Effect of temperature and cardiopulmonary bypass on the pharmacokinetics of remifentanil

D. RUSSELL, D. ROYSTON, P. H. REES, S. K. GUPTA AND G. N. C. KENNY

Summary

Sixteen patients undergoing coronary revascularization requiring cardiopulmonary bypass received remifentanil 2 µg kg\(^{-1}\) or 5 µg kg\(^{-1}\) by infusion over 1 min after sternotomy but before commencing cardiopulmonary bypass, during hypothermic cardiopulmonary bypass and during cardiopulmonary bypass after rewarming. Hypothermic cardiopulmonary bypass reduced the clearance of remifentanil by an average of 20%, and this was attributed to the effect of temperature on blood and tissue esterase activity. Reductions in arterial pressure occurred with administration of both doses during normothermia only. (Br. J. Anaesth. 1997; 79: 456–459).

Key words

Infusions of fentanyl, alfentanil and sufentanil have become established for use during induction and maintenance of anaesthesia in patients undergoing cardiac and vascular surgery.1–3 Remifentanil hydrochloride is a synthetic mu receptor agonist with an analgesic potency similar to that of fentanyl, 4 but with an ultra-short duration of action because of rapid hydrolysis by plasma and tissue esterases. Westmoreland and colleagues5 administered remifentanil 1 µg kg\(^{-1}\) over 1 min followed by infusion of 0.05–1.0 µg kg\(^{-1}\) until the end of surgery in 29 patients after induction of anaesthesia with propofol. Despite the variation in infusion rate, the times to onset of spontaneous respiration after discontinuation of remifentanil were similar, suggesting that remifentanil was not rate limiting in recovery from anaesthesia.

Remifentanil might therefore be attractive for use in circumstances where varying degrees of intense opioid activity are required, and where after discontinuation of infusion of opioid, blood concentrations, and hence opioid receptor occupancy, decrease rapidly and predictably irrespective of the dose or duration of infusion. Another potentially attractive feature is that the pharmacokinetics of remifentanil are unlikely to be affected significantly by hepatic8,9 or renal impairment.10

Esmolol is a short-acting β-adrenergic blocking agent which is metabolized extensively by esterases present in the cytosol of red blood cells.11 Kramer and colleagues12 investigated the pharmacokinetics of esmolol in patients undergoing cardiac anaesthesia and observed that clearance was reduced during hypothermic cardiopulmonary bypass (CPB). They attributed this to reduced enzymatic hydrolysis associated with hypothermia, and as remifentanil undergoes hydrolysis by similar enzyme systems we hypothesized that similar principles might apply. This might significantly affect remifentanil requirements during hypothermic CPB. The aim of this study was to assess the effect of temperature and CPB on the pharmacokinetics and pharmacodynamics of remifentanil in patients undergoing coronary revascularization.

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Patients and methods

After obtaining Ethics Committee approval, 16 male or female patients, aged 18–65 yr, undergoing elective coronary revascularization requiring CPB gave written informed consent to take part in the study. Exclusion criteria were a recent history of unstable angina or myocardial infarction, significant left main stem coronary artery disease, significant valvular heart disease, significant hepatic or renal disease, recent history of major opioid use, personal or family history of cholesterase deficiency and obesity (greater than 25% above ideal weight for height).

Concomitant cardiovascular medication was continued up to and including the day of surgery. Patients received benzodiazepine–opioid remedication and anaesthesia was induced and maintained using an opioid–hypnotic–neuromuscular blocker technique. In all cases the CPB pump was primed with 2 litre of crystalloid, diastolic cardiac arrest was induced with cold crystalloid cardioplegia, and during CPB arterial blood pH was maintained at 7.4 (measured at 37 °C).

REMITFENTANIL ADMINISTRATION

Remifentanil was delivered from a motorized syringe driver over 60 s via a central venous catheter into the superior vena cava. Each patient was scheduled to receive three i.v. bolus doses of remifentanil, at distinct times during surgery.

Period A (normothermic, pre-bypass) after sternotomy but before commencing CPB, with a core (nasopharyngeal) temperature >35 °C.

Period B (hypothermic, on bypass) during hypothermic CPB, with a core temperature of 28–30 °C for at least 15 min.

Period C (normothermic, on bypass) before discontinuation of CPB, with a core temperature of >36 °C for at least 5 min.

The study had a dose escalation design, with the first eight patients receiving three bolus doses of 2 µg kg⁻¹, and the remaining eight patients receiving three doses of 5 µg kg⁻¹. Haemodynamic indices were recorded during the period immediately after administration of remifentanil.

SAMPLE COLLECTION AND ANALYSIS

Blood samples (5 ml) were obtained from a radial artery cannula immediately before administration of remifentanil, and at 1, 2, 3, 4, 5, 10, 15, 20 and 30 min after the start of administration or until the criteria for periods A, B or C no longer applied (mainly discontinuation of CPB). The samples were heparinized and two duplicate 2.5-ml aliquots were placed in tubes containing 50 µl of 50% citric acid. Each tube was vortexed vigorously for 10 s, inverted several times and frozen at −20 °C. Concentrations of remifentanil in whole blood were measured by GC high resolution mass spectrometry, with a lower limit of detection of 0.1 ng ml⁻¹. The inter-day coefficient of variation was less than 8.5% at 0.25 ng ml⁻¹, and 4.6% at 80 ng ml⁻¹.

Compartmental data analysis involved fitting the blood concentration–time data for each phase to a two- or three-compartment model with zero order input rate using the non-linear least squares regression analysis program PCNONLIN.¹³ A weighting scheme of 1/C_pred was used. The choice of 1/C_pred rather than 1/C_observed was made because we believe that the true variance of the observations (and hence the weighting) is estimated better from the entire data set (the model predicted values) than from an individual observation. Model selection was based on the following goodness of fit measures: visual inspection of the residual plots, magnitude of the standard error of variable estimates and Akaike’s information criteria.¹⁴

Comparison between dose groups (2 and 5 µg kg⁻¹) was conducted using the two sample t test (SAS PROC TTEST) on un-transformed and log-transformed variables, and with a non-parametric method (Wilcoxon Rank Sum, SAS PROC NPAR/WA). Treatment group comparisons (normothermia pre-bypass compared with hypothermic CPB) were conducted using analysis of variance of un-transformed data (SAS PROC GLM).

Results

PHARMACOKINETIC DATA

The pharmacokinetics of remifentanil 2 µg kg⁻¹ were determined in eight patients during period A (pre-bypass, normothermia), in seven patients during period B (CPB, hypothermia) and in four patients during period C (CPB, normothermia) (table 1). Results were obtained in eight, seven and 4 patients during periods A, B, and C, respectively.

Table 1 Mean (SD) pharmacokinetic variables following administration of remifentanil 2 µg kg⁻¹ during period A (pre-bypass, normothermia), period B (cardiopulmonary bypass (CPB), hypothermia) and period C (CPB, normothermia).

<table>
<thead>
<tr>
<th>Period</th>
<th>n</th>
<th>Cl (l min⁻¹ kg⁻¹)</th>
<th>V₁ (l)</th>
<th>V₂ (l)</th>
<th>t₁/2 (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>8</td>
<td>37 (15.6)</td>
<td>28 (8.78)</td>
<td>41 (26.9)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>7</td>
<td>39 (13.6)</td>
<td>64 (78.4)</td>
<td>40 (24.0)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>4</td>
<td>22 (9.7)</td>
<td>32 (10.0)</td>
<td>31 (7.6)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 Mean (SD) pharmacokinetic variables following administration of remifentanil 5 µg kg⁻¹ during period A (pre-bypass, normothermia), period B (cardiopulmonary bypass (CPB), hypothermia) and period C (CPB, normothermia).

<table>
<thead>
<tr>
<th>Period</th>
<th>n</th>
<th>Cl (l min⁻¹ kg⁻¹)</th>
<th>V₁ (l)</th>
<th>V₂ (l)</th>
<th>t₁/2 (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>6</td>
<td>26 (8.3)</td>
<td>22 (9.7)</td>
<td>30 (6.8)</td>
<td></td>
</tr>
</tbody>
</table>
six patients receiving remifentanil 5 µg kg⁻¹ during periods A, B and C, respectively (table 2). Remifentanil concentrations immediately before the doses administered during bypass were at or below the limit of analytical detection and were therefore considered to be zero. The fraction AUC extrapolated using the two-compartment terminal elimination rate constant was less than 20%.

Blood remifentanil concentration–time profiles were fitted to a two- or three-compartment pharmacokinetic model. Statistical evaluation of the goodness of fit demonstrated that the three-compartment model offered no significant improvement over the two-compartment model. Therefore, the data were represented by a two-compartment model for further comparison between dose groups and treatment periods.

There were no significant differences in the pharmacokinetics of remifentanil between the two dose groups (ANOVA; \( P > 0.05 \)). Data for the two groups were therefore pooled and are shown in table 3. Mean blood concentration–time profiles for the two doses are shown in figure 1A and 1B. Clearance of remifentanil was similar in periods A and C (fig. 2), but was reduced by an average of 20% during period B compared with period A in the same individuals (ANOVA; \( P = 0.0057 \)). This was attributed to reduced hydrolytic enzyme activity at the lower temperatures associated with hypothermic CPB. No significant difference in volume of distribution at steady state (\( V_{SS} \)) was detected between treatment periods.

**Table 3** Mean (SD) combined pharmacokinetic variables following administration of remifentanil 2 and 5 µg kg⁻¹ during period A (pre-bypass, normothermia), period B (cardiopulmonary bypass (CPB), hypothermia) and period C (CPB, normothermia). \( t_{1/2}^{\text{d1}} \) = distribution half-life, \( t_{1/2}^{\text{e2}} \) = elimination half-life, \( V_1 \) = volume of distribution (central compartment), \( V_{SS} \) = volume of distribution at steady state, \( Cl \) = clearance. *\( P = 0.0057 \) compared with period A (analysis of variance).

<table>
<thead>
<tr>
<th></th>
<th>Period A (n = 16)</th>
<th>Period B (n = 14)</th>
<th>Period C (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( t_{1/2}^{\text{d1}} ) (min)</td>
<td>0.6 (0.19)</td>
<td>0.8 (0.51)</td>
<td>0.6 (0.22)</td>
</tr>
<tr>
<td>( t_{1/2}^{\text{e2}} ) (min)</td>
<td>6.4 (1.76)</td>
<td>11.9 (7.31)</td>
<td>7.2 (2.40)</td>
</tr>
<tr>
<td>( V_1 ) (ml kg⁻¹)</td>
<td>61 (49.6)</td>
<td>86 (113.9)</td>
<td>89 (96.3)</td>
</tr>
<tr>
<td>( V_{SS} ) (ml kg⁻¹)</td>
<td>1767 (96.2)</td>
<td>329 (443.4)</td>
<td>246 (224.6)</td>
</tr>
<tr>
<td>( Cl ) (ml min⁻¹ kg⁻¹)</td>
<td>32 (13.4)</td>
<td>25 (9.1)*</td>
<td>35 (17.2)</td>
</tr>
</tbody>
</table>

**HAEMODYNAMIC DATA**

Brief reductions in arterial pressure of 14–25% occurred during periods A (fig. 3) and C after administration of remifentanil 2 and 5 µg kg⁻¹. Mean arterial pressure was unchanged during period B with both doses. No clinically relevant alterations in heart rate occurred with administration of remifentanil at either dose.
Pharmacokinetics of remifentanil

Discussion

The mean value for clearance of remifentanil in the 2-μg kg⁻¹ dose group was consistent with that observed in previous studies, while the value observed after administration of 5 μg kg⁻¹ was somewhat lower than typically seen. Previous studies with remifentanil have demonstrated linear pharmacokinetics over a wide range of doses in both healthy volunteers and anaesthetized patients. Therefore, we believe that the lower clearance in the 5-μg kg⁻¹ group reflected inter-patient variability in a study of this nature using eight patients in each group, rather than being caused by dose-dependent (non-linear) pharmacokinetics. As such, we considered using pooled data from the two groups to be appropriate. The pooled dose group analysis was consistent with the individual group analyses and demonstrated a modest, but consistent, reduction in remifentanil clearance during hypothermic CPB compared with matched pre-bypass values.

As the pharmacokinetics of remifentanil were only modestly altered by hypothermic CPB, administration of remifentanil during cardiac anaesthesia can therefore be based on anticipated or observed patient need without the concern for major dosage adjustment during bypass.

References


Figure 3  Mean (±SD) mean arterial pressure (MAP) after administration of remifentanil 2 or 5 μg kg⁻¹ during the period between sternotomy and commencing cardiopulmonary bypass. Remifentanil was administered over 60 s between 0 and 1 min.