The μ-opioid receptor agonist remifentanil induces acute dysphoria irrespective of its analgesic properties

KJ Wagner *Klinik für Anaesthesiologie, Technische Universität München, Klinikum rechts der Isar, München, Germany.*

M Valet *Neurologische Klinik und Poliklinik, Technische Universität München, Klinikum rechts der Isar, München, Germany.*

EF Kochs *Klinik für Anaesthesiologie, Technische Universität München, Klinikum rechts der Isar, München, Germany.*

M Kriner *Institut für Medizinische Statistik und Epidemiologie, Technische Universität München, Klinikum rechts der Isar, München, Germany.*

TR Tölle *Neurologische Klinik und Poliklinik, Technische Universität München, Klinikum rechts der Isar, München, Germany.*

T Sprenger *Neurologische Klinik und Poliklinik, Technische Universität München, Klinikum rechts der Isar, München, Germany.*

Abstract

μ-opioidergic agonists are believed to induce euphoria, whereas κ-agonists are thought to lead to dysphoria. Our study investigated mood effects of remifentanil, a μ-receptor opioid agonist, in healthy male volunteers. Moreover, we examined interactions between mood and pain. Three conditions were investigated in 21 volunteers: saline, 0.05 and 0.15 µg kg^{-1} min^{-1} remifentanil. Each condition was investigated during non-painful heat and during painful heat stimulation. Mood was measured with the von Zerssen's mood scale (Bf-S score) and pain intensity using a Visual Analogue Scale (VAS). High Bf-S scores are reflecting discontent and dysphoria. Changes were tested for significance using a linear mixed model approach. Remifentanil significantly increased Bf-S scores during painful heat (+91.4%), indicating a negative mood effect, although it reduced VAS scores of painful heat intensity (−49.0%). The type of sensory stimulation (non-painful versus painful) had no effect on mood. There was no interaction between remifentanil dose and type of stimulation. Our results provide evidence for negative mood effects of remifentanil. These effects occur with and without pain. Taken into account that remifentanil reduces pain, one could have expected analgesia-related amelioration of mood instead. In clinical practice, these remifentanil effects should be considered and a comedication might be advisable.

Key words

dysphoria; mood; μ receptor; opioids; pain; remifentanil

Introduction

Opioids are widely used in acute and chronic pain therapy, clinical anaesthesia and intensive care. μ, δ, κ and nociceptin opioid receptor subtypes have been cloned and characterised during the last decades (Bodnar and Klein, 2006). Although these receptors all belong to the group of opioid receptors, differential functions with different brain distributions have been reported (Hiller and Fan, 1996). In clinical pain management, mostly drugs acting at the μ-receptor are applied, as activation of this receptor produces potent analgesia. Besides the analgesic properties, it is well known that μ-receptor agonists can lead to side effects such as respiratory depression, nausea and constipation. Concerning mood related effects, euphoria and addiction are well established and have been investigated in drug abusers and non-drug abusing volunteers for a variety of opioids with different receptor profiles. Dysphoric effects are well accepted for κ-agonists (Pfeiffer, *et al.*, 1986; Corbett, *et al.*, 2006) and have also been reported for μ-agonists (Lasagna, *et al.*, 1955). However, results of other consecutive previous studies on short- and long-term negative consequences on mood were non-uniform and these effects have not been extensively studied so far.

Remifentanil is a synthetic opioid and a member of the 4-anilidopiperidine class that is used for anaesthesia and analgesia. It exhibits specific μ-agonist pharmacodynamic effects comparable to other potent μ-opioid receptor agonists (James, *et al.*, 1991). The pharmacokinetic profile with a rapid onset and peak effect and a short duration of action due to metabolism by non-specific esterases provides fast and reproducible steady-state concentrations, which are advantageous in experimental settings when administering different dosages (Glass,

Corresponding author: Klaus Jürgen Wagner, Klinik für Anaesthesiologie, Klinikum rechts der Isar der Technischen Universität München, Ismaninger Strasse 22, D-81675 München, Germany. Email: K.Wagner@lrz.tum.de

et al., 1999). Its context-sensitive half-life is 3–6 min, and its terminal elimination half-life is 10–20 min (Hughes, *et al.*, 1992; Kapila, *et al.*, 1995; Westmoreland, *et al.*, 1993). Thus, minimal latency between dose administration and observed effect translate into an opioid that is easy to titrate and thus provides suitable conditions for short-term psychophysical investigations.

In two previous positron emission tomography (PET) imaging studies, we were able to show the cerebral sites of action of remifentanil during rest but also in the context of pain stimulation (Wagner, *et al.*, 2001; Wagner, *et al.*, 2007). Thereby, we observed a prominent activation of the cingulo-frontal cortex. This brain region is known to contribute not only to analgesia but also to strongly modulate the individual affective state. This poses the question whether and to what extent remifentanil modulates affect. Generally, µ-opioid agonists are believed to primarily induce euphoria (Corbett, *et al.*, 2006); however, there have been sporadic case reports about dysphoric effects of remifentanil in the clinical setting (Crozier, *et al.*, 2004).

In the present study we therefore investigated the acute effects of remifentanil on mood in healthy volunteers in a well-controlled experimental setting using a double-blinded, placebo-controlled, randomised study design with a reproducible and individually adapted experimental heat pain stimulus. We expected remifentanil to produce a µ-opioid receptor-mediated antinociceptive and euphoric mood effect.

Methods and materials

Ethical approval for this study was obtained from the Ethics Committee of the Technische Universität München, Germany.

Volunteers

A total of 442 individual data sets were acquired in 21 male volunteers (mean age 35 ± 4.7 years). Per subject, a mean number of 21 data sets (range: 12–46 data sets) were acquired. In a subgroup of the volunteers, the data were acquired during PET scanning sessions. These PET scanning results have been published elsewhere (Wagner, *et al.*, 2007). All subjects gave written informed consent acknowledging that 1) they would experience experimental pain stimuli, 2) they would receive a potent analgesic in different dosages, 3) all methods and procedures were clearly explained and 4) they were free to withdraw from the experiment at any time.

Volunteers with any chronic or ongoing pain condition, previous or actual neurological, psychiatric and medical condition, a history of drug abuse or any other severe disease (American Society of Anesthesiology [ASA] physical status >I) were excluded from the study. Volunteers were asked to refrain from consuming alcoholic or caffeinated beverages for 12 h before the experiment.

Experimental setting

The volunteers had fasted for at least 6 h before the study. Electrocardiograms and arterial oxygen saturation (SaO_2) were measured and continuously recorded (Capnomac Ultima, Datex, Helsinki, Finland). Non-invasive blood pressure measurements were performed at 5-min intervals (Dinamap™ 1846 SX; Criticon, Tampa, Florida, USA). End-tidal CO_2 ($etCO_2$) concentrations were measured using a Capnomac Ultima monitor via a catheter placed at the nasopharyngeal border.

Opioid administration

During experimental pain stimulation, a total of three different drug infusion regimes were investigated: saline [control], $0.05\ \mu g\ kg^{-1}\ min^{-1}$ remifentanil [low-dose remifentanil] and $0.15\ \mu g\ kg^{-1}\ min^{-1}$ remifentanil [moderate-dose remifentanil]. According to its short half-life, remifentanil was delivered intravenously by an infusion pump (Combimat 2000, Döring, München, Germany) in a blinded, randomised order with a time interval of >30 min between the two remifentanil infusion rates. The average duration of infusion was 187.6 min (range: 145–226 min), whereas the average total dose of remifentanil administered was 18.8 µg/kg (range: 14.4–24.3 µg/kg).

At the beginning and during each drug condition as well as before filling out the mood scales after each condition, volunteers were asked about symptoms of nausea (yes/no answer). The occurrence of signs of regurgitation or vomiting was registered during the entire experiment.

Painful stimulation

The use of a Visual Analogue Scale (VAS) was explained to the volunteers. A temperature-controlled contact thermode (surface area 1.6×3.6 cm; contact pressure 0.4 Newton/cm^2; PATH-tester MPI 100, PHYWE, Göttingen, Germany) was used for the two stimulus conditions (non-painful heat, painful heat) in the three drug conditions ('control', 'low-dose remifentanil' and 'moderate-dose remifentanil'). The thermode was attached to the right volar forearm, and the position was changed in clockwise direction after each condition to avoid habituation effects and skin damage.

Determination of the thermal pain threshold was accomplished by an adjustment procedure. Thereby the subjects used a heating and a cooling button to determine the temperature just being barely painful starting from a baseline temperature of 37 °C. Seven consecutive trials were performed 1 h before the investigation, and the average temperature of the last six trials was considered as the pain threshold.

Thermal stimuli were applied with a frequency of 0.6 Hz and a duration of 5 min. From the individual pain threshold (mean: 44.98 °C, SD ± 0.67, range 43.88–46.2 °C), the heat pulses changed between a maximum of 1 °C above the pain threshold to a minimum of 0.3 °C below the pain threshold for the painful heat stimulation (amplitude 1.3 °C, Figure 1a).
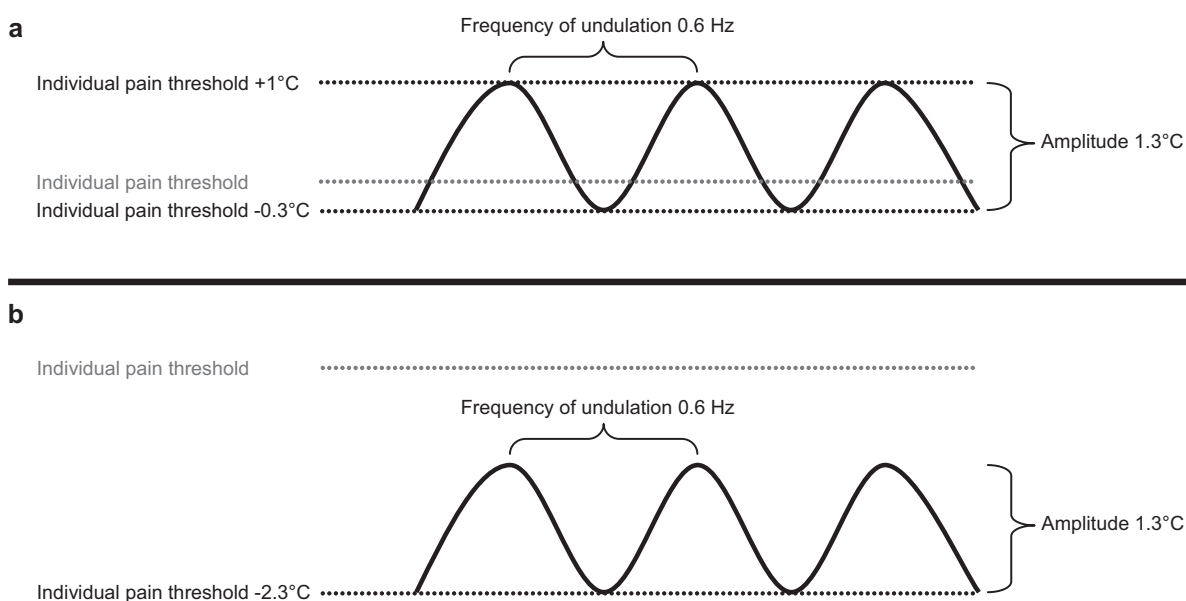
Figure 1 Experimental thermal stimulation for painful (a) and non-painful heat stimulation (b).

For the non-painful heat stimulation, the temperature undulated with the identical frequency and amplitude starting 2.3 °C below the individual pain threshold (Figure 1b). This kind of thermal stimulation was chosen to avoid skin damages (Lautenbacher, *et al.*, 1995).

After each stimulation, subjects rated their individually experienced pain intensity by moving a slide along a 100 mm VAS (0–100; 0 = no pain, 100 = unbearable pain).

Mood testing

The patient's subjective state of well-being was measured by a multidimensional scaling of verbal descriptor items, the von Zerssen mood scale (28 items, Befindlichkeits-Skala [Bf-S], Hogrefe Verlag, Göttingen, Germany). It consists of two statistically equivalent parallel questionnaire versions (Bf-S, Bf-S`). Each version contains a list of 28 pairs of antonymous words (e.g., lethargic – active, satisfied – dissatisfied, solemn – cheerful, happy – sad, energetic – weak, etc.) (von Zerssen, *et al.*, 1970). The scale has been shown to possess sufficient reliability and validity and has been used in many psychopharmacological studies (von Zerssen, *et al.*, 1970, Pfeiffer, *et al.*, 1986, Crozier, *et al.*, 2004).

Volunteers were familiarised with the test before the study and were instructed how to use and fill out the questionnaires which takes approximately 1–3 min. Bf-S and Bf-S' were given to the volunteers in a randomised order to counteract habituation and to minimise learning effects. After each of the six different conditions (2 heat conditions × 3 drug conditions), the volunteers completed the test in an ambient, quiet surrounding by deciding which, if any, adjective of each pair most closely describes his current mood. Choosing the negative term gives two points, the positive term gives zero points and indecision gives one point. Low-sum scores represent a subjective feeling of well-being/euphoria, whereas high scores indicate dysphoria and depression.

The median score of a normal population is 9; 25% of subjects have a score of 4 or less, 75% have a score of 17 or less. In clinical routine, a score over 27 (90th percentile) provides strong evidence for depression. Heimann, *et al.* (1975) considered a score between 7 and 17 to be consistent with an emotionally balanced state.

Statistical analysis

As the experimental paradigm provided repeated measurements per individual, the influence of the remifentanil dose and the mode of stimulation (non-painful versus painful) on the Bf-S scores and VAS ratings was estimated using Linear Mixed Models (Laird and Ware, 1982) in SPSS 15.0 (SPSS Inc., Chicago, Illinois, USA). This approach allows to investigate serial measurements with inclusion of variable numbers of measurements per condition. As all measurements were performed consecutively, a compound symmetry correlation structure was used, that is, variance and correlation between the elements are homogenous. The statistical threshold was set at $p < 0.05$ for all comparisons.

Results

All volunteers completed the study without complications. In particular, no nausea or vomiting was noted.

The results of the Linear Mixed Models are reported as estimated regression coefficients beta (β) together with their corresponding 95% confidence intervals (CI). Here, β can be

Table 1 Mood score and pain rating during the different experimental conditions

	Saline/control		Low-dose remifentanil		Moderate-dose remifentanil	
	Non-painful heat	Painful heat	Non-painful heat	Painful heat	Non-painful heat	Painful heat
Mood score (Bf-S, 0–56)	12.42 ± 8.64	10.32 ± 8.35	15.65 ± 11.50	15.78* ± 11.58	19.09** ± 14.48	19.75* ± 14.17
Pain score (VAS, 0–100)	n.a.	60.73 ± 23.68	n.a.	43.38* ± 20.70	n.a.	31.00* ± 22.66

Mean values ± standard error of the mean of mood scores (Bf-S) and pain ratings (VAS) during the different experimental conditions.
Bf-S, Befindlichkeits-Skala; VAS, Visual Analogue Scale; n.a. = not applicable.
*$p < 0.001$ versus painful heat during saline/control.
**$p < 0.001$ versus non-painful heat during saline/control.

regarded as effective change in the score due to the particular situation in comparison to the baseline group.

Bf-S scores and VAS ratings

Non-painful stimulation   Concerning the experiments with non-painful stimulation, the moderate dose of remifentanil significantly increased the Bf-S mood scores (β = 5.86, 95%-CI = [2.68; 9.04], $p < 0.001$) indicating dysphoria (Table 1, Figure 2). Low-dose remifentanil increased the Bf-S ratings non-significantly (trend only).

Painful stimulation   Regarding the experiments with painful stimulation, already the low dose of remifentanil significantly increased the Bf-S mood scores (β = 5.81, 95%-CI = [2.76; 8.86], $p < 0.001$) (Table 1, Figure 3) and decreased the values of the VAS pain ratings (β = −22.03, 95%-CI = [−27.69; −16.37], $p < 0.001$) (Table 1, Figure 4). The moderate dose increased the Bf-S scores (β = 9.70, 95%-CI = [6.66; 12.74], $p < 0.001$) and decreased the VAS ratings (β = −34.53, 95%-CI = [−40.19; −28.87], $p < 0.001$) even more.

On the individual level, only 2 of 21 volunteers reported opposite mood changes than the group mean, that is, decreases

instead of increases on the Bf-S scale, indicating euphoria rather than dysphoria.

Analysis of the whole data set (Interaction analysis)   When analysing the data of the non-painful and painful stimulation of all volunteers together and considering a possible interaction between dose and mode of stimulation, that is, including all experimental data in the analysis, only the medication with remifentanil had a significant influence on the Bf-S mood scores (low dose: β = 4.91, 95%-CI = [1.87; 7.95], $p = 0.002$; moderate dose: β = 8.82, 95%-CI = [5.78; 11.85], $p < 0.001$). Neither the mode of stimulation (β = 2.02, 95%-CI = [−0.89; 4.94], $p = 0.174$) nor the interaction between medication and stimulation (low dose*painful: β = −2.16, 95%-CI = [−6.05; 1.73], $p = 0.276$; moderate dose*painful: β = −2.69, 95%-CI = [−6.57; 1.20], $p = 0.175$) had an effect on Bf-S mood scores.

Cardiorespiratory parameters

The haemodynamic and respiratory values are presented in Table 2. Systolic blood pressure and $etCO_2$ did not change irrespective of the applied remifentanil dose. Minor but significant remifentanil-related changes were detected when SaO_2,
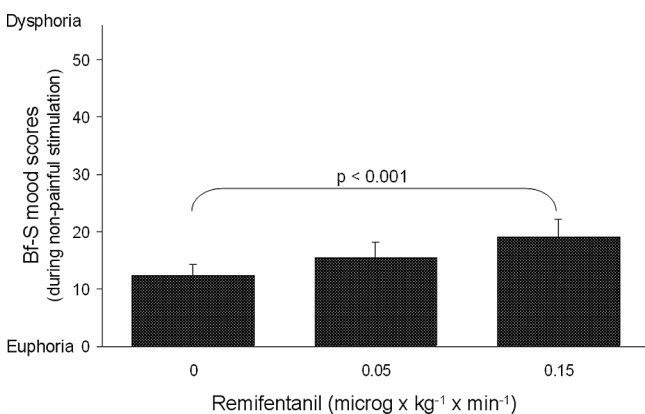

Figure 2 Mood ratings (Bf-S scores) during non-painful heat and the different concentrations of remifentanil (saline, low-dose remifentanil, moderate-dose remifentanil).
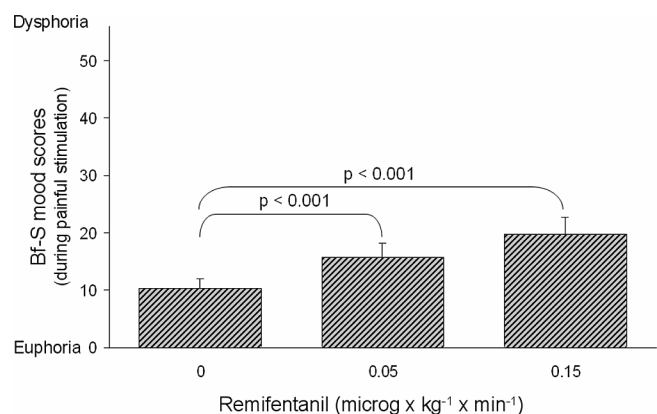

Figure 3 Mood ratings (Bf-S scores) during painful heat and the different concentrations of remifentanil (saline, low-dose remifentanil, moderate-dose remifentanil).
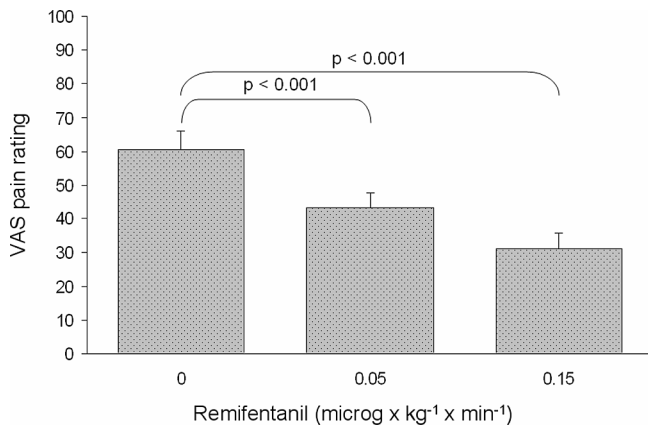
Figure 4 VAS rating of pain intensity during the different concentrations of remifentanil (saline, low-dose remifentanil, moderate-dose remifentanil).

diastolic arterial blood pressure and heart rate were statically analysed by the Linear Mixed Model. In spite of significant differences, none of the cardiorespiratory parameters were out of the normal physiological range.

The stimulus had no statistically significant effect on cardiovascular parameters.

Discussion

We used remifentanil hydrochloride which is a specific µ-opioid receptor agonist with pharmacodynamic properties comparable to those of fentanyl and its derivates to investigate drug effects on mood. The maximal dose of remifentanil was based on the findings of previous studies using remifentanil with continuous infusion and omitting a bolus application in healthy subjects (Wagner, *et al.*, 2001; Wagner, *et al.*, 2007). The applied doses are similar to what is commonly used in anaesthetic practice and intensive care. This regimen allowed investigation of

spontaneously breathing volunteers who were able to follow commands, to indicate the VAS ratings and to fill out mood questionnaires without problems. Moreover, important confounding factors in terms of mood disturbances such as nausea or vomiting, which are well known side effects of µ-opioid receptor agonists, were avoided in our current study because of zero order infusion kinetics. A bolus dose for loading before infusion was not necessary because steady-state concentrations are reached within 10 min with the continuous infusion approach.

Opioid effects on mood and other neuropsychological variables have been increasingly studied recently (Gruber, *et al.*, 2007). However, investigations mainly focused on the population of addicts or postaddicts, and only little research has examined the subjective effects of opioids in healthy volunteers. The pain relieving and euphorigenic properties of µ-opioidergic drugs have been well known for centuries and studies from the 90s of the last century have again stressed these positive subjective effects (Zacny, *et al.*, 1992). In contrast, activation of the κ-receptor is thought to produce dysphoria (Pfeiffer, *et al.*, 1986).

Lasagna, *et al.* (1955) were the first to describe dysphoric effects of opiates (morphine and heroin) acting predominantly on the µ-receptor in normal subjects, which was confirmed by further research (Hill and Zacny, 2000; Zacny, *et al.*, 1998). In a previous and methodologically sound study by Black, *et al.* (1999) the authors found a remifentanil-related increase in 'lysergic acid diethylamide' scores as a measure of dysphoric drug effects. The authors themselves attributed this mood change to nausea, which occurred in a significant number of subjects with remifentanil application. However, nausea cannot explain the results of our study as we did not notice nausea or vomiting. The difference in the amount of nausea and vomiting between the studies is best explained by differences in infusion kinetics. Black, *et al.* used a target-controlled infusion scheme (with bolus) of remifentanil, whereas we omitted a bolus application.

Other possible explanations for the conflicting results might be differences in the study design, for example, time of testing postdrug exposure and drug dosage. Another essential factor

Table 2 Cardiorespiratory parameters during the different experimental conditions

	Saline/control		Low-dose remifentanil		Moderate-dose remifentanil	
	Non-painful heat	Painful heat	Non-painful heat	Painful heat	Non-painful heat	Painful heat
Syst BP (mm Hg)	125 ± 2.7	123 ± 1.8	126 ± 3.2	127 ± 3.7	129 ± 3.3	129 ± 3.2
Dia BP (mm Hg)	75 ± 1.5	76 ± 1.3	71* ± 1.7	72* ± 1.7	72* ± 1.8	72* ± 1.8
HR (beats/min)	65 ± 1.5	67 ± 1.3	61* ± 1.3	62* ± 1.3	63 ± 1.7	63 ± 1.7
End-tidal CO_2 (mm Hg)	42 ± 0.3	42 ± 0.3	42 ± 0.7	42 ± 0.7	42 ± 0.7	42 ± 0.7
Oxygen saturation (%)	98 ± 0.2	97 ± 0.2	98* ± 0.2	98 ± 0.2	97* ± 0.3	97 ± 0.3

Mean values ± standard error of the mean of cardiorespiratory parameters during the different experimental conditions. Significant changes between the painful heat conditions are marked with asterisks (painful heat during remifentanil application versus painful heat during saline/control). The same applies to significant changes between the non-painful heat conditions (non-painful heat during remifentanil application versus non-painful heat during saline/control).
Syst BP = systolic blood pressure, dia BP = diastolic blood pressure, HR = heart rate.

explaining the discrepancy between our results and the textbook doctrine of euphorigenic μ-effects might be related to a dynamic interaction of a number of different personality variables. Hereby, the personal background, present situation and observer activities might play a critical role in the subjective perception of drug effects (Lindemann and Felsinger 1961).

Last but not least, many previous studies used unspecific agonists, which preclude conclusions about receptor specific effects.

Our study results highlight the substantial mood changes that occur during infusion of remifentanil. Quite contrary to the expectation that remifentanil would induce euphoria in most volunteers during rest (i.e., non-painful heat), we observed clearly dysphoric mood ratings in 19 of 21 subjects. One might argue that the pre-study affective state might predict remifentanil mood effects. However, in one of the two volunteers evidencing mood conversion toward a euphoric state, the pre-study mood was within normal limits (Bf-S = 8) and in the other one, it was dysphoric (Bf-S = 24). Hence, this argumentation is unlikely to explain the different behaviour of these two volunteers concerning mood modulation.

Concerning analgesia, remifentanil performed well during both dosages, exhibiting dose-related analgesia during the painful heat conditions. However, the analgesic properties were not associated with an improvement in mood, and thus, analgesia-related positive effects on mood were outweighed by opioid-related dysphoric effects.

Remifentanil is increasingly popular for ambulatory surgery for minor to moderate procedures and is expected to minimise postoperative complications (White, *et al.*, 2007; Wilmore and Kehlet, 2001). However, its dysphoric effects are disadvantageous in this context and have to be considered by the clinician before patients are given it.

A systematic clinical approach about mood effects of remifentanil failed to show postanaesthetic dysphoria on the first postoperative day (Crozier, *et al.*, 2004). However, in such a clinical perioperative study setting, various factors like the use of a volatile (Gupta, *et al.*, 1996; Pollard, *et al.*, 1994) or intravenous anaesthetic (Kalman, *et al.*, 1993; Marshall, *et al.*, 1992; Oxorn, *et al.*, 1994), the diagnosis and the procedure itself are influencing the mood of the patient. This might, therefore, blur the effects of remifentanil itself on mood, necessitating a very large study cohort to provide sufficient statistical power.

The remifentanil associated mood change in our study cohort must be considered as substantial as Bf-S scores were nearly doubled by the application of remifentanil, and there was clearly a conversion from an emotionally balanced state (Heimann, *et al.*, 1975) to dysphoria. This view is underlined by the results of a recent pharmacologic study on the effects of the selective serotonin reuptake inhibitor citalopram on depression using the same psychological scale that we used (Bf-S) in addition to the Hamilton Depression Scale. In the cited study, the Bf-S scores decreased by 13 points after 6 weeks of treatment with citalopram and were regarded as clinically relevant (Gastpar, *et al.*, 2006). The change on the Bf-S scale was accompanied by a mean change of 11.4 points on the Hamilton Depression Scale.

Considering these substantial dysphoric effects of remifentanil, it seems to be unsuitable for monotherapy and a pre- or comedication should be considered to minimise dysphoric effects in the clinical setting. In this regard, the addition of midazolam to remifentanil analgesia might be a feasible approach because this combination has been shown to result in less side effects such as anxiety while providing adequate analgesia with reduced dosing of remifentanil (Gold, *et al.*, 1997).

Opioids bear the risk of addiction not only in patients but also in medical personnel (Domino, *et al.*, 2005). Thereby opioids with strong positive effects on mood are thought to have a greater abuse liability (Baylon, *et al.*, 2000). Hence, one might conclude that the dysphoric effects of remifentanil on mood together with the need for intravenous constant infusion argue for a relatively low abuse potential of this drug in clinical practice. To our knowledge, no remifentanil abuse has been reported so far. However, it must be kept in mind that in the current study we exclusively investigated healthy volunteers without a history of drug abuse and volunteers who are prone to addiction might behave differently.

Acute pain perception in normal subjects is distinct from that seen in patients with chronic clinical pain conditions (Apkarian, *et al.*, 2005). Therefore, our results of dose-related dysphoric effects of remifentanil during acute pain in humans are restricted to healthy subjects without pre-existing chronic pain conditions.

In conclusion, the application of the selective μ-opioid receptor agonist remifentanil during experimental pain induces dose-dependent dysphoric mood in healthy, non-drug abusing volunteers. These effects should be considered in the clinical management of patients receiving remifentanil.

Acknowledgments

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