Title:

Study to evaluate the optimal dose of remifentanil required to ensure apnea during magnetic resonance imaging of the heart under general anesthesia.

Running Title:

Dosing of Remifentanil for Cardiac Imaging

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Abstract

Background: Magnetic resonance (MRI) scanning of the heart is an established part of the investigation of cardiovascular conditions in children. In young children sedation is likely to be needed and multiple controlled periods of apnea are often required to allow image acquisition. Suppression of spontaneous ventilation is possible with remifentanil, however the dose required is uncertain.

Aims: To establish the dose of remifentanil, by infusion, required to suppress ventilation sufficiently to allow a 30 second apnea during MRI imaging of the heart.

Method: Patients aged 1 to 6 years were exposed to different doses of remifentanil and the success in achieving a 30 second apnea was recorded. A dose recommendation was made for each patient, informed by responses of previous patients using an adaptive Bayesian dose escalation design. Other aspects of anesthesia were standardized. A final estimate of the dose needed to achieve a successful outcome in 80% of patients (ED80) was made using logistic regression.

Results: 38 patients were recruited, and apnea achieved in 31 patients. The estimate of the ED80 was 0.184 µg/kg/min (95% CI 0.178-0.190). Post-hoc analysis revealed that higher doses were required in younger patients.

Conclusion: The ED80 for this indication was 0.184 µg/kg/min (95% CI 0.178-0.190). This is different from optimal dosing identified for other indications and dosing of remifentanil should be specific to the clinical context in which it is used.

Keywords

General anesthesia, congenital heart disease, remifentanil, magnetic resonance imaging

What is Already Known about this topic

- Different anesthetic techniques can be applied to children undergoing imaging of their cardiovascular system in the MRI scanner.
- The dose of remifentanil described in previous studies is widely variable depending on the indication for use and end point studied.

What new information this study adds

- The dose required to produce apnea in 80% of children aged 1 to 6 years undergoing MRI scan is 0.184 µg/kg/min (95% CI 0.178-0.190).
- Across this age range there is variability in the dose required to produce apnea.

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Declaration of Conflicts of Interest

I confirm that I have no conflicts of interest to declare.

Trials Registration

Registered at Clinicaltrials.gov NCT02481791

Introduction

Magnetic resonance imaging (MRI) of the heart is an established part of the investigation of children with congenital heart disease or other cardiovascular conditions. Due to the need for patient cooperation and the duration of the scans, small children are likely to require inhibition of consciousness, commonly involving general anesthesia. Patient factors, the unique environment of the MRI scanner and the need to reduce artefacts and allow acquisition of adequate imaging requires modification of the anesthetic management (1). Though scans may be conducted in a sedated and spontaneously breathing child (2), it remains common to request multiple periods of apnea to reduce motion artefacts. There is currently little data to support any particular anesthetic approach. A common technique at Alder Hey Children's Hospital is to mechanically ventilate, whilst maintaining anesthesia and suppression of the patient's respiration using continuous infusions of propofol and remifentanil. There is, however, variation in practice including dosing of sedative medications. The objective of this study is to identify the dose of remifentanil required to ensure apnea (and therefore avoid movement artefact) in the majority of children during MRI scans. More precisely, the dose that will ensure an apnea of at least 30 seconds duration when co-administered with a standardized dose of propofol in 80% of children.

The dose of remifentanil has not been described in this situation. Previous studies have examined dosing in other situations, both by continuous infusion and bolus administration. Studies that identified a dose for infusion, in children, are summarized in Table 1 (3-11). The dose described is highly variable. Pharmacokinetic and pharmacodynamics differences will exist in the different populations studied. A greater source of variation is likely to be the different indications and end points studied. It seems reasonable that the dose at which a patient will continue to breath during dental extraction will be less than the dose required to suppress neurohormonal responses during heart surgery. There is a need to adapt dosing to specific situations.

Method

Authorization for the study was obtained from the Research Ethics Committee and from the Medicines and Health Care Product Regulatory Agency Informed consent was obtained from each child's parent(s) or legal guardian(s) after distribution of verbal and written information. Formal assent was not obtained from the children themselves due to their young age, however a written and graphical information sheet designed for use by young children was given to the children and their guardians.

Study participants were children from one year of age up to their seventh birthday who were scheduled for MRI imaging of their heart, requiring multiple breath holds. Contraindications were children with previous hypersensitivity to any of the study drugs; known abnormal response to opioid analgesics; conditions associated with abnormal control of breathing; or any other contraindication to proposed anesthetic technique (at the discretion of the responsible anesthesiologist).

The study utilized an adaptive model-based Bayesian dose-escalation design (12, 13). A dose recommendation was made for each patient (an infusion rate described in µg /kg/minute) representing the best estimate of the ED80 (the dose that will produce the desired response in 80% of patients) determined by the response of previous patients. There are several key features to this

design. Firstly, an interim Bayesian analysis was performed after each new patient response became available to inform dosing of the next patient (12-14). Only doses of remifentanil in the set 0.1, 0.11, … 0.3 µg/kg/min could be recommended to prevent recommendations of doses outside of the clinical accepted range. To further ensure that only acceptable doses were administered, the anesthesiologist responsible for the clinical care of the patient, was able to deviate from this recommendation if they believed it to be in the interest of the patient. Further that escalation of the dose above 0.22 µg/kg/min would only be allowed after consideration by the Trial Monitoring Group. Secondly, prior opinion on the appropriate remifentanil dose was accounted for in order to determine the dose to be given to patients early in the study. Finally, the study continued until the estimate of the ED80 was sufficiently precise. Simulations were conducted prior to the study to estimate the likely sample size and viability of the study and are detailed in the supplemental material.

Figure 1 illustrates the anesthetic management for the study. Either intravenous induction (with propofol 4mg/kg but modified according to the judgment of the anesthesiologist) or gaseous induction (with sevoflurane up to 8%) was allowed according to the preference of the anesthesiologist and patient. A dose of remifentanil (1 µg/kg) was given to facilitate intubation of the trachea and additional doses of remifentanil (0.5 µg/kg) and propofol (1-2 mg/kg) were allowed during this period. Other medications, including neuromuscular blocking drugs, were not given. The patient was then transferred into the MRI scanner. Infusion of propofol at 130 µg/kg/min and remifentanil at the test dose were administered from infusion pumps placed within the control room (separate but adjacent to the room containing the MRI scanner) and connected via long extensions (6 meters in length). Preparation of the infusions was standardized (1% neat propofol and 20 µg/ml remifentanil in saline). The infusion lines were connected independently to a single intravenous line. All lines were flushed with study drug to reduce dead space. Positive pressure ventilation was with air and oxygen via a circle system and MRI compatible ventilator located next to the patient. The breathing circuit was adapted such that the inspiratory limb was extended to loop via the control room, allowing the anesthesiologist seated in the control room to interrupt ventilation. Standard MRI compatible monitors were connected. For the first five minutes ('settling period') after transfer to the MRI scanner further bolus administration of remifentanil and propofol were allowed. Subsequent to this, the propofol infusion was reduced to 100 µg/kg/min ('equilibrium period'). The need for further modification of infusion rates or bolus administration after this point were only allowed in the presence of persistent patient movement such that safe conduct of the scan could not proceed. This judgment was made by the anesthesiologist in charge of the case. This was classed as an 'early failure' of the dosing being tested.

After a period of 20 minutes, patients entered a test period. The MRI protocol included an ECG gated respiratory navigated volumetric sequence. The MRI scanner detects movement of the diaphragm and acquires images only when the diaphragm movement is absent or minimal (within a set window of up to 5 mm). Interruption of ventilation allows image acquisition. For the purpose of the study, movement of the diaphragm detected by the MRI scanner, during a 30 second breath hold, was taken as failure of the dose to adequately inhibit respiration. Absence of movement was considered a success, assuming that dosing had not already been deemed an 'early failure'. The radiographers making the assessment of diaphragm movement were blinded to the study dose, the anesthesiologist was not.

Dose allocation

The dose administered and the success or failure of the dosing (as described above) was entered into bespoke software that then made a recommendation for the dose to be administered to the next patient, using a Bayesian Logistic Regression model (13-15). The software used and instructions on use can be viewed at https://github.com/iwadsworth/DoseEscalationApp. In order to make a dose recommendation for patients early in the study, prior opinions of appropriate dose are accounted for. In this case there is no previous published data on the required dose of remifentanil in this clinical situation. Before conducting the study, the opinions of clinicians at Alder Hey were that a dose of 0.18 µg/kg/min would be sufficient to ensure apnea in 80% of patients and 0.13 µg/kg/min to ensure apnea in 50% of patients. These priors are represented in the Bayesian model as pseudo-data: three 'patients' receiving 0.13 µg/kg/min of whom 1.5 have a successful outcome (as defined above) and three 0.18 µg/kg/min with 2.4 having a successful outcome. With the recruitment of real patients, the importance of these pseudo-data to the estimate of the ED80 decreases.

Sample size, stopping rule and pre-study simulation

Due to the adaptive design of the study, the number of patients required was not fixed. Rather the study would end when a sufficiently accurate estimate of the dose giving 80% response could be made or once a maximum of 60 patients had been recruited. The estimate of the ED80 was deemed sufficiently accurate if the ratio of the upper and lower limits of the 95% Bayesian credibility interval (incorporating prior pseudo-data and observed data) was less than 1.3. Prior to the study, simulations were conducted and it was found that under the expected conditions (ED80 of 0.18 and ED50 of 0.13) around 36 patients would be required to meet the stopping criteria. Details of these simulations (conducted by LH) are provided in the supplementary material.

Quality of imaging

The objective of performing the scan is to achieve diagnostic imaging in order to inform future treatment. A formal assessment of the image quality of the respiratory gated sequence was conducted by two pediatric cardiac radiologists. Visualization of coronary arteries, delineation of endocardial and pericardial ventricular borders and a general subjective impression of the scan quality was graded on a five-point scale (non-diagnostic, borderline, diagnostic, good or excellent) (16). Where there was difference in the grading of left and right sided structures an arithmetic mean was taken but rounded down to the lower category.

Monitoring of safety

The objective of the study was not to determine the safety or superiority of the described anesthetic technique. Given the nature of the population studied, adverse events are expected. An independent trial monitoring group was established to have oversite of patient safety during the study. The committee was asked to convene in the event of:

- Drop in heart rate below 60/minute
- Drop in systolic blood pressure below 60 mmHg
- Any cardiovascular event judged to be serious by the clinical team
- Need to repeat the scan due to low quality images

Final statistical analysis

The primary quantity of interest was the ED80 of remifentanil under the conditions described above. A frequentist logistic regression model (i.e. without priors) was used to estimate the ED80. The logistic regression model was fitted to the observed data using maximum likelihood estimation and confidence intervals were derived using the delta method(17).

$$\log\left\{\frac{p(d)}{1-p(d)}\right\}=\theta_1+\theta_2\log(d)$$

Secondary statistical analyses included general descriptions of the patient population. A comparison was made between patients in whom the dosing was successful and those in whom it was not, in order to identify factors other than dosing that may be predictive of success. Exploratory post hoc analyses were conducted after examination of the data. Simple descriptive statistics will be used to describe cardiovascular effects of the study medication.

Results

A total of 38 patients were recruited to the trial and treatment was successful in 31. Of the seven patients in whom the treatment failed, four were early failures. The final estimate of the ED80 was 0.184 µg/kg/min (95% CI 0.178-0.190). The ED50 is estimated as 0.175(0.169-0.183) mcg/kg/min and the ED90 as 0.187(0.176-0.2) mcg/kg/min. The estimated dose-response relationship was steeper than had been anticipated (the difference between the dose at which 50% of subjects would have a successful response and the dose at which 80% would have a successful response was smaller than the prior values for these parameters). Figure 2 illustrates the effective dose required to produce a range of responses from an ED50 to an ED95 together with the pointwise 95% confidence interval.

The conduct of the trial is illustrated in Figure 3. On each occasion, the dose recommended by the software was administered. Failure of treatment led to a higher dose being recommended for the next patient whilst success led to a reduced estimate. This difference was larger at the beginning of the trial. The trend is for the 95% credibility interval for the ED80 (incorporating prior opinion and observed data)(18) to become narrower as the study progresses. Results that are less consistent with the model expectations (for example two consecutive failures in patients 12 and 13), led to widening of the credibility interval.

Table 2 describes the characteristics of the study subjects and compares these characteristics between those who responded and those who did not. Of note, patients in whom the treatment failed were younger, lower weight and more likely to have received a gas induction. They were less likely to have previously been exposed to opioid analgesics, principally during previous heart surgery or intensive care. Gas induction and lower weight were also more common in younger patients, whilst older children were more likely to have undergone previous surgery. When weight was standardized to age (using the UK 1990 dataset (19)) there appeared to be little difference between the two groups. In an exploratory analysis, the regression was repeated using age as an additional explanatory variable. Care is required in use of these estimates due to the small number of patients and the low event rate (seven treatment failure). The estimated ED80 is lower with increasing age. In a 2-year-old child, the ED80 was estimated as 0.19 µg/kg/min (0.184-0.197), whilst in a 5 year old as 0.173 (0.163-0.184). The addition of age improved the goodness of fit of the regression model ($p<0.05$, log likelihood test).

Also shown in Table 2 are estimates of plasma concentrations of the remifentanil and of propofol. Plasma concentrations were not measured during the study but have been derived from existing pharmacokinetic (PK) models (20, 21). Care is required in interpretation of these values and true variation is likely to be greater than shown, due to variation in PK parameters within the population. For this reason, it is not valid to make a statistical comparison between the two groups. Estimated propofol concentration was slightly lower in the 'failed' group, however the difference was small, less than 10%.

An attempt was made to keep EtCO2 in the range 35 to 45 mmHg (4.7to 6 kPa). At the time of the test breath hold the mean EtCO2 was 5.22 kPa. Four patients had values below this range (in all of whom the study treatment was successful) and one had a value above this range (in whom the study treatment failed). The highest value was 6.27 kPa.

A formal analysis of imaging quality was possible in 34 of 38 patients. In other patients a complete respiratory gated sequence was not required. Overall, the scan quality was not diagnostic or borderline in 10 patients (29%) across at least one of the three domains: four of six patients in whom the dosing failed (67%) and six of 29 in whom dosing succeeded in producing apnea (21%). Factors other than respiratory movement may have accounted for poorer quality in some cases. Such factors include adverse effect of high or variable heart rate on efficacy of ECG gating and signal susceptibility related to high flow or surgical material. In no patient was it necessary to repeat the scan on a separate occasion due to suboptimal quality of imaging.

The median lowest systolic blood pressure was 70 mmHg (range of 57 to 87) and lowest heart rate 82 beats/min (range of 60 to 129). Adverse events (as defined by the study protocol) occurred in two patients. In one patient the systolic blood pressure fell during the conduct of the anesthetic below 60 mmHg. The patient subsequently recovered well and was discharged home that day. In a second child, a more serious adverse event occurred during induction of anesthesia, prior to initiation of the study infusion. The child had complex disease with a severe Ebstien's anomaly and had suffered significant cardiovascular instability during a previous anesthetic. Shortly after induction of anesthesia he became severely bradycardic and pulses were not palpable. He received a single dose of adrenaline (10 µg/kg) and short period of CPR. Subsequent to this, he had return of spontaneous cardiac output and it was possible to continue with limited imaging. He returned normally to consciousness after imaging and was discharged home the next day. Both cases were reviewed by the safety monitoring committee prior to recommencing recruitment. In the second case, causation was considered to be uncertain, however the bolus dose of remifentanil may have been a contributary factor. The study protocol was revised to include additional caution in recruitment of patients likely to exhibit significant instability. The second patient was not included in further analysis as the study drug had not been administered.

One further patient was excluded from the analysis. This patient received the study drug, however a technical fault in the connection of the ventilator meant the results were not interpretable. Other than this only minor protocol violations occurred: unintended small alterations in the propofol infusion rate and in the timing of the test breath hold.

Discussion

The dose of any drug will be determined by a number of considerations, principally the efficacy of the dose and toxicity. In anesthetic practice it is common to titrate the dose to achieve a particular effect. As a starting point for such titration an estimate of the dose is required. The dose will vary according to the desired end point and clinical situation. For this reason, the dose of remifentanil described previously (Table 1) has ranged from 0.06 to 1.0 µg/kg/min.

In this study an adaptive study design using a Bayesian Logistic Regression was used. Other methodologies could have been applied and each would have advantages and disadvantages(22). It is likely that this type of adaptive design is advantageous over other adaptive study designs (for example "biased coin" or "up and down method")(22) as the response of all previous patients is accounted for in dose determination. Advantages of an adaptive design over randomization include improving the estimate of the primary outcome (by ensuring that more patients received a similar dose) and reducing the impact on study subjects' clinical care. Our objective was not to 'prove' that one dosing was superior to another but rather to 'learn' more about optimal dosing of this drug. Plasma concentrations of remifentanil were not measured. Plasma level may have helped to explain differences in response to the drug in patients given similar dosing at the cost of increasing the complexity of the study. Given the relatively simple pharmacokinetics of remifentanil (23) we considered our approach justified. We believe that the methodology employed is valid and provides a useful tool in determination of dosing. Relatively precise estimates can be achieved with small numbers of study subjects. Conducting such trials in different clinical situations would allow for a more 'multi-dimensional' view of drug dosing.

There are limitations to our study. By ensuring that most patients receive a dose approximating the ED80 the estimates of doses needed to obtain other responses (such as the ED50 or ED95) are less precise. Choosing a higher EDx would ensure efficacy in a larger proportion of patients but at the risk of increased toxicity, while choosing a lower EDx would necessitate greater dose titration to achieve an effect. We believe that an ED80 is a reasonable compromise in this clinical situation. In other clinical contexts, different EDx values will be appropriate.

The expectation had been that most patients would reach the 'test period' and the assessment of efficacy would be made by the radiographer on the basis of diaphragm movement. This was not always the case and 4 patients were classed as "early failures". This leads to two possible limitations. Firstly, the anesthesiologist determined if it was not possible to continue. The anesthesiologist had not been blinded in an attempt to allow greater acceptability of the study and to allow the anesthesiologist to modify the dose estimate if they felt that to administer the recommended dose might be unsafe for the patient. Secondly, it is possible that the treatment was assessed to have failed prior to the remifentanil concentration reaching a steady state. We feel that these considerations were unlikely to have produced a bias in the result, as previous descriptions of the PK of remifentanil in children, indicate that steady state concentrations will be achieved very rapidly. In addition, considerable effort was made to continue at the test dose of remifentanil. The dosing was abandoned only when it was clear that it was not working.

The effect of age and weight on response was not fully anticipated. In previous studies higher doses of remifentanil dosing were required in infants, however in the age range studied here the dosing was less dependent on age(11). In our study younger and smaller children were more likely to

continue breathing when receiving similar doses of remifentanil, and in an exploratory multiple logistic analysis required higher doses than older children. This is consistent with allometrically scaled PK models of remifentanil. Given the small number of patients and of events (failures), care is taken in accounting for multiple covariates in the regression model. Use of target controlled (TCI) models for both propofol and remifentanil may have allowed for pharmacokinetic difference due to age and size. Use of automated TCI pumps would have been cumbersome due to the need to transfer patients into the MRI scanner and frequent use of gaseous induction.

A further limitation may be the impact of method of induction and EtCO2 on the success of treatment. All patients in whom treatment failed underwent gaseous induction compared to 54.8% of those in whom treatment succeed. Gas induction was also more common in younger children which may in part explain this association. Due to the length of time between induction and the test period a direct impact of method of induction on success seems less likely. Whilst it had been the intention to control EtCO2 closely this was not possible in all cases. The need for frequent breath holds was inevitably associated with an increase in CO2 and it was necessary to increase ventilation to compensate for this. It is of note that the EtCO2 appeared higher in the three patients in whom treatment failed at the test breath hold. Further modelling based on this co-variate would not be appropriate due to the small number of data points. The magnitude of this difference is not however great (a mean of 5.91 compared to 5.15 kPa) and it seems unlikely that this impacted greatly on the study outcomes.

The trial was not designed to establish the superiority, in terms of safety or efficacy, of the described technique. Choice of an anesthetic technique is likely to be determined by multiple factors. The purpose of undergoing a Cardiac MRI scan was to gain information to guide patient treatment. The suboptimal quality of scans in over a quarter of cases is disappointing. The assessment, of scan quality, was only performed in a single sequence, and the required information could often be gained from other sequences during the scan, or after correlation with other sources of clinical data. A number of factors were recognized to impact on the imaging quality other than those modifiable by anesthetic technique. In our practice we have found this to be a useful approach and have continued to apply this technique. Though we now tend to use MRI compatible infusion pumps within the scan room and will use rocuronium at induction to limit need for a remifentanil bolus in patients with more severe cardiovascular disease.

Conclusion

We estimate that a dose of 0.184 µg/kg/min of remifentanil, with 95% confidence intervals of 0.178-0.19, is adequate to ensure apnea in 80% of young children undergoing MRI scan under general anesthesia. A slightly higher dose may be more appropriate in younger children and a slightly lower dose as the child approaches age seven.

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Study	Study Methodology	Clinical context	Other sedatives	Patients	Objective	End point	Dose (µg/Kg/min)
Anssermino (3)	Individual patient dose titration	Dental surgery		2-7 years	Maximum dose allowing spontaneous breathing	TD50	0.127 (0.053-0.3)
Foubert (4)	RCT of 0.2 µg/Kg/ min and 0.3 µg/Kg/min	Cardiac Catheterisatio n		1.5 to 20 months	Heamodynamic stability (greater than 20% change in HR or BP)	N/A	Similar in both groups
He (5)	Randomised to none,0.1,0.2 or 0.3 µg/Kg/min.	Endotracheal intubation	Sevoflurane	3-8 years	Success of endotracheal intubation	N/A	Reduction in sevoflurane dose with increasing dose of remifentanil.
Litman (6)	Individual patient dose titration	Conscious sedation for painful procedures	Midazolam	2-12 years	Need for additional sedation	ED50	0.4 µg/Kg/min (s.d 0.2 µg/Kg/min)
Park (7)	Bias Coin design. Logistical regression/ PAVA	Extubation following tonsillectomy	Other agents discontinued	3-12 years	Prevention of coughing on extubation	ED95	0.06 µg/Kg/min (95% CI 0.037-0.068)
Shin (8)	RCT 0.1 vs 0.25 µg/Kg/min	Painful procedures in ventilated neonates	None	Preterm Infants	Premature infant pain profile score	N/A	0.25 more effective than 0.1 µg/Kg/min
Teksan (9)	RCT 0.1 vs 0.2 µg/ Kg/min	Rigid bronchoscopy for foreign body removal	Propofol and Mivacurium	3-13 years	Stable hemodynamics.	N/A	0.2 µg/Kg/min considered superior
Weale (10)	RCT 0.25,1,2.5, or 5 µg/Kg/min	Cardiac Surgery		Less than 5 years	Inhibition of stress response	N/A	1.0 µg/Kg/min
Barker 2007(11)	Individual dose titration	Strabismus Surgery	Propofol	0.5-3 years	Ventilation rate >10 per minutes	RD50	0.192
				3-6 years			0.095
				6-9 years			0.075

Table 1. Previous studies to identify dosing of remifentanil in children. RCT is randomized controlled trial. EDx is effective dose associated with a successful outcome is x% of patients. TDx is the dose considered to produce toxicity in x% of patients. RD50 is Individual rate tolerated. PAVA is pooled-adjacent-violators algorithm.

Labels	Successful	Failed	Comparison	Total
Age (months)	46.6 (17.6)	27 (13)	19.6 (6.9 to 32)	43 (18.4)
Age <30 months	6 (19.4%)	5 (71.4%)	0.1 (0 to 0.6)	11 (28.9%)
Weight (kg)	15.4 (3.2)	11.9 (2.8)	3.4 (0.7 to 6.2)	14.7 (3.4)
Z score weight	-0.49 (1.44)	-0.79 (1.43)	0.3 (-1.05 to 1.65)	-0.55 (1.42)
Premed	5 (16.1%)	1 (14.3%)	1.2 (0.1 to 12)	6 (15.8%)
Cyanotic	5 (16.1%)	0 (0%)		5 (13.2%)
Gas Induction	17 (54.8%)	7 (100%)		24 (63.2%)
Previous opioid exposure	18 (58.1%)	2 (28.6%)	3.5 (0.6 to 21)	20 (52.6%)
$EtCO_2$ at time of test breath hold (kPa)	5.15 (0.49)	5.91 (0.34)	-0.76 (-1.45 to -0.07)	5.22 (0.52)
Details of Drug dosing				
Remifentanil dose µg/kg/min	0.19 (0.01)	0.18 (0.01)	0.01 (0 to 0.01)	0.19 (0.01)
Total Remifentanil Bolus Dose µg/kg	1.53 (0.47)	3.42 (1.76)	-1.89 (-3.53 to -0.26)	1.88 (1.11)
Additional Propofol Bolus Dose mg/kg	1.08 (1.07)	2.06 (1.88)	-0.98 (-2.7 to 0.77)	1.26 (1.28)
Exploratory pharmacokinetic Analysis				
Estimated Propofol concentration µg/ml	1.8 (0.41)	1.7 (0.37)		1.78 (0.4)
Estimated steady state Remifentanil concentration ng/ml	3.03 (0.18)	2.74 (0.17)		2.97 (0.21)

Table 2: Patient characteristics. Results shown as either mean and standard deviation or as a number and percentage (of those in whom treatment was successful or not who had this characteristic). In the comparison column the mean difference or odds ratio (odds of success given the characteristic compared to odds if did not have that characteristic) and 95% confidence intervals. Weight z scores are in comparison to the growth tables (weight against age) using the UK1990 data set(19). 'Remi steady state' describes the expected steady state concentration of remifentanil given previous described PK (20). 'Propofol µg/ml' describes the expected plasma propofol concentration according to the Paedfusor dataset(21). As the concentration of neither drug was measured these values are intended to be illustrative only. Mean difference is not given as unknown variation in drug concentration cannot be accounted for.

Figure 1: Illustrates the management of individual cases. This is separated into four time periods. An induction period of indeterminant length, a settling period of five minutes immediately after transfer into the MRI scanner, an equilibrium period of 20 minutes and then a test period. Changes to infusion rate of additional boluses are only allowed during the induction and settling period. During the test period a test breath hold is conducted whilst diaphragm movement is detected by the MRI scanner.

Figure 2. The dose of remifentanil required to produce the response in x% of patients. The shaded area is the 95% confidence interval for each estimate. Inferences are based on the observed data alone.

Figure 3: Illustrates the conduct of the trial. The blue circles represent individual patients in whom the dosing (on left axis) was successful and red triangles patients in whom it was not. The smaller black dot and lines represent each Bayesian posterior modal estimate of the ED80 and corresponding 95% credibility interval (combining prior pseudo-data and observed data). The actual dose given was rounded to the nearest 0.01 µg/kg/min.