

## USE OF REMIFENTANIL FOR ANALGESIA DURING DRESSING CHANGE IN SPONTANEOUSLY BREATHING NON-INTUBATED BURN PATIENTS

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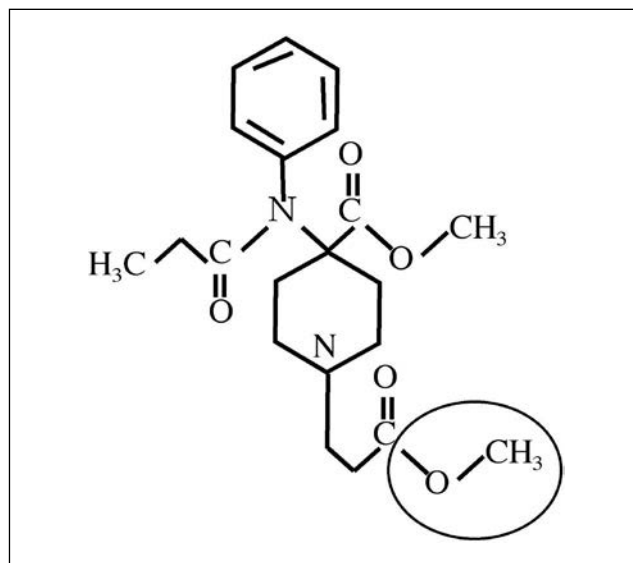
**SUMMARY.** We report our experience in using remifentanyl as sole agent for the analgesia of spontaneously breathing non-intubated burn patients during dressing changes. Sixty procedures were collected and analysed. Remifentanyl was used during monitoring of vital functions, with oxygen inhalation throughout the procedure, at the bedside in the intensive care unit ward. Infusion speed was varied by the nurse in charge, depending on pain, analgesia, and adverse effects. The dosage of continuous infusion ranged from 0.125 to 1  $\mu\text{g.kg}^{-1}.\text{mn}^{-1}$  (average, 0.42). All patients received intravenously morphine 30 min before the end of the procedure (average, 10 mg). The main side effects were hypoxia and drowsiness, always quickly reversed when the doses were reduced. All patients had low levels of pain during and after the procedure, and were satisfied with the analgesia protocol. We conclude that remifentanyl is another possible manner of analgesia in the dressing of burn patients, but that it must be used in an “anaesthesiological” environment.

### Introduction

Management of pain is an important part of burns treatment, and a complete chapter is devoted to the subject in “Total Burn Care”.<sup>1</sup> Pain at rest seems quite easy to treat, especially since long-lasting oral morphine sulphate has been available. On the other hand, pain during dressing changes is more difficult to treat, and some burn patients report that during their hospitalization it is their worst pain experience.<sup>2</sup> In some patients, pain remains unbearable, even if they receive acetaminophen as well as high doses of morphine before the procedure and nitrous protoxide during it. Since repeated general anaesthesia for these procedures is not possible in our unit (besides the fact that the fasting necessary for general anaesthesia is not desirable for patient nutrition and cicatrization), the use of a powerful, quick-acting, and lasting opioid such as remifentanyl (RF) is a possibility. After using RF to dress patients under mechanical ventilation, when the morphine used for sedation proved to be insufficient (even in large amounts) for dressing-related pain, we decided to use RF in conscious, non-intubated patients. We report here our experience of 60 procedures in a five-month period.

### Pharmacology of remifentanyl

Remifentanyl<sup>3</sup> is a 4-anilidopiperidine derived from fentanyl. The methyl ester function circled in *Fig. 1* is the target of non-specific esterases, present in numerous tissues that transform RF to G190291, which is 1,000 times



**Fig. 1** - Structure of remifentanyl.

less powerful than RF and therefore does not provide analgesia or respiratory side effects, even if its urinary elimination is impaired by renal insufficiency. The metabolism of RF is not influenced by age or by kidney or liver failure. This metabolism explains the very short half-life (initial 1', terminal 30') of RF. Contrary to fentanyl, no redistribution occurs with RF, and its action does not last longer if the duration of infusion increases. The very high tissue diffusion index explains why the peak concentration

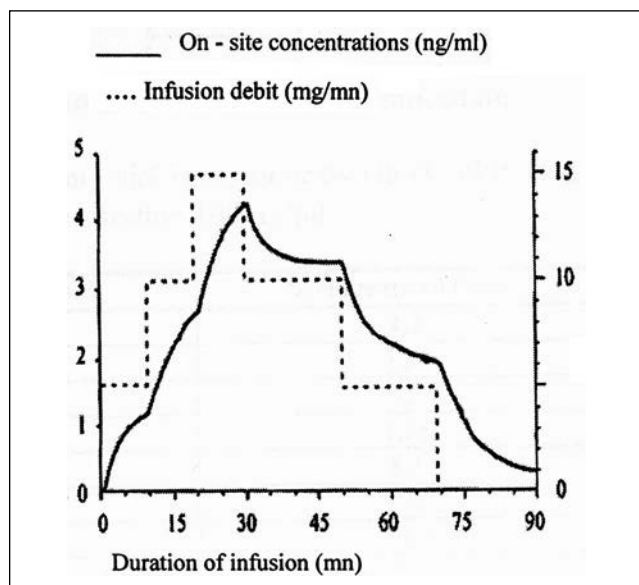


Fig. 2 - Evolution of onsite concentrations with various infusion debits.

at the site of action is obtained within 1'30'' and the balance of concentrations, when used in continuous infusion, is reached within 10'. The onsite concentrations are therefore quite parallel to infusion speed (Fig. 2).<sup>4</sup> The intrinsic analgesic power is evaluated in the same order as fentanyl, i.e. eight<sup>3</sup> to forty<sup>5</sup> times that of alfentanil. The context-sensitive halftime is 3' and is independent of the duration of the infusion, and the clinical effects last 3 to 5'. RF does not provide any post-procedural analgesia. It has no hypnotic effect, respiratory depression is parallel to its analgesic power, and muscular rigidity (also involving the respiratory muscles) contraindicates use of RF boluses in non-intubated patients. Hypotension and deep bradycardia are likely if used in hypovolaemic patients.

Finally, RF provides a powerful analgesia, achieved in a few minutes and lasting some minutes in any patient (although the elderly are more susceptible to RF, as also to other opioids), with a respiratory depression that is as deep as its analgesic effect is high.

### Patients and methods

Between November 2004 and March 2005, 60 procedures of dressing changes were compared. They all concerned patients who had no tracheal tube.

The patients selected included some whose tracheal tube had been removed the day before, since intubated patients receive RF for the procedure. It should be noted that these patients - when having dressing changes during mechanical ventilation - received 0.2 to 0.3  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{mn}^{-1}$  RF and that these dosages were anaesthetic dosages. Some other selected patients had suffered considerable pain during pre-

vious procedures although they had received high doses of oral morphine sulphate (50 to 70 mg), plus 1 g acetaminophen and usually 10 mg midazolam (or 100 mg hydroxyzin) before the procedure, and  $\text{N}_2\text{O}$  during it. Some others were patients for whom the scheduled procedure was known to be notably painful (e.g. removing greased gauze for first dressing after hospitalization, first dressing after excision or on donor sites in large areas, removing numerous staples from extensive grafted areas, etc.).

Once selected, the patients were informed the day before of the scheduled protocol. Also the day before the anaesthesiologist prepared a personalized table (Fig. 3) providing the nurse with some warnings, an explanation of the dilution of remifentanyl, a dosage table, instructions on the use of remifentanyl infusion, a prescription of morphine, the date, the patient's name, and the name of the prescribing doctor who signed the form.

On the day of the procedure, the nurse in charge made sure that an anaesthesiologist would be available at all times during the procedure. If the patient was not already hospitalized in the intensive care unit (ICU) ward, he was taken there for the duration of the procedure and for one

#### Caution

- Connect the syringe closest to the patient (10 cm)
- Use an anti-return valve
- Thoroughly clear out the infusion site at the end of procedure

Dilution of remifentanyl: one 2 mg vial in 20 ml or two in 40 ml (water, 5% dextrose, normal saline). Concentration, 100  $\mu\text{g}/\text{ml}$ .

Weight (kg)	Dosage ( $\mu\text{g}/\text{kg}/\text{mn}$ )	Syringe speed (ml/h)
70	0.1	4.2
	0.125	5.25
	0.15	6.3
	0.175	7.35
	0.2	8.4
	0.225	9.45
	0.25	10.5
	0.275	11.55
	0.3	12.6
	0.35	14.7
	0.4	16.8
	0.45	18.9
	0.5	21
	0.55	23.1
	0.6	25.2
	0.65	27.3
	0.7	29.4
	0.75	31.5
	0.8	33.6
	0.85	35.7
	0.9	37.8
	0.95	39.9
	1	42

Day 1: Start on first line. If pain, go to following line, wait 2', go on with procedure, and so on. During the procedure, if patient does not respond, or pulse oxymetry decreases, go to previous line.

Other days: Start one line above that used the day before.

Morphine: 10 mg IV 30' before end of procedure.

Date Patient's name Doctor's name and signature

Fig. 3 - Example of remifentanyl prescription form.

**Table I** - Variation of vital parameters

	Before	Min. during	Z test	Max. during	Z test
Heart rate (beats/min)	130	92	0.81 NS	119	0.95 NS
MAP (mm Hg)	84	81	0.32 NS	97	0.87 NS
SpO <sub>2</sub>	99	95	0.71 NS	100	0.72 NS

Z test is calculated compared to the value "before".

NS = nonsignificant.

hour thereafter, in order to perform monitored surveillance. Before the procedure the patient had to fast. The dressing was changed "early" (9 a.m.) in order to let the patient have breakfast soon after.

The patient received oxygen via a disposable mask, in order to obtain 40% of the inspired fraction. If the patient did not already have one, a peripheral venous route was installed. If the patient already had a multi-lumen catheter, one of the lumina was dedicated to remifentanyl. An anti-reflux device was installed in this route. RF infusion was initiated after at least 5' of oxygen inhalation at a dose of  $0.1 \mu\text{g.kg}^{-1}.\text{mn}^{-1}$ . The procedure started 5' later. If the patient expressed pain of over 4 on a verbal rating scale (VRS) from 0 to 10, the procedure was discontinued and the dose of RF was increased by  $0.025 \mu\text{g.kg}^{-1}.\text{mn}^{-1}$ , with the procedure being continued 3' later, and so on if the VRS remained over 4. If the patient exhibited drowsiness, the dose was reduced in steps of  $0.025 \mu\text{g.kg}^{-1}.\text{mn}^{-1}$ , repeated every 3' if necessary. In the event of reduced pulse oxygen concentration, the dose was reduced in steps of  $0.05 \mu\text{g.kg}^{-1}.\text{mn}^{-1}$ , also repeated every 3' if necessary. 30' before the scheduled end of the procedure, the patient received the prescribed dose of morphine via IV route. If the patient was in pain after the procedure, he received additional 3 mg doses of morphine every 5' until he rated his pain under 4. Monitored surveillance went on for 1 h after the last dose of morphine.

We recorded the following: pulse oxymeter value (SpO<sub>2</sub>), mean arterial pressure (MAP), and heart rate (HR) before the procedure, as well as the same values at the highest and lowest levels reached during the procedure. We also recorded the highest and lowest VRS values during the procedures. The values of SpO<sub>2</sub>, MAP, and HR were compared, using the Z test. Any side effect was also recorded.

## Results

Twenty-seven patients underwent 60 dressing changes under an analgesia with RF, and solely with RF. No hypnotic or anxiolytic or analgesic drug of any kind was added except morphine, as described before. The average dosage of RF at which the patients had pain evaluated below 4 as the procedure was in progress was  $0.42 \pm 0.22 \mu\text{g.kg}^{-1}.\text{mn}^{-1}$ . The duration of the procedure length was  $93 \pm 30'$ . A total number of 88 vials of RF were opened.

The highest VRS during the procedure was  $5.92 \pm 2.38$ ; the lowest was  $1.07 \pm 1.51$ . No patient rated his pain at continuously over 4. Even those patients who at some time of the procedure expressed high levels of pain were very satisfied with the analgesia provided. *Table I* shows the variations in vital signs during the procedure compared with before. None of these was statistically significant. The patients were given  $10.11 \pm 7.25$  mg morphine, and 67 10-mg vials were used.

A total number of 38 adverse effects were noted, concerning 19 procedures - some occurred more than once during the same procedure. There were 14 episodes of drowsiness and 18 falls of SpO<sub>2</sub> below 95% (never below 90% except during three apnoeas, of which the deepest was 75%, all three due to a random bolus after folding of the infusion tube during mobilization of the patient). There were three episodes of decrease in MAP (between 65 and 70). All these episodes were rapidly reversed with a reduction or brief interruption of infusion of RF. The anaesthesiologist never had to prescribe anything or provide anything else, such as artificial ventilation, vascular filling, or RF reversal with naloxone.

## Discussion

According to Joly, writing in 2003, "the use of RF in spontaneously breathing patients is not nowadays recommended",<sup>6</sup> but it is possible to find data attesting its use. As early as 1999, Torres<sup>7</sup> stated that studies were needed to assess the possibility and safety of RF in spontaneously breathing patients, as Gold had done in 1997.<sup>8</sup> However, RF has infrequently been used for analgesia (and more often for sedation in an ICU, which is beyond our purpose). Papers on the subject are even more uncommon as regards adults. RF has been used in continuous infusion for shock wave lithotripsy, at a rate of  $0.05 \mu\text{g.kg}^{-1}.\text{mn}^{-1}$ .<sup>9</sup> For the fiberoptic intubation of conscious patients, dosages ranged from 0.1 to  $0.5 \mu\text{g.kg}^{-1}.\text{mn}^{-1}$ .<sup>10</sup> For colonoscopy,<sup>11</sup> administered at  $0.2 \mu\text{g.kg}^{-1}.\text{mn}^{-1}$ , RF provided a good analgesia, with a better haemodynamic profile and a faster recovery than propofol, although hypoventilation was frequent (55% of the patients). In radiology,<sup>12</sup> RF was successfully used at very low doses of  $0.01$  to  $0.05 \mu\text{g.kg}^{-1}.\text{mn}^{-1}$ , without marked respiratory depression. With regard to burns, though mentioned by Latar-

jet<sup>13</sup> after his work with alfentanil,<sup>14</sup> we have not found any papers related to RF.

In our study, the mean dosage was much higher than that seen in the literature, apart from Gold's paper.<sup>8</sup> This probably explains the frequency (about one-third) of cases of respiratory depression, albeit less than that observed by Calvo,<sup>12</sup> even if our dosages were higher and the respiratory depression did not seem to be correlated to the average dosage of RF. This has to be compared with its efficacy, and the balance turns in favour of its positive effects, since all patients had good analgesia and the side effects - even the three apnoeas - reversed spontaneously, rapidly, and without medical intervention. The nurses in the unit found it easy to learn to manipulate RF in this manner for the following reasons: 1. they were used to its utilization in intubated patients; 2. the anaesthesiologists provided training about RF and its practical use; 3. guidelines were written on the prescription form for each patient. The nurses

were soon asking us to use RF because the quality of the analgesia permitted improvement in the quality of the dressing itself and provided a good experience for the patient. Until now, over 150 dressings have been changed using this technique, which has become routine in our unit.

## Conclusion

The infusion of remifentanyl in conscious non-intubated patients is a new weapon against pain during dressing change in burn patients. Like any weapon, it has its side effects (i.e. respiratory depression), which can be minimized with preoxygenation and anaesthetic-type monitoring (with an anaesthesiologist on standby). Nurses and anaesthesiologists should be trained in the treatment of intubated patients before starting on non-intubated ones. Nurses too should have courses and training before the onset of such a protocol.

**RÉSUMÉ.** Nous rapportons notre expérience de l'utilisation du rémifentanyl comme agent unique d'analgésie durant le pansement des patients brûlés, non intubés, ventilant spontanément. Soixante procédures ont été analysées. Le rémifentanyl a été utilisé sous monitoring des fonctions vitales chez des patients respirant de l'air enrichi en oxygène, au lit du patient en chambre de réanimation. La posologie était adaptée par l'infirmière réalisant le pansement selon le niveau de douleur ou d'analgésie et l'apparition d'effets ad-verses. Les posologies variaient de 0,125 à 1 µg.kg-1.mn-1, en moyenne 0,42, par voie intraveineuse. Les principaux effets ad-verses observés étaient la somnolence et l'hypoxie, toujours rapidement réversibles avec la diminution des doses. Tous les patients re-levaient de la morphine 30 min avant la fin du pansement, en moyenne 30 mg IV. Tous les patients ont eu des niveaux de douleur bas, pendant et après la procédure, et se disaient satisfaits de cette technique. Nous concluons que le rémifentanyl est une autre pos-sibilité d'analgésie pour le pansement des brûlés, mais qu'il doit être utilisé dans un environnement de type "anesthésie".

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*Acknowledgements.* To the nurses of the Unit for their involvement in this study, and to Dr Jean François Arnould. The idea of using remifentanyl in this indication is his.

This paper was received on 8 February 2006.

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