Problems in obtaining sufficient anaesthesia with propofol and remifentanil: three cases, a test infusion, and a review

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Editor’s key points

- Three patients with an apparently decreased response to remifentanil.
- Two of these patients subsequently tested with a step-up infusion of remifentanil.
- They had a normal analgesic response but limited respiratory and consciousness responses.
- The cause of this impaired effect is not clear.

Background. Over a 5 yr period, we have encountered three patients in whom remifentanil appeared to have no clinical effect during general anaesthesia (GA). We describe seven anaesthetics in these three patients.

Methods. We reviewed the literature on this subject. A simple reproducible test to explore this response was designed. This involved a controlled infusion of increasing doses of remifentanil while observing respiratory variables, pain threshold, pupil size, and Glasgow coma scale score. In addition, blood was sampled for genotyping.

Results. No description of this impaired response was found in the review of the literature. Two of the patients agreed to participate in the test. In both patients, we found a seemingly normal analgesic response but a lack of respiratory depression and almost no depression of consciousness, even at doses well above the recommended level for clinical use. The genotyping did not explain the results of the test.

Conclusions. The potential causes of this effect are discussed. We advise clinicians to be aware of this unusual response to remifentanil. If such a response is suspected, we recommend the use of another opioid. If this is suspected before GA, we propose the use of our test as a diagnostic tool.

Keywords: awareness; drug resistance; drug tolerance; general anaesthesia; remifentanil

Accepted for publication: 29 October 2012

Remifentanil is one of the most potent clinically used opioids, with a short half-life and context-sensitive half-life time which is independent of the duration of the infusion. Remifentanil is metabolized to a much less potent metabolite via non-specific esterases.1 Owing to these unique properties, remifentanil has gained increasing importance during daily anaesthesia practice. Thus, an increasing number of patients receive remifentanil, and thus even rare complications require attention.

Over a 5 yr period, we encountered three patients at hospitals in the Copenhagen area in whom a sufficient level of anaesthesia seemed impossible to achieve using a combination of propofol and remifentanil. We suspected that the cause was a very low effect or lack of effect of remifentanil.

We describe seven inductions of anaesthesia in these patients and review the literature. A controlled infusion test of remifentanil was given to two of the patients and the possible causes and clinical implications are discussed.

Case 1

A 61-yr-old Caucasian male (82 kg) with a recent diagnosis of prostate cancer, but who was otherwise healthy and free of any medication, was undergoing planimetric volumetry and a biopsy of the prostate gland. General anaesthesia (GA) was induced with propofol 200 mg and alfentanil 1 mg. A continuous infusion of propofol was started at 0.125 mg kg⁻¹ min⁻¹ and after 1 min, a laryngeal mask (LM) was placed. As the arterial pressure and heart rate increased, fentanyl 0.1 mg and alfentanil 2 mg were given, and the infusion rate of propofol was increased to 0.2 mg kg⁻¹ min⁻¹ and increased to 1.9 μg kg⁻¹ min⁻¹ over a period of ≏15 min without any effect. Additional boluses of remifentanil were given, but even after a bolus of 2.5 mg, the patient moved, showed respiratory effort, and had dilated pupils.

Four months later, the patient was rescheduled for planimetric volumetry of the prostate gland. Anaesthesia was
induced with propofol 200 mg and continuous infusions of propofol 0.2 mg kg\(^{-1}\) min\(^{-1}\) and remifentanil 1.2 \(\mu\)g kg\(^{-1}\) min\(^{-1}\). An LM was easily placed, but even with these infusion rates, the heart rate was 85 beats min\(^{-1}\) and the arterial pressure was 128/86 mm Hg. Despite increasing the infusion rates to 0.26 mg kg\(^{-1}\) min\(^{-1}\) of propofol and 1.5 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) of remifentanil, the arterial pressure and the relatively high heart rate did not decrease. Anaesthesia was supplemented with fentanyl 0.2 mg, after which the heart rate and arterial pressure decreased significantly. The duration of the total procedure was 22 min.

One month later, the patient was undergoing brachytherapy with Iodine 125 implantation. Anaesthesia was induced with propofol and alfentanil and maintained with desflurane 12% and a continuous infusion of remifentanil 1.2 \(\mu\)g kg\(^{-1}\) min\(^{-1}\). However, additional alfentanil 1 mg, fentanyl 0.4 mg, and propofol 200 mg were required to maintain adequate anaesthesia during the 1 h procedure.

**Case 2 (Subject A)**

A 30-yr-old otherwise healthy Caucasian female (66 kg), who was treated with prednisolone and levetiracetam for epilepsy, was undergoing a partly awake craniotomy for an intracranial tumour. Anaesthesia was induced with continuous infusions of propofol 0.13 mg kg\(^{-1}\) min\(^{-1}\) and remifentanil 0.45 \(\mu\)g kg\(^{-1}\) min\(^{-1}\), and also a bolus of propofol 120 mg, but insufficient depth of anaesthesia was indicated by her arterial pressure, heart rate, and readings on a Cerebral State Monitor\textsuperscript{TM} (CSM) (Danmeter Aps, Odense, Denmark). I.V. access was replaced and a new remifentanil solution was mixed. However, despite increased infusion rates of propofol to 0.15 mg kg\(^{-1}\) min\(^{-1}\) and remifentanil to 1.5 \(\mu\)g kg\(^{-1}\) min\(^{-1}\), the patient required several supplemental boluses of propofol (a total of 170 mg) during the first part of the surgery that lasted 2 h. The readings on the CSM indicated that the patient was intermittently still awake.

**Case 3 (Subject B)**

A 34-yr-old healthy Caucasian female (65 kg) was undergoing breast lift surgery. Anaesthesia was induced with continuous infusions of propofol 0.09 mg kg\(^{-1}\) min\(^{-1}\) and remifentanil 0.5 \(\mu\)g kg\(^{-1}\) min\(^{-1}\), and after 30 s, boluses of propofol 150 mg and of remifentanil 180 \(\mu\)g. After 1 min without ventilation, an LM was easily introduced and inspiratory airway pressure was normal. After a few minutes, spontaneous respiration occurred, but the patient coughed, moved her extremities, and developed increased secretion of sputum. Additional boluses of propofol 50 mg and remifentanil 180 \(\mu\)g were given, but these relieved the symptoms for only 1–2 min. The infusions were moved to an i.v. access in the opposite arm and the symptoms remained despite additional boluses of propofol 50 mg and remifentanil 300 \(\mu\)g. The anaesthesia was stopped, and within 5 min, the patient was fully awake with sufficient respiration. Three hours later, the patient was anaesthetized again. An extra person inspected the mixing of the remifentanil solution.

The GA was induced with thiopental 450 mg and a bolus of remifentanil 240 \(\mu\)g. Mask ventilation was easy, and after administration of succinylcholine, she was intubated. Continuous infusions of propofol 0.1 mg kg\(^{-1}\) min\(^{-1}\) and remifentanil 0.6 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) were started, but the similar symptoms appeared again after a few minutes. The diameter of the pupils was 7 mm. These symptoms were unchanged despite further boluses of propofol 100 mg and remifentanil 240 \(\mu\)g. The procedure was therefore abandoned, and the patient was alert with sufficient spontaneous respiration after 5 min.

Two months later, the patient was rescheduled for the surgery under GA. An infusion of remifentanil was started at a rate of 0.6 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) and increased up to 1.2 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) over 10 min. Her only experience was that her ‘breathing felt heavy’. A further bolus of remifentanil 240 \(\mu\)g had no effect, and the infusion was stopped. After 7 min of observation, sufentanil 30 \(\mu\)g was given, and the classic opioid effects, including miosis, were observed. The anaesthesia was now induced with propofol and was uneventfully maintained with propofol and sufentanil.

**Review of the literature**

We searched the PubMed database using the key words ‘resistance’ or ‘tolerance’ or ‘awareness’ or ‘lack of effect’ or ‘reduce effect’ or ‘diminish effect’ or ‘less effect’ or ‘low effect’ or ‘weak effect’ or ‘remifentanil’, which resulted in 402 references. The Cochrane Library was searched using the same keywords with the search restriction ‘search all text’. This search produced 42 more references. Finally, Google Scholar was searched using the same keywords in the article title, and 29 more references were added. Titles and abstracts were screened, but the only possible explanation of our findings was ‘acute opioid tolerance’. This is relatively well studied but still controversial. The results of one double-blinded study,\textsuperscript{3} one single-blinded randomized controlled clinical study,\textsuperscript{4} one prospectively paired volunteer-blinded study,\textsuperscript{5} and one prospective observational clinical study\textsuperscript{6} argue for the existence of acute opioid tolerance after remifentanil infusion. In contrast, one double-blinded placebo-controlled study,\textsuperscript{7} one randomized placebo-controlled double-blinded cross-over design study,\textsuperscript{8} one single-blinded randomized controlled clinical study,\textsuperscript{9} and one prospective observational clinical study\textsuperscript{10} could not confirm its existence. The earliest detection of what may have been acute tolerance was reported at 45\textsuperscript{5} and 120 min\textsuperscript{5} after stopping the remifentanil infusion. In our cases, however, no effect or a very limited effect was found and there were no signs of a developing tolerance (i.e. an initial effect waning over time).

The PubMed database was then searched using the word ‘remifentanil’ limited by ‘case reports’. Titles and abstracts of 409 case reports were found and screened but only one seemed relevant.\textsuperscript{11} However, while that patient showed signs of consciousness while receiving a relatively high
remifentanil dose, this was noted after a longer period of infusion of remifentanil.

Methods

Our three patients were offered a remifentanil infusion test and blood samples. The protocol for this study was approved by the Danish Regional Scientific Ethics Committee of the Capital Region # H-3-2010-137. The remifentanil infusion test was performed in an operating theatre with standard anaesthetic equipment available. I.V. access was obtained, and oxygen 5 litre min$^{-1}$ was given by a nasal catheter. ECG, arterial oxygen saturation ($\text{Sa}_O_2$), respiratory rate, and end-tidal carbon dioxide concentration ($\text{ET}_\text{CO}_2$) were monitored. Non-invasive arterial pressure was measured every 2 min, and the Glasgow coma scale (GCS) score every minute. The pain threshold was measured every minute on the fourth finger of the right hand by applying pressure using an algometer (Somedic, Sollentuna, Sweden).$^{11}$ Pupil size was measured continuously with a video camera. We encouraged the subjects to verbalize their subjective experience before and during the test and asked if they felt any discomfort. Baseline values were recorded and a continuous infusion of remifentanil 0.5 $\mu$g kg$^{-1}$ min$^{-1}$ was started. After 4 min, the infusion rate was increased stepwise by 0.25 $\mu$g kg$^{-1}$ min$^{-1}$ every 2 min. At 16 min, the infusion rate was 2.0 $\mu$g kg$^{-1}$ min$^{-1}$ and remained unchanged thereafter. Bolus doses of remifentanil 60, 120, and 240 $\mu$g were given at 16, 17, and 18 min, respectively. During the infusion, if $\text{Sa}_O_2$ < 90% or apnoea (>10 s) was observed, the subject was encouraged to breathe. If this failed, the infusion of remifentanil was stopped, and ventilation was restored as necessary. Likewise, the infusion was stopped if the GCS score was < 9. If none of these observations occurred, the infusion was stopped after 20 min. Blood samples were drawn from each subject immediately after stopping the infusion. Genotyping of the A118G (rs179971) SNP in the opioid $\mu$-receptor gene was performed by analysing genomic DNA obtained from whole-blood samples collected in EDTA vacuum tubes. Genotyping was performed by the use of a pre-made TaqMan genotyping assay (Applied Biosystems 7500 Fast Real Time PCR, Applied Biosystems, Lincoln, CA, USA).

Results

Subjects A and B (Cases 2 and 3) agreed to participate in the investigation and signed an informed consent. The infusion regimes, the calculated plasma concentrations, and target concentrations are shown in Figure 1.

Subject A felt dizzy 2 min and 45 s (2:45) after the infusion was started but maintained a GCS score of 15 throughout the entire test. She did close her eyes for up to 5 s a few times. She was encouraged to breathe at 5:52 and again at 7:52 because of apnoea. At 10:34, $\text{Sa}_O_2$ < 90% was observed, and despite encouragement to breathe, apnoea was observed at 11:00. The infusion was stopped at 11:10. A total dose of remifentanil 612 $\mu$g was given and a calculated peak plasma concentration of 25.6 ng ml$^{-1}$ was reached. Subject B, although feeling tired and distant after 4 min, had a GCS score of 15 during the first 7 min of the infusion test. Although orientated and obeying commands, she closed her eyes most of the time when she was not disturbed. Apnoea was observed at 14:35 and she was encouraged to breathe. At 17:00, muscle rigidity seemed to develop, and it was difficult to evaluate her consciousness. She had open eyes and followed commands up until 19:20 but had no verbal response (GCS score 11). After the test, she explained that she remembered everything from the 18th and the 19th min but was unable to speak. Muscle rigidity increased at 18:10, and despite encouragement to breathe, apnoea developed. The infusion was stopped at 18:24. A total dose of remifentanil 1718 $\mu$g was given and a calculated peak plasma concentration of 67.9 ng ml$^{-1}$ was reached. After a further 26 s, naloxone 0.4 mg was administered to ensure ventilation. One minute later, breathing and speech had fully returned to normal.

We observed a minimal respiratory depression in both subjects (Fig. 1). Pupil constriction was found in Subject A but was minimal in Subject B. Increased values for algometry were found in both subjects. A detailed description of past medical history and clinical observations in Subjects A and B during the remifentanil infusion test is given in the Supplementary material. A118G-polymorphism testing showed that Subject A was homozygous AA and Subject B was heterozygous AG.

Discussion

A combination of propofol and high-dose remifentanil was used in the three patients. Nevertheless, all patients showed signs of insufficient anaesthesia. In two of the patients, other opioids were required to achieve sufficient anaesthesia. Anaesthesia was cancelled twice in one patient. These events are likely to be related to an unusual effect profile of remifentanil.

The threshold for a pain stimulus increased after 1–2 min during the infusion test in both subjects. An increase in analgesic tolerance of 100% was seen after 3–4 min in both subjects. Two studies in young volunteers on the effect on pain perception (tibial algometry) of a remifentanil bolus reported analgesic effect onset times of 1–2 min and increased algometry thresholds of up to 100% after 3 min.$^{12}$ $^{13}$ Thus, the analgesic effect of remifentanil in our subjects did not seem to be markedly reduced.

Despite the high doses of remifentanil, no or only a slight sedative effect was found. It is known that the central effects of high dose of remifentanil infusions vary between individuals. Thus, when remifentanil 2–20 $\mu$g kg$^{-1}$ was infused at a constant rate over 2 min, the effective dose for 50% of the volunteers to lose consciousness (defined as failure to respond to three consecutive commands) was estimated to be 12 $\mu$g kg$^{-1}$ or a whole blood concentration of 53.8 ng ml$^{-1}$. The same study showed that only two of five volunteers receiving 20 $\mu$g kg$^{-1}$ lost consciousness, although five
of five volunteers receiving 15 \( \mu g \) kg\(^{-1}\) lost consciousness.\(^{14}\) Changes in the diameter of the pupil may be an estimate of the central nervous effect of opioids.\(^{15}\) Subject A showed a reduced diameter after 2–3 min to a maximum reduction of 32%. In Subject B, the immediate reaction was a dilated pupil at 1 and 2 min followed by a gradual contraction to below the baseline diameter after 8 min to a maximum reduction of 26%. Studying constant rates of infusions of remifentanil targeting plasma levels of 0.75, 1.5, and 3 ng ml\(^{-1}\) in healthy volunteers, a dose-dependent decrease in pupil diameter was observed.\(^{16}\) Compared with the estimated plasma levels of our subjects, these plasma levels were relatively low.

Subject A showed a gradual and slight increase in E\(^{\prime}\)CO\(_2\) from 5 to 14 min and a reduction in respiratory rate to 6 bpm after 11 min. Respiratory depression occurred in Subject B first after 14 min, when a decrease in respiratory rate and an increasing E\(^{\prime}\)CO\(_2\) over the next 3 min were observed. The E\(^{\prime}\)CO\(_2\) increased markedly after boluses of 60 and 120 \( \mu g \) of remifentanil. In a study of a single bolus of
Remifentanil (25–200 μg) in healthy young volunteers breathing room air, dose-dependent decreases in oxygen saturation and respiratory rate were observed within 2–4 min. It is possible that the oxygen supplementation and the encouragement to breathe (in the case of apnoea) masked the observation of respiratory depression in our subjects. However, Subject B did not require encouragement to breathe until after almost 15 min, indicating an unusual lack of respiratory depression after remifentanil.

The result of the AG-polymerism test does not explain the markedly reduced effect of remifentanil because neither Subject A nor Subject B had the variant of homozygote GG, which is associated with a reduced effect from morphine. In the remifentanil infusion test, Subject A showed no muscular rigidity, and Subject B showed, what we interpreted as, apnoea secondary to muscular rigidity after 18 min. In a study of 10 young healthy volunteers, remifentanil was given at infusion rates of 1–8 μg kg⁻¹ min⁻¹ over 20 min. Despite pretreatment with 0.5 mg pancuronium, all of the subjects showed moderate muscular rigidity requiring succinylcholine by continuous infusion to facilitate controlled ventilation. Hence, the muscular rigidity we observed seems to be far less than expected.

Thus, in seven anaesthetics in three subjects, an uncharacteristic effect of remifentanil was observed. Infusion of remifentanil in two subjects showed a normal analgesic response but confirmed a lack of respiratory depression and almost no depression of consciousness, even at high doses. The cause of this cannot be explained based on our cases or the tests and may be difficult to isolate. Possible explanations could be increased metabolism as a result of supranormal activity of esterases, and also reduced receptor sensitivity or a low permeability of the blood–brain barrier. Although the mechanism is unknown, the clinical implications may be significant.

In six of seven anaesthetics in our patients, propofol was the hypnotic used for maintenance. Remifentanil is known to produce a potent synergy with propofol. For example, only modest remifentanil concentrations dramatically reduce the concentration of propofol required to ablate the response to laryngoscopy or to reduce BIS values. Therefore, the lack of clinical effect in our cases does not necessarily have to be exclusively associated with remifentanil, but an additional factor might also be an altered interaction between propofol and remifentanil. In addition to the problems of achieving a sufficient depth of anaesthesia, one could speculate that some cases of awareness may be explained by a markedly reduced effect of remifentanil.

In conclusion, it is possible that Subjects A and B simply represent extreme outliers in a population known to have a wide range of reactions to remifentanil. However, regardless of which mechanism is responsible for this, it is important in the clinical setting to be aware of this unusual response and to understand that it may be impossible to obtain sufficient anaesthesia using the combination of propofol and high doses of remifentanil. This problem seemed to be resolved by replacing remifentanil with another opioid. If this problem is suspected before a subsequent anaesthetic, we propose the use of our test at induction to allow the choice of the right opioid or the right dose of remifentanil.

Supplementary material
Supplementary material is available at British Journal of Anaesthesia online.

Acknowledgement
We would like to thank MSc Tom De Smet from Demed Medical in Temse, Belgium, for his support with the Rugloop programming.

Declaration of interest
None declared.

Funding
This work was supported by departmental sources only.

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Handling editor: C. S. Reilly