*British Journal of Anaesthesia* **110** (5): 741–6 (2013)
Advance Access publication 20 December 2012 · doi:10.1093/bja/aes474

BJA

CLINICAL PRACTICE

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

S. Bache[1]*, L. Stendell[1], N. V. Olsen[2] and K. S. Olsen[1]

[1] Department of Anaesthesiology, University Hospital of Copenhagen (Glostrup Hospital), Copenhagen, Denmark
[2] Department of Neuroanaesthesia, The Neuroscience Centre, University Hospital of Copenhagen (Rigshospitalet), Copenhagen, Denmark

* Corresponding author. E-mail: sbache@webspeed.dk

## 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 $kg^{-1}$ $min^{-1}$. As the patient still showed signs of inadequate anaesthesia, a continuous infusion of remifentanil was started at 1.0 μg $kg^{-1}$ $min^{-1}$ 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 μg $kg^{-1}$ $min^{-1}$. 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 μg $kg^{-1}$ $min^{-1}$ 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 μg $kg^{-1}$ $min^{-1}$. 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 μg $kg^{-1}$ $min^{-1}$, 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™ (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 μg $kg^{-1}$ $min^{-1}$, 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 μg $kg^{-1}$ $min^{-1}$, and after 30 s, boluses of propofol 150 mg and of remifentanil 180 μg. 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 μg 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 μg. 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 μg. 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 μg $kg^{-1}$ $min^{-1}$ 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 μg. 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 μg $kg^{-1}$ $min^{-1}$ and increased up to 1.2 μg $kg^{-1}$ $min^{-1}$ over 10 min. Her only experience was that her 'breathing felt heavy'. A further bolus of remifentanil 240 μg had no effect, and the infusion was stopped. After 7 min of observation, sufentanil 30 μg 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' and '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,[2] one single-blinded randomized controlled clinical study,[3] one prospectively paired volunteer-blinded study,[4] and one prospective observational clinical study[5] argue for the existence of acute opioid tolerance after remifentanil infusion. In contrast, one double-blinded placebo-controlled study,[6] one randomized placebo-controlled double-blinded cross-over design study,[7] one single-blinded randomized controlled clinical study,[8] and one prospective observational clinical study[9] could not confirm its existence. The earliest detection of what may have been acute tolerance was reported at 45[5] and 120 min[4] 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.[10] However, while that patient showed signs of consciousness while receiving a relatively high