(Acta Anaesth. Belg., 2006, 57, 265-270)

Practical aspects of the use of target controlled infusion with remifentanil in neurosurgical patients : predicted cerebral concentrations at intubation, incision and extubation

D. A. Ferreira (*), C. S. Nunes (**), L. Antunes (***), F. Lobo (****) and P. Amorim (****)

Summary : Remifentanil has important side effects and it is not easy to know what remifentanil concentrations should be used during different endpoints of anaesthesia. We analyzed the remifentanil predicted effect-site concentrations (RemiCe) at different events during neurosurgical procedures and assessed if the concentrations used were clinically adequate. BIS and haemodynamic parameters were collected every 5 seconds. Predicted cerebral concentration of propofol (PropCe) and RemiCe were analyzed immediately prior to respective stimulus, and 30, 60 and 90 seconds after. RemiCe were 2.2 ± 0.3, 6 ± 2.6 and 2.2 ± 0.9 ng ml^{-1} at intubation, incision and extubation, respectively. PropCe observed in the same periods were 5 ± 1, 2.6 ± 0.9 and 1 ± 0.3 µg ml^{-1}, also respectively. The remifentanil concentrations used in our patients were lower than reported concentrations, while being clinically adequate to minimize the haemodynamic response to stimulation.

Key words : Remifentanil ; intubation ; incision ; extubation.

Introduction

Total intravenous anaesthesia (TIVA) is widely used. Some advantages of this technique have contributed to its acceptance by anaesthesiologists : it allows each component of anaesthesia to be regulated independently and adapted to noxious stimulation during surgery, it is very easy to use, provides good haemodynamic stability and a smooth recovery from anaesthesia (4, 7). Target-controlled infusion (TCI) with propofol and remifentanil is a common anaesthetic choice for neurosurgical procedures (6). TCI with these two drugs based on published pharmacokinetic/pharmacodynamic models (11, 13, 17) is being widely studied (2, 14, 15). Although remifentanil allows easy titration of analgesic levels and easy adaptation to different levels of stimulation, when combined with propofol it may cause hypotension and bradicardia (10).

TCI is a recent technique for the administration of intravenous agents based on real-time pharmacokinetic simulations. Its aim is to control and maintain adequate levels of drugs and effects. However, the therapeutic window is narrow with IV agents. Concentrations below the minimal threshold have the risk of awareness, recall and/or movement. By the contrary, an overconcentration leads to hypotension and ventilatory depression (20). When anaesthesiologists begin to use TCI systems some difficulties are usually encountered, namely in selecting the appropriate target concentrations for remifentanil at specific key points, such as intubation, incision and extubation. Nevertheless, anaesthesiologists have been prone to use TCI due to its great potential (5, 14, 16).

In this study, we assessed if remifentanil concentrations based on our previous clinical experience were sufficient to prevent haemodynamic responses to stimulation at different events during neurosurgical procedures in patients under general anaesthesia with TCI with propofol and remifentanil.

Methods

Patients and equipment

Data were collected during twenty-five neurosurgical interventions (Research Committee

D. A. Ferreira, D.V.M., C.E.C.A.V., U.T.A.D. ; C. S. Nunes, Ph.D., C.E.C.A.V. ; L. Antunes, Ph.D., C.E.C.A.V.-U.T.A.D. ; F. Lobo, M.D. ; P. Amorim
(*) Secretaria de Zootecnia, Apartado 1013, 5000-911 Vila Real, Portugal. E-mail : davidor@utad.pt.
(**) Departamento de Matemática Aplicada, Faculdade de Ciências da Universidade do Porto, Rua do Campo Alegre, 687, 4169-007 Porto, Portugal.
(***) Apartado 1013, 5000-911 Vila Real, Portugal.
(****) Serviço de Anestesiologia, Hospital Geral de Santo António, Largo Prof. Abel Salazar 4050, Porto, Portugal.
Correspondence address : David A. Ferreira, Secretaria de Zootecnia, Quinta dos Prados, Apartado 1013, 5000-911 Vila Real. E-mail : davidor@utad.pt.

approval and informed consent), under general anaesthesia with target controlled infusion using propofol (Fresenius) and remifentanil (GSK, Ultiva). Two anaesthesiologists blinded to the objective of the study were involved. Patients with severe cardiac pathologies, uncontrolled hypertension or under medications influencing the central nervous system were not included in the study.

Electroencephalographic data was collected using an A-2000XP BIS monitor (Aspect Medical Systems) with BIS-Sensors® (Aspect medical Systems) placed on the forehead of each patient according to the manufacturer instructions. Haemodynamic data was collected using an AS3 Datex monitor (Datex –Engstrom). Propofol and remifentanil were administered using two Asena Alaris syringe pumps. Both monitors and the syringe pumps were connected by a RS-232 interface to a personal computer running RugLoop II® software (developed by Tom De Smet (Demed Engineering, Temse, Belgium) and Michel Struys (Ghent University, Gent, Belgium)). RugLoop II® with the Minto and colleagues (12, 13) and Schnider and colleagues (17) pharmacokinetic/pharmacodynamic models for remifentanil and propofol, respectively, was used to control the syringe pumps. Blood pressure measurements during induction of anaesthesia and intubation were performed non-invasively using the AS3 continuous measurements mode ("STAT" mode). Patients subjected to craniotomies had arterial invasive measurements following intubation. Patients subjected to non-craniotomies procedures had non-invasive blood pressure monitoring every minute after induction of anaesthesia.

Anaesthetic protocol

Propofol and remifentanil were administered using a peripheral venous cannula inserted in the forearm of each patient. A saline solution was administered at a constant infusion rate of 400 ml h^{-1} to assure the homogeneous administration of the anaesthetic drugs. All other required drugs and fluids were administered in a separate venous line.

Patients were pre-medicated with 10 mg of diazepam *per os,* two hours before entering the surgery room. Induction of anaesthesia was performed by a continuous infusion rate of 200 ml hr^{-1} of propofol until loss of consciousness. At this moment, propofol infusion was changed to TCI with a propofol effect-site target equal to that observed at loss of consciousness ; based on our previous experience in the operating theatre with neurosurgical patients, a remifentanil infusion was also initiated at a plasmatic concentration target of 2.5 ng ml^{-1} until intubation. A 1 mg kg^{-1} rocuronium IV was administered before tracheal intubation. After intubation, propofol concentrations were titrated to a BIS target level of hypnosis of 40 to 60 and remifentanil concentrations were adjusted to a minimum, maintaining heart rate and mean arterial pressure values stabilized according to the individual patient's needs. Before skin incision, the anaesthesiologists increased the remifentanil target concentration to a level that they felt adequate for each individual patient, provided that the remifentanil effect site concentrations were above 3 ng ml^{-1}. The skin was not infiltrated with any anaesthetic solution. During the maintenance phase of anesthesia (time between incision and the stop of propofol infusion), propofol was adjusted to a BIS target level of hypnosis of 40 to 60 ; remifentanil was adjusted to surgical stimuli. After skin closure, propofol infusion was stopped. Extubation was performed after the patients were awake and breathing spontaneously. Remifentanil infusion was maintained during extubation and continued for one hour, with decreasing rate in the recovery room. Paracetamol (1 gr) and parecoxib (40 mg) were given about one hour before the end of surgery. No opioids other then remifentanil were given before extubation.

Data analysis

Data of propofol and remifentanil predicted cerebral concentrations, BIS, heart rate and systolic blood pressure were analyzed immediately prior to the respective stimulus (intubation, incision and extubation) and at 30, 60 and 90 seconds after the respective using repeated measurements analysis of variance. The software of MATLAB 6.5.1 (The MathWorks®, Natick, MA) was used for statistical analysis ; $P < 0.05$ was considered significant. Data are quoted as mean ± sd.

Results

Twenty two ASA I-III patients, age 46 ± 12 years (age range 20-74), weight 67 ± 13 kg, height 163 ± 8 cm, thirteen females were studied. Eleven patients were submitted to craniotomies procedures with invasive blood pressure measurements (starting after intubation) ; eleven patients were submitted to non-craniotomies procedures (8 spinal, 1 cranioplasty and 2 ventricular-peritoneal shunts)

Table I

Predicted propofol (PropCe) and remifentanil (RemiCe) cerebral concentrations at intubation, incision and extubation. Systolic blood pressure values (SBP ; mmHg), heart rate (HR ; bpm) and BIS at the time immediately prior (T0) to intubation, incision and extubation, and 30 (T30), 60 (T60) and 90 (T90) seconds after. After intubation, systolic blood pressure (ANOVA *P = 0.003*) and heart rate (ANOVA *P = 0.006*) increased significantly. Values are expressed in mean ± sd. °Values of 21 patients.
Pairwise comparisons *P < 0.05

	T0	T30	T60	T90
RemiCe (ng ml^{-1})				
Intubation	2.2 ± 0.3	2.3 ± 0.2	2.3 ± 0.2	2.3 ± 0.2
Incision	6.1 ± 2.6	5.8 ± 2.7	5.2 ± 2.1	4.6 ± 1.7
Extubation	2.2 ± 0.9	—	—	—
PropCe (µg ml^{-1})				
Intubation	5 ± 1	4.9 ± 1	4.9 ± 1	4.9 ± 1
Incision	2.6 ± 0.9	2.6 ± 0.9	2.6 ± 0.9	2.6 ± 0.9
Extubation	1 ± 0.4	—	—	—
SBP (mmHg)				
Intubation	112.8 ± 21.1	119.9 ± 22.2	123.2 ± 19.7*	122.1 ± 20*
Incision	103.6 ± 21.3	108.1 ± 26.2	111.7 ± 26.9	110.7 ± 25.3
Extubation°	137.3 ± 38.1	139 ± 34.2	140.9 ± 34.4	139.4 ± 30.4
HR (bpm)				
Intubation	67.6 ± 13.8	75.7 ± 18.5	74.9 ± 17.9	72.8 ± 7.5
Incision	58.3 ± 10.8	57.8 ± 10.4	58.6 ± 10.7	58.8 ± 9.9
Extubation	73.6 ± 22.3	75.9 ± 19.5	78 ± 19.5	73.8 ± 22.5
BIS				
Intubation	32.2 ± 7.5	34.4 ± 7.6	32.2 ± 7.7	31.4 ± 6.8
Incision	36.6 ± 7.3	37 ± 5.6	39.1 ± 7	40.2 ± 7.2
Extubation	88.6 ± 10.9	87.4 ± 10.6	88.6 ± 9.1	87.3 ± 10.1

with non invasive blood pressure measurements throughout the entire procedures. Three patients were excluded due to failures in the protocol. Rocuronium 1 mg kg^{-1} was administered 3.1 ± 0.8 minutes before intubation.

Table I shows the remifentanil and propofol predicted cerebral concentrations, systolic blood pressure, heart rate and BIS at intubation, incision and extubation and at each 30 seconds after. At intubation, systolic blood pressure and heart rate increased significantly (*P < 0.01*) ; remifentanil and propofol predicted effect site concentrations at intubation were 2.2 ± 0.3 ng ml^{-1} and 5 ± 1 µg ml^{-1}, respectively. All other variables did not show any significant change during all time periods studied. Individual haemodynamic and BIS changes observed at intubation, incision and extubation are shown in figure 1.

Discussion

We observed a maximum increase of 9% in systolic blood pressure 60 seconds after orotracheal intubation and a 12% maximum increase in heart rate 30 seconds after orotracheal intubation. Although the remifentanil plasma target of 2.5 ng ml^{-1} had been achieved in all patients before intubation, in some patients the effect site concentration was slightly below 2.5 ng ml^{-1} at the time of intubation. Guignard and colleagues (8) reported that remifentanil prevented increases in haemodynamic variables associated with laryngoscopy and tracheal intubation in a dose-dependent fashion : effect site concentrations of 4 ng ml^{-1} attenuated or even abolished the haemodynamic responses to intubation. In our study, the remifentanil predicted effect site concentrations at intubation were 2.2 ± 0.3 ng ml^{-1} which can be considered adequate if we look at the haemodynamic responses. The increase in systolic blood pressure (9%) and heart rate (12%) observed in our study following intubation, although statistically significant, occurred during a brief period of time and may be considered clinically acceptable. The use of higher doses of remifentanil would probably result in marked hypotension (10) pre-laryngoscopy, without clinically relevant attenuation of the haemodynamic responses to orotracheal intubation.

The intensity of noxious stimuli varies in a very significant way throughout a given procedure, requiring frequent dose adjustments. It is difficult to completely abolish the haemodynamic responses without taking unnecessary risks, such as severe hypotension and bradicardia. At skin incision, when the noxious stimulus is intense, the target concentration of the opioid must be increased. At any target change it must be taken into account the period

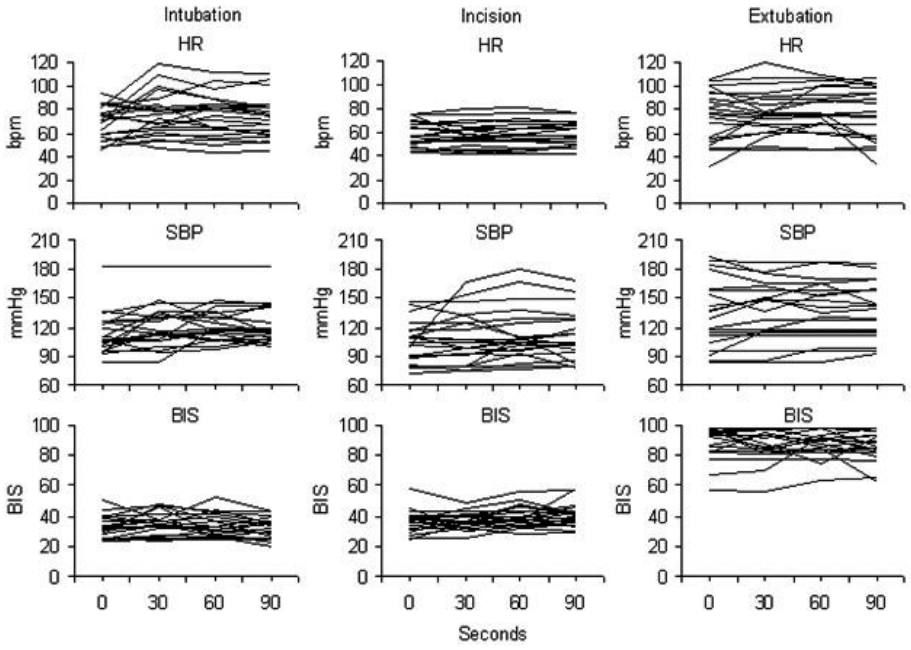

Fig. 1. — Heart rate (HR) (bpm), systolic blood pressure (SBP) (mmHg) and BIS values of each individual patient at intubation, incision and extubation (0 seconds) and 30, 60 and 90 seconds after. At intubation it was observed a statistically significant increase in systolic blood pressure *(P = 0.003)* and heart rate *(P = 0.006)*.

of time required to achieve equilibration between plasma and effect concentrations of the drugs (20). This period depends on the value of the pharmacokinetic parameter k_{e0} which also influences the time to peak compartment effect after bolus administration (18). For remifentanil, a period of approximately 2 minutes after a bolus is sufficient to allow the equilibrium between plasma and effect concentrations (13). At skin incision, there were no significant changes in heart rate or blood pressure suggesting that the remifentanil concentrations used were adequate to prevent significant haemodynamic responses to the noxious stimulus. We did no test if lower remifentanil concentrations would allow us to achieve the same results. However, the fact that the blood pressure and heart rate did not drop as response to the increasing remifentanil concentrations also suggests that the remifentanil concentrations were adequate when incision was performed.

At emergency from anaesthesia, anaesthetic concentrations must be compatible with spontaneous ventilation while still providing good residual analgesia. Tolerance to analgesia during remifentanil infusion is profound and develops very rapidly (19). It is also known that intraoperative use of remifentanil may result in increased postoperative pain (9). Although the effects of remifentanil dissipate rapidly after ending an IV infusion (5-10 minutes), remifentanil provides more effective postoperative analgesia than does intraoperative treatment with morphine followed by morphine boluses (21). Postoperative pain should be treated according to the patient's needs, eventually using non-steroid drugs or longer acting opioids (1).

Predicted effect site concentrations are probably meaningless to the anaesthesiologists who have never used TCI systems and are only accustomed to infusion rates. This is particularly true with remifentanil, since only recently commercial systems became available. In order to help one understand how remifentanil predicted concentrations (ng ml^{-1}) translate into infusion rates (µg kg^{-1} min^{-1}) we have calculated the infusion rates used in our patients at several time periods (table II). The remifentanil infusion rate used after extubation in our study was 0.05 ± 0.02 µg kg^{-1} min^{-1}. This infusion rate is much lower than what has been reported. Bowdle and colleagues (3) used a remifentanil infusion rate from 0.05 µg kg^{-1} min^{-1} to 0.15 µg kg min^{-1} to provide postoperative analgesia following abdominal, spine, joint replacement or thoracic surgery. Yarmush and colleagues (21) suggested similar remifentanil infusion rates for surgery procedures excluding cardiac, neurosurgery and peripheral vascular surgery, with a reported maximum infusion rate of 0.23 µg kg^{-1} min^{-1}. The lower doses used in our study could be due to the administration of paracetamol and parecoxib one hour before the end of surgery or to a difference in post-operative analgesia requirements for neurosurgical procedures.

Table II

Remifentanil minimum, maximum, mean and standard deviation (St Dev) infusion rates in μg kg^{-1} min^{-1}. Remi to Int- Time period between the beginning of remifentanil infusion until intubation ; Int to Inc- Time period between intubation and incision ; Mph- Maintenance phase of anaesthesia ; Prop0 to Ext- Time period between the end of Mph and extubation. Ext to 3 min after- Three minutes time period after extubation. *Data from 19 patients

Time periods	Remifentanil infusion rates (μg kg^{-1} min^{-1})				Time (min)
	Minimum	Maximum	Mean	St Dev	
Remi to Int	0.11	0.24	0.17	0.03	4.7 ± 1.4
Int to Inc	0.03	0.12	0.08	0.02	65.4 ± 35.5
Mph	0.08	0.19	0.13	0.03	187.7 ± 132.2
Prop0 to Ext*	0.02	0.16	0.07	0.04	12 ± 6.6
Ext to 3 min after*	0.02	0.09	0.05	0.02	3 ± 0

In conclusion, the remifentanil predicted concentrations used during the different phases of the procedures proved to be clinically adequate to minimize the haemodynamic response to stimulation. The remifentanil concentrations used in our patients tend to be lower than reported or recommended concentrations which, with the exception of intubation, may be due to the fact that the patients in our study were neurosurgical patients. We believe that demonstrating that remifentanil concentrations around 2.2 ng ml^{-1} for intubation, 6.1 ng ml^{-1} for incision and 2.2 ng ml^{-1} for extubation may be of clinical use for anaesthesiologists who are starting to use TCI systems in neurosurgical patients. Our results also showed that it was safe to extubate patients with remifentanil predicted cerebral concentrations around 2 ng ml^{-1} while maintaining blood pressure near awake values and a propofol predicted effect site concentration of 1 μg ml^{-1}. It is worth to note that there is no such thing as an "optimum recipe" for adequate anaesthesia, nor this work tries to do so. There are a large number of possible combinations of target levels that will also produce good anaesthesia. Only experience will allow the achievement of a smooth anaesthesia. Other departments and countries certainly have slightly different approaches, all of which are valid. TCI with propofol and remifentanil is a safe anaesthetic technique for neurosurgical procedures. It allows an easy control of patients' haemodynamic and electroencephalographic variables, and a smooth awakening.

Acknowledgements

The authors wish to acknowledge the Portuguese Foundation for Science and Technology (Lisbon, Portugal) for their financial support under project POSI/EEA-SRI/57607/2004.

References

1. Albrecht S., Schuttler J., Yarmush J., *Postoperative pain management after intraoperative remifentanil*, Anesth. Analg., **89**, S40-45, 1999.
2. Bagshaw O., *TIVA with propofol and remifentanil*, Anaesthesia, **54**, 501-502, 1999.
3. Bowdle T. A., Camporesi E. M., Maysick L., *et al., A multicenter evaluation of remifentanil for early postoperative analgesia*, Anesth. Analg., **83**, 1292-1297, 1996.
4. Camu F., Kay B., *Why total intravenous anaesthesia (TIVA) ?* Amsterdam, Elsevier, 1991.
5. Egan T. D., Kern S. E., Muir K. T., *et al., Remifentanil by bolus injection : a safety, pharmacokinetic, pharmacodynamic, and age effect investigation in human volunteers*, Br. J. Anaesth., **92**, 335-343, 2004.
6. Ferreira D. A., Nunes C. S., Antunes L. M., *et al., The effect of a remifentanil bolus on the bispectral index of the EEG (BIS) in anaesthetized patients independently from intubation and surgical stimuli*, Eur. J. Anaesthesiol., **23**, 305-310, 2006.
7. Fragen F., *Total intravenous anesthesia*, Philadelphia, Lippincott-Raven, 1996.
8. Guignard B., Menigaux C., Dupont X., *et al., The effect of remifentanil on the bispectral index change and hemodynamic responses after orotracheal intubation*, Anesth. Analg., **90**, 161-167, 2000.
9. Guignard B., Bossard A. E., Coste C., *et al., Acute opioid tolerance : intraoperative remifentanil increases postoperative pain and morphine requirement*, Anesthesiology, **93**, 409-417, 2000.
10. Koitabashi T., Johansen J. W., Sebel P. S., *Remifentanil dose/electroencephalogram bispectral response during combined propofol/regional anesthesia*, Anesth. Analg., **94**, 1530-1533, 2002.
11. Marsh B., White M., N. M., *et al., Pharmacokinetic model driven infusion of propofol in children*, British Journal of Anaesthesia, **67**, 41-48, 1991.
12. Minto C. F., Schnider T. W., Shafer S. L., *Pharmacokinetics and pharmacodynamics of remifentanil. II. Model application*, Anesthesiology, **86**, 24-33, 1997.
13. Minto C. F., Schnider T. W., Egan T. D., *et al., Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development*, Anesthesiology, **86**, 10-23, 1997.
14. Nunes C., Ferreira D., Antunes L., *et al., Regular clinical use of BIS monitoring may result in average higher BIS values*, Eur. J. Anaesthesiol., **21** (Suppl 32), 39, 2004.
15. O'Hare R., McAtamney D., Mirakhur R. K., *et al., Bolus dose remifentanil for control of haemodynamic response to*

tracheal intubation during rapid sequence induction of anaesthesia, Br. J. Anaesth., **82**, 283-285, 1999.
16. O'Hare R. A., Mirakhur R. K., Reid J. E., *et al.*, *Recovery from propofol anaesthesia supplemented with remifentanil*, Br. J. Anaesth., **86**, 361-365, 2001.
17. Schnider T. W., Minto C. F., Shafer S. L., *et al.*, *The influence of age on propofol pharmacodynamics*, Anesthesiology, **90**, 1502-1516, 1999.
18. Shafer S. L., Varvel J. R., *Pharmacokinetics, pharmacodynamics, and rational opioid selection*, Anesthesiology, **74**, 53-63, 1991.
19. Vinik H. R., Kissin I., *Rapid development of tolerance to analgesia during remifentanil infusion in humans*, Anesth. Analg., **86**, 1307-1311, 1998.
20. Viviand X., Léone M., *Induction and maintenance of intravenous anaesthesia using target-controlled infusion systems*, Best. Pract. Res. Clin. Anaesthesiol., **15**, 19-33, 2001.
21. Yarmush J., D'Angelo R., Kirkhart B., *et al.*, *A comparison of remifentanil and morphine sulfate for acute postoperative analgesia after total intravenous anesthesia with remifentanil and propofol*, Anesthesiology, **87**, 235-243, 1997.