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Review Article

Remifentanil tolerance and hyperalgesia: short-term gain, long-term pain?

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Summary

The unique pharmacology of remifentanil makes it a popular intra-operative analgesic. Short-acting opioids like remifentanil have been associated with acute opioid tolerance and/or opioid-induced hyperalgesia, two phenomena which have different mechanisms and are pharmacologically distinct. Clinical studies show heterogeneity of remifentanil infusion regimens, durations of infusion, maintenance of anaesthesia, cumulative dose of remifentanil and pain measures, which makes it difficult to draw conclusions about the incidence of acute tolerance or hyperalgesia. However, it appears that intra-operative remifentanil infusion rates of above 0.25 $\mu g.kg^{-1}.min^{-1}$ are associated with higher postoperative opioid consumption, suggesting tolerance. Infusion rates greater than 0.2 $\mu g.kg^{-1}.min^{-1}$ are characterised by lower mechanical/pressure/cold/pain thresholds, which suggests hyperalgesia. The use of concurrent multimodal analgesia, especially N-methyl-D-aspartate receptor antagonists, may be an effective preventive strategy. The clinical significance and long-term consequences of these entities is still uncertain.

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Introduction

Remifentanil is an ultra-short-acting phenylpiperidine opioid analgesic that has high lipid solubility and hence a rapid onset of effect; it is rapidly metabolised by non-specific blood and tissue esterases, which also ensures rapid recovery. It is commonly used by infusion (either manual or target-controlled) during surgery since it can be given in high doses and is easily titratable, enabling potent intra-operative analgesia and a fast postoperative recovery. It is primarily a mu-opioid receptor agonist with pharmacodynamic properties in-keeping with all drugs of this class, namely analgesia, dose-dependent respiratory depression, nausea and constipation, although the latter two are not relevant during general anaesthesia [1]. Rapid dissipation of effects means that it is crucial to provide a 'bridge' to postoperative analgesia either during, or at completion of, surgery, before the infusion is terminated.

In the peri-operative population, opioid use has also been associated with postoperative opioid-induced hyperalgesia or acute opioid tolerance. There are concerns that short-acting opioids are particularly likely to lead to the development of these important (but distinct) phenomena [2]. Studies performed both in animals and human volunteers have shown that acute

analgesic opioid tolerance develops a couple of hours after the initiation of a continuous infusion of remifentanil [3]. It may be associated with high-dose infusions and high cumulative doses [1, 4–6]. Correlation with duration of exposure seems equivocal [4, 7–10]. In this article, we aim to provide a narrative review of tolerance and hyperalgesia, their definitions, cellular mechanisms and preventive strategies. The evidence for remifentanil and the development of acute opioid tolerance or opioid-induced hyperalgesia from clinical studies is also examined.

Methods

A search for clinical trials, systematic reviews or meta-analyses was performed using PubMed and Ovid MEDLINE to identify all articles, using 'remifentanil', 'tolerance', 'hyperalgesia', 'operative' and 'surgery' as keywords. Articles were included if they were published in English before December 2015.

Abstracts of retrieved citations were then reviewed to shortlist those which met the inclusion and exclusion criteria. Clinical studies which were further evaluated (as summarised in Table 2) were selected if: the manuscript reported a randomised study and was written in English; the study was performed in humans with an intra-operative or peri-operative focus; and the study compared either high-dose vs. low-dose remifentanil infusion, or remifentanil infusion vs. placebo. Studies were excluded if they recruited healthy volunteers or children, and if there had been co-administration of neuro-axial analgesia or pre-medication with analgesics.

Clinical importance of remifentanil

Widespread extravascular metabolism of remifentanil means it does not accumulate in the periphery and undergoes very high clearance. This results in a short, consistent context-sensitive half time (3–5 min), independent of organ function and infusion duration [11]. These distinct characteristics make it very popular in both intravenous and inhalational anaesthesia (it is often used as a substitute for nitrous oxide in the latter). A remifentanil infusion of 0.17 $\mu g.kg^{-1}.min^{-1}$ is as effective as 70% nitrous oxide in attenuating intra-operative pain, without a difference in postoperative pain scores [12]. Commonly accepted current practice utilises intra-operative infusions ranging between 0.1 $\mu g.kg^{-1}.min^{-1}$ and 0.5 $\mu g.kg^{-1}.min^{-1}$. Although the manufacturer's guidelines suggest a range as high as 2 $\mu g.kg^{-1}.min^{-1}$, in clinical practice, doses above 0.2 $\mu g.kg^{-1}.min^{-1}$ are unlikely to confer any additional benefit and will be more likely to be associated with haemodynamic instability [13]. Using a target controlled infusion (TCI), a dose range of 3–7 $ng.ml^{-1}$ is usual. Boluses of 1 $\mu g.kg^{-1}$ or TCI up to around 12 $ng.ml^{-1}$ can be used in healthy patients to attenuate the short-term stress of particularly noxious stimuli such as tracheal intubation [8, 14].

Acute opioid tolerance and opioid-induced hyperalgesia

Tolerance and hyperalgesia are pharmacologically distinct (Table 1). Tolerance is defined as a progressive decrease in the pharmacodynamic response to a drug and can be compensated for by increasing the dose. Opioid tolerance not only develops to the analgesic properties of opioids but also to the side-effects, such as respiratory depression, pruritus, sedation and nausea [1, 9]. It is possible for tolerance to occur in the absence of hyperalgesia [15]. Opioid tolerance is a desensitisation of pain signalling pathways to opioids, equating to a loss in potency from a pharmacological perspective. It is defined as an increase in the dose required to maintain analgesia in patients receiving opioids for pain relief in the clinical setting [1]. Acute opioid tolerance has been found to develop a couple of hours after the initiation of remifentanil administration through continuous infusion [3].

Hyperalgesia, in contrast, is a state of nociceptive sensitisation and is defined by the International Association for the Study of Pain as 'increased pain from a stimulus that normally provokes pain'. The umbrella term 'hyperalgesia' is not restricted to a consequence of opioid use, but can also be a result of tissue trauma and inflammation [16, 17]. Hyperalgesia may be primary (in the area of tissue injury from local sensitisation) or secondary (when uninjured tissue around the area becomes sensitised I added) [18, 19]. The term 'allodynia', which previously was not defined as being distinct from hyperalgesia, is now reserved for those forms of pain which are clearly caused by excitation of low-threshold sensory nerve fibres [16].

Table 1 Important clinical differences between acute opioid tolerance and opioid-induced hyperalgesia.

Acute opioid tolerance	Opioid-induced hyperalgesia
Decreasing efficacy of the drug; desensitisation to opioids	Form of drug-induced pain sensitisation which occurs within the central nervous system
Can be overcome by increasing the dose	Cannot be overcome by increasing the dose; dose escalation will make it worse
Development of tolerance to some adverse side-effects (caused by opioids) may be observed over time	May be stimulus-specific (e.g. heat stimuli)

Opioid-induced hyperalgesia, specifically, cannot be overcome by increasing the opioid dose as this will actually exacerbate the problem; this is in contrast to acute opioid tolerance [20]. In opioid-induced hyperalgesia, the type of increased pain sensitivity experienced is usually similar to, but may be different from, the original underlying pain, such as surgical wound pain [9]. Some authors also suggest that the definition of opioid-induced hyperalgesia should not be confined to an increase in pain sensitivity to external stimuli, but should occur in conjunction with increased pain sensitivity over time as well as the spread of pain to other locations [21]. While a widely accepted clinical definition of opioid-induced hyperalgesia does not yet exist, opioid-induced hyperalgesia is said to be characterised by a paradoxical increase in pain, associated with hyperalgesia and allodynia [22, 23].

Cellular mechanisms of acute opioid tolerance and opioid-induced hyperalgesia

The underlying mechanism of acute opioid tolerance is still unclear. At least two different processes at the cellular level have been proposed. The first involves a 'within process', where opioid administration elicits an opposing reaction within the same system where the opioid elicits its primary action. This response will progressively neutralise the effect of the opioid via desensitisation, internalisation, down-regulation and phosphorylation of opioid receptors or heterodimerisation with other receptors [24]. Acute receptor desensitisation is thought to occur via uncoupling of the receptor and G-protein, which is followed by internalisation of the receptor from the cell membrane. This process occurs after a few minutes of agonist exposure. Receptor-G-protein uncoupling is mediated via phosphorylation of putative sites on the intracellular loops of activated receptors. Acute desensitisation and down-regulation of receptors both result in a reduction of agonist efficacy [25]. Despite this, some researchers have suggested that increased internalisation may, in contrast, decrease tolerance by removing desensitised receptors from the membrane and causing resensitisation via creating new or substituting recycled receptors [26].

The second process is the 'between process' adaptation, whereby opioids recruit different neuronal circuits, which oppose the primary drug effect. Specific pro-nociceptive processes are activated by opioid administration, such as engaging N-methyl-D-aspartate (NMDA) receptors, which counteract the analgesic effects [17, 24, 27]. Remifentanil may stimulate the NMDA receptors, and μ-opioid receptors, δ-opioid receptors of remifentanil or glycine (an additive in remifentanil preparations) could directly stimulate NMDA receptors [28]. It has also been noted that the magnitude of tolerance is unrelated to opioid potency [29]. Different opioid agonists have shown differences in the ability to down-regulate or desensitise opioid receptors, attributed to the intrinsic efficacy of the opioid agonist. Intrinsic efficacy relates the number of receptors occupied with the magnitude of the receptor-mediated response. Each opioid has a given intrinsic efficacy for the different types of opioid receptors. The 'fractional receptor occupancy' is the number of receptors that need to be occupied out of the total population to generate a given effect [30]. The smaller the number of occupied receptors that a drug needs to generate analgesia, the higher is its intrinisic efficacy; this is inversely related to the degree of tolerance after continuous infusion [30–32]. Remifentanil has a high fractional receptor occupancy and a low intrinsic efficacy, also related to its short duration of action and dose, which causes a comparatively larger rightward

shift in dose–response. These characteristics have been suggested to down-regulate more receptors.

Opioid-induced hyperalgesia may result from a number of mechanisms. Understanding these may help with prevention, as treatment is particularly difficult. This was summarised in a review by Lee et al. [9].

Central glutaminergic systems

This is the most researched putative mechanism of opioid-induced hyperalgesia. Certain opioids and their metabolites are agonists at NMDA receptors, which activate the central glutaminergic system. This causes an influx of calcium ions into neurons, which increases neuronal excitability. These neurons more readily transmit pain impulses initiated by substance P and other noxious stimuli. Prolonged opioid administration induces down-regulation of spinal glutamate transporters in the spinal cord which, in turn, increases levels of glutamate available for NMDA receptors. Increased NMDA activity has been demonstrated in spinal neurons after remifentanil exposure. NMDA antagonists such as MK801 have been shown to block opioid-induced hyperalgesia [9, 33, 34].

Spinal dynorphins

These are endogenous opioid peptides which not only bind mainly to kappa-opioid receptors but also, to a lesser extent, μ-opioid receptors and NMDA receptors. Levels of spinal dynorphins increase after continuous infusion of μ-opioid receptor agonists. This increased level of spinal dynorphins leads to the release of the excitatory neuropeptides calcitonin gene-related peptide receptor and cholecystokinin, which enhance pro-nociceptive input at the spinal level. Animal studies have shown that using dynorphin antiserum blocks opioid-induced allodynia and hyperalgesia [9, 35–37].

Descending facilitation

This is a shift in the balance between descending inhibitory control towards more pro-nociception. Normally, when a pain signal is received by the skin or viscera, this is relayed to the dorsal column and then transferred to higher centres in the brain. This transfer can be affected by a network of descending pathways from the brain which can either enhance this pain signal transfer (descending facilitation) or inhibit it (descending inhibition). Enhancement of descending facilitation to the dorsal horn of the spinal cord is possibly mediated by cholecystokinin and dynorphin. This is thought to originate at the level of the rostral ventral medulla, where there are certain subsets of neurons which mediate pain transmission. These comprise 'on' cells, which are stimulated by opioids and increase pain signal transmission in the spinal cord and 'off' cells, which inhibit pain signals. The 'on' cells are implicated in promoting nociception and the development of opioid-induced hyperalgesia [9, 36, 38–40].

Genetics

Catechol-O-methyltransferase (COMT) is an enzyme involved in the breakdown of catecholamines, including dopamine and noradrenaline. There are three genotypes. Breakdown of dopamine and noradrenaline is altered in those with different genotypes, therefore causing differing levels of catecholamines in the synapse after neurotransmitter release. Those homozygous for the met158 allele have increased pain sensitivity after opioid administration. In individuals with a met–met polymorphism, more pain is experienced if a painful stimulus is given after prior opioid administration. Abcb 1b glycoprotein drug transporter gene studies in mice have shown that certain genetic haplotypes are more likely to develop hyperalgesia after opioid administration. Also implicated are variants of the β_2-adrenergic receptor gene. Chronic exposure to opioids has been shown to enhance expression of β_2-adrenergic receptors. Experiments in mice have shown that certain variants of the β_2-adrenergic receptor gene are associated with opioid-induced hyperalgesia which is enhanced by the selective β_2-adrenergic agonist, isoproterenol, and blocked by β_2-adrenergic antagonists [41–44].

Transient receptor potential cation channel, subfamily V (TRPV1)

This is a non-selective cation channel found mainly in the peripheral nervous system but also in high quantities in the central nervous system. Antagonists to TRPV1 have been found to reverse hyperalgesia. In animal studies, mice with TRPV1 'knock out' were

found to have no tactile or thermal hypersensitivity to chronic morphine administration [45].

5-Hydroxytryptamine (5HT3)

The 5HT3 antagonist, ondansetron, has been shown to block opioid-induced hyperalgesia in animals. A possible mechanism of action is via a shift in balance favouring nociception over inhibition in the descending pathways from the brainstem [46].

Measurements

Acute opioid tolerance is demonstrated by requiring an increased opioid dose to achieve analgesia. When analgesia is achieved with a higher opioid dose, this response helps to distinguish it from hyperalgesia (Table 1).

As opioid-induced hyperalgesia is a state of paradoxical increase in pain associated with hyperalgesia and allodynia [23], detecting the presence and severity of opioid-induced hyperalgesia is not straightforward. To date, there are no widely accepted diagnostic criteria. Studies often use pain intensity and opioid consumption as surrogate markers. While these parameters are perhaps important practically in the clinical setting, they may not distinguish opioid-induced hyperalgesia reliably from other phenomena associated with increased pain and opioid consumption. Various studies have used quantitative measurements to evaluate secondary hyperalgesia, such as mechanical (pressure, touch, injection), thermal (cold or heat), electrical or other stimuli (e.g. ischaemia). Levels of glutamate, cytokines and dynorphin have also been used [21, 47].

No single approach has yet been validated or considered as the definitive standard in the measurement of hyperalgesia in clinical trials [21]. Chen et al. studied responses to different quantitative sensory testing methods including temperature (heat/cold sensation, heat/cold pain threshold) and mechanical (von Frey filament and pinprick). They found that only one (heat pain threshold) showed a significant difference between a group of patients with chronic pain who had no opioid treatment in the preceding 3 months and another group who were currently on opioid therapy, suggesting that hyperalgesia may be stimulus specific [48]. A systematic review compared the responsiveness of quantitative measurements in detecting opioid-induced hyperalgesia in 14 clinical studies of patients with chronic pain taking long-term opioids [21]. A variety of measurements were studied, including mechanical (pressure and touch – von Frey filament, pinprick, algometry and injection), thermal (cold pressor tolerance/threshold, heat pain tolerance/threshold/intensity), electrical or other stimuli (ischaemia). Although the authors identified heat stimuli as a potentially good test for opioid-induced hyperalgesia, none of the methods tested were found to have sufficient statistical power to determine hyperalgesia. They concluded that better study designs, testing protocols and large sample sizes are needed for formal meta-analyses in the future.

Evidence of acute opioid tolerance/opioid-induced hyperalgesia from clinical studies

A small number of clinical studies have been carried out to evaluate the effect of peri-operative remifentanil infusion on the induction of acute opioid tolerance and/or opioid-induced hyperalgesia (Table 2).

From a total of 17 randomised trials which met the criteria outlined under Methods above, five examined opioid-induced hyperalgesia, three acute opioid tolerance and the remaining nine explored both. Among all studies, postoperative analgesic requirement was considered in all but one (eye surgery) [60]. Postoperative opioids were either nurse-initiated as required, or patient-controlled. Of patient-controlled opioids, all used intravenous morphine with the exception of two, which used oxycodone and fentanyl, respectively. Nurse-initiated opioids included morphine, fentanyl and pethidine.

The incidence of acute opioid tolerance in these studies was most commonly defined by an increase in postoperative opioid requirements. A few studies also measured the time of first request for analgesia postoperatively. Of the 12 studies that addressed acute opioid tolerance, one was said to support the presence of acute opioid tolerance [50], while another four inferred its presence [54–57]. These five studies all measured (and found) greater postoperative opioid requirements in groups receiving higher compared with lower remifentanil doses or control. There was heterogeneity

Table 2 Characteristics of included studies.

Study	Type of study	Patients/ surgery	Patients in high-dose group (n)	Patients in low-dose/ control group (n)	Intervention intravenous remifentanil dosages)	Remifentanil infusion mode	Cumulative remifentanil dose (higher dose group)/ Duration of procedure	Primary pain outcome	Secondary pain outcome	Mode of anaesthesia	In high-dose remifentanil group			
											Acute opioid tolerance	Opioid-induced hyperalgesia (mechanism of inducing)	Postop opioid	Postop pain
Cortinez [49]	Randomised, controlled	Gynaecological non-laparoscopic	30	30	0.25 $\mu g.kg^{-1}.min^{-1}$ vs. None	CI	Mean 98 min	Postop VAS on coughing at 0, 15, 30, 45, 60, 90, 120 min and 24 h	Cumulative postop PCA morphine consumption	Sevoflurane + nitrous oxide	No	/	NS	NS
Guignard [50]	Randomised	Major abdominal surgery	24	25	0.25 $\mu g.kg^{-1}.min^{-1}$ titrated by 0.05 $\mu g.kg^{-1}.min^{-1}$ increments vs. 0.1 $\mu g.kg^{-1}.min^{-1}$	CI	Median 4.3 h	VAS at 0 h, 2 h, 4 h, 8 h, 16 h, 24 h postop. Cumulative postop morphine consumption	Timing to 1st postop analgesia	Desflurane	Yes	Yes ↑ pain scores observed despite higher opioid requirement	Greater + required earlier	Greater
Jo [51]	Randomised, double-blinded, controlled	Abdominal hysterectomy	20	20	3-4 $ng.ml^{-1}$ vs. saline	TCI	Mean 145 ± min (anaesthesia)	PCA fentanyl consumption at PACU and over 48 h	VAS at rest and cough in PACU and over 48 h	Total intravenous propofol	?	?	Greater in PACU only Total opioid: NS	Greater in PACU only Total opioid: NS
Joly [52]	Randomised, double-blinded	Major abdominal surgery	25	25	0.4 $\mu g.kg^{-1}.min^{-1}$ vs. 0.05 $\mu g.kg^{-1}.min^{-1}$	CI	At least 2 h	VAS 15-min interval 1st hour then hourly for 3 h Mechanical pain threshold (von Frey) peri-incision + forearm Pressure pain threshold (pressure algometer) peri-incision + forearm	Mechanical static (punctate) hyperalgesia to von Frey peri-incision Dynamic allodynia with soft brush peri-incision PCA morphine consumption VAS during peak flow	Desflurane	/	Yes ↓ mechanical pain threshold proximal to wound↑ extent in opioid induced hyperalgesia to von Frey	Greater	NS
Lahtinen [53]	Randomised, double-blinded, controlled	Cardiac bypass graft surgery	45	45	0.3 $\mu g.kg^{-1}.min^{-1}$ vs. saline	CI	179 ± 29 min	Cumulative PCA oxycodone consumption	Time to 1st opioid VAS score at 0,8,16,24,32,40 h	Propofol continuous infusion ± isoflurane	No	No	NS	Less in remifentanil group
Lee [54]	Randomised, controlled	Tonsillectomy	30	30	0.3 $\mu g.kg^{-1}.min^{-1}$ vs. saline	CI	54.8 ± 5.0 min	VAS during swallowing at 30 min, 1 h, 6 h, 12 h, 24 h	Time 1st postop Analgesic Total Pethidine and Ketorolac requirement	Sevoflurane	Inf	Inf	Greater (pethidine) + required earlier	Less in remifentanil group
Lee [55]	Randomised, controlled	Robotic laparoscopic Prostatectomy	25	25	0.3 $\mu g.kg^{-1}.min^{-1}$ vs. saline	CI	296.8 ± 17.4 min	VAS at rest 30 min, 6 h, 12 h, 24 h, 36 h	PCA morphine 36 h	Desflurane	Inf	Inf	Greater + required earlier	Less in remifentanil group
Lee [56]	Randomised	Laparoscopic vaginal hysterectomy	29	28	0.3 $\mu g.kg^{-1}.min^{-1}$ vs. 0.05 $\mu g.kg^{-1}.min^{-1}$	CI	141.6 ± 15.7 (duration of anaesthesia)	VAS at rest 1 h, 6 h, 12 h, 24 h Mechanical hyperalgesia threshold peri-incision 24 h (von Frey)	PCA morphine 36 h Time to 1st analgesia Cumulative. ketorolac in recovery	Desflurane	Inf	Yes Mechanical hyperalgesia threshold ↓	Greater + required earlier	Less in bigger dosed group

(continued)

Table 2 (*continued*)

Study	Type of study	Patients/ surgery	Patients in high-dose group (n)	Patients in low-dose/ control group (n)	Intervention intravenous remifentanil dosages)	Remifentanil infusion mode	Cumulative remifentanil dose (higher dose group)/ Duration of procedure	Primary pain outcome	Secondary pain outcome	Mode of anaesthesia	In high-dose remifentanil group			
											Acute opioid tolerance	Opioid-induced hyperalgesia (mechanism of inducing)	Postop opioid	Postop pain
Lee [57]	Randomised	Urology	29	30	0.3 $\mu g.kg^{-1}.min^{-1}$ vs. 0.05 $\mu g.kg^{-1}.min^{-1}$	CI	186.6 ± 10.8 min (duration of anaesthesia) 3400 ± 300 μg	VAS during movement 1 h, 6 h, 12 h, 24 h Mechanical hyperalgesia threshold on arm + peri-incision 24 h (von Frey) Area of hyperalgesia peri-incision 24 h	PCA morphine 24 h	Desflurane	Inf	Yes ↑ area of hyperalgesia ↓ mechanical hyperalgesia threshold	Greater + required earlier	Less in bigger dosed group
Rauf [58]	Randomised, controlled	Coronary artery bypass surgery	10	10	0.1 $\mu g.kg^{-1}.min^{-1}$ vs. saline	CI	Mean 499.4 min (anaesthesia)	Morphine used 1st hour postop	Total postop morphine (nurse titrated) VAS scores	Total intravenous propofol	?	/	Greater (only 1st hour postop) Total opioid: NS	NS
Richebé [59]	Randomised, double-blinded	Elective cardiac surgery	TCI 19	CI 19	TCI 7 $ng.ml^{-1}$ vs. CI 0.3 $\mu g.kg^{-1}.min^{-1}$	TCI or CI	TCI group: mean 3661.1 μg CI group: Mean 5329.7 μg Duration ~280 min	Mechanical dynamic hyperalgesia perpendicular to wound (von Frey)	Dynamic, punctuate hyperalgesia till postop day 7 VAS and VRS at rest and coughing Total morphine consumption till postop day 2	Total intravenous propofol	/	Yes Extent of opioid induced hyperalgesia ↓ in TCI group	NS	NS
Schmidt [60]	Randomised	Eye surgery	21	21	0.4 $\mu g.kg^{-1}.min^{-1}$ vs. 0.1 $\mu g.kg^{-1}.min^{-1}$	CI	Average 70 min	Deep pressor pain tolerance thresholds Cold pressor pain (hand in ice water bath)	Post op VNRS	Isoflurane	/	Yes ↑ sensitivity to deep pressure stimuli	/	NS
Shin [61]	Randomised, double-blinded	Breast surgery	42	48	4 $ng.ml^{-1}$ vs. 1 $ng.ml^{-1}$	TCI	Mean 235.6 min (anaesthesia) Mean 2070.9 ± 126 μg	PCA morphine 1st 24 h	VAS in 24 h	Sevoflurane	/	Yes	Greater at least till 12 h post op	Greater 30 min post op. After 30 min: NS
			46	50	4 $ng.ml^{-1}$ vs. 1 $ng.ml^{-1}$	TCI	Mean 231.1 min (anaesthesia) Mean 2064.3 ± 680.9 μg			Total intravenous propofol	No	No	NS	NS

(continued)

Table 2 (*continued*)

Study	Type of study	Patients/ surgery	Patients in high-dose group (n)	Patients in low-dose/ control group (n)	Intervention intravenous remifentanil dosages)	Remifentanil infusion mode	Cumulative remifentanil dose (higher dose group)/ Duration of procedure	Primary pain outcome	Secondary pain outcome	Mode of anaesthesia	In high-dose remifentanil group			
											Acute opioid tolerance	Opioid-induced hyperalgesia (mechanism of inducing)	Postop opioid	Postop pain
Song [62]	Randomised	Thyroidectomy	28	28	0.2 $\mu g.kg^{-1}.min^{-1}$ vs. 0.05 $\mu g.kg^{-1}.min^{-1}$	CI	84 ± 29 min 1118 ± 390 μg	Mechanical pain threshold (von Frey) peri-incisional area + forearm 24 h, 48 h	Pain intensity by VNRS at PACU, 6 h, 24 h, 48 h Fentanyl by nurses	Sevoflurane	/	Yes ↓ mechanical pain threshold peri-incision	NS	NS
Song [63]	Randomised	Laparoscopic gynaecology surgery	25	25	0.3 $\mu g.kg^{-1}.min^{-1}$ vs. 0.1 $\mu g.kg^{-1}.min^{-1}$	CI	Mean 168.4 ± 9.4 min Mean 2980 ± 200 μg	Mechanical and evoked pain(von Frey) + tactile pain threshold to upper arm + peri-incisional areas at 24 h	Time to first postop analgesic VAS on movement 1st hour postop Ketorolac consumption 1st hour Total PCA (morphine + ketorolac) 24 h	Desflurane	/	Yes ↓ tactile pain threshold ↑ area of hyperalgesia	NS	NS
Treskatsch [64]	Randomised, double-blinded	Laparotomy	17	15	0.2 (+increments of 0.05) $\mu g.kg^{-1}.min^{-1}$ vs. 0.1 $\mu g.kg^{-1}.min^{-1}$ (+increase MAC of volatile if required)	CI	Mean 275 min (anaesthesia)	Observed BPS and VRS by study nurses until 4 h postop NRS by patient at 0 h, 1 h, 2 h, 3 h, 4 h, 6 h	Total postop morphine consumption	Sevoflurane	No	No	NS	NS
Yeom [65]	Randomised, double-blinded	Spinal fusion	20	20	0.03 $\mu g.kg^{-1}.min^{-1}$ vs. 0.16 $\mu g.kg^{-1}.min^{-1}$	CI	2.9 ± 0.6 h	PCA fentanyl consumption	VNRS at rest at 1 h, 24 h, 48 h	Sevoflurane + nitrous oxide	No	/	NS	NS

/, not investigated or not commented on; NS, not significant; ?, inconclusive; Inf, inferred; PCA, patient-controlled analgesia; VAS, visual analogue scale; VNRS, verbal numerical rating scale; VRS, visual rating scale; TCI, target controlled infusion; CI, continuous infusion; BPS, behavioural pain scale; PACU, post anaesthesia care unit.

in the type of operations, ranging from major abdominal to laparoscopic, as well as duration of surgery. All of the positive studies used volatile anaesthesia, and the intra-operative reminfentanil dosage was at or above 0.25 $\mu g.kg^{-1}.min^{-1}$. Of note, none of the studies addressing acute opioid tolerance which employed a target-controlled infusion mode for remifentanil, or used continuous propofol infusion for maintenance of anaesthesia, reported acute opioid tolerance. However, results may be difficult to interpret because patients may have different individual pain thresholds.

Of the 14 studies which addressed opioid-induced hyperalgesia, nine supported the presence of opioid-induced hyperalgesia and another two inferred its presence. Of these eleven studies, seven employed quantitative sensory testing methods to evaluate secondary hyperalgesia, while four used only surrogate markers in the form of pain intensity and opioid consumption. Of the seven which employed quantitative sensory testing methods, six used von Frey filaments to measure either mechanical pain threshold (three studies) or the area of hyperalgesia (three studies). Of note, where two of these six studies found significant differences using von Frey filaments, the same studies did not find any significance when using a pressure algometer for pressure pain [52] or tactile pain thresholds [63]. The one study which did not use von Frey filaments [60] chose to measure deep pressure pain tolerance and cold pain from an ice bath. Its findings were positive for pressure stimuli but not for cold. Referring to the 'Measurements' section above, hyperalgesia may be stimulus-specific. It is of interest that no studies here used heat stimuli as their quantitative sensory testing method even when current evidence suggests that heat stimuli may be useful to detect the presence of hyperalgesia [21, 48].

Another interesting point to note is the low correlation between quantitative sensory testing methods and surrogate opioid-induced hyperalgesia markers. All studies which employed quantitative sensory testing methods to detect opioid-induced hyperalgesia also measured surrogate markers such as postoperative pain intensity and/or postoperative opioid consumption. Out of these seven studies, only two found positive opioid-induced hyperalgesia with both quantitative sensory-testing methods and surrogate markers [56, 57]. Five studies found positive opioid-induced hyperalgesia only through quantitative sensory-testing methods, while the differerence in postoperative pain and/or opioid consumption was not significant. This further questions the validity of surrogate markers to detect hyperalgesia in general.

The number of patients in each study arm was relatively small. Most studies have included sample sizes of 20–30 patients, with the highest being 50 [61] and the lowest being 10 [58]. These studies have compared the effect of a higher dose of remifentanil compared with either a lower dose or a control. A few of these studies also involved randomly allocating patients into three groups; two treatment groups (one high remifentanil dose and one low-dose group) along with another group such as ketamine [52], adenosine [54], dexmedetomidine [56], pregabalin [57], magnesium [62] and amantadine [64]. Surgical specialties also varied and include major abdominal, gynaecological, breast, urological, thyroid, orthopaedic and eye as well as cardiac surgery.

On the whole, there is huge heterogeneity; studies have used a variety of infusion regimens, durations of infusion, maintenance of anaesthesia, cumulative dose of remifentanil as well as outcomes of pain measurement.

Two factors deserve specific mention. The first is the dose of remifentanil. Previous research suggested that acute opioid tolerance and opioid-induced hyperalgesia were induced when remifentanil was infused at $> 0.1\ \mu g.kg^{-1}.min^{-1}$ [3]. Specific to peri-operative studies that employed high- vs. low-dose remifentanil infusions, exposure to a high rather than to a low intra-operative remifentanil dose was associated with higher postoperative opioid consumption. This phenomenon is most likely explained by the development of acute opioid tolerance. In these studies, acute opioid tolerance developed above a remifentanil infusion rate of $0.25\ \mu g.kg^{-1}.min^{-1}$. In studies that found opioid-induced hyperalgesia to be significant, remifentanil was infused at $> 0.2\ \mu g.kg^{-1}.min^{-1}$ characterised by lower mechanical/pressure/cold pain thresholds, a larger area of hyperalgesia or through reporting higher pain scores despite higher postoperative opioid requirements. A comprehensive analysis of quantitative sensory testing methods used to detect opioid-induced hyperalgesia in

these studies has been given above. Many studies compared a higher and lower remifentanil dose (and the relative effects of each) without a proper control, which makes it hard to determine the exact remifentanil dose/range needed for acute opioid tolerance and opioid-induced hyperalgesia to be significant.

The second factor is the mode of remifentanil infusion and maintenance of anaesthesia. The most common methods of administering remifentanil intraoperatively are by continuous infusion or TCI. In most reports, authors infused remifentanil continuously; two studies used TCI. Richebe and colleagues found that, while a 7 $ng.ml^{-1}$ TCI has an equivalent effect site concentration to 0.3 $\mu g.kg^{-1}.min^{-1}$ of continuous infusion, using TCI mode significantly reduced intraoperative mean remifentanil use and showed a lower incidence of opioid-induced hyperalgesia [59]. This is in line with recent recommendations favouring TCI for achieving more precise drug delivery.

Studies reporting positive results have shown that acute tolerance to remifentanil-mediated analgesia develops with higher dose infusions and only becomes evident when total opioid exposure is quite high; these studies were performed in animals and human volunteers [3]. Most of these studies used the volatile agents sevoflurane or desflurane as the maintenance anaesthetic. Five studies used propofol infusion. None of the studies involving propofol demonstrated acute opioid tolerance. Only one concluded that opioid-induced hyperalgesia occurred in the higher remifentanil dose group who received propofol anaesthesia [59]. Shin et al. divided their study population into using sevoflurane or propofol for maintenance of anaesthesia before randomly allocating patients to receive high- or low-dose intra-operative remifentanil. The sevoflurane plus high-dose remifentanil group demonstrated increased postoperative pain despite greater postoperative opioid consumption in the first 30 min, implying opioid-induced hyperalgesia. No significant findings were reported for the propofol groups regardless of remifentanil dose [61]. Findings from a systematic review have also suggested that propofol may have a preventative effect on the development of remifentanil-induced hyperalgesia [9].

It may be difficult to compare studies with different types of surgery as postoperative pain intensities, and hence postoperative analgesic requirements are expected to be different. It has been suggested that opioid-induced hyperalgesia can lead to the development of chronic pain. There was no follow-up in these studies to see if chronic pain was a problem, despite observations from animal studies proposing mechanisms relating the transition from acute opioid analgesia exposure to changed receptor signalling to chronic pain and the loss of analgesic efficacy [66].

Non-opioid adjuncts in preventing remifentanil-induced acute opioid tolerance and opioid-induced hyperalgesia

By definition, opioid dose escalation would be expected to overcome acute opioid tolerance. Studies with a particular focus on acute opioid tolerance prevention or treatment are few in number, perhaps because it is easier to manage by increasing the opioid dose. With regard to opioid-induced hyperalgesia, opioid tapering, opioid rotation, detoxification, multimodal analgesia and other adjuncts have been evaluated in an attempt to reduce or prevent opioid-induced hyperalgesia. Opioid tapering, rotation and detoxification are more applicable to patients with chronic pain [9] and are beyond the scope of this article. This section has a particular focus on non-opioid adjuncts for which there is a growing body of research and evidence.

Systematic reviews were unable to draw conclusive evidence on the exact susceptible patient population, prevention or dosing strategy in regard to opioid-induced hyperalgesia with remifentanil [10, 20].

The first group of drugs that have been examined is NMDA receptor antagonists, including ketamine, magnesium sulphate and amantadine. A meta-analysis evaluated the effectiveness of NMDA receptor antagonists in reducing postoperative pain and consumption of analgesics after remifentanil-based analgesia [67]. This included eight studies of peri-operative ketamine and another five where a pre-operative magnesium sulphate bolus was followed by an infusion throughout surgery. Studies with ketamine showed higher heterogeneity in comparison with those used to consider effects of magnesium sulphate. In particular, the range of ketamine boluses and intraoperative infusion rates varied from 0.15 to 0.5 $mg.kg^{-1}$ and 2 to 5

5 $\mu g.kg^{-1}.min^{-1}$ respectively. One trial also used low-dose ketamine as postoperative patient-controlled analgesia with a bolus dose of 0.5 mg ketamine per 1 mg morphine; however, it did not show any additional analgesic benefit compared with control. In the trials studying magnesium sulphate, a regimen of an initial intravenous bolus of 30–50 $mg.kg^{-1}$ 15% magnesium sulphate followed by 8–15 $\mu g.kg^{-1}.min^{-1}$ infusions were used. All studies involved an intra-operative continuous infusion of remifentanil at rates between 0.1 $\mu g.kg^{-1}.min^{-1}$ and 0.5 $\mu g.kg^{-1}.min^{-1}$. The authors concluded that compared with placebo: NMDA receptor antagonists reduced pain scores at 0 h, 4 h, 6 h, 8 h, 12 h and 24 h postoperatively; reduced the cumulative analgesic use up to 48 h postoperatively; prolonged the first time to first analgesic request; and improved satisfaction scores. Compared with control, NMDA receptor antagonists did not influence postoperative nausea and vomiting or produce adverse effects such as nightmares, hallucinations, diplopia or shivering. The comparative efficacy of ketamine and magnesium sulphate was not mentioned [67].

Only one study looked at the effect of pre-operative amantadine on pain outcomes in patients undergoing elective major lower abdominal surgery using a three-arm study. The three groups were low-dose remifentanil, high-dose remifentanil and high-dose remifentanil with pre-operative amantadine [64]. Postoperative pain intensity and morphine consumption did not differ significantly between groups.

Secondly, we report on the use of non-steroidal anti-inflammatory drugs. These have appeal because activation of spinal cyclo-oxygenase (COX) may play a role in the development of opioid-induced hyperalgesia. Prostaglandins, in particular prostaglandin E2, have been shown to stimulate glutamate release both from astrocytes and the spinal cord dorsal horn in healthy human volunteers. This is inhibited by COX inhibitors, which have also been shown to functionally antagonise NMDA receptors A small study involving 16 healthy adults showed that pre-treatment with intravenous parecoxib (a selective COX-2 inhibitor) or ketorolac (a COX-1 and 2 inhibitor) before remifentanil infusion reduced the area of pinprick hyperalgesia compared with control. Parecoxib reduced the area significantly more than ketorolac ($p = 0.009$), suggesting that COX-2 inhibition is perhaps more important than COX-1 inhibition in reducing hyperalgesia. It is notable that the same pre-treatment produced no significant difference for cold pressor pain [68], demonstrating that hyperalgesia may be stimulus specific.

Another older study demonstrated that only pre-treatment with 40 mg parecoxib (over 10 min intravenously) before remifentanil infusion, but not when given at the same time as remifentanil, produced a significantly diminished hyperalgesic response upon remifentanil withdrawal. This suggests adequate timing may be of importance in the antihyperalgesic effect of COX-2 inhibitors [69]. The analgesic and antihyperalgesic actions of COX inhibitors/NSAIDs are attributed to inhibition of peripheral prostaglandin synthesis in inflamed tissue as well as COX inhibition in the central nervous system [70].

Yalcin et al. evaluated the effect of paracetamol 1 g given before surgery on remifentanil-induced hyperalgesia, in comparison with ketamine. This study randomly assigned 90 patients undergoing total abdominal hysterectomy to receive either a saline infusion, a ketamine bolus or a paracetamol infusion before the induction of anaesthesia. They concluded that 1 g paracetamol was as effective as a 0.5 $mg.kg^{-1}$ ketamine intravenous bolus plus intra-operative maintenance infusion of 5 $\mu g.kg^{-1}.min^{-1}$ in terms of postoperative pain scores, morphine consumption and satisfaction with anaesthesia. Pain thresholds in the area of the incision were also significantly higher at 24 h and 48 h postoperatively in the control group, suggesting hyperalgesia [71].

Gabapentinoids have also been studied. When given before and after surgery, gabapentin has been shown to significantly decrease postoperative pain scores [72]. Stoicia et al. reviewed the effects of gapapentin on opioid-induced hyperalgesia and concluded that, while the efficacy of gabapentin in reducing or preventing opioid-induced hyperalgesia has been demonstrated in animal models and some human case studies, no large-scale prospective, randomised, controlled trials have been performed to corroborate these findings [73]. As an adjunct to short-term remifentanil use, only a recent animal study demonstrated a reduction in the minimum alveolar concentration (MAC) by

gabapentin (150–300 mg.kg^{-1}) when using sevoflurane, and enhanced the MAC reduction produced by remifentanil (2–4 μg.kg^{-1}.min^{-1}). This enhancement suggests the possibility of limiting acute opioid tolerance. Another study showed no antihyperalgesic and no opioid-enhancing effect from a single 600 mg dose of gabapentin in healthy volunteers receiving low-dose remifentanil infusions at 0.08 μg.kg^{-1}.min^{-1} for 40 min [74].

Pregabalin has a more rapid onset and more linear pharmacokinetics than gabapentin. It has been shown in 'off label' use to be effective for treating incisional and inflammatory pain [75]. A study investigated the differences in thresholds and areas of hyperalgesia between low- and high-dose remifentanil infusions and the effects of gabapentin. This involved a three-group comparison of placebo with low-dose remifentanil, placebo with high-dose remifentanil and gabapentin with high-dose remifentanil. A pre-operative dose of 300 mg pregabalin given to these patients undergoing laparo-endoscopic single-site urological surgery showed a reduction in the mechanical hyperalgesia threshold and the area of hyperalgesia around the surgical incision at 24 h postoperatively compared with control, with a remifentanil infusion at 0.3 μg.kg^{-1}.min^{-1} [57]. This supports an earlier study which found that giving pre-operative pregabalin (150 mg) was associated with lower fentanyl patient-controlled analgesia use 48 h after propofol–remifentanil anaesthesia [51].

Drugs acting on the sympathetic nervous system have also been explored. Genetic analysis in mice suggests that the β_2-adrenergic receptor gene is associated with the expression of opioid-induced hyperalgesia and intra-operative infusion of esmolol can reduce postsurgical opioid requirements [76]. In humans, a small randomised, controlled trial demonstrated that intracutaneous electrical and heat stimulation produced a smaller area of secondary hyperalgesia when remifentanil TCI (3 ng.ml^{-1}) was combined with propranolol vs. remifentanil alone. The administration of propranolol (target plasma concentration of 15 ng.ml^{-1}) began 30 min before the remifentanil infusion and was shown to have only minor haemodynamic effects [77].

Likewise, α_2-adrenergic agonists may offer some promise. Dexmedetomidine is a highly selective α_2-adrenergic receptor agonist, often used for sedation, which produces a unique arousable sedative effect via its action on the locus coeruleus. It also has mild analgesic properties and its systemic administration has been reported to enhance the analgesic effect of opioids, thus reducing opioid requirements. Dexmedetomidine has been reported to depress NMDA receptor-mediated synaptic transmission in animal models as well as reduce spinal NMDA receptor phosphorylation in the dorsal horn, which was found to be up-regulated after remifentanil infusion [78].

In the only human study currently available in English, 90 patients who underwent laparoscopic vaginal hysterectomy were randomly allocated to receive groups receiving either: placebo with low-dose remifentanil (0.05 μg.kg^{-1}.min^{-1}); placebo with high-dose remifentanil (0.3 μg.kg^{-1}.min^{-1}); or dexmedetomidine with high-dose remifentanil infusions. Compared with the placebo plus high-dose remifentanil group, those who received pre-induction dexmedetomidine (two-step infusion; an initial dose of 1.0 μg.kg^{-1} for 10 min, followed by a continuous infusion of 0.7 μg.kg^{-1}.h^{-1}) had a significantly higher mechanical hyperalgesia threshold around the surgical incision 24 h after surgery, as measured using von Frey filaments on peri-incisional areas [56].

Anaesthetic agents may affect the body's response to remifentanil. For instance, when propofol anaesthesia was used, high-dose remifentanil was not associated with differences in morphine consumption or postoperative pain at 24 h, suggesting that propofol infusion may itself have a preventive effect on remifentanil-induced hyperalgesia. This was in comparison to studies using regional and inhalational anaesthesia [10]. This antihyperalgesic property has been attributed to inhibition of the NMDA subtype of the glutamate receptor [10, 67, 79]. In addition, as nitrous oxide is an NMDA receptor antagonist, one might expect it to affect pain transmission. Intra-operative 70% nitrous oxide administration during propofol–remifentanil (0.3 μg.kg^{-1}.min$^{-1)}$ anaesthesia was found to significantly reduce postoperative opioid-induced hyperalgesia in a study of 50 adults as determined by hand-held von Frey filaments and measured with a visual analogue scale [80].

NMDA receptors also seem to be involved in δ-opioid receptor activity. A rat model study found

increased membrane trafficking of δ-opioid receptor antagonists in the spinal cord after high-dose remifentanil administration (1 $\mu g.kg^{-1}.min^{-1}$) and surgery. δ-opioid receptor antagonists may, therefore, prevent the enhancement effect of remifentanil on the NMDA receptor-mediated miniature excitatory post synaptic current in dorsal horn neurons. Naltrindole, a δ-opioid receptor antagonist, at a dose of 30 nM infused 10 min before remifentanil, was found to attenuate remifentanil-induced mechanical and thermal hyperalgesia, without affecting baseline nociceptive threshold [81].

A variety of other drugs have been investigated. Adenosine is a purine compound which has complex effects on pain transmission, with actions at both peripheral and spinal sites. Intravenous adenosine may attenuate peri-operative pain through anti-inflammatory actions mediated by peripheral adenosine A2a or A3 receptors. Centrally, A1 receptor-mediated antinociceptive actions have been found to contribute to long-lasting peri-operative pain relief [82, 83]. Moreover, adenosine A2a receptors also inhibit NMDA receptor conductance [84]. In a study of 90 patients undergoing tonsillectomy, when an intra-operative infusion of adenosine 80 $\mu g.kg^{-1}.min^{-1}$ (compared with a saline control) was added to sevoflurane-based anaesthesia along with remifentanil at 0.1 $\mu g.kg^{-1}.min^{-1}$, it was found that first postoperative analgesia was requested later and total pethidine requirement in the first 24 h was significantly less [54]. Finally, a new study on a rat model investigated the tricyclic antidepressant amitriptyline (10 $mg.kg^{-1}$ and 50 $mg.kg^{-1}$), the microglia activation inhibitor minocycline (30 $mg.kg^{-1}$ and 100 $mg.kg^{-1}$) and the neurokinin-1 antagonist maropitant (10 $mg.kg^{-1}$ and 30 $mg.kg^{-1}$). These drugs have previously been shown to be effective in the treatment of morphine tolerance [85]. When combined with a very high remifentanil infusion rate of 4 $\mu g.kg^{-1}.min^{-1}$, these drugs did not significantly alter postoperative hind paw withdrawal response to electronically calibrated von Frey filaments compared with control [86]. The authors note that it may be difficult to extrapolate these results to humans, as the doses used in the rat study were adjusted to obtain desired clinical effects and are much higher than the therapeutic range for humans.

Conclusion

In conclusion, remifentanil, in common with other opioids, can induce acute opioid tolerance and opioid-induced hyperalgesia. These are pharmacologically distinct concepts and have different cellular mechanisms. Tolerance can be overcome by increasing the opioid dosage, whereas, in contrast, dose escalation will worsen hyperalgesia. Numerous studies have shown that concurrent use of multimodal analgesia may prevent remifentanil-induced acute opioid tolerance and opioid-induced hyperalgesia, which may be partly due to a subsequent reduction in intra-operative remifentanil requirements. There is substantial heterogeneity amongst currently published studies in evaluating the effect of peri-operative remifentanil infusions on the induction of acute opioid tolerance and/or opioid-induced hyperalgesia, making it difficult to compare results and draw clear conclusions. This comprises: different drugs used for anaesthetic maintenance; no differentiation between minor or major operations with their different magnitudes of postoperative pain, using TCI or continuous infusions of remifentanil; and different methods of pain testing and assessment of opioid-induced hyperalgesia or acute opioid tolerance. Also the sample sizes are small. Much larger scale studies with a larger number of patients are needed; these should be randomised with placebo controls. Although it appears possible for acute opioid tolerance and opioid-induced hyperalgesia to be induced when remifentanil is infused at > 0.1 $\mu g.kg^{-1}.min^{-1}$, in the peri-operative setting, it seems that this dose needs to be at least 0.25 $\mu g.kg^{-1}.min^{-1}$ for acute opioid tolerance and 0.2 $\mu g.kg^{-1}.min^{-1}$ for opioid-induced hyperalgesia for a sustained period of time. It is difficult to simply attribute higher postoperative opioid consumption to acute opioid tolerance, as intra-operative opioids or other analgesia given may not have been of an adequate dose to attenuate the original surgical pain once the remifentanil effects have worn off. Apart from needing higher doses of analgesics to control pain in the immediate short-term period, it is difficult to assess the clinical significance of tolerance and whether there are long-term consequences. In instances where there are significant differences in postoperative opioid requirement, this does not always translate to increased self-reported postoperative pain,

suggesting that clinically significant opioid-induced hyperalgesia is actually very rare. Hyperalgesia may also be stimulus-specific. To date, no single approach has been validated as the definitive standard in hyperalgesia, be it with surrogate markers like pain intensity and opioid consumption or the use of quantitative sensory testing. Long-term follow-up of patients who show signs of postoperative hyperalgesia would be useful to assess whether chronic pain is a significant clinical consequence.

Competing interests

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