatively large patient accrual, and the choice of a set of doses with unacceptably high rates of ROA may not be discovered until an undesirably large number of patients have been treated at those dose levels. Alternatively, the trial could be conducted using adaptive rules that select drug dose levels for successive cohorts of patients based on outcomes of patients treated previously in the trial. Fewer patients are needed to determine the MTD, a suboptimal range of nalmefene doses having unacceptably high probabilities of ROA can be detected earlier, and fewer patients are treated at suboptimal dose levels. The novel modified continual reassessment method (MCRM), is such an adaptive strategy. It is a Bayesian model-based algorithm that, in the current setting, aims to choose a dose level having a mean ROA probability \( P_{\text{ROA}} \) closest to a previously specified target \( P_{\text{ROA}} \).

This report describes the usefulness of the MCRM for determining the MTD of nalmefene, which spares analgesia in an acceptable number of patients receiving epidural fentanyl and dilute bupivacaine for postoperative pain control.
Materials and Methods

This study was approved by the Institutional Review Board of The University of Texas M. D. Anderson Cancer Center. Written informed consent was obtained from 27 patients, classified as American Society of Anesthesiologists physical status II or III, who were scheduled to undergo operations for which an epidural catheter was indicated for postoperative pain control. Patients were ineligible to participate in the study if they were younger than 18 yr or older than 80 yr of age; were pregnant; displayed uncontrolled hypertension with a sustained diastolic blood pressure above 115 mmHg; had known coronary artery disease that placed them in New York Heart Association functional class 3 or 4; or were receiving α2-agonist antihypertensive therapy, long-term opioid therapy, or antiemetic therapy. All patients were instructed preoperatively in the use of the patient-controlled epidural analgesia infusion pump, Baxter model APII (Baxter Health Care, Deerfield, IL), and in the use of a printed 11-point (integer) visual analog scale (VAS) in which 0 was no pain and 10 was the worst pain imaginable.

Before induction of general anesthesia in each patient, an indwelling epidural catheter for postoperative pain control was inserted during local anesthesia (1% lidocaine without epinephrine) at a segmental level appropriate for the proposed surgery and secured to the patient’s back and shoulder. If necessary, midazolam (1–2 mg) was administered intravenously to facilitate epidural catheter placement. Subarachnoid or intravenous placement of the epidural catheter was ruled out by testing it with 3 ml lidocaine, 1.5%, plus 1:200,000 epinephrine. After induction of general anesthesia with sufentanil (0.2–1.0 μg/kg) and sodium thiopental (3–5 mg/kg) or etomidate (0.2 mg/kg), patients received rocuronium, isoflurane (0.5%), or desflurane (2–8%); air; oxygen; and a sufentanil infusion (0.2–0.5 μg·kg−1·h−1). Antiemetics were avoided, and stomach contents were suctioned with a nasogastric or orogastric tube.

One hour before completion of surgery, fentanyl (100–150 μg) in 10 ml normal saline was administered through the epidural catheter. A continuous infusion of fentanyl (10 μg/ml) in 0.075% bupivacaine was initiated at 5–10 ml/h with the patient-controlled epidural anesthesia pump. The patient’s age, weight, and epidural catheter location were factors involved in setting the starting infusion rate. The demand dose was set for 0.5 ml every 15 min. At the end of the operation, residual muscle relaxation was antagonized with glycopyrrolate and neostigmine. Patients were extubated in the operating room or shortly after arriving in the postanesthesia care unit.

In the unit, each patient’s pain intensity was brought to a VAS score of 3 or lower, if necessary, by administering boluses of the epidural infusion or by adjusting the basal infusion rate. At this time, patients were removed from the study and were ineligible to receive nalmefene if we were unable to reduce the VAS score to 3 or less without the aid of intravenous opioids; for example, because of epidural failure. Only patients eligible to receive nalmefene were assigned study numbers in sequence.

If a patient who was eligible for the drug was able to adequately assess his or her pain and the VAS score was maintained at 3 or lower for a minimum of 30 min, the patient’s baseline VAS score was recorded. The patient then received a single intravenous injection of one of the following four doses of nalmefene: 0.25, 0.50, 0.75, or 1.00 μg/kg given over 2 min. The patient was unaware of the dose given. Pain intensity was assessed at least hourly for 4 h and once again at 8 h by the department of anesthesiology’s acute pain nurse or the study chairman. At each assessment, the patient indicated pain intensity by placing a mark at the appropriate number on the VAS. In addition, the nursing staff was instructed to inform us of an increase in the patient’s pain occurring at any time other than the scheduled assessment times. ROA was defined as an increase in the VAS score of 2 or more integers above the patient’s baseline score after administration of nalmefene and could occur at any time during the 8-h observation period. We attempted to ensure that any increase in VAS score was not just a reflection of an increase in patient movement or other physical activity. The epidural infusion rate was adjusted to maintain the VAS score at 3 or less. If needed in patients experiencing nalmefene-induced ROA, intravenous ketorolac tromethamine was used as an adjuvant analgesic.

Patients requesting treatment for pruritus were initially given diphenhydramine (12.5 mg) intravenously every 4–6 h. Patients with nausea and vomiting were treated with intravenous droperidol (0.625 mg) every 6 h as needed. Ondansetron (4 mg) was substituted if droperidol failed to relieve the nausea and vomiting. In the event that these medications were unsuccessful in relieving pruritus or nausea and vomiting, a dilute solution of naloxone was added as an infusion by injection into the
patient's bag of intravenous maintenance fluid. If the fluid volume in the bag exceeded 500 ml, 0.4 mg naloxone was added; 0.2 mg was injected if the volume was less than 500 ml. The infusion was kept at the rate previously ordered by the surgeon to achieve adequate fluid maintenance in the patient.

Nalmefene, similar to naloxone, can lead to nausea and vomiting, although the incidence should be low at the dose levels used in this investigation. Nausea and vomiting suspected of being caused by nalmefene administration were not considered to be equivalent to ROA unless ROA was present and could not be explained by the physical activity of retching or patient movement.

Somnolence level was assessed using the four-point sedation scale outlined in Table 1. Sedation was reduced by decreasing the epidural infusion rate until the patient became more alert. Epidural patients were monitored routinely with continuous pulse oximetry for at least 24 h postoperatively. Respiratory depression was defined as a respiratory rate less than 10 breaths/min or an arterial oxygen saturation less than 85%. In response to the occurrence of respiratory depression, we temporarily discontinued the epidural infusion and, if necessary, administered intravenous naloxone in 80-μg increments.

Table 1. Somnolence (Sedation) Score

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No sedation: Patient fully awake and oriented.</td>
</tr>
<tr>
<td>1</td>
<td>Mild sedation: Patient aroused by verbal stimuli; oriented to time, place, and person.</td>
</tr>
<tr>
<td>2</td>
<td>Moderate sedation: Patient aroused by physical stimuli; oriented when awakened.</td>
</tr>
<tr>
<td>3</td>
<td>Marked sedation: Patient aroused by physical stimuli; disoriented when awakened.</td>
</tr>
</tbody>
</table>

Somnolence (Sedation) Score

We assumed a unit exponential before (starting) distribution for α and estimated an initial \( P_{ROA} \) for each dose. With this model, an increase in the nalmefene dose causes an increase in \( P_{ROA} \). Estimated mean posterior \( P_{ROA} \) values at the respective four dose levels change as the patient data accumulate during the trial, so that the estimated dose-response curve more accurately reflects the true dose-response relation with each additional piece of information.\(^7\) Posterior probability refers to the fact that \( P_{ROA} \) is a function of α, the drug dose, and patient response observed at any point in the trial; that is, the \( P_{ROA} \) of each nalmefene dose level is updated repeatedly as the response of each successive patient is observed.

The interactive, menu-driven computer program used to implement the MCRM and specific details about its operation can be obtained directly from the third author (P. F. T.) at rex@mdanderson.org. For our trial, we entered the trial's title, our target \( P_{ROA} \) of 0.20, the four nalmefene dose levels (0.25, 0.50, 0.75, and 1.00 μg/kg), patient identification numbers, nalmefene doses received, and whether analgesia was reversed. Starting estimates of \( P_{ROA} \) were necessary for the four doses. The choice of these initial probabilities was not critical to the method, but they had to begin below the targeted \( P_{ROA} \) increase with the dose levels and end above the targeted \( P_{ROA} \). In general, these starting probabilities are chosen to obtain a statistical design with good operating characteristics, including a high probability of selecting the correct MTD in a variety of possible dose–adverse event scenarios.\(^7\) The computer program enables one to simulate the trial in different scenarios during the planning stage, and these starting probabilities may be adjusted as appropriate before the trial begins. Consequently, we selected 0.10, 0.20, 0.40, and 0.80 as the starting \( P_{ROA} \) values.

Patients were treated in cohorts of one individual, beginning with the lowest of the four nalmefene doses. We did not allow an untried dose to be skipped before escalating the dose in the next patient.\(^5\) With the MCRM, there are no restrictions, however, on dosage decreases, and the next recommended dose at any stage of the trial may be larger, smaller, or the same as the current dose. After observing the binary outcome (ROA/no ROA) for a

\[
\begin{align*}
\frac{\exp(3 + \alpha d(i))}{1 + \exp(3 + \alpha d(i))}
\end{align*}
\]

Anesthesiology, V 92, No 4, Apr 2000

\( p_{ROA} \)
patient, the updated distribution of $\alpha$ was calculated via Bayes’s theorem. From that distribution, a new estimate of the dose-ROA curve was obtained, which was used to assign the next patient to the dose level whose associated mean posterior $P_{\text{ROA}}$ was closest to the target $P_{\text{ROA}}^* = 0.20$. In other words, for each patient in the trial, the drug dose and whether analgesia was reversed were entered to allow computation of the next patient’s nalmefene dose. The $P_{\text{ROA}}$ of each dose level was updated repeatedly as the data from successive cohorts were accumulated. The MTD of nalmefene was defined as that dose among the four chosen doses that had a final mean $P_{\text{ROA}}$ closest to 0.20.

The MCRM continues until a stopping criterion is satisfied. Three possible stopping criteria may be used: a minimum number of patients: The trial continues until at least this number of patients is treated; a maximum number of patients: The trial stops if at most this number of patients is treated; or a minimum number of patients at the MTD: The trial stops if at least this number of patients is treated at the MTD of the study drug. In our trial, the MTD of nalmefene was determined after 25 patients were treated and evaluated for ROA.

A logistic regression analysis of the data from all 25 patients was performed to assess the influence of nalmefene dose, patient age and sex, and type of surgery on $P_{\text{ROA}}$. Nonpaired, two-tailed Student $t$ tests were used to compare at the time of nalmefene administration, hourly epidural fentanyl infusion rates, epidural fentanyl-bupivacaine infusion volumes, epidural boluses necessary to achieve a VAS score of 3 or less, and fentanyl doses received for the group of patients experiencing ROA and the group of patients without ROA. A significance level of $P < 0.05$ was applied. Unless otherwise stated, numerical values are reported as the mean ± SD.

### Results

Two patients were removed from the study before the administration of nalmefene because of our inability to reduce their VAS scores to 3 or less without the aid of intravenous hydromorphone. In both cases, testing the epidural with 10-20 ml of 0.125% bupivacaine produced no reduction in pain intensity, and the catheters were considered to have been placed incorrectly. Of the remaining 25 patients (11 men, 14 women, mean age 57 yr), five patients had a baseline VAS score of 0, 13 had a VAS score of 1 or 2, and seven had a score of 3. There were no additional epidural failures during the 8-h study period in the these patients.

The time from admission to the postanesthesia care unit until administration of nalmefene was 91 ± 30 min. Table 2 shows the sequence of nalmefene doses assigned by the MCRM as the program accumulated data on the effects of preceding doses on the corresponding patients’ analgesia. After 25 patients were treated, the final mean posterior $P_{\text{ROA}}$ values for the four dose levels were, respectively, 0.09, 0.18, 0.37, and 0.79, and the corresponding final median values were, respectively, 0.11, 0.21, 0.41, and 0.80 (fig. 1). Because the targeted $P_{\text{ROA}}^*$ was 0.20, the MTD of nalmefene was selected to be the second dose level, 0.50 μg/kg.

If present, ROA resulting from nalmefene administration usually occurred by the first hourly assessment, and in all cases the decrease in analgesia was successfully managed by administering boluses of the epidural fentanyl-bupivacaine solution, increasing the infusion rate, or both. Supplementation with a single intravenous dose of 15-30 mg ketorolac was necessary by four of the five patients experiencing drug-induced ROA to decrease their VAS score to 3 or less.

Table 3 summarizes, at the time of nalmefene admin-
administration, the initial baseline VAS scores, the hourly epidural fentanyl infusion rates, the volumes of epidural fentanyl-bupivacaine infusion given as boluses to obtain a baseline VAS score of 3 or less, the volumes of epidural infusion administered since activation of the epidural, and the fentanyl doses received for the group with ROA and the group without ROA. Differences in these variables between the two groups were statistically and medically insignificant.

For patient groups receiving the same nalmefene dose level, the median infusion rates for the hour immediately preceding drug administration were 8.5, 8.0, and 8.5 ml/h for the 0.25, 0.50, and 0.75 µg/kg dose levels, respectively. Analgesic demand doses were included in the calculation of these rates.

Eighteen patients received 0.50 µg/kg of nalmefene. Of these, three patients experienced ROA (the VAS score increased 3 integers above predrug baseline in all three), 13 patients had thoracic procedures, and five received upper abdominal operations. The three incidences of ROA occurred in thoracic patients, whereas no ROA was observed in the upper abdominal patients. Of the three patients receiving 0.75 µg/kg of nalmefene, ROA was noted in two (the VAS score increased 3 points in one patient and 6 points above baseline in the other). Figure 1 illustrates the 95% posterior \( P_{ROA} \) or credibility intervals (vertical bars) for the four nalmefene doses, based on the data from all patients receiving nalmefene. The formal probability statement corresponding to the interval for 0.50 µg/kg nalmefene is \( P(0.073 < P_{ROA} < 0.055 \mid \text{final data}) = 0.95 \). The median \( P_{ROA} \) values are represented by the round dots. The figure shows clearly why the 1.00 µg/kg dose was never tried because its extrapolated median \( P_{ROA} \) and probability interval were estimated to be far above the targeted 0.20.

A logistic regression analysis of the patient data in table 2 indicated that \( P_{ROA} \) increased with nalmefene dose, as expected \((P = 0.01)\). Neither sex \((P = 0.54)\) nor type of surgery \((P = 0.32)\) were predictive of \( P_{ROA} \). The \( P_{ROA} \) decreased with age, but this effect was only marginally significant \((P = 0.06)\) and may have been an artifact of the small sample size of 25 patients.

No patient developed nausea or vomiting after the

---

**Table 3. Comparison, at the Time of NAL Administration, of VAS Scores and Epidural Fentanyl Infusion Rates, Fentanyl Doses and Fentanyl–Bupivacaine Volumes Received by the Patient Group Experiencing ROA and the Patient Group without ROA**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group with ROA</th>
<th>Group without ROA</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n = 5 )</td>
<td>( n = 20 )</td>
<td></td>
</tr>
<tr>
<td>Pre-NAL, baseline VAS score*</td>
<td>2 ± 1</td>
<td>2 ± 1</td>
<td></td>
</tr>
<tr>
<td>Hourly epidural fentanyl infusion rate at NAL administration (µg · kg(^{-1}) · h(^{-1}))</td>
<td>1.13 ± 9.31</td>
<td>1.09 ± 9.41</td>
<td>0.84</td>
</tr>
<tr>
<td>Epidural fentanyl–bupivacaine bolus volume to achieve a VAS score ≤3 (ml)</td>
<td>8.0 ± 7.6</td>
<td>9.4 ± 7.2</td>
<td>0.71</td>
</tr>
<tr>
<td>Total fentanyl–bupivacaine volume from epidural activation to NAL administration (ml)†</td>
<td>39.5 ± 11.3</td>
<td>39.1 ± 11.8</td>
<td>0.81</td>
</tr>
<tr>
<td>Total fentanyl dose from epidural activation to NAL administration (µg/kg)</td>
<td>5.89 ± 12.2</td>
<td>5.13 ± 14.9</td>
<td>0.25</td>
</tr>
</tbody>
</table>

* Values are rounded off to the nearest integer.
† Values include epidural fentanyl–bupivacaine bolus volumes.
‡ Differences between the two groups are not significant.

NAL = nalmefene; ROA = reversal of analgesia; VAS = visual analog scale.
administration of nalmefene that was not present initially. Somnolence of a potentially problematic level (sedation score of 2 or 3) was observed in none of the patients. At no time during the evaluation period was respiratory depression noted in any patient, nor was a naloxone infusion necessary to treat an adverse side effect.

Discussion

The objective of this dose-finding study was to establish the MTD of nalmefene that spares analgesia in an acceptable number of patients receiving epidural fentanyl and dilute bupivacaine for postoperative pain control. Confirmatory assessment of the safety and efficacy of nalmefene necessitates the results of a large double-blinded, placebo-controlled trial, which is currently underway, to determine the effectiveness of our MTD in ameliorating epidural fentanyl-induced side effects (e.g., pruritus, nausea, vomiting, and somnolence).

During the early phases of designing our study, several approaches were considered. A traditional approach would have involved four groups of patients randomized among the four preselected nalmefene doses (e.g., 0.25, 0.50, 0.75, and 1.00 µg/kg). All patients in a particular group would have received the same nalmefene dose in double-blinded fashion. This idea was abandoned for several reasons: If a minimum of 10 patients per group were included, then a total of 40 patients would be needed (even more if a placebo group were considered), and more efficient study designs requiring fewer patients were available; the selection of a suboptimal range of doses would not be discovered until the study was completed; and selecting doses for patients adaptively, using the dose-outcome data from patients treated previously in the trial, would expose fewer patients to a drug dose with an unacceptably high $P_{ROA}$. One adaptive approach is the standard "3 + 3" algorithm often used by medical oncologists to evaluate the MTD of a new chemotherapeutic agent in cancer patients. Although fewer patients would be necessary to determine a nalmefene MTD, an inherent weakness of this algorithm is its relatively high probability of either underestimating the MTD or obtaining inconclusive data. The recently developed MCRM has been used by medical oncologists as a desirable alternative for determining the MTD of a new chemotherapeutic agent. Extensive simulation studies indicate that the MCRM is, in fact, superior to the 3 + 3 design in estimating a reliable MTD and is more likely to treat patients in the trial with doses at or close to the MTD.

The MCRM necessitates preselection of a target adverse event probability value before the trial begins. We theorized that a nalmefene dose that reversed analgesia in only 5–10% of patients ran the risk of being ineffective in reducing epidural opioid-induced side effects in a large placebo-controlled, double-blinded trial. On the other hand, a dose that reversed analgesia in 25–50% of patients might make pain management difficult or impractical. As a compromise, we targeted a nalmefene dose that would reverse analgesia in 20% of our patients. A search of the literature for an approximate dose revealed several previous studies that used nalmefene in doses of 0.25–0.75 µg/kg to either prevent or treat opioid-induced side effects, but these studies involved patients receiving neuraxial morphine.

Initially, we defined the stopping criteria for our trial to have no minimum patient number, a maximum patient number of 21, and a minimum number of patients treated at MTD of six. Pertinently, it is standard practice in conventional toxicity trials using the 3 + 3 algorithm to stop after six subjects have been treated at the MTD of the study drug. After only 11 patients were treated in our trial, the MTD of nalmefene was estimated to be 0.50 µg/kg. However, at this point we were substantially uncertain about the $P_{ROA}$ associated with the 0.50 and 0.75 µg/kg dose levels because only one patient had been treated with the higher dose. As a result, the trial was extended to 25 patients. The MTD of nalmefene remained the same, and notably, the MCRM treated the last seven patients (numbers 19–25) at the MTD.

Although the MCRM algorithm, as implemented in our trial, allowed testing of nalmefene dose levels with ROA probabilities much in excess of our target $P_{ROA}$, the MCRM only treated 3 of 25 patients at the 0.75 µg/kg dose level and none at 1.00 µg/kg dose level. In fact, after ROA was observed in two of the three patients receiving the 0.75 µg/kg dose, the algorithm would no longer escalate to that dose. Because the extrapolated $P_{ROA}$ associated with the 1.00 µg/kg dose was estimated to be far above 0.20, that dose was not even tested. This intended safety feature does not exist in the more traditional randomized double-blinded trial described previously, in which all of the patients in those groups assigned to dose levels with ROA probabilities exceeding our acceptable $P_{ROA}$ would be exposed to an increased risk of ROA.

Several concerns about the MCRM in our study must be addressed. A problem with practical implementation...
of the MCRM arises from the need to know the outcome from the previous cohort in order to determine the recommended dose for the next cohort. For example, during evaluation of the MTD of a new chemotherapeutic agent, toxicity often is not observed immediately after treatment, and the MCRM might need considerable time to complete. Moreover, this problem exists regardless of the dose-finding algorithm whenever decisions are made adaptively and becomes primarily a logistic problem if one or two individuals are used in a cohort. On the other hand, selected analgesic or anesthetic agents with desirable as well as adverse dose-dependent effects are ideal drugs to be evaluated by the MCRM because their effects are evident after a very short time.

The MCRM as employed in our trial was unblinded for the evaluator, and the potential exists for knowledge of the drug dose to bias the evaluator’s interpretation of the patient’s response. A way to reduce this bias would be to deny the evaluator knowledge of the administered drug dose. In our study, at the time of nalmefene administration, the five patients with nalmefene-induced ROA and the remaining patients without ROA received similar epidural fentanyl–bupivacaine infusion volumes, epidural boluses, and fentanyl doses. However, because our sample size is small, caution is exercised in stating that the ROA was not likely a result of the possibility that those five patients received less opioid or bupivacaine than the remaining patients without ROA.

In summary, we have used the recently-developed MCRM to determine that the MTD of nalmefene is 0.50 μg/kg. This dose, if administered to patients receiving epidural fentanyl in dilute bupivacaine for postoperative pain control, reverses analgesia in approximately 20% of. More generally, we suggest that the MCRM may be an effective and probably safe statistical tool for determining the best doses of new analgesic or anesthetic drugs that cause dose-dependent adverse effects.

References