Effective dose of nefopam in 80% of patients (ED_{80}): a study using the continual reassessment method

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What is already known about this subject

- Dixon's up-and-down technique allows the calculation of the median effective dose (ED_{50}) of a drug with a limited number of patients.
- However, it is not possible to calculate the effective dose in more than 50%, i.e. in 80% or 90% (ED_{80} or ED_{90}) of the patients with this technique.

What this study adds

- We used the continual reassessment method, which is a Bayesian method to determine ED_{80} , the dose of nefopam relieving pain in 80% of postoperative patients. The ED_{80} was close to 60 mg, higher than the usual dose of 20 mg.

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Aims

The effective dose in 50% of patients (ED_{50}) is far from being relevant for clinical purposes. We used the continual reassessment method (CRM) to determine the effective dose of nefopam in 80% of the patients suffering from moderate pain in the postoperative period (ED_{80}).

Methods

Patients with a pain intensity >3 on a 1–10 numerical pain score (NPS) received increasing or decreasing doses of nefopam (20, 30, 40, 60, 80 mg) postoperatively. The criterion of success was a NPS ≤ 3 , 30 min after the beginning of infusion. The initial dose was 20 mg and the subsequent doses were determined by the continuous reassessment method (CRM). The data were also fitted *a posteriori* with the maximum likelihood technique.

Results

Twenty-four patients were enrolled. Nefopam 60 mg gave a probability of success of 0.818 (95% credibility interval 0.606–0.941). Using the maximum likelihood technique, we determined an ED_{50} of 27.3 mg and a dose leading to a probability of 0.8 (ED_{80}) of 74.4 mg. We did not observe a high incidence of side-effects.

Conclusions

The ED_{80} of nefopam, close to 60 mg is higher than the usual dose of 20 mg. The CRM allowed us to determine the ED_{80} of nefopam with reasonable accuracy in a small number of patients as compared with the classical dose-probability curve fitting. We did not observe an increased incidence of side-effects when compared with the literature or to our previous studies.

Introduction

Nefopam is an analgesic agent used to treat mild to moderate postoperative pain [1–3]. It acts principally by inhibiting serotonin, dopamine and noradrenaline reuptake [4, 5]. Numerous studies have consistently shown a 30–40% decrease in opioid consumption when nefopam is used in the postoperative period [1–3]. We have recently shown that its association with morphine was infra-additive, whereas its association with ketoprofen showed an important synergy [6, 7]. However, in these two studies, the median effective dose (ED₅₀) of nefopam was measured (in the following, effect is the probability of success and ED_i is the dose effective in *i* percentage of the patients). Because in daily clinical practice, it is necessary to obtain satisfactory pain relief in at least 80–90% of the patients, we aimed to determine the effective dose in 80% of the patients, ED₈₀. Dixon's up-and-down method [8] is not the best technique for measuring ED₈₀. The shape of the dose-probability curve may vary and the up-and-down technique that focuses only on the dose leading to 50% of the effect does not provide information on the more clinically relevant parts of the curve (Figure 1). Moreover, the accuracy of the estimates given by the up-and-down technique has been questioned [9, 10]. We used the continual reassessment method (CRM) [11] to estimate ED₈₀. The CRM has already been used for dose-finding, particularly in phase I trials for cytotoxic drugs [11–13]. This method uses the Bayes formula to calculate the probability of success of predetermined doses. Contrary to the up-and-down technique, this method uses all the information gained by incorporating data from consecutive patients. Therefore, the number of patients required to calculate the ED₈₀ (or the dose leading to any other probability of success) of a drug is markedly reduced when the CRM is used as compared with any other technique [14, 15]. Contrary to the up-and-down technique, which is a memory-less procedure, the CRM is a Bayesian technique that retains the memory of all previous events. The CRM is commonly used in dose-finding studies to establish the maximum tolerated dose of a new drug [15], and also to determine adequate dosing of various drugs in phase III or IV studies [16–18].

Methods

Patients

After Ethics Committee approval (Cochin-Port-Royal Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France) and written informed consent was obtained from the patients, 24 American Society of Anaesthesiologists physical status I or II patients were enrolled. The

Figure 1

Dose-probability curves obtained with different parameters of the logistic equation. In this case, ED₅₀, the dose leading to 50% probability of success is the same (10 units), but the probability at dose = zero (placebo effect) and the probability of correctly treating 80% of the patients markedly differ. When Dixon's up-and-down technique is used, only the probability of 50% success is known. The clinical needs, i.e. correctly treating more than 80 or 90% of the patients, cannot be approached by this technique. Conversely, the CRM allows the calculation of any predetermined probability (—, $a_0 = -4$, $\theta = 0.4$; ---, $a_0 = -1$, $\theta = 0.1$; ···, $a_0 = -0.5$, $\theta = 0.05$)

protocol design considered the total number of patients to be enrolled should be between 24 and 36, the final number being determined by the stopping criteria of the CRM. All patients were scheduled for moderately painful surgery. Non-inclusion criteria were as follows: 1) contra-indications to the use of nefopam, including pregnancy; 2) age under 18 years; 3) postoperative pain less than or equal to 3 on a numeric pain scale (NPS) (0 = no pain to 10 = the worst possible pain) upon arrival in the post anaesthesia care unit (PACU).

Anaesthetic protocol

The evening before surgery, patients were instructed on how to use the NPS. All patients received general anaesthesia with propofol or thiopental and desflurane or sevoflurane. Remifentanyl or sufentanyl were used based on the preferred choice of the attending physician. All patients received 1 mg droperidol intravenously at the end of surgery to prevent nausea and vomiting.

Analgesia

The study was double-blind and prospective. Blinding was ensured by using syringes freshly prepared by an anaesthesiologist not involved in the patient's pain assessment. Immediately after arrival in the PACU, pain

intensity was assessed using the NPS. As soon as the pain score was greater than 3 [19], the patient was included and received one of the following doses of nefopam as a continuous 15 min intravenous infusion: 20, 30, 40, 60, 80 mg. The dose of nefopam received in each cohort was determined by the response of the previous patients and automatically defined by the CRM software (see statistical analysis). The range of doses used was based on previous studies [6, 7].

The efficacy of the study drug was assessed using the NPS 30 min after the beginning of drug administration. Two outcomes were considered: effective analgesia: NPS less or equal to 3/10 or ineffective analgesia: NPS greater than 3. At this time (30 min after the beginning of nefopam administration), patients who complained of ineffective analgesia were given rescue analgesia and morphine titration was started according to the usual rules of our PACU.

Adverse effects

Known adverse effects of nefopam (sweating, nausea, vomiting, dizziness, tachycardia, dry mouth, high blood pressure, local pain due to drug infusion) were recorded every 15 min after the injection until the patient's discharge from the PACU.

Modelling procedure and statistical analysis

Nefopam ED_{80} (probability of efficacy in 80% of the patients) was first modelled using the continual reassessment method (CRM) [11]. We considered that the probability of response (P) followed a logistic model:

$$P = \frac{\exp(a_0 + \theta \text{Dose})}{1 + \exp(a_0 + \theta \text{Dose})}$$

where a_0 and θ are, respectively, the intercept and the slope of the logit and Dose is the dose of nefopam injected. With this model, the probability of response for Dose = 0 (placebo effect) is

$$P_0 = \frac{\exp(a_0)}{1 + \exp(a_0)}$$

and the dose leading to a probability of 50% is

$$ED_{50} = \frac{-a_0}{\theta}$$

In addition, a logistic model was fitted at the end of the trial using the procedure glm of S-PLUS [20].

Continuous reassessment method (CRM)

The software BPCT uses the Bayes formula and a one parameter logistic model (θ). The doses, the associated prior probabilities, the intercept of the logit (a_0), the

number of patients in the cohorts are chosen *a priori* according to the clinical experience of the investigator(s). The software gives the posterior probability for each dose and the credibility interval of the probability associated with each dose. A set of predetermined doses with their expected probabilities of success are first chosen. Then, the principle exists to give a dose to the first patient (or cohort of patients) and to increase or decrease the dose for the next patient (or cohort of patients) according to the posterior conditional probability of success (or failure) calculated by the software using the Bayes formula. We used the software BPCT [21] with cohorts of three patients, one-step escalation (the next cohort receives the next higher dose, even if a much higher dose seems adequate according to the probabilities calculated by the software) and a low initial dose in order to have the maximum number of patients treated in a wide range of the dose-probability curve. In order to have better information on the lower and higher parts of the dose-probability curve, we decided to begin with two cohorts of three patients receiving the lower dose (20 mg) and to finish with an additional cohort of three patients receiving the highest dose (80 mg). *A priori* probabilities of 0.40, 0.55, 0.70, 0.85 and 0.90 were associated with the following doses: 20, 30, 40, 60 and 80 mg, respectively. These doses and probabilities have been chosen in order to have a wide range of probabilities and doses with minimal deviation from our previous results [6, 7]. We made the choice of a target probability of success of 80%. The prior distribution was exponential with a mean of 1 and the (fixed) intercept of the logit was -3 . We considered a minimum number of patients of 21 and a maximum of 33. Between these two numbers, we decided to use the following stopping rules (adapted from Zohar & Chevret [22]):

- 1 A posterior probability of response lower than the lower dose (inappropriate dosing scheme).
- 2 A posterior probability of response higher than the higher dose (inappropriate dosing scheme).
- 3 A width of the 95% credibility interval (the Bayesian credibility (or credible) interval is the probability given the data that the true value is in this interval) of the probability less or equal to 0.15 (i.e. the interval between two consecutive doses).

With the mandatory additional final cohort of three patients at the highest dose, the total number of patients possibly entering the study was then between 24 and 36.

Although not independent, the data were also fitted *a posteriori* using the function glm of S-PLUS considering a binomial distribution with a logit link. We used the one parameter and the full two parameter logistic

equation. This procedure uses the maximum likelihood (assuming independence) maximization process. It has been shown that the use of the Bayes formula or of a repetitive fitting by the maximum likelihood rapidly leads to similar results [13]. We also performed an *a posteriori* fitting of a two-parameter equation (full logistic model) to draw a full dose-effect curve. In order to assess better the number of patients needed to obtain the same degree of precision of the target probability with the logistic regression than with the CRM, we performed simulations. Monte Carlo simulations (5000 replicates) were then conducted to calculate the 95% confidence intervals associated with data sets containing an increasing number of patients. These simulations were done using the two parameters (intercept and slope of the logit) initially calculated by fitting the full logistic model. Bernoulli variables with probabilities of success equal to those calculated by fitting the two-parameter model were generated. Simulations were done with 5000 repetitions, considering data sets of 100, 200, 400 and 800 subjects receiving doses of 20, 30, 40, 60 and 80 mg (equally distributed in each dose group, i.e. 20, 40, 80 and 160 patients/group, respectively).

The data are reported as the probability of success and 95% credibility interval, as the fitted parameter(s) of the logit and their 95% confidence interval calculated by a non parametric Bootstrap stratified by cohorts with 1000 replicates and as the 95% confidence interval of the parameters of the logit after Monte Carlo simulations.

Demographic data and adverse effects are reported as the mean $\pm$ SD or counts and proportions. Figures are given with three significant digits.

Results

Two patients had a NPS lower than three upon arrival in the PACU and were not included. Demographic data (age, sex ratio, body weight, type and duration of surgery) are shown in Table 1. The NPS at the time of inclusion and 30 min later are shown in Table 2. Seven patients (29%) had nausea, two patients presented with sweating (8%) and one patient had a transient decrease in blood pressure not related to the medication. No respiratory depression was noted. None of these patients was excluded. The procedure converged rapidly (Figure 2). Because of a misinterpretation of the results given by the software, the trial was stopped prematurely, i.e. after 24 patients including the three additional patients who received 80 mg (Table 3).

With the Bayesian method, a dose of 60 mg of nefopam gave a probability of success of 0.818 with a 95% credibility interval between 0.606 and 0.941 (Figure 3).

Table 1

Demographic data for the 24 patients

Sex (%)	
Female	18 (75%)
Male	6 (25%)
Age (years)	41 $\pm$ 14
Surgery (%)	
Tympanoplasty	10 (42%)
Thyroidectomy	8 (33%)
Parotidectomy	1 (4%)
Endoscopic cholecystectomy	5 (21%)
Duration of surgery (min)	120 $\pm$ 42
Intraoperative analgesia (%)	
Remifentanyl (%)	15 (62%)
Sufentanil (%)	9 (38%)

Table 2

Pain intensity and analgesia

Pain score (NPS: 0–10)	
0 min	5 (4–9)
30 min	2 (1–5)
Analgesia	
Effective	17 (71%)
Ineffective	7 (29%)

Data are expressed as median and range or count (%) as appropriate. NPS (numerical pain scale) ranges from 0 = no pain to 10 = worst possible pain.

With the maximum likelihood method used to fit the one parameter equation, the slope of the logit was $\theta = 0.0724$ (95% confidence interval 0.0529, 0.111) (Figure 3).

With the two parameter logistic model, the intercept of the logit was -0.803 (95% confidence interval: -3.39 , 1.33) and the slope was 0.0294 (95% confidence interval -0.013 , 0.085). These figures gave a probability at dose = 0 mg (ED₀, placebo effect) of 0.309 and a dose leading to a probability of 0.5 (ED₅₀) of 27.3 mg, respectively. Similarly, the dose leading to a probability of 0.8 (ED₈₀) was 74.4 mg. The results of the Monte Carlo simulations are reported in Table 4 and are also displayed in a graphic form in Figure 4.

Discussion

The main finding of this study is that the ED₈₀ of nefopam administered intravenously as a sole agent in

Figure 2

Probability of success of the 60 mg dose according to the number of patients included. The dashed lines are the limits of the 95% credibility interval. The symbols used show the dose supposed to be closest to the target probability of 0.80 computed for the next patient: triangle 30 mg, square 40 mg, circle 60 mg. At the end of the fifth cohort (15th patient), the dose associated with the target probability remained constant and the credibility interval remained nearly constant

postoperative patients with moderate pain is close to 60 mg. This dose is higher than the dose used based on recommendations from the manufacturer [1, 2].

ED₅₀, the dose leading to the probability of successful treatment in 50% of the patients is the parameter usually measured to quantify the potency of a drug. For that purpose, two different approaches may be used: 1) the construction of a complete dose–probability curve, or 2) a method focusing on the target parameter such as the up-and-down technique, which is memory-less like all processes based on a Markov chain. The construction of a full dose–probability curve has the advantage of allowing the calculation of the dose leading to any probability of interest (ED₂₀, ED₈₀, ED₉₀, ...). However, the number of patients required is important. The rather large 95% confidence interval contours displayed in Figure 4 clearly show that several hundred patients are needed if one wants to draw a complete dose–probability curve, mainly because of the binomial nature of the response. When a simulation is done with 800 patients (five groups of 160 patients each receiving the 20, 30, 40, 60 and 80 mg doses) the coefficient of variation of the two parameters are 43% and 25% for the intercept and the slope of the logit, respectively. This is due to the 0/1 response and to the heteroscedastic nature of the logit with a variance dependent on the probability itself. However, the loss of information due to the transformation of the data from categorical (NPS from 0 to 10) to binomial (0/1) is only due to the interindividual

variability and will not be solved by using the dose–effect curve rather than the dose–probability curve. Only stratification of the data or incorporation of covariates in a mixed-effect modelling process may decrease this variability if the full NPS information is used.

Dixon's up-and-down method needs fewer patients, but gives information only on a specific point (ED₅₀) of the curve. This dose is only a median value and a large interindividual variability (obvious from the graphs of sequential results) is often observed (see Figure 2 [6] and Figure 3 [7]). In addition, although the calculation of a parameter of interest different from the ED₅₀ is possible by the up-and-down method, the number of patients required becomes rapidly unreasonable when the probability of interest deviates from the ED₅₀.

The continual reassessment method, which is a Bayesian method, has the advantage of focusing on a specific probability using all the information given by the entire cohort of patients. Therefore, the probability of interest may be calculated with a very small group of patients. In the present study, the 60 mg dose was rapidly found to be the dose closest to the ED₈₀ and the width of the 95% credibility interval rapidly decreased (Table 3 and Figure 2). Our choice of an intercept of –3 was dictated by the fact that this value is the most commonly used in the literature probably because computations are stable in this case and because this value leads to a negligible intercept of the dose–probability curve (placebo effect).

Because it has been shown that the traditional CRM using the Bayes formula or a method using the maximum likelihood rapidly gave the same results [14], we fitted *a posteriori* the one parameter logistic equation used with the CRM with the procedure glm of S-PLUS. This fitting was performed with the original cohort, i.e. with correlated data and an unequal number of patients in each dose group so the results should be interpreted with care. The results were similar between the two methods for the target probability of 0.8 (Figure 3). However, because the effect of the prior probabilities and the choice of the intercept of the logit has an uncertain effect on the resulting posterior probabilities when the Bayesian CRM is used as compared with the maximum likelihood method [11–15, 22], this procedure must be favoured to the modification using the maximum likelihood. The only limitation to the use of the technique seems to be a weak dose–response curve [16–18]. In the clinical trials where the CRM failed, an *a posteriori* analysis of the data showed that no clear relationship was present between dose and effect or probability. In the field of anaesthesia, effects are usually clearly related to the dose (either with muscle relaxants

Table 3

Dose administered to each cohort and probability of success (P) of the 60 mg dose after the n^{th} subject (cf. Figure 2)

Subject	NPSTO	Posterior probability for the 60 mg dose				
		Dose (mg)	P (60 mg)	CI low	CI high	CI percentage
0–3	5	20	0.862	0.141	0.997	99
4–6	5	20	0.733	0.166	0.973	110
7–9	5	30	0.776	0.347	0.962	79
10–12	6	40	0.784	0.369	0.960	75
13–15	5	60	0.852	0.561	0.970	48
16–18	6	60	0.816	0.555	0.951	49
19–21	5	60	0.790	0.549	0.933	49
22–24	5	80	0.818	0.606	0.941	41

Dose is the dose administered to the cohort, P is the posterior probability for the 60 mg dose, CI low and CI high are the lower and upper values of the 95% credibility interval, CI percentage is the credibility interval normalized by P in percentage, NPSTO is the median baseline NPS for the cohort.

Figure 3

Result of the CRM and the corresponding *a posteriori* maximum likelihood fitting of the one parameter equation (after the 24th patient). The filled circle is the probability of success of the 60 mg dose with its credibility interval calculated by the CRM. The thick dashed line is the dose–probability curve fitted by the maximum likelihood method with the procedure glm of S-Plus (one parameter logistic link) and the thin dashed lines are the contour of the 95% confidence interval

or with analgesic drugs) and the CRM appears to be a method leading to a precise response with a minimal number of patients.

With the CRM, we measured a probability of success (adequate analgesia) of 82% in patients receiving 60 mg nefopam for relieving moderate postoperative pain. These results are in accordance with our previous findings of an ED₅₀ of 28 mg when we used Dixon's up-and-down technique [7] and with the ED₅₀ calculated by fitting the full two-parameter logistic model (27.3 mg as

Table 4

95% confidence interval of the parameters of the full logistic equation simulated with 100, 200, 400 and 800 patients. The typical values were: intercept $a_0 = -0.803$ and $\theta = 0.0294$ (see Figure 4)

Number of subjects	a_0	θ
100	-1.89 0.147	0.010 0.0550
200	-1.53–0.102	0.0154 0.0457
400	-1.32–0.342	0.0196 0.0406
800	-1.16–0.469	0.0223 0.0371

compared with the 0.55 probability of success of the 30 mg dose calculated with the CRM, Table 3). It seems at first glance that our data do not concur with previous information [1–3], particularly because the dose recommended by the manufacturer is 20 mg. Surprisingly, however, it is hard to find the rationale for recommending this dose as no dose–response study has been published or is available in the manufacturer files. The recommendation to use 20 mg intravenously may result from dose-comparison studies such as the study by Sunshine & Laska in which 20 mg of nefopam was found to be equipotent to 12 mg of morphine sulphate [23]. However, other studies have not found such a high potency of nefopam and Tigerstedt *et al.* found 15 mg of nefopam equipotent to 50 mg meperidine [24]. In this case, 20 mg of nefopam would be equipotent to 6.6 mg morphine. In another study, Tigerstedt *et al.* [25] administered nefopam 15 mg intravenously every 10 min up to

Figure 4

Probability of response fitted by the two-parameter logistic equation (thick line at the centre, labelled typical value in the inset). The triangles on the x-axis are the doses given to the patients and used in the data sets generated for the simulations. Using the parameters calculated by the logistic regression, data sets of 100, 200, 400 and 800 patients have been generated considering a Bernoulli distribution and the logistic model was fitted to those data. The procedure was repeated 5000 times, thus allowing the calculation of confidence intervals. The different dashed lines around the line corresponding to the typical values are the 95% confidence interval contours. The inset shows for each line (upper and lower 95% CI) the number of subjects used for the data set. Even, when as many as 800 subjects are used, the 95% CI interval remains wide. Typical value (—); 100 low (—); 100 high (—); 200 low (---); 200 high (---); 400 low (---); 400 high (---); 800 low (---); 800 high (---)

90 mg. Interestingly, they obtained a maximum analgesic effect with 60 mg and no additional benefit when increasing the dose to 90 mg.

The manufacturer's recommendation of 20 mg can possibly be explained by a high incidence of side-effects with large doses. Again, as no dose-response curve is available, it is difficult to ascertain the relation between dose and incidence or severity of side-effects and the results from the literature are not conclusive [23–27]. The occurrence of adverse effects was not increased in the present study as compared with our previous results [6, 7]. However, because of the small number of patients studied, we are unable to draw any definite conclusion.

In conclusion, the use of the CRM allowed us to determine the ED_{80} of nefopam using a limited number of patients. Because we do not know if this dose (60 mg infused intravenously in 15 min) significantly increases

the incidence of side-effects, further studies are needed to determine which dose possesses the better analgesic vs side-effects profile.

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References

- McIntock TT, Kenny GN, Howie JC, McArdle CS, Lawrie S, Aitken H. Assessment of the analgesic efficacy of nefopam hydrochloride after upper abdominal surgery: a study using patient controlled analgesia. *Br J Surg* 1988; 75: 779–81.
- Mimoz O, Incagnoli P, Josse C, Gillon MC, Kuhlman L, Mirand A, Soilleux H, Fletcher D. Analgesic efficacy and safety of nefopam vs. propacetamol following hepatic resection. *Anaesthesia* 2001; 56: 520–5.
- Du Manoir B, Aubrun F, Langlois M, Le Guern ME, Alquier C, Chauvin M, Fletcher D. Randomized prospective study of the analgesic effect of nefopam after orthopaedic surgery. *Br J Anaesth* 2003; 91: 836–41.
- Piercey MF, Schroeder LA. Spinal and Supraspinal sites for morphine and nefopam analgesia in the mouse. *Eur J Pharmacol* 1981; 74: 135–40.
- Rosland JH, Hole K. The effect of nefopam and its enantiomers on the uptake of 5-hydroxytryptamine, noradrenaline and dopamine in crude rat brain synaptosomal preparations. *J Pharm Pharmacol* 1990; 42: 437–8.
- Beloeil H, Delage N, Negre I, Mazoit JX, Benhamou D. The median effective dose of nefopam and morphine administered intravenously for postoperative pain after minor surgery: a prospective randomized double-blinded isobolographic study of their analgesic action. *Anesth Analg* 2004; 98: 395–400.
- Delage N, Maaliki H, Beloeil H, Benhamou D, Mazoit JX. Median effective dose (ED_{50}) of nefopam and ketoprofen in postoperative patients: a study of interaction using sequential analysis and isobolographic analysis. *Anesthesiology* 2005; 102: 1211–6.
- Dixon WJ. Staircase bioassay: the up-and-down method. *Neurosci Biobehav Rev* 1991; 15: 47–50.
- Paul M, Fisher DM. Are estimates of MAC reliable? *Anesthesiology* 2001; 95: 1362–70.
- Lu W, Ramsay JG, Bailey JM. Reliability of pharmacodynamic analysis by logistic regression: mixed-effects modeling. *Anesthesiology* 2003; 99: 1255–62.
- O'Quigley J, Pepe M, Fisher L. Continual reassessment method: a practical design for phase 1 clinical trials in cancer. *Biometrics* 1990; 46: 33–48.
- Kramar A, Lebecq A, Candall E. Continual reassessment methods in phase I trials of the combination of two drugs in oncology. *Stat Med* 1999; 18: 1849–64.

- 13 Storer BE. An evaluation of phase I clinical trial designs in the continuous dose–response setting. *Stat Med* 2001; 20: 2399–408.
- 14 O’Quigley J, Shen LZ. Continual reassessment method: a likelihood approach. *Biometrics* 1996; 52: 673–84.
- 15 Whitehead J, Zhou Y, Stallard N, Todd S, Whitehead A. Learning from previous responses in phase I dose-escalation studies. *Br J Clin Pharmacol* 2001; 52: 1–7.
- 16 Fabre E, Chevret S, Piechaud JF, Rey E, Vauzelle-Kervodan F, D’Athis P, Olive G, Pons G. An approach for dose finding of drugs in infants: sedation by midazolam studied using the continual reassessment method. *Br J Clin Pharmacol* 1998; 46: 395–401.
- 17 Desfrere L, Zohar S, Morville P, Brunhes A, Chevret S, Pons G, Moriette G, Rey E, Treluyer JM. Dose-finding study of ibuprofen in patent ductus arteriosus using the continual reassessment method. *J Clin Pharm Ther* 2005; 30: 121–32.
- 18 Dougherty TB, Porche VH, Thall PF. Maximum tolerated dose of nalmeferene in patients receiving epidural fentanyl and dilute bupivacaine for postoperative analgesia. *Anesthesiology* 2000; 92: 1010–6.
- 19 Dihle A, Helseth S, Paul SM, Miaskowski C. The exploration of the establishment of cutpoints to categorize the severity of acute postoperative pain. *Clin J Pain* 2006; 22: 617–24.
- 20 Venables WN, Ripley BD. *Modern Applied Statistics with S-PLUS*. Statistics and Computing Series 3rd edn. New York, Springer-Verlag, 1999.
- 21 Zohar S, Latouche A, Taconnet M, Chevret S. Software to compute and conduct sequential Bayesian phase I or II dose-ranging clinical trials with stopping rules. *Comput Meth Programs Biomed* 2003; 72: 117–25.
- 22 Zohar S, Chevret S. The continual reassessment method. comparison of Bayesian stopping rules for dose-ranging studies. *Stat Med* 2001; 20: 2827–43.
- 23 Sunshine A, Laska E. Nefopam and morphine in man. *Clin Pharmacol Ther* 1975; 18: 530–4.
- 24 Tigerstedt I, Sipponen J, Tammisto T, Turunen M. Comparison of nefopam and pethidine in postoperative pain. *Br J Anaesth* 1977; 49: 1133–8.
- 25 Tigerstedt I, Tammisto T, Leander P. Comparison of the analgesic dose-effect relationships of nefopam and oxycodone in postoperative pain. *Acta Anaesthesiol Scand* 1979; 23: 555–60.
- 26 Scherpereel P. Utilisation pratique des analgésiques non morphiniques dans le traitement de la douleur aiguë postopératoire. *Ann Fr Anesth Réanim* 1985; 4: 446–50.
- 27 Phillips G, Vickers MD. Nefopam in postoperative pain. *Br J Anaesth* 1979; 51: 961–5.