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A mixture of alfentanil and morphine for rapid postoperative loading with opioid: theoretical basis and initial clinical investigation

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Summary

Pharmacokinetic modelling of estimated central nervous system concentrations was used to devise the optimal mixture of morphine and alfentanil for the treatment of postoperative pain. Modelling revealed that an intravenous opioid pain protocol using an alfentanil−morphine mixture in the proportions 0.75 : 10 mg would provide a profile of analgesia of rapid onset, yet slow offset. The regimen was evaluated in 58 patients in the recovery ward who were randomly allocated to receive analgesia using pain protocols with either morphine or the mixture. Groups were well matched for age, weight and initial pain scores. The mean (SD) time to patient comfort was 27.6 (20.2) min for the mixture and 41.2 (18.6) min for morphine ($p = 0.01$). Multiple regression analysis revealed that that initial pain score ($p = 0.009$) and drug group ($p = 0.02$), but not age, weight or gender were independent predictors of the time to comfort. Drug group was not a significant predictor of adverse effects.

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Postoperative pain and current dose regimens

Despite the best efforts of anaesthetists, many patients still experience moderate to severe pain in the recovery room. This is frequently managed using intravenous opioids titrated to analgesic effect, and nurse-administered 'pain protocols' involving repeated intravenous bolus doses of opioid given at fixed 'lock-out periods' can be very effective in this setting [1, 2].

However, commonly used opioids, such as morphine and pethidine, have a relatively slow onset to peak effect even after intravenous bolus dose administration. When repeated doses are given during titration regimens, the 'lock-out period' between doses must allow for at least some of the effect of each dose to be seen before another is given. This can result in considerable delays before adequate analgesia is achieved. Increasing the frequency of administration of boluses may speed the onset of analgesia, but will also increase the risk of accumulation [3] and adverse effects such as respiratory depression. Choosing an opioid with a more rapid onset, such as alfentanil, may provide more rapid onset of analgesia, but will result in a brief duration of effect.

The aim of this study was therefore to explore the feasibility of a mixture of opioids to produce the features of rapid onset, yet slow offset.

Kinetic and dynamic basis of a mixture of alfentanil and morphine

The concepts used here arose from a recent review of the opioid pharmacokinetic literature by the authors [3]. A data set of kinetic parameters was compiled from the literature (with various assumptions) and used to simulate the time-course of blood and estimated central nervous system (CNS) concentrations of opioids in various settings. It was noted that, after intravenous bolus administration, the estimated CNS concentrations of opioids were delayed relative to their blood concentrations to different extents depending on their rate of

blood/CNS equilibration. Of the four opioids examined, alfentanil was the most rapid, with maximal CNS concentration achieved between 1 and 3 min after injection, whereas morphine was the slowest with maximal concentrations achieved between 6 and 102 min after injection. Maximal concentrations in this context refer to concentrations between 80 and 100% of the peak estimated CNS concentration. This is consistent with clinical experience, with alfentanil recognised as having a rapid onset but short duration of action, and morphine as having a slow onset but a longer duration of action.

On this basis, it was proposed that an injectable solution containing a mixture of morphine and alfentanil in the appropriate proportions would produce an 'apparent' opioid with the properties of rapid onset of analgesia but relatively long duration of action. An opioid with these properties would speed the titration of opioid dose against pain scores in situations such as the recovery ward. The aims of this study were to: (i) describe the theoretical kinetic basis of the mixture, (ii) determine the theoretical optimal ratio of morphine and alfentanil in such a mixture, and (iii) report an initial investigation of the efficacy of the mixture compared with morphine alone in the recovery ward of a large hospital.

Methods

Simulations

Simulations of the behaviour of the proposed mixture were performed using the 'Scientist for Windows' (Micromath Scientific Software, Salt Lake City, UT, USA) modelling software package. The following assumptions were made: (i) the blood concentrations of morphine and alfentanil could be predicted using the parameter values and compartmental models of both drugs described previously [3]; (ii) the CNS equilibration half-times of morphine and alfentanil were 34 and 1 min, respectively, as assumed previously [3, 4]; (iii) morphine (10 mg) and alfentanil (0.75 mg) were equipotent in that they would produce a similar *maximum* analgesic effect after intravenous bolus administration [5]; (iv) the maximum estimated CNS concentrations for these two doses were therefore equipotent.

The last two assumptions were used to scale all doses and CNS concentrations of alfentanil to the equivalent 'apparent' concentrations of morphine. The fraction of morphine in the alfentanil–morphine mixture was designated by a ratio (F). Thus, an F-value of 0.75 would indicate that 75% of the apparent morphine dose was due to the morphine, and 25% due to the alfentanil.

Simulation 1

Simulations were performed to compare the apparent CNS concentration time-curves for F-values of 0, 0.25, 0.5, 0.75 and 1. The total dose of the mixture was 10 mg of apparent morphine and was injected intravenous over 30 s. CNS concentrations were predicted for 120 min following the injections.

Simulation 2

A simulation was also used to examine the hypothetical titration of a patient to the same level of analgesia using a dose ratio for the mixture (F) of 0.5 and 'lock-out' intervals of 2 and 5 min. This was compared with morphine alone used with the standard lock-out interval of 5 min. The target CNS level was 0.02 $mg.l^{-1}$ of apparent morphine, and the dose unit for titration was 2 mg for morphine and 3 mg for the mixture.

Study design

Approval was obtained from the ethics committee of the Royal Adelaide Hospital. Patients scheduled by the attending anaesthetist to receive intravenous morphine using a protocol for pain relief after surgery were identified pre-operatively and enrolled in the trial after informed consent had been obtained. Patients were then randomly allocated to two groups, each receiving nurse-administered opioid via intermittent intravenous bolus titrated according to the patient's reports of pain. Patients in the morphine group were administered the drug by nurses using the standard Royal Adelaide Hospital intermittent intravenous opioid administration protocol [1]. The standard concentration of morphine in a syringe for this protocol is 10 mg of morphine in 10 ml. Patients in the mixture group received a mixture of 7.5 mg morphine and 500 μg alfentanil in 10 ml, providing an easily prepared mixture with an F-value close to 0.5. The lock-out interval for the morphine group was 5 min, and for the mixture group was 2 min. These intervals were used to minimise the risk of opioid accumulation after repeated boluses over time and are based on the blood/CNS equilibrium half-times of alfentanil and morphine [3].

Both opioid regimens were administered by nurses experienced in the use of intravenous pain protocols. Blinding of the nurses to the contents of the syringes was not possible because of differences in the lock-out intervals. Nurses were instructed that both opioids were approximately equipotent on a volume basis, but that the mixture may produce more rapid onset of analgesia. They were asked to base their initial doses (within a 0.5–4 ml range) on the parameters they used for the conventional morphine protocol. These included pain scores, patient's

age [1, 2], and onset of adverse effects, in particular excess sedation.

For each patient, the data collected were patient age, weight, gender and initial pain score (verbal numerical rating scale, 0–10). Prior to each incremental dose of opioid, blood pressure, heart rate, haemoglobin saturation and sedation score (0–3) were recorded. Patients were asked prior to each dose if they were comfortable, with the time of the first 'yes' response recorded as the time to comfort. The total volume of opioid used to that point was then recorded. Power analysis assumed a difference of 10 min in the time to comfort to be clinically significant, a SD in the time to comfort of 13 min (from data from our recovery room), a β-value of 0.2, and an α-value of 0.05. This suggested that 54 patients would need to be enrolled to examine the issue of time to onset of comfort.

Statistical analysis

The effect of the drug group and patient characteristics on the dependent variables time to comfort, minimum heart rate, minimum systolic blood pressure, minimum haemoglobin oxygen saturation and maximum sedation score were analysed using the Visual General Linear Modelling module of the Statistica software package [StatSoft, Inc. (1999) STATISTICA for Windows, OK, USA]. The dependent variables were examined separately in models in which the categorical predictors were gender and drug used, and the continuous predictors were age, weight and initial pain score. Sigma restricted parameters, normal distribution of parameter values and log link functions were used. In addition, the times to achieve comfort in the two groups were compared using a paired *t*-test. The significance level was 95% throughout.

Results

Simulation 1

The effect of altering the ratio of morphine and alfentanil in the mixture on the time-course of the apparent CNS concentrations after an intravenous bolus is shown in Fig. 1. In Fig. 1A, the first 20 min after the dose is shown. Note that when $F = 0$ (alfentanil alone) the apparent CNS concentrations peak at ≈ 2 min but decrease relatively rapidly. When $F = 1$ (i.e. morphine alone) the peak CNS concentration occurs at ≈ 20 min, although it is close to this maximum value by ≈ 5–10 min. An F-value of 0.5 produces the desired rapid onset (peak at 2 min) but also produces a progressive and relatively slow decrease from this peak.

This shape of an apparent CNS concentration curve would be expected to produce rapid but predictable titration of opioid dose to effect. Note, however, that the total 'amount' of analgesia produced (the area under the CNS concentration curve) of this dose (5 mg of

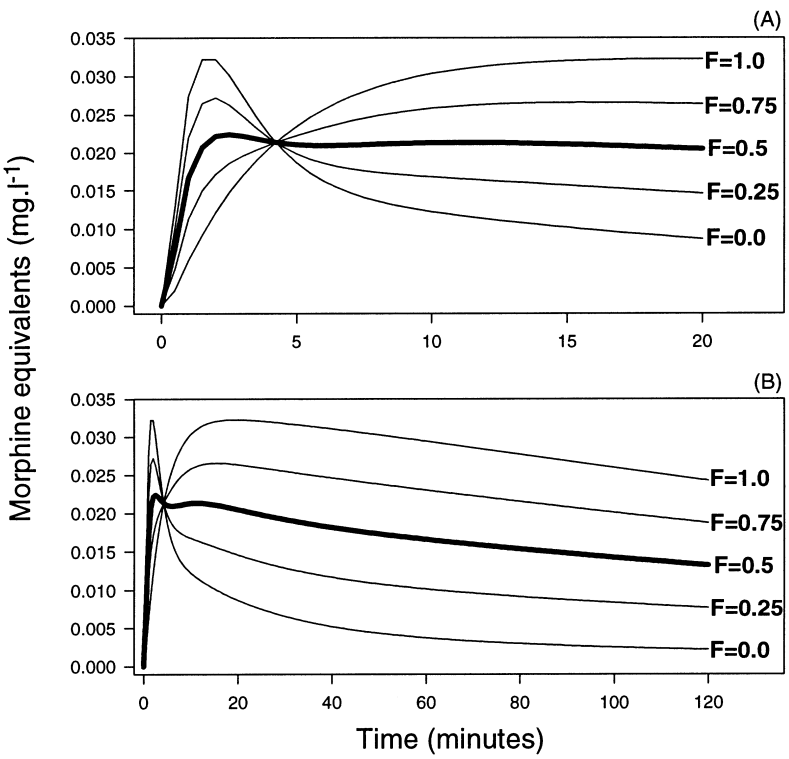

Figure 1 (A) The predicted apparent CNS concentrations of a mixture of alfentanil and morphine. Alfentanil concentrations are expressed as morphine equivalents using the assumptions described in the text. F is the ratio of morphine in the mixture, where 0 is alfentanil alone and 1 is morphine alone. (B) The same data shown on a longer time scale.

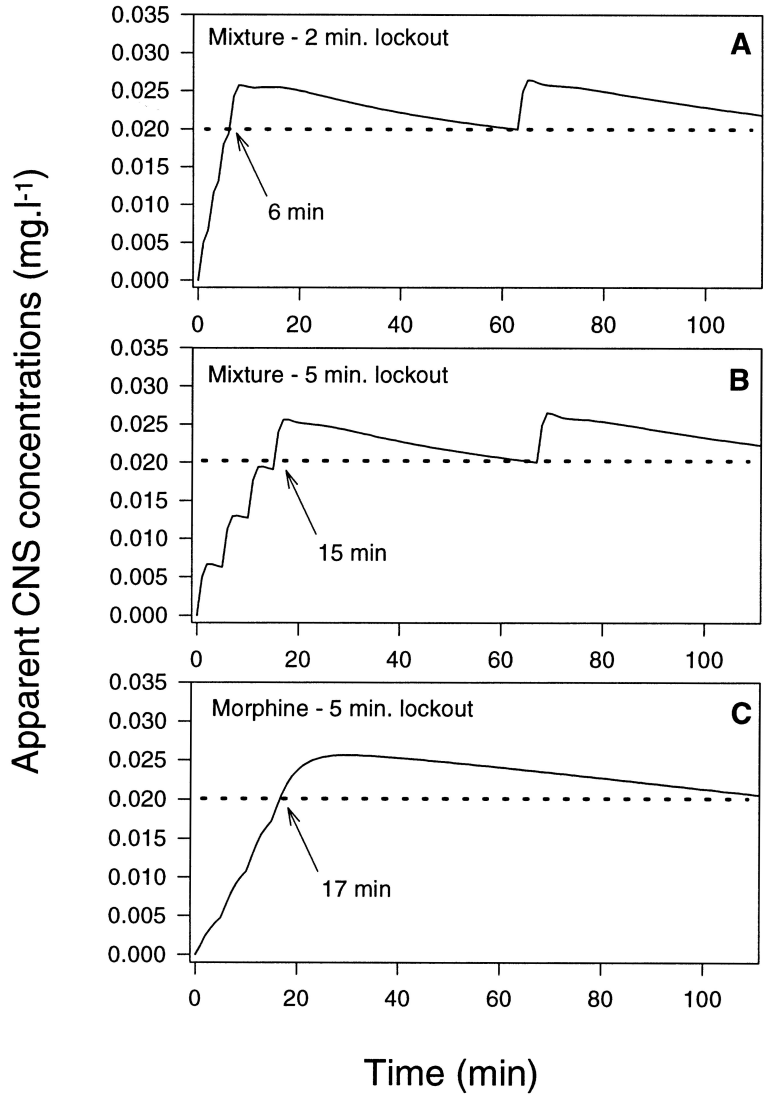

Figure 2 Simulation of the titration of a hypothetical patient using intravenous bolus doses with an apparent target concentration in the CNS of 0.02 mg.l^{-1}. (A) The drug used was a mixture of alfentanil and morphine (F = 0.5), with bolus doses of 3 ml and a lock-out interval of 2 min. (B) The drug used was a mixture of alfentanil and morphine (F = 0.5), with bolus doses of 3 ml and a lock-out interval of 5 min. (C) The drug used was morphine alone, with bolus doses of 2 mg and a lock-out interval of 5 min.

morphine and 0.375 mg of alfentanil) is less than for the equivalent 10 mg of morphine alone. This suggests that the alfentanil serves to 'fill the early gap' in the morphine curve rather than contribute greatly to later analgesia produced by morphine. Alternatively, it could be considered that the effects of alfentanil would have worn off by the time the morphine has reached its peak effect. Thus, the total 'apparent' morphine dose of the mixture could be increased to 15 mg to be equivalent to 10 mg of morphine alone in terms of achieving equivalent peak CNS concentrations, and the bolus doses for Simulation 2 were devised accordingly.

Simulation 2

Titration for the case of morphine alone (2 mg dose size with a 5-min lock-out intervals) is shown in Fig. 2C. For the optimal mixture (F = 0.5, 3 mg apparent morphine dose size) the results for titration using 5 min and 2 min lock-out intervals are shown in Fig. 2A and B, respectively. The times required to reach the target CNS concentration were 17, 15 and 6 min, respectively, for these three dose regimens.

Table 1 Patient characteristics. Data are shown as mean (SD) for the mixture group (MA) and the morphine alone group (M).

Drug	*n*	Age; years	Weight; kg	Sex ratio M : F	Initial pain score
MA	33	51.8 (17.9)	84.8 (15.8)	19 : 14	7.2 (2.3)
M	25	48.2 (19.7)	77.9 (17.0)	14 : 11	7.1 (2.0)

Table 2 The effect of covariates on dependent variables for the general linear model. Data are shown as the p-value of the regression.

Covariate	Time to comfort	Minimum oxygen saturation	Maximum sedation score	Minimum heart rate	Minimum systolic blood pressure
Age	0.698	0.614	0.194	0.564	0.518
Weight	0.230	0.951	0.385	0.720	0.960
Initial pain score	0.009*	0.181	0.060	0.238	0.533
Gender	0.565	0.196	0.676	0.637	0.907
Drug	0.02*	0.286	0.914	0.735	0.534

*Significant effect at 95% significance level.

Clinical study

Seventy-three patients were enrolled and consented. The data from 15 of these were not used in the data analysis; seven because they experienced no pain in recovery, three because of protocol violations and five because the protocol was interrupted owing to concerns over respiratory rate while pain was still being reported (three in the mixture group and two in the morphine group). This left 25 patients in the morphine group and 33 patients in the mixture group. The two groups were matched for age, weight, sex distribution and initial pain score (Table 1) with no statistically significant differences in patient characteristics between drug groups.

In some patients, the full data set could not be collected. The numbers of missing measurements in the mixture and morphine groups were: initial pain score, 6; sedation scores, 1; heart rate, 1; blood pressure, 1.

All patients included in the data analysis reached the point of reporting comfort. However, the patients in the mixture group became comfortable more rapidly, with a mean (SD) time to comfort of 27.6 (20.2) min for the mixture, and 41.2 (18.6) min for morphine alone ($p = 0.01$). The results of the visual general linear modelling are shown in Table 2. Initial pain score ($p = 0.009$) and drug group ($p = 0.02$) were significant predictors of time to comfort. No covariates, in particular the drug group, were significant predictors of potential adverse opioid effects (minimum heart rate, minimum systolic blood pressure, minimum haemoglobin oxygen saturation and maximum sedation score).

Discussion

Alfentanil and morphine produce their analgesic and other effects by acting predominantly on μ-opioid receptors in the CNS, and the time-course of their activity in the CNS, and most specifically at the μ-receptor, should be governed by the time-course of the average opioid concentration in the CNS. Although direct evidence for this assumption is not extensive, there are at least data suggesting that the EEG effect of alfentanil relates to its CNS concentration [6]. For two opioids administered together, therefore, their cerebral effects should be additive and the net effect should therefore be proportional to the sum of their two CNS concentration curves. This was the fundamental premise of our study.

Although the simulations included some significant assumptions, the results were consistent with clinical experience and revealed two important properties of the mixture. First, an optimal ratio of the two drugs could be determined that gave an apparent time-course of CNS concentrations with both a rapid onset and long duration of action. Importantly, when the ratio in terms of assumed potency of the two drugs was 1 : 1, there was no 'trough' in the CNS concentrations between the two drugs that would complicate the titration process. The benefits of the mixture over morphine were predicted to be a more rapid onset of analgesia and an earlier time for the peak apparent CNS concentration. If the latter is taken to be the principle determinant of the lock-out period [3], this could be exploited as a shorter lock-out interval (e.g. 2 vs. 5 min). In a titration setting, this can substantially decrease the time to achieve adequate analgesia should multiple doses of opioid be required, with a maximum theoretical reduction to 40% of normal.

The second property revealed by the simulation analysis was that the role of alfentanil was to 'fill in the gap' in the early CNS concentrations of morphine. As a corollary, the addition of the alfentanil to the mixture had little impact on the time-course of the CNS concentrations once the target CNS concentration had been reached, and therefore had minimal effect on the interval between doses at steady state. Thus, for maintenance purposes the mixture should behave much like morphine alone.

It was felt that it was important to make use of these two predicted properties of the mixture in the clinical trial so that the full potential benefits of a mixture could be examined. Therefore, a shorter lock-out interval was used in the mixture group. This decision meant that nurses

could not be effectively blinded to the drug group but also that more frequent dosing might well have contributed to the findings of a reduced time to comfort in the mixture group. We considered, and rejected, reducing the interval of administration of morphine to 2 min. Dosing with morphine at this frequency risks significant accumulation and 'overshoot' in the target CNS concentrations. Certainly this is supported by our clinical experiences that, even with a lock-out interval of 5 min, the use of morphine can be associated with late-onset sedation. Although not particularly dangerous in a controlled setting such as the recovery room, excessive sedation can significantly delay discharge to the ward. More importantly perhaps, was that we aimed in this study to determine whether a new technique would reduce the time patients spent in pain compared with current common practice. This appears to have been successfully achieved.

A recent study compared the efficacy of morphine alone and an alfentanil–morphine mixture in the setting of patient-controlled analgesia (PCA), finding no difference in reported pain scores over a 24-h period [7]. Although the timing of recording pain scores used would not be expected to be particularly sensitive at detecting onset of analgesia, patients in the mixture group reported that they felt that the onset of pain relief was 'fast' more frequently than those in the morphine alone group. The analysis in our study, however, suggests two reasons why the dose regimen used was not optimal. First, the ratio of alfentanil to morphine was around half that used in our study and, as suggested in Fig. 1, this will limit the rate of onset of effect. Second, the lock-out interval used was 8 min, which the kinetic analysis used in our study would suggest was excessive. In fact, lock-out intervals of 2 min have been used successfully with alfentanil alone in patient-demand systems and target controlled infusions, and have proven both safe and effective [8, 9]. Thus, it may be that an alfentanil–morphine mixture with a higher proportion of alfentanil and with a shorter lock-out period may prove significantly more effective than morphine alone when used for PCA.

The issue of the incidence of adverse effects has not been addressed completely in this study, despite the fact that the drug group was not a significant predictor of possible physiological adverse effects of rapid opioid administration. There were five patients (three in the mixture group) in whom the study was stopped because of concern over excessive sedation, and these were not included in the regression analysis. Furthermore, it is possible that adverse effects may be exaggerated in some pathophysiological states, such as hypovolaemia. It should be noted, however, that the incidence of adverse events with alfentanil in patient-demand analgesic dose regimens has been shown to be similar to that reported for PCA morphine [8, 9]. Extensive analysis of adverse effects is the subject of a larger trial during the second phase of the assessment of an alfentanil–morphine mixture for post-operative pain. If the outcome is satisfactory, it is planned to expand the scope of this mixture, as it would appear suitable for other settings in which intravenous opioids are administered, such as patient-controlled analgesia, and the treatment of incident pain such as during burns dressings.

As a final comment, it is interesting to note the enthusiasm of nursing staff exposed to this dose regimen. The feedback from those nurses who have used it regularly is very positive, with a strong impression that it overcomes some of the limitations of morphine pain protocols. Although a subjective measure of effectiveness, it certainly seems to have passed at least this measure of clinical utility.

Acknowledgment

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