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Effect site concentrations of remifentanil and pupil response to noxious stimulation

L. Barvais[1]*, E. Engelman[1], J. M. Eba[1], E. Coussaert[2], F. Cantraine[2] and G. N. Kenny[3]

[1]*Department of Anaesthesia, Erasme Hospital, 808 route de Lennik, 1070, Anderlecht, Belgium.* [2]*Faculty of Medicine, Free University of Brussels, 808 route de Lennik, 1070, Anderlecht, Belgium.* [3]*Glasgow Royal Infirmary, Alexandra Parade, Glasgow, UK*

*Corresponding author. E-mail: lbarvais@ulb.ac.be

Background. Opioid drugs block reflex pupillary dilatation in response to noxious stimulation. The relationship between the target effect site concentration (Ce_T) of remifentanil and the pupil diameter and reactivity in response to a standard noxious stimulus were evaluated.

Methods. Anaesthesia was induced with propofol TCI to obtain loss of consciousness (LOC) in 12 ASA I/II patients. Thereafter, remifentanil Ce_T was titrated by increments of 1 up to 5 ng ml^{-1}. In the awake state, at LOC and at each plateau level of remifentanil Ce_T, arterial pressure, heart rate, and BIS (A2000) were recorded. Pupil size and dilatation after a 100 Hz tetanic stimulation (T100) were measured at LOC and at each plateau level of remifentanil Ce_T.

Results. LOC was observed at a mean propofol Ce_T of 3.53 (SD 0.43) μg ml^{-1}. Arterial pressure and heart rate decreased progressively from LOC to 5 ng ml^{-1} remifentanil Ce_T without any statistical difference between each incremental dose of remifentanil. Mean BIS values decreased from 96 (2) in the awake state, to 46 (12) at LOC ($P<0.05$) and then remained unchanged at all remifentanil Ce_T. Pupil dilatation in response to 100 Hz tetanic stimulation decreased progressively from 1.55 (0.72) to 0.01 (0.03) mm and was more sensitive than pupil diameter measured before and after 100 Hz tetanus. An inverse correlation between pupil dilatation in response to 100 Hz tetanus and an increase in remifentanil Ce_T from 0 to 5 ng ml^{-1} was found ($R^2=0.68$).

Conclusions. During propofol TCI in healthy patients, the decrease in pupil response to a painful stimulus is a better measurement of the progressive increase of remifentanil Ce_T up to 5 ng ml^{-1} than haemodynamic or BIS measurements.

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Estimation of the μ-agonist effect of opioids during anaesthesia is often based upon imprecise clinical measurements such as arterial pressure and heart rate variation, tear formation, sweating, and movement. The sympathetic response can be obtunded by β-adrenergic blocking agents, and EEG-derived data such as the BIS index is not affected by low opioid concentrations.[1] Moreover, movement is abolished in paralysed patients.

Larson and colleagues[2] have demonstrated that alfentanil does not diminish the light reflex but blocks reflex pupillary dilatation in response to noxious stimulation. These workers reported a good correlation between plasma alfentanil concentration and the magnitude of pupil dilatation. Remifentanil is an opioid drug with a short onset and duration of action. Minto and colleagues described the pharmacokinetics and pharmacodynamics of remifentanil in 65 healthy adult volunteers, using the electroencephalogram to measure the opioid effect.[3] The predictive performance of their population pharmacokinetic set had an acceptable accuracy.[3]

TCI systems calculate and target the effect compartment concentration (Ce_T) of i.v. anaesthetic drugs.[4 5] Recently, an accurate and easy to use pupillometer has been marketed, which allows measurement of pupil size without any

influence on the light reflex (Colvard infrared pupillometer; OASIS Medical Inc., Glendora, CA, USA). The aim of this study was to investigate the relationship between calculated Ce_T of remifentanil and pupil size or dilatation in response to repetitive, standard noxious stimulation. The changes in BIS and haemodynamic measurements were also recorded and compared with remifentanil Ce_T.

Methods

After approval by the local ethics committee and written informed consent, 12 ASA physical status I and II patients (six females; six males) undergoing minor peripheral surgery were studied. All patients were free of eye disease, taking no medication and received oral alprazolam 0.5 mg as pre-medication. One-way valves were used for the remifentanil and propofol TCI systems.

A software system, called TOOLBOX, designed in the Department of Computer Sciences of our faculty, was used to infuse propofol and remifentanil.[5] This TCI system allows the Ce_T of i.v. anaesthetic drugs to be targeted. The software is programmed in Visual Smalltalk, one object orientated language (VisualAge for Smalltalk version 6.0, IBM) and is run on a Windows-based PC. It has been implemented with the same algorithms as those proposed by Shafer.[4]

Induction of anaesthesia was obtained by increasing propofol Ce_T progressively until loss of consciousness (LOC) using the population pharmacokinetic set of Schnider.[6] This set was selected because a propofol TCI, which controlled the effect site rather than the plasma drug concentration, more accurately produced the desired effect.[7] In all patients, the initial Ce was 2 µg ml^{-1}, which was progressively increased by steps of 1 µg ml^{-1} until LOC. Thereafter, the propofol Ce_T associated with LOC was maintained at the same level during the whole study period and cisatracurium 0.15 mg kg^{-1} was administered.

The Ce_T of propofol was titrated without any restriction on the peak plasma concentration, using propofol 1% and a maximum pump flow rate of 1200 ml h^{-1}. Figure 1 describes the progressive increase in the Ce_T of propofol in a 40-yr-old patient with a weight of 70 kg and a height of 170 cm using the pharmacokinetic set of Schnider,[6] with a $T_{1/2keo}$ of 1.8 min. In this patient, the initial target Ce_T of 2 µg ml^{-1} is generated by a bolus of 38 mg administered over 10 s, which is associated with a short peak plasma overshoot of 8 µg ml^{-1}.

The infusion of remifentanil was started and titrated progressively in stepwise increments of 1 up to 5 ng ml^{-1} without any restriction on the remifentanil plasma overshoot. Figure 2 depicts the method of remifentanil administration. Table 1 gives the bolus doses of remifentanil administered to achieve the plateau levels and the doses given by continuous infusion during the plateau phase to maintain remifentanil Ce_T constant in a 40-yr-old patient (weight 70 kg and height of 170 cm). Each pupil assessment was performed when 100% of the required Ce_T was attained. The pupil assessment took approximately 1 min. The next plateau level of remifentanil Ce_T was selected at the end of each pupil assessment.

In the awake state, at LOC and at each plateau level of remifentanil Ce_T, arterial pressure, heart rate, and BIS (A2000) (Aspect Medical systems, Natick, MA) were recorded. At LOC and at each plateau of remifentanil Ce_T, the pupil diameter was measured before the noxious stimulus. The diameter of the pupil at maximal dilatation was recorded again at the end of a 100 Hz tetanic stimulation (T100) applied to the ulnar nerve (DIGISTIM at 60 mA) for 10 s. The pupil size was measured using an
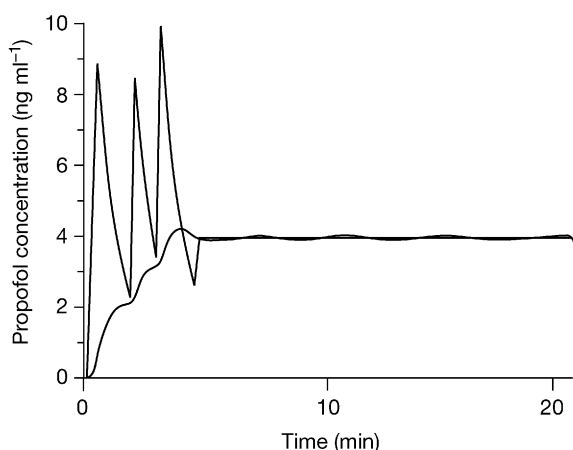
Fig 1 Pharmacokinetic simulation of the calculated peak plasma concentrations associated with a progressive increase in the calculated effect site concentrations of propofol in a 40-yr-old patient with a weight of 70 kg and a height of 170 cm, using the pharmacokinetic set of Schnider and colleagues.[6]
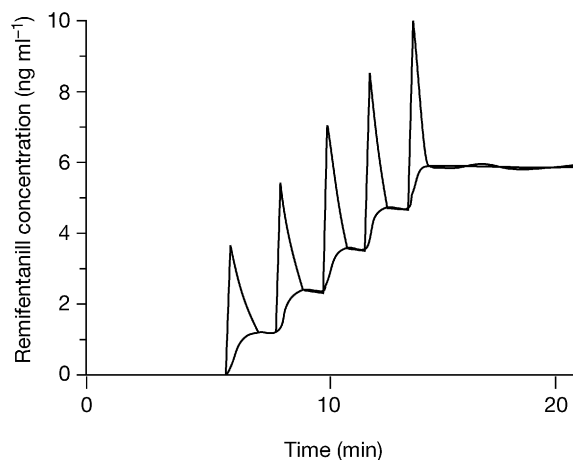
Fig 2 Pharmacokinetic simulation of the calculated peak plasma concentrations associated with a progressive increase in calculated effect site concentrations of remifentanil by stepwise increments of 1 up to 5 ng ml^{-1} without any restriction of remifentanil plasma overshoot in a 40-yr-old patient with a weight of 70 kg and a height of 170 cm, using the pharmacokinetic set of Minto and colleagues.[3]

infrared commercially portable pupillometer (OASIS, Colvard). The resolution of the device was 0.1 mm. Pupil size was always assessed by the same investigator after controlling the correct positioning of the pupillometer by moving it up and down or to the left and right. Normocapnia was controlled by manual ventilation between each time point measurement. The differences between the pupil size measured before and after 100 Hz tetanus were calculated for each time point.

All data are given as mean (SD). Statistical analysis was performed using analysis of variance for repeated measures across all measurements. $P<0.05$ was considered as statistically significant. When a P value <0.05 was obtained, a Tukey post hoc analysis was performed to compare individual points.

Results

The mean (SD) (range) age of the population studied was 40.5 (11.5) (22–65) yr. The mean (SD) (range) weight was 64.7 (12.4) (50–78) kg and mean (SD) (range) height was 167.7 (7.8) (154–186) cm. The mean Ce_T of propofol at LOC was 3.53 (0.43) (range 3–4) $\mu g\ ml^{-1}$.

Systolic arterial pressure decreased progressively from the awake state to a remifentanil Ce_T of 5 ng ml^{-1}. Compared with the value at LOC, systolic arterial pressure decreased significantly at a remifentanil Ce_T of 3, 4, and

Table 1 Bolus doses of remifentanil administered to achieve the plateau levels and the doses given by continuous infusion during the plateau phase to maintain the effect site concentration (Ce_T) in a 40-yr-old patient (weight 70 kg and height 170 cm) over 1 min

Remifentanil Ce_T (ng ml^{-1})	Bolus dose (µg)	Dose given to maintain Ce_T over 1 min (µg)	Total dose given before the next dose increase (µg)
1	16	4	20
2	20	6	46
3	22	10	78
4	24	14	116
5	28	16	160

5 ng ml^{-1} (Table 2). No statistical difference between each successive plateau level of remifentanil Ce_T was found.

Diastolic arterial pressure and heart rate decreased progressively from the awake state until remifentanil Ce_T of 5 ng ml^{-1}. Compared with the values at LOC, a decrease was found at a remifentanil Ce_T of 2, 3, 4, and 5 ng ml^{-1}. Compared with the diastolic pressure measured at a remifentanil Ce_T of 1 ng ml^{-1}, the diastolic pressures recorded at 4 and 5 ng ml^{-1} were significantly decreased (Table 2).

Compared with the heart rate values recorded at LOC, a significant decrease was measured at a remifentanil Ce_T of 4 and 5 ng ml^{-1}. Compared with the values at a remifentanil Ce_T of 1 ng ml^{-1}, a significant decrease in heart rate was only measured at 5 ng ml^{-1} (Table 2).

The BIS decreased statistically from 95.6 (2.3) in the awake state to 45.5 (11.5) at LOC and remained low, varying little at the increasing levels of remifentanil Ce_T (Table 2).

In the absence of any noxious stimulus and compared with the reference size at LOC (4.14 (1.42) mm), pupil size was statistically decreased from remifentanil Ce_T of 2 ng ml^{-1} (2.07 (0.48) mm) (Fig. 3A). Compared with the pupil size at 1 ng ml^{-1} (3.02 (1.24) mm), the pupil size before 100 Hz tetanic stimulus was statistically smaller at remifentanil Ce_T of 3, 4, and 5 ng ml^{-1} (Fig. 3A). Compared with the pupil diameter after T100 at LOC (5.69 (1.42) mm) and at a remifentanil Ce_T of 1 ng ml^{-1} (4.25 (1.21) mm), all subsequent measurements of the pupil size after T100 were less than 2.5 mm and statistically significantly smaller (Fig. 3B).

A progressive decrease in pupil dilatation in response to 100 Hz tetanus from 1.55 (0.72) mm to 0.01 (0.03) mm was found (Fig. 4A). Compared with the pupil dilatation in response to T100 at LOC and at a remifentanil Ce_T of 1 ng ml^{-1}, pupil dilatation became statistically significantly less responsive from a remifentanil Ce_T of 2 ng ml^{-1}. At a remifentanil Ce_T of 5 ng ml^{-1}, the pupil dilatation was also statistically smaller than at 2 ng ml^{-1} (Fig. 4A). A linear relation between the pupil dilatation to T100 and remifentanil Ce_T was found ($y=1.46+-0.324x$; $R^2=0.68$; $\rho=-0.82$)

Table 2 Haemodynamic variables (systolic arterial pressure (SAP), diastolic arterial pressure (DAP), heart rate (HR)) and Bispectral index (BIS) in the awake state, at LOC under propofol TCI alone and at progressive effect site concentrations (Ce_T) of remifentanil up to 5 ng ml^{-1} (mean (SD)). Ce_T 1 ng ml^{-1} =calculated effect site concentration of remifentanil at 1 ng ml^{-1} using the set of Minto et al.[3] T100=100 Hz tetanic stimulation applied to the ulnar nerve during 10 s. SAP=systolic arterial pressure; DAP=diastolic arterial pressure; HR=heart rate. *$P<0.01$ compared with awake. +$P<0.05$ compared with LOC. †$P<0.01$ compared with LOC. ‡$P<0.05$ compared with remifentanil Ce_T of 1 ng ml^{-1}. §$P<0.01$ compared with remifentanil Ce_T of 1 ng ml^{-1}

$n=12$	SAP (mm Hg)	DAP (mm Hg)	HR (beats min^{-1})	BIS
Awake	122.5 (13.0)	75.9 (9.1)	73.4 (10.7)	95.6 (2.3)
LOC	112.5 (13.1)	68.7 (7.5)	71.2 (8.1)	45.5 (11.5)*
Ce_T 1 ng ml^{-1}	107.9 (10.0)	63.2 (8.2)	68.0 (8.7)	38.4 (8.7)*
Ce_T 2 ng ml^{-1}	101.1 (8.7)	56.0 (8.0)+	62.2 (8.2)	40.8 (10.5)*
Ce_T 3 ng ml^{-1}	95.3 (10.1)†	52.2 (7.1)†	59.6 (8.6)	39.9 (9.2)*
Ce_T 4 ng ml^{-1}	91.6 (8.7)†	49.8 (5.7)†§	58.1 (5.9)+	39.1 (5.9)*
Ce_T 5 ng ml^{-1}	91.7 (11.8)†	48.1 (5.7)†§	54.9 (5.7)†‡	38.7 (10.3)*
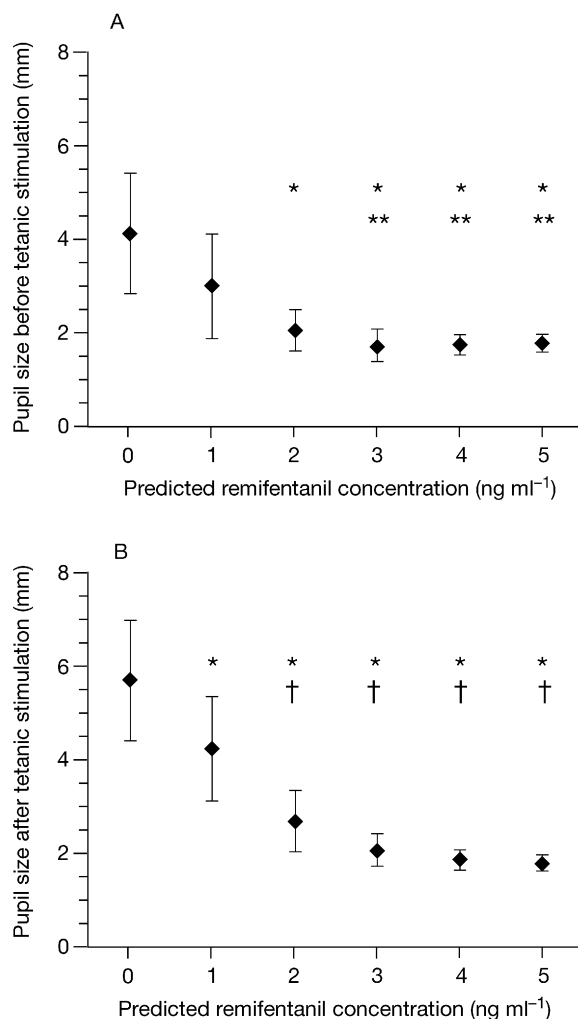
Fig 3 Mean (SD) pupil size (mm) in 12 patients measured before (A) and after (B) a tetanic stimulation of 100 Hz for 10 s applied to the ulnar nerve, after loss of consciousness under propofol TCI alone (0), and at different plateau levels of theoretical calculated effect site concentrations (Ce_T) of remifentanil of 1, 2, 3, 4, 5 ng ml^{-1}, using the pharmacokinetic set of Minto and colleagues.[3] *$P<0.01$ compared with loss of consciousness; **$P<0.05$ compared with remifentanil Ce_T of 1 ng ml^{-1}; †$P<0.01$ compared with remifentanil Ce_T of 1 ng ml^{-1}.

(Fig. 4B). The 95% CI for the slope of the regression line was −0.377 to −0.271 (Fig. 4B).

Compared with pupil reactivity at LOC in the absence of remifentanil, a 50% reduction in the maximal pupil dilatation to T100 was obtained at a theoretical remifentanil Ce_T of 2.3 ng ml^{-1}. A large inter-individual variation in pupil dilatation in response to tetanic stimulation was present at LOC before the start of the remifentanil infusion and at a remifentanil Ce_T of 1 ng ml^{-1} (Fig. 3).

Discussion

Pupil size is determined by the opposing action of smooth muscles in the iris innervated by the sympathetic and parasympathetic divisions of the autonomic nervous system. The parasympathetic system (cholinergic innervation) of the iris originates exclusively in the midbrain, innervates the circular fibres of the iris, and has a constrictive action. In contrast, the polysynaptic sympathetic system, mediated by alpha-1 adrenergic receptors, innervates the radicular fibres of the iris and dilates the pupil.[8]

Noxious stimulation dilates the pupil in both unanaesthetized and anaesthetized humans and is mediated primarily by the sympathetic system in the awake state. However, during desflurane anaesthesia, pupil dilatation in response to a noxious stimulus appears to involve either inhibition of the pupilloconstrictor nucleus located in the central pathway as high as the rostral mesencephalon, or a previously undescribed non-cholinergic, non-adrenergic synapse with neuromuscular junctions within the iris.[9] The halogenated agents (halothane, isoflurane, sevoflurane, desflurane), the catecholamines and atropine provoke mydriasis.[10 11] Propofol, thiopental, lidocaine, and the neuromuscular blocking agents do not alter pupil reactivity.[12 13] The neuroleptic and opioid drugs have a pupilloconstriction effect.

During isoflurane anaesthesia, alfentanil did not diminish the light reflex but produced a substantial dose-dependent depression of pupillary dilatation after a noxious stimulus. Dilatation was reduced to 50% of control values at alfentanil concentrations around 20 ng ml^{-1}, and was almost abolished at concentrations approaching 100 ng ml^{-1}.[2] Larson and colleagues[10] have demonstrated that pupil dilatation is a more sensitive measure of noxious stimulation than the commonly used variables of arterial pressure and heart rate during isoflurane and propofol anaesthesia. The effect of opioids on pupil dilatation in response to a painful stimulus is not mediated via the α2 receptors.[14]

TCI propofol combined with a continuous opioid infusion has become the standard European technique for total i.v. anaesthesia. Synergy between propofol and the opioid drugs permits administration of lower doses of each.[15] Adjustments of the hypnotic or analgesic components are made in response to the intensity of the surgical stimulus, to the haemodynamic changes that occur during surgery, and also according to the respective pharmacokinetic profiles and duration of infusion of each drug.[15]

As yet, there have been only two clinical reports of improving opioid titration and decreasing the variability in individual responsiveness during adequate administration of propofol.[17 18] BIS variability in response to a nociceptive input has been shown to decrease when opioid doses were increased in healthy volunteers.[17] BIS is as sensitive as haemodynamic responses after a painful stimulus for detecting deficits in the analgesic component of anaesthesia,[18] and it may help to monitor depth of anaesthesia in patients who are incapable of heart rate and arterial pressure responses because of cardiovascular medication.[18] But the BIS index cannot help the anaesthetist to titrate remifentanil analgesia during propofol TCI.
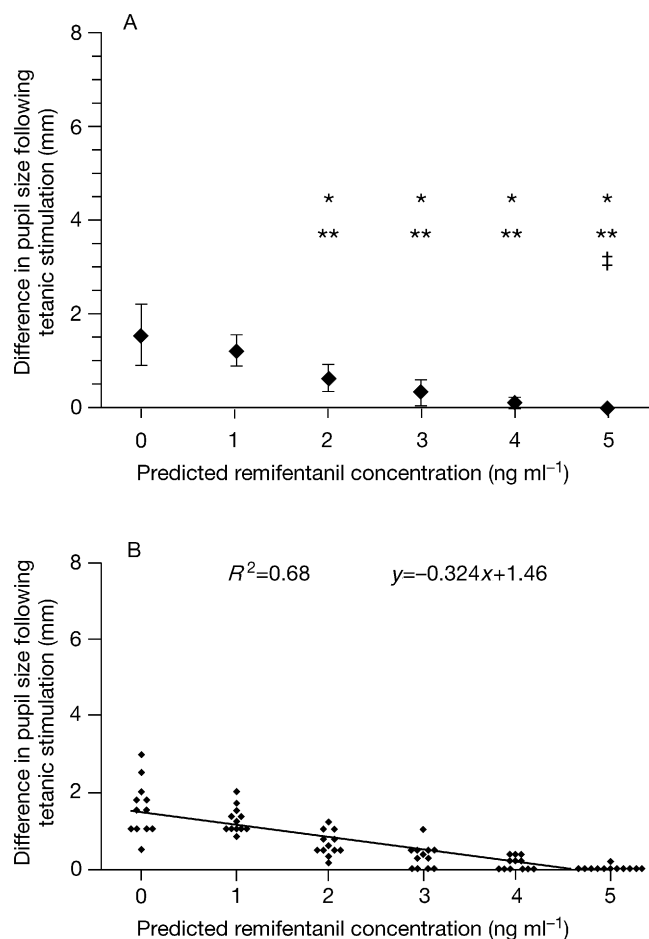
Fig 4 (A) Mean (SD) difference in pupil size (mm) in 12 patients measured before and after a tetanic stimulation of 100 Hz for 10 s applied to the ulnar nerve, after loss of consciousness under propofol TCI alone (0) and at different plateau levels of theoretical calculated effect site concentrations (Ce_T) of remifentanil of 1, 2, 3, 4, 5 ng ml^{-1}, using the pharmacokinetic set of Minto and colleagues.[3] *$P<0.01$ compared with loss of consciousness; **$P<0.05$ compared with remifentanil Ce_T of 1 ng ml^{-1}; ‡$P<0.01$ compared with remifentanil Ce_T of 2 ng ml^{-1}. (B) Regression line of the differences in the pupil size (mm) measured before and after a tetanic stimulation of 100 Hz for 10 s applied to the ulnar nerve in 12 patients and the calculated effect site concentrations (Ce_T) of remifentanil of 0, 1, 2, 3, 4, 5 ng ml^{-1}, using the pharmacokinetic set of Minto and colleagues.[3]

During general anaesthesia, pupillary changes to light or a painful stimulus are rarely studied because of the lack of a convenient and accurate method of recording pupillary activity in the operating room. As a new portable and easy to use pupillometer has been marketed and validated,[19] this clinical study was undertaken to evaluate the relationship between the remifentanil effect site concentration and haemodynamic responses, changes in BIS, and pupil dilatation to a noxious and repetitive stimulus.

In the 12 patients studied, systolic and diastolic arterial pressures and heart rate decreased progressively from the awake state until a remifentanil Ce of 5 ng ml^{-1}, without any statistical difference between each successive plateau level

of remifentanil (Table 2). This decrease in arterial pressure may not be related to the progressive increase in remifentanil Ce and is probably caused by the delayed effects of propofol combined with a dose-dependent, synergistic action of remifentanil. Kazama and colleagues[20] have compared the effect site equilibration constants (keo) of propofol with BIS and arterial pressure in elderly and younger patients. They demonstrated that the decrease in arterial pressure is delayed compared with EEG depression, independently of the age of the patient.[20]

A linear relationship between pupil dilatation in response to T100 and the calculated remifentanil Ce using the population pharmacokinetic data set of Minto[3] was demonstrated clearly in this study. This relation is similar to the results of Larson and colleagues who measured reflex pupil dilatation and plasma alfentanil concentrations.[2] To exclude any reduction in pupil dilatation caused by the repetition of the same noxious stimulus, we studied a control group of five ASA I patients anaesthetized with the same propofol effect site TCI profile without any opioid administration. Pupillary dilatation was evaluated five times every 2 min after the same tetanic stimulus of 100 Hz. No sign of fade of pupil dilatation in response to 100 Hz tetanus was detected.

In conclusion, during propofol TCI anaesthesia in young healthy patients, the addition of remifentanil up to a 5 ng ml^{-1} effect site concentration produces a dose-dependent depression in pupil dilatation after a noxious stimulus. Pupil dilatation in response to 100 Hz tetanus is a more sensitive measurement of remifentanil Ce than arterial pressure, heart rate, or BIS variations.

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