Feasibility study for the administration of remifentanil based on the difference between response entropy and state entropy†

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Background. Facial electromyography (FEMG) may have utility in the assessment of nociception during surgery. The difference between state entropy (SE) and response entropy (RE) is an indirect measure of FEMG. This study assesses an automated algorithm for remifentanil administration that is based on maintaining an entropy difference (ED) that is less than an upper boundary condition and greater than a lower boundary condition.

Methods. The algorithm was constructed with a development set (n=40), and then automated and studied with a validation set (n=20) of patients undergoing anterior cruciate ligament repair. The percentage of time that the ED was maintained between the two boundary conditions was determined. Remifentanil and propofol predicted effect-site concentrations (Ce) were determined at surgical milestones and, after drug discontinuation, the time to response to verbal stimulation and orientation was measured.

Results. The median (25th–75th percentile) per cent of time that the ED was recorded between the boundary conditions was 99.3% (98.1–99.8%). Predicted propofol (μg ml−1) and remifentanil (ng ml−1) Ce (so), respectively, were 3.5 and 4.0 at induction, 1.9 (0.8) and 7.2 (3.7) at the end of surgery, and 1.1 (0.5) and 3.2 (2.2) at eye opening. The median time to eye opening and orientation was 3.8 and 6.8 min, respectively.

Conclusion. This feasibility study supports the concept that remifentanil may be delivered using an algorithm that maintains the difference between SE and RE between the upper and lower boundary condition.


Keywords: anaesthetic techniques, i.v. infusion; anaesthetics i.v., propofol; analgesics, opioid, remifentanil; drug delivery, computerized; monitoring, depth of anaesthesia

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Current thinking about the anaesthetic state considers ‘depth of hypnosis’ separately from ‘depth of analgesia’ or, perhaps more accurately, ‘depth of anti-nociception’. It has become common practice to attend to the ‘depth of hypnosis’ by titrating hypnotic agents to the output from electroencephalographic-based monitors. Determining the appropriate ‘depth of anti-nociception’ is more problematic, as there is wide opioid requirement variability among patients. In addition, it is not clear which assessment of nociception has greatest utility for this purpose. Adequacy of anti-nociception is usually assessed by observing patient responses to surgical stimulation, such as movement, lacrimation, or sympathetic nervous system stimulation. These assessment methods are not ideal: movement and lacrimation are quantal, they are...

†Declaration of interest. A patent application has been submitted by the principal author for the algorithm utilized in the investigation.
either present or absent, and while their presence indicates an inadequate anti-nociceptive state, their absence does not guarantee an adequate state. In addition, the sympathetic nervous system can be affected by a variety of medications, such as beta-blockers or vasodilators, making it a less reliable marker of opioid adequacy. Additional criteria to assist in judging the adequacy of opioid administration could prove to be useful.

A potential source of information is the level of facial electromyographic (FEMG) activity during surgical stimulation. Facial muscles are innervated by both cortical motor pathways and brainstem emotive pathways. In a conscious person, the facial expressions of pain are universal. In an anaesthetized patient, an increase in FEMG activity occurs with stimulation and, in some studies, has been shown to predict arousal. Opioids may be titrated to suppress FEMG, and FEMG activity can guide opioid administration in the opioid-exposed patient. While intriguing, these observations have not been demonstrated to have utility during routine clinical care.

A possible source of objective information about FEMG activity is provided by the difference between state entropy (SE, M-Entropy, GE Healthcare, Helsinki, Finland) and response entropy (RE). SE is calculated from the electroencephalographic power between 0.8 and 32 Hz, or the range of frequencies associated with cortical activity. RE is derived from the activity between 0.8 and 47 Hz. The difference between the entropy readings (RE - SE), or entropy difference (ED), represents activity from 32 to 47 Hz, frequencies among those seen with facial muscle activity. Increases in the ED are associated with painful stimulation. There is some preliminary information that opioid dosage can be titrated to the ED: in a recent clinical utility study of the entropy monitor, alfentanil was administered to keep the ED below 10.

This preliminary, feasibility study describes the development of an algorithm for remifentanil administration that utilizes the difference between RE and SE as a surrogate marker for adequacy of the level of anti-nociception. The specific goal of the study was to characterize the performance of the system in terms of the percentage of suggested changes in remifentanil Ce that were clinically acceptable, and the percentage of the time that the algorithm was able to maintain the ED between the upper and lower boundary conditions. In addition, the predicted effect-site concentration of remifentanil and propofol at surgical milestones was determined, as was the time to response to verbal stimulation and orientation, the incidence of patient movement, the haemodynamic response of the patient during surgery, and the incidence of awareness after surgery.

Methods

The study was approved by the hospital Institutional Review Board and all patients gave signed informed consent. The study consisted of a developmental set (n=40) and a validation set (n=20) of patients undergoing anterior cruciate ligament repair. For both sets, inclusion criteria were age between 18 and 55 yr, body mass index 18–30 kg m⁻², no overt cardiopulmonary disease, no opioid consumption within the past month and consumption of fewer than eight alcoholic beverages per week, no use of neuropsychiatric medications, and no known neurological disorder.

For both patient sets, on arrival in the operating theatre, i.v. access was secured and routine monitors were placed: 3-lead ECG, pulse oximeter, non-invasive arterial pressure. An entropy sensor (GE Healthcare, Helsinki, Finland) was placed according to the manufacturer’s specifications and passed the initial impedance check. Midazolam 0.05 mg kg⁻¹ was administered and, 3 min later, a series of three arterial pressure determinations were performed per minute to establish baseline haemodynamic measurements. After preoxygenation, anaesthesia was induced using target-controlled infusions via RUGLOOP II-TCI. RUGLOOP II-TCI simultaneously collected information from operating theatre monitors and, using a three-compartment model enlarged with an effect-site compartment, instructed two infusion pumps to maintain predicted Ce of pharmaceutical agents. Propofol and remifentanil infusion were administered using two Harvard 22 infusion pumps (Harvard Instruments, Cambridge, MA, USA). For propofol, an initial Ce of 3.5 μg ml⁻¹ was targeted and for remifentanil, an initial Ce of 4 ng ml⁻¹ was targeted. Remifentanil Ce limits of 2 and 15 ng ml⁻¹ were utilized. The M-Entropy module exported SE and RE data to RUGLOOP every 5 s via the serial port of the S/5 monitoring system (GE Healthcare, Helsinki, Finland). In both sets, propofol Ce was adjusted to maintain a SE reading of 50.

Developmental set

Each ED was calculated and entered in real time into an Excel spreadsheet that contained the experimental variables of the upper and lower boundary conditions. These variables were investigated via the Dixon’s up-and-down methodology as described below.

The lower boundary conditions were developed at times with no surgical stimulation. The average ED and the median percentage of EDs equal to zero during these times were determined. When these conditions occurred during surgical stimulation, the remifentanil Ce was lowered by a percentage, starting with a 10% decrease. If, within 10 min, the remifentanil decrease resulted in the ED continuing below these boundary conditions, this was considered a negative response and the next remifentanil decrease was increased by 2.5% (i.e. 12.5%). If, within 10 min, the remifentanil decrease resulted in an ED that was greater than the lower boundary condition, it was considered a positive response and the subsequent remifentanil decrease was decreased by 2.5%, to 7.5%.
The upper boundary conditions were developed initially when the opioid level was inadequate: during patient movement or when the heart rate or blood pressure were greater than 20% above baseline. From these observations, an ED of 9 was selected as the upper boundary condition. Differences in time-windowing between the two entropy measurements required that the ED be averaged over several readings, as choosing too small a number of EDs would result in changes in remifentanil concentration that may not be needed, and choosing too great a number would result in a system that reacts too slowly to change in nociception. The number of EDs that should be averaged was analysed by considering each occasion, ED >9, and determining the number of EDs associated with a 95% specificity of representing a ‘true’ increase, rather than a temporary increase that quickly resolved. Next, the appropriate increase in remifentanil Ce was determined by the Dixon’s up-and-down methodology, with the initial increase being 20%. If, within 10 min, the remifentanil increase resulted in a decrease in the ED value below the upper boundary condition, it was considered a positive response and the subsequent increase was lowered by 5% (i.e. 15%). If the increase did not result in the ED decreasing below boundary conditions, it was considered a negative response, the subsequent remifentanil increase was increased by 5% (i.e. 25%). Finally, the lockout period after a remifentanil increase, during which no further increases would be allowed, was determined by examining each positive result and measuring the duration of time between the increase and when the ED decreased below the upper boundary condition. The time by which 95% of the positive results occurred was selected as the lockout period.

The automated remifentanil algorithm

After the determination of the variables, the treatment algorithm was automated, creating the automated remifentanil algorithm (ARA) as a modular subunit of RUGLOOP II. With each new ED, the ARA determined whether the criterion for either remifentanil increase or decrease was met. If so, an alert appeared, which the anaesthetist responded to and effected the suggested change. If the anaesthetist decided not to accept the suggested change, the suggestion remained in place for a default period of 1 min. After a change, a ‘lockout’ period began, which prevented a further similar change for a prescribed period of time. If the criterion for neither an increase nor a decrease was met, no change in remifentanil concentration was suggested (Fig. 1).

Validation set

Two anaesthetists were involved in the patients’ care: one ran the ARA system and the other gave patient care. Both anaesthetists had to agree for changes suggested by the ARA to be implemented. Changes were accepted if there was no clinical reason to reject the suggestion. During surgical preparation, the ARA was set to maintain a remifentanil Ce of 4 ng ml\(^{-1}\), unless criteria for a remifentanil increase were met. The propofol Ce was adjusted to a SE of 50. After surgical incision and during the procedure, the ARA was set to allow both increases and decreases in remifentanil Ce. Non-invasive blood pressure was obtained every minute. Patient movement was treated by increasing the propofol Ce by 25% and by agreeing to the suggested remifentanil Ce increase. At the end of the procedure, keterolac 60 mg i.v. was administered and a femoral nerve block was performed with a nerve stimulator: bupivacaine 0.5%, 30 ml and lidocaine 2%, 10 ml were instilled. The propofol and remifentanil were then discontinued simultaneously, and time to response to verbal stimulation, LMA removal, and orientation were determined. Verbal stimulation was performed by calling the patient’s name loudly every 20 s, and the LMA was removed when the patient responded to commands and had a respiratory rate of at least 6 min\(^{-1}\). The patients were considered oriented when they responded with the correct location and date. Patients were questioned about awareness using the modified Brice protocol\(^{16}\) on the day of surgery in the post-anaesthesia care unit and at 1 week after operation by telephone.

For each patient, the number of remifentanil increases and decreases was determined as was the percentage of ARA-suggested changes that were accepted. The percentage of time that the algorithm maintained the ED between the boundary conditions was determined. The predicted propofol and remifentanil Ce at the end of preparation, average during surgery, at the end of surgery, at drug discontinuation, and upon awakening to verbal stimulation were determined. The average heart rate and arterial pressure under tourniquet were determined as was the percentage of arterial pressure values that were within 20% of baseline.

Remifentanil and propofol Ce at each time point were compared with repeated ANOVA. Correlation between emergence times and length of surgery and propofol and remifentanil predicted Ce was done by linear regression (SigmaStat 3.0, SPSS, Chicago, IL, USA). Effect of gender on emergence times was evaluated with chi-square analysis. A P value of <0.05 was considered significant.

Results

Developmental set

In the 40 patients, the lower boundary condition was met 122 times. Changes in remifentanil concentration ranged from 17.5 to 2.5%; the median change was 10%, which was utilized in the ARA. The upper boundary condition was exceeded 157 times and the remifentanil increase ranged from 10 to 50%; the median result was 25%.
which was utilized in the ARA. In addition, it was determined that the number of elevated EDs needed to have a 95% specificity for a true increase was 4, and the duration for 95% of positive remifentanil increases to decrease the ED below the upper boundary condition was 5.5 min. These values were also incorporated into the ARA.

Validation set
Twenty patients were studied, 15 male, aged 35 (10) [mean (SD)], mean height 174 (8) cm, and mean weight 76 (12) kg. The mean time from induction to start of surgery was 22.3 (18.2) min, time of surgery with tourniquet 89.6 (28.1) min, and time from tourniquet deflation to drug discontinuation was 16.1 (8.2) min.

The range of number of remifentanil increases was 0–7; the median (25th–75th percentile) was 4 (2–5). The range of number of decreases was 0–7, median 4 (1–5). Of the 62 suggested decreases, all were accepted. Of the 76 suggested increases, 75 were accepted; in one patient, an increase was suggested as the dressings were being applied. Examples of the ED and the predicted remifentanil Ce are presented (Fig. 2). The ED was maintained between the boundary conditions for 99.3% (98.1–99.8%) of the time.

Remifentanil Ce at the end of surgery was significantly greater than the average during surgery (Table 1). Both remifentanil and propofol Ce were significantly different at response to verbal stimulation compared with drug discontinuation. Remifentanil Ce at response was similar to the level at induction of anaesthesia.

The ARA resulted in wide interpatient variability of propofol and remifentanil Ce combinations at drug discontinuation and response to verbal stimulation (Fig. 3). The median (25th–75th percentile) time to response to verbal stimulation after drug discontinuation was 3.8 (2.9–7.2) min, the time to LMA removal 4.5 (3.3–7.3) min, and time to orientation 6.8 (4.7–9.0) min. Fourteen of 20 patients responded to verbal stimulation within 5 min of drug discontinuation; the remaining 6 required 6.8–16.9 min. No relationship was found between any of the emergence time measurements and gender, the duration of surgery, or the propofol or remifentanil Ce at any of the time points listed above. The mean heart rate ranged from 42 to 71 beats min$^{-1}$, median 53 (changes from baseline of $-38\%$ to $-4\%$, median $-19\%$). Mean arterial pressure ranged from 64 to 110 mm Hg, median 91 (changes from baseline of $-21\%$ to $18\%$, median $-2\%$). The median (25th–75th percentile) percentage of mean blood pressure readings that were $<20\%$ below baseline was 1.0% (0–6.2%); the percentage of those $>20$ above baseline was 0% (0–2.9%).

Four patients moved transiently during surgical stimulation (Table 2). In all four patients, the ARA suggested a remifentanil increase, and the movement was successfully
treated by accepting this increase and by increasing the propofol Ce by 25%. There were no adverse surgical sequelae as a result of the patient movement. No patient had recall of intraoperative event the day of surgery or at 1 week after operation.

Discussion

This study demonstrated that in healthy patients undergoing ACL reconstruction surgery it was possible to adjust remifentanil Ce utilizing an algorithm based on maintaining a RE–SE difference between upper and lower boundary conditions. When automated, the algorithm made suggested changes in remifentanil Ce that were clinically acceptable, and the algorithm maintained the ED between the boundary conditions the majority of the time. The use of the algorithm resulted in stable haemodynamics and clinically acceptable times to emergence, although the incidence of patient movement requires discussion. These preliminary results also suggest that the ED, as an indication of FEMG activity, may have potential to be used as a surrogate marker for adequacy of anti-nociception.

The ARA does not utilize a direct measurement of FEMG, but rather is based on the premise that the difference between the SE and RE reflects the degree of ongoing FEMG activity. For this to be true, it is likely that the SE needs to be relatively constant. There are three reasons for this: first, the entropy readings are unitless and an ED value may not reflect the same degree of FEMG activity with different SE values. Second, there is a difference in the time-windowing of SE and RE, which are not time aligned. The time windows for SE vary between 15 and 60 s depending on the preponderance of frequencies being analysed: lower frequencies result in a longer overall window. RE is windowed more rapidly, from 15.36 to 1.92 s, with the higher frequencies, 32–47 Hz, analysed in 1.92 s. A sudden increase in FEMG is reflected in an increase RE and an increase in ED. If there is also a change in cortical arousal, the SE will eventually increase

<table>
<thead>
<tr>
<th>Time point</th>
<th>Propofol Ce (SD) (µg ml⁻¹)</th>
<th>Remifentanil Ce (SD) (ng ml⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>3.5 (0.7)*</td>
<td>4.0 (0.3)</td>
</tr>
<tr>
<td>End surgical preparation</td>
<td>2.8 (0.6)*</td>
<td>4.1 (0.3)</td>
</tr>
<tr>
<td>Average surgery</td>
<td>2.0 (0.6)*</td>
<td>5.3 (1.9)*</td>
</tr>
<tr>
<td>End surgery</td>
<td>1.9 (0.8)</td>
<td>7.2 (3.7)*</td>
</tr>
<tr>
<td>Eye opening</td>
<td>1.1 (0.5)*</td>
<td>3.2 (2.2)*</td>
</tr>
<tr>
<td>Orientation</td>
<td>0.9 (0.4)</td>
<td>2.3 (1.5)</td>
</tr>
</tbody>
</table>

Table 1 The predicted propofol and remifentanil Ce and different time points during progression of surgery. *Value is significantly different (P<0.05) from the value preceding it.
as well, and the ED may then decrease. Thus, a short increase in ED may represent only FEMG activation from inadequate anti-nociception, or may represent an incipient change in hypnotic state from inadequate hypnosis and anti-nociception. In either event increased opioid medication may be appropriate. During the development of the ARA, we sought to minimize the issue of time-windowing by considering the ED averaged over time. The third reason to require stable SE values is that there can be overlap between frequencies associated with FEMG and EEG; the frequency band 32–47 Hz also includes γ waves of the EEG, which are associated with consciousness and mentation. With a high SE, the ED could reflect both FEMG and γ activity.

We achieved a stable SE in this study, as SE increase followed by ED increase occurred only with patient movement and awakening after drug discontinuation. All other ED increases were followed by no change in SE values. This is different from the data described by Wheeler and colleagues in which all increases in RE were followed by increases in SE. Thus, changes in ED found in this study probably reflected FEMG change.

Other recent studies have provided insights about the potential utility of the ED as an assessment of nociception. In a study using a propofol–nitrous oxide (N₂O)–alfentanil anaesthetic, alfentanil administration was guided either by routine haemodynamic monitoring or by haemodynamic monitoring and maintaining the ED <10. While the ED-monitored group was given less propofol and emerged more quickly from anaesthesia, there was no difference in alfentanil administration. In a comparison of propofol–N₂O–remifentanil and propofol–N₂O–esmolol, the difference between RE and SE was similar in both groups, suggesting that the ED lacked utility. However, the esmolol group received more propofol and all patients received rocuronium, either of which may account for the lack of effect. In a study of patients receiving one of four concentrations of end-tidal sevoflurane and increasing degrees of electrical stimulation to their forearms, the ED increased in each group with increasing stimulation, but the prediction coefficient of the relationship between ED and degree of stimulation was not high, ranging from 0.528 to 0.686. The authors concluded that the difference seemed to be useful in estimating the nociception, but should be interpreted carefully during anaesthesia. Finally, Ranatan and colleagues described an index of nociception that contains several physiologic variables, one of which was the ED.

Anaesthesia control systems are usually evaluated by their ability to maintain around a set point. The ARA cannot be evaluated this way, as it is designed to maintain the ED between an upper and lower boundary condition, not around a set point. Nevertheless, both the percentage of suggested remifentanil changes that were clinically acceptable and the time that the ED was maintained between the boundary conditions suggest that as a control system, the performance of the automated algorithm was acceptable.

Care guided by the algorithm resulted in a wide variation in remifentanil and propofol Ce that may reflect patient variability, or may represent an unidentified instability in the algorithm. Without a control group, we cannot comment on whether care determined by the ARA was different from routine clinical care and cannot suggest that the algorithm be utilized in the care of patients. However, the median time to emergence, 3.8 min, compared favourably with other control systems using propofol and remifentanil.

Tourniquet use is associated with progressive sympathetic stimulation and increasing heart rate and arterial pressure. In this study, almost all heart rate and mean arterial blood pressure readings were >20% above baseline, suggesting good haemodynamic stability. Patient movement occurred at low combinations of propofol and remifentanil, combinations usually associated with sedation, not general anaesthesia. In the future, movement could be averted by increasing the lower boundary for remifentanil or propofol. This may result in longer emergence from anaesthesia, but should prevent patient movement. An experienced anaesthetist can anticipate changes in the level of nociception and adjust the anaesthetic accordingly; a control system does not have this ability. The surgical model chosen for this study, ACL reconstruction, is associated with moderate and relatively stable degrees of nociception. The behaviour of the algorithm during procedures associated with more intense or variable nociception requires further investigation.

The variables of the algorithm were determined through the developmental set of patients. It is not clear whether these are the ‘ideal’ values for these control variables, and further work will optimize these values. Some clinical situations required multiple remifentanil increases to bring the ED below the upper boundary condition. This is not unexpected, as the percentage increase in remifentanil was determined from the median amount in the validation set. The surgical model also intentionally minimized three factors that could negatively affect ARA performance: neuromuscular blocking drugs, electrocautery, and physical contact of the sensor by the surgical team. The relationship between FEMG response and level of

<table>
<thead>
<tr>
<th>Patient movement time</th>
<th>Remifentanil Ce (ng ml⁻¹)</th>
<th>Propofol Ce (ng ml⁻¹)</th>
<th>Duration at these settings before movement (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 h 26 min</td>
<td>3.6</td>
<td>0.9</td>
<td>20</td>
</tr>
<tr>
<td>1 h 15 min</td>
<td>2.7</td>
<td>1.0</td>
<td>4</td>
</tr>
<tr>
<td>2 h 11 min</td>
<td>2.8</td>
<td>1.3</td>
<td>11</td>
</tr>
<tr>
<td>46 min</td>
<td>2.9</td>
<td>1.2</td>
<td>6</td>
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</table>
stimulation has not been determined. The ARA may allow some degree of neuromuscular block: Wheeler and colleagues\textsuperscript{11} described eight patients who had an increase in ED during painful stimulation when the train-of-four had not returned to normal. Further work will clarify how these factors affect system performance.

In conclusion, this preliminary evaluation of an algorithm that guided remifentanil administration during propofol anaesthesia based on the difference between the SE and RE resulted in clinical care characterized by stable anaesthesia based on the difference between the SE and RE. Further work will clarify how these factors affect system performance.

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References