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Tramadol

A Review of its Use in Perioperative Pain

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Data Selection

Sources: Medical literature published in any language since 1993 on tramadol, identified using AdisBase (a proprietary database of Adis International, Auckland, New Zealand) and Medline. Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: AdisBase search terms were 'tramadol' or 'CG-315' or 'CG-315E' or 'U-26225A'. Medline search terms were 'tramadol'. Searches were last updated 26 May 2000.

Selection: Studies in patients with perioperative moderate to severe pain who received tramadol. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Tramadol, analgesia, pain, pharmacodynamics, pharmacokinetics, therapeutic use.

Contents

Summary

Abstract

Tramadol is a synthetic, centrally acting analgesic agent with 2 distinct, synergistic mechanisms of action, acting as both a weak opioid agonist and an inhibitor of monoamine neurotransmitter reuptake. The 2 enantiomers of racemic tramadol function in a complementary manner to enhance the analgesic efficacy and improve the tolerability profile of tramadol.

In several comparative, well designed studies, oral and parenteral tramadol effectively relieved moderate to severe postoperative pain associated with surgery. Its overall analgesic efficacy was similar to that of morphine or alfentanil and superior to that of pentazocine. Tramadol provided effective analgesia in children and in adults for both inpatient and day surgery.

Tramadol was generally well tolerated in clinical trials. The most common adverse events (incidence of 1.6 to 6.1%) were nausea, dizziness, drowsiness, sweating, vomiting and dry mouth. Importantly, unlike other opioids, tramadol has no clinically relevant effects on respiratory or cardiovascular parameters at recommended doses in adults or children. Tramadol also has a low potential for abuse or dependence.

Conclusions: The efficacy of tramadol for the management of moderate to severe postoperative pain has been demonstrated in both inpatients and day surgery patients. Most importantly, unlike other opioids, tramadol has no clinically relevant effects on respiratory or cardiovascular parameters. Tramadol may prove particularly useful in patients with poor cardiopulmonary function, including the elderly, the obese and smokers, in patients with impaired hepatic or renal function, and in patients in whom nonsteroidal anti-inflammatory drugs are not recommended or need to be used with caution. Parenteral or oral tramadol has proved to be an effective and well tolerated analgesic agent in the perioperative setting.

Pharmacodynamic Profile

Tramadol is a synthetic, centrally acting analgesic agent with 2 distinct, synergistic mechanisms of action. It is both a weak opioid agonist with selectivity for the μ-receptor and a weak inhibitor of the reuptake of noradrenaline (norepinephrine) and serotonin (5-hydroxytryptamine; 5-HT). This dual mechanism of action may be attributed to the 2 enantiomers of racemic tramadol. The (+)-enantiomer has a higher affinity for the μ-receptor and is a more effective inhibitor of 5-HT reuptake, whereas the (–)-enantiomer is a more effective inhibitor of noradrenaline reuptake and increases its release by autoreceptor activation.

In healthy volunteers, oral tramadol 100mg provided superior analgesia compared with placebo. The peak analgesic effect occurred 1 to 4 hours after drug administration, with analgesia persisting for 3 to 6 hours.

Tramadol is extensively metabolised in the liver, with the *O*-desmethyl (M1) metabolite of tramadol having an ≈200-fold higher affinity for opioid receptors than the parent drug. The *O*-desmethylation of tramadol is dependent on the cytochrome P450 enzyme CYP2D6 sparteine-oxygenase (deficient in ≈8% of Caucasians). Studies in healthy volunteers deficient in this enzyme (poor

tramadol metabolisers) provided evidence for the possible contribution of the M1 metabolite to the analgesic effects of tramadol, with reduced analgesia in poor metabolisers compared with extensive metabolisers.

The two enantiomers of tramadol act synergistically to provide analgesia. In both clinical and animal studies, the (+)-enantiomer provided similar analgesia to that of racemic tramadol and superior analgesia compared with the (–)-enantiomer. However, racemic tramadol showed an improved tolerability profile compared with the (+)-enantiomer in these studies.

Several comparative, double-blind studies, in both adults and children, indicated that unlike other opioids (such as morphine, pethidine, oxycodone and nalbuphine) postoperative tramadol was not associated with clinically relevant respiratory depression. In addition, although one study demonstrated a statistically significant increase in both systolic and diastolic blood pressure, these were not considered clinically relevant. There were also no clinically relevant effects on heart rate with tramadol and it reduced shivering in postoperative patients.

Pharmacokinetic Profile

Tramadol is rapidly absorbed following single or multiple oral 100mg doses in adult volunteers. The mean absolute bioavailability of tramadol was ≈68% and increased to >90% with multiple doses and with intramuscular administration. Food intake had no clinically relevant effects on its bioavailability. In healthy adult volunteers administered a 100mg single oral dose of tramadol, the maximum plasma concentration (C_{max}) was 308 μg/L at 1.6 hours and with a single intramuscular dose was 193 μg/L attained at 0.75 hours. C_{max} for the M1 metabolite after a single oral 100mg dose was 55 μg/L and was reached in ≈3 hours. Tramadol has a high tissue affinity, with an apparent volume of distribution after parenteral administration of ≈260L.

Tramadol undergoes extensive first-pass metabolism in the liver, with ≈10 to 30% of an oral dose excreted unmetabolised in healthy volunteers. Both tramadol and its metabolites are primarily excreted via the kidneys (90%). The terminal elimination half-life ($t_{½\beta}$) value for tramadol after a single oral (100mg) or parenteral (50mg) dose was ≈5.5 hours. $t_{½\beta}$ values for the M1 metabolite following oral single or multiple 100mg doses were 6.69 and 6.98 hours, respectively. $t_{½\beta}$ is increased ≈2-fold in patients with renal or hepatic impairment. Concomitant administration with carbamazepine, an inducer of hepatic enzymes, reduced the $t_{½\beta}$ of tramadol by ≈50%.

Clinical Efficacy

The analgesic efficacy of intravenous, intramuscular and oral tramadol has been established in several randomised, double-blind, parallel-group, comparative studies in adult patients with moderate to severe acute postoperative pain, and in a limited number of studies in paediatric patients.

Parenteral or oral tramadol effectively relieved moderate to severe postoperative pain associated with several types of surgery (including abdominal, orthopaedic and cardiac surgery), reducing pain intensity by 46.8 to 57.6% within 4 to 6 hours (assessed using a 100mm or 100-point visual analogue scale). There is also a dose-dependent reduction in the severity and prevalence of postoperative shivering with tramadol treatment.

The overall analgesic efficacy with tramadol was comparable to that achieved using equianalgesic doses of parenteral morphine or alfentanil. Intramuscular tramadol also provided similar efficacy compared with intramuscular ketorolac in postoperative patients.

Concomitant use of intravenous tramadol 50 or 100mg with dipyrone 25 or

50mg (a nonsteroidal anti-inflammatory drug; NSAID) using patient controlled analgesia provided better analgesia than intravenous piritramide 0.75 or 1.5mg (an opioid agent). A continuous infusion of tramadol 10 mg/h with concomitant oral propacetamol 2g 4 times daily achieved superior analgesic efficacy compared with tramadol monotherapy.

In children, intramuscular tramadol 2 mg/kg as required provided analgesia similar to that of intramuscular pethidine 1 mg/kg or nalbuphine 0.1 mg/kg following lower abdominal surgery. Furthermore, a single caudal injection of tramadol 2 mg/kg provided similar analgesia 3 to 12 hours postoperatively to that of caudal bupivacaine 2 mg/kg (a local anaesthetic) or tramadol 2 mg/kg with concomitant bupivacaine 2 mg/kg, although at the 3-hour time point bupivacaine provided superior analgesia.

Tramadol provided effective postoperative pain relief in patients after day surgery (including groin and gynaecological surgery). The majority of these studies involved complex treatment regimens, with the concomitant administration (pre-, intra- and/or postoperatively) of several other analgesic agents (both opioids and NSAIDs). In a large multicentre study, perioperative intravenous and oral tramadol 100mg provided superior analgesic efficacy for the first 24 hours compared with a combination of intraoperative fentanyl 100μg and postoperative oral codeine 16mg/paracetamol 1000mg. Tramadol 100mg (administered intra- and post-operatively) also provided similar analgesic efficacy compared with naproxen sodium 500mg in 91 patients. Furthermore, intravenous tramadol 1.5 mg/kg, administered at the induction of anaesthesia, provided superior pain relief compared with intravenous ketorolac 10mg in 60 patients after laparoscopic surgery.

Results from early studies investigating the intraoperative use of tramadol were controversial, with reports of increased recall of intraoperative events following its use. However, several recent studies using volatile or intravenous anaesthetic techniques, in both inpatients and day surgery patients, have not shown any clinically significant lightening of anaesthesia depth sufficient to cause accidental awareness while undergoing surgery.

Tolerability

In general, tramadol was well tolerated in clinical trials. The most common adverse events with single or multiple dose oral or parenteral administration of tramadol were nausea (6.1% of patients), dizziness (4.6), drowsiness (2.4), tiredness (2.3), sweating (1.9), vomiting (1.7) and dry mouth (1.6). Adverse events occurred in ≈15% of patients. Unlike other opioids, notably morphine, tramadol did not cause clinically relevant respiratory depression at recommended therapeutic doses. The incidence of seizures in patients receiving tramadol is estimated to be <1%.

The risk of dependence or abuse with tramadol is low (0.7 to 1.5 cases of abuse per 100 000 individuals). The most common symptoms associated with an overdose were lethargy (30% of patients), nausea (14%), tachycardia (13%), agitation (10%), seizures (8%), coma (5%), hypertension (5%) and respiratory depression (2%). Naloxone treatment reversed sedation and apnoea in 50% of patients. No serious cardiotoxicity was observed with tramadol overdose.

Dosage and Administration

Tramadol is recommended for the management of acute or chronic moderate to severe pain. In adults and adolescents, the usual dosage is 50 to 100mg every 4 to 6 hours as required, with a maximum dosage of 400 mg/day. It may be administered orally or parenterally, although only an oral formulation is available

in the US. Dosage adjustments may be required in patients with renal or hepatic impairment and in those >75 years of age. Recommendations for the use of tramadol in paediatric patients may vary between individual countries. For example, tramadol is not recommended for use in children <12 years of age in the UK or in those <16 years of age in the US, whereas in Germany some formulations are approved for use in children aged ≥1 year.

Tramadol is not recommended in patients receiving monoamine oxidase inhibitors and is contraindicated in cases of acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic drugs. The risk of seizure with tramadol administration may be enhanced in patients receiving monoamine oxidase inhibitors, neuroleptics, other drugs that reduce the seizure threshold, patients with epilepsy or patients otherwise at risk of seizure. Tramadol should be used with caution in patients with increased intracranial pressure and when treating patients with respiratory depression or if concomitant central nervous system depressant agents are being administered. When used with concomitant carbamazepine, dosages of tramadol may require adjustment.

1. Introduction

Tramadol is a centrally acting analgesic agent that is structurally related to morphine and codeine. The pharmacodynamic and pharmacokinetic properties, and therapeutic potential of this drug in acute and chronic pain treatment were previously reviewed in *Drugs* in 1993.[1] This review focuses on the perioperative use of tramadol in the treatment of patients with acute moderate to severe pain.

2. Pharmacodynamic Profile

2.1 Mechanism of Action

Tramadol is a synthetic, centrally acting analgesic agent with 2 distinct but complementary mechanisms of action; these have been extensively reviewed elsewhere and are briefly summarised in table I.[1,4,29,30] It acts as an opioid agonist with selectivity for the μ-receptor and also binds weakly to κ- and δ-receptors.[2-4] The affinity of tramadol for the μ-receptor is ≈6000-fold less than that of morphine and 10-fold less than codeine.[2,4] Tramadol is extensively metabolised in the liver (see section 3), although only the *O*-desmethyl (M1) metabolite is pharmacologically active, with an ≈200-fold higher affinity for opioid receptors than the parent drug.[1,26,27]

Evidence from both human and animal studies indicates that tramadol-mediated antinociceptive and analgesic effects are only partially antagonised (≈30%) by the opioid antagonist naloxone, suggesting nonopioid mechanisms of action are also involved.[1,2,5] Thus, at the same concentrations at which it binds to opioid receptors, tramadol acts on monoamine systems to inhibit the reuptake of noradrenaline (norepinephrine) and serotonin (5-hydroxytryptamine; 5 HT).[2,4,6,7] Evidence, mainly from preclinical studies, supporting the monoamine mechanism of action of tramadol has been reviewed previously (table I).[1,5-7,9,23,31,32]

Tramadol is structurally related to codeine and morphine (fig. 1). Like codeine, tramadol has a methyl substitution on the phenolic moiety, which accounts for its affinity for opioid receptors.[1]

Opioid and nonopioid mechanisms of action of tramadol are thought to act synergistically on descending inhibitory pathways in the central nervous system (CNS), resulting in the modulation of second order neurones in the spinal cord.[1,2] These inhibitory pathways, mediated by the raphe nuclei, periaqueductal grey, locus coeruleus and reticulospinal projections, involve both opioid and monoamine neurotransmitters.

The dual mechanism of action associated with the analgesic and antinociceptive effects of tramadol

Table I. Summary of pharmacodynamic properties of tramadol

Overall mechanism of action	Modulation of opioid and monoamine descending inhibitory pathways mediated by the raphe nucleus, periaqueductal grey, locus coeruleus and reticulospinal projections[1,2]
Opioid effects	Selectivity for μ-receptor, although it binds weakly to the δ- and κ-receptors[2-4]
	Affinity for the μ-receptor is ≈6000-fold less than morphine and 10-fold less than codeine[2,4]
	≈30% of analgesic activity is antagonised by naloxone (an opioid antagonist)[1,2,5]
Monoamine effects	Inhibits reuptake of noradrenaline (norepinephrine) and 5-HT[2,4,6,7]
	Does not bind to α_2-adrenoceptors, 5-HT, N-methyl-D-aspartate or benzodiazepine receptors[5,8]
	In healthy volunteers, tramadol analgesia is significantly decreased by yohimbine[9]
	The effects of tramadol in a rat tail-flick test are antagonised by yohimbine (an α_2-adrenoceptor antagonist) and ritanserin (5-HT antagonist)[5]
	In vitro, cocaine (a norepinephrine uptake inhibitor) and 6-nitroquizapine (a 5-HT uptake inhibitor) block the synaptosomal reuptake of monoaminergic neurotransmitters in the presence of tramadol[7,10]
Respiratory effects	Tramadol caused no clinically relevant respiratory depression in adults[11-14] or children[1,15,16] undergoing surgery
	There were also no clinically significant changes in oxygen saturation in adults and children receiving tramadol[11,16]
	Effects of tramadol on inspiratory-expiratory oxygen difference, end-tidal CO_2 concentration, minute volume and respiratory rate were similar to those observed with placebo[13]
	No clinically relevant effects on blood pressure or heart rate in adults and children undergoing surgery[13-15]
Other effects	In healthy volunteers, tramadol decreased the sweating, vasoconstriction and shivering thresholds.[17] These effects were only partially reversed by naloxone
	In healthy adult volunteers[18-21] and patients who underwent abdominal surgery,[22] tramadol had no clinically relevant effects on gastrointestinal functioning.
Contribution of individual enantiomers and metabolites of tramadol to analgesia	
(+)-enantiomer	Higher affinity for μ-receptor than (–)-enantiomer[1,5,6,10,23,24]
	More potent inhibitor of 5-HT reuptake than (–)-enantiomer[1,5,6,10,23,24]
	In postoperative patients using PCA, tramadol (+)-enantiomer provided similar efficacy to racemic tramadol, with both treatments providing superior analgesia compared with the (–)-enantiomer ($p = 0.0006$)[25]
(–)-enantiomer	More potent inhibitor of noradrenaline reuptake than the (+)-enantiomer and increases its release by autoreceptor activation[2,5-7,24]
O-desmethyl (M1) tramadol metabolite	The only pharmacologically active metabolite[1]
	≈200-fold higher affinity for μ-receptor than racemic tramadol[1,26,27]
	In healthy volunteers, tramadol is demethylated by the liver enzyme CYP2D6 sparteine-oxygenase to the pharmacologically active metabolite *O*-desmethyl tramadol[27,28]
	In healthy volunteers deficient in CYP2D6 enzyme (≈8% of Caucasian population), analgesia with tramadol is reduced compared with that in extensive metabolisers[27,28]

CYP= cytochrome P450; **5-HT** = serotonin (5-hydroxytryptamine); **PCA** = patient controlled analgesia.

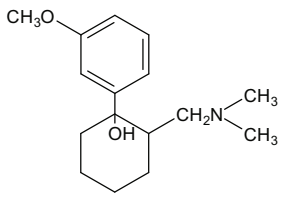
may be a reflection of the actions of the 2 enantiomers that form the therapeutic racemic mixture.[2,29] Thus, the (+)-enantiomer has a higher affinity for the μ-receptor and is a more effective inhibitor of 5-HT reuptake,[1,5,6,10,23,24] whereas the (–)-enantiomer is a more effective inhibitor of noradrenaline reuptake and increases its release by autoreceptor activation.[2,5-7,24] The inhibitory constants for the binding of the tramadol enantiomers and other opioids to opioid receptors and for monoamine uptake are summarised in table II.[5,23]

2.2 Analgesic Effects

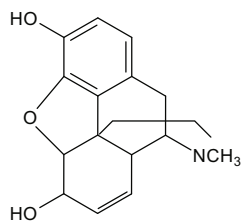
The analgesic effects of tramadol in healthy volunteers have been reviewed previously in *Drugs*.[1] As discussed in the previous review, results of

double-blind controlled studies indicated that oral tramadol 100mg provided analgesia superior to that of placebo.[1] The peak effect occurred 1 to 4 hours after drug administration and analgesia persisted for 3 to 6 hours after onset.[1] Furthermore, intravenous tramadol 2 mg/kg provided similar effects on detection-, pain- and tolerance-thresholds to that of intravenous pethidine 1 mg/kg in 16 healthy volunteers.[33]

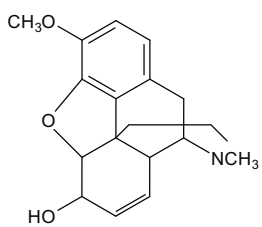
Recent evidence suggests that hepatic demethylation of tramadol by the liver enzyme cytochrome P450 (CYP) 2D6 sparteine-oxygenase may play a major role in mediating the analgesic effects of this agent (see section 3.2).[27,28] Since



Tramadol



Morphine



Codeine

Fig. 1. Chemical structures of tramadol, morphine and codeine.

≈8% of Caucasians are deficient in CYP2D6 (poor metaboliser), tramadol may have reduced opioid analgesic effects in these patients.[34] In a randomised, double-blind, placebo-controlled, crossover study in healthy volunteers who were either extensive (n = 15) or poor (n = 12) metabolisers of sparteine, tramadol 2 mg/kg increased pain pressure detection ($p < 0.05$), tolerance thresholds and thresholds for eliciting nociceptive reflexes following single ($p < 0.001$) and multiple stimulations of the sural nerve in extensive metabolisers.[28] In contrast, with poor metabolisers, only the thresholds to pain tolerance and nociceptive reflexes after a single stimulation were increased, although the increase in reflexes was lower than that observed in extensive metabolisers.[28] In addition, extensive metabolisers showed a reduction in peak pain levels ($p < 0.001$) and pain area in the cold pressor test.[28] These increased responses observed in extensive metabolisers compared with poor metabolisers correlated with higher serum concentrations of the M1 metabolite in the former group [median area under the plasma concentration-time curve (AUC) for 0 to 10 hours was 274 *vs* 142 mg/L · h; $p < 0.00005$].

Furthermore, studies in mice indicated that the M1 metabolite may contribute to the analgesic effects of tramadol.[26] Although *ex vivo* studies using rat brain slices containing the caudal part of the locus coeruleus indicated that both the M1 and M5 metabolites of tramadol bind to opioid receptors, only the M1 metabolite showed analgesic effects *in vivo* (measured using the tail-flick response test; no data values presented in abstract).[26] The M5 metabolite of tramadol shows poor penetration of the blood-brain barrier and this may account for its lack of analgesic efficacy in this study.[26]

Although both enantiomers of tramadol produce an antinociceptive effect, the (+)-enantiomer provides superior analgesia compared with the (–)-enantiomer.[23,25] As a racemic mixture, these enantiomers act synergistically. In rats administered tramadol by intrathecal injection, the 50% effective dose (ED_{50}) for the racemic mixture was 8.9 μmol/L, a value lower than the theoretical ED_{50}

Table II. Comparative inhibition of opioid receptor binding and monoamine uptake by tramadol, its enantiomers, and codeine and morphine[5,23]

Opioid agent	Inhibitory constant (K_i; μmol/L)				
	opioid receptor			noradrenaline (norepinephrine) uptake	5-hydroxytryptamine uptake
	μ	δ	κ		
(+/–)-Tramadol	2.1	57.6	42.7	0.79	0.99
(+)-Tramadol	1.3	62.4	54.0	2.51	0.53
(–)-Tramadol	24.8	213	53.5	0.43	2.35
Codeine	0.2	5.1	6	NA	NA
Morphine	0.00034	0.092	0.57	NA	NA

NA = not active at a concentration of 10 μmol/L.

(20.1 μmol/L) produced by addition of the antinociceptive effects of the enantiomers [ED_{50} = 14.1 and 35 μmol/L for the (+) and (–)-enantiomers, respectively].[23]

Results from a double-blind randomised study indicated that the two enantiomers of tramadol may act synergistically in humans,[25] confirming results reported in previous preclinical studies.[2,23] In 98 patients recovering from gynaecological surgery, the (+)-enantiomer provided similar analgesia compared with racemic tramadol. However, both treatments provided superior analgesia compared with the (–)-enantiomer ($p = 0.006$).[25] Responder rates according to the primary efficacy criterion (a decrease in pain intensity from severe to ≤mild 1 hour after the loading dose) in the (+/–), (+) or (–)-enantiomer groups were 48, 67 and 38%, respectively, and 76, 82 and 41% according to the secondary efficacy criterion (% of patients who considered pain relief was satisfactory over the 24-hour study period). Although the (+)-enantiomer provided analgesic efficacy similar to that of racemic tramadol, it was associated with a significantly higher incidence of nausea than the racemic drug ($p = 0.005$). Thus, taking into account the efficacy and tolerability profiles of these agents, it was concluded that racemic tramadol was superior to the (+)-enantiomer.[25] In this study, patients initially received intravenous 50mg doses of (+/–), (+) or (–) tramadol up to a maximum of 200mg (loading dose), followed by patient-controlled analgesia (PCA) for 24 hours with a demand dose of 20mg, lockout time of 5 minutes and a daily maximum dose of 600mg.[25]

The minimum effective serum concentration (MEC) of tramadol required to provide effective analgesia has been determined in 40 patients who underwent orthopaedic or gynaecological surgery.[35] Patients received a loading dose of intravenous tramadol of 50mg (maximum dose 200mg; median loading dose 97.5mg), followed by PCA for 24 hours with a demand dose of 20mg (maximum 500 mg/4 hours) and lockout time of 5 minutes. The MEC of tramadol was best described by a log-normal distribution and demonstrated high interindividual variability and, to a lesser extent, intraindividual variation. The MEC for tramadol ranged from 20.2 to 986.3 μg/L (median 287.7 μg/L), with the MEC for the M1 metabolite being 0.9 to 190.5 μg/L (median 36.2 μg/L).[35]

2.3 Effects on Respiration

Opioid analgesics are generally associated with respiratory depression. This is mediated through a decrease in the sensitivity of the respiratory centre to CO_2 which results in a decrease in respiratory rate and tidal volume.[1] Importantly, evidence from studies in healthy volunteers and surgical patients have shown that tramadol, unlike other opioids, is unlikely to produce clinically relevant respiratory depression at the recommended dosage. However, respiratory depression may occur if the recommended dosage is considerably exceeded (see section 5.3).[36] The discussion in this section

focuses on the effects of tramadol on respiration in postoperative patients.

The respiratory effects of tramadol have been compared with those of other opioids in double-blind, randomised studies involving postoperative patients.[11-14,37] A dose-response study in 30 patients indicated that intravenous tramadol, at a higher dose than an equianalgesic dose of morphine, transiently depressed the rate of respiration but had no effect on end-tidal CO_2 tension (fig. 2).[14] However, using a potency ratio of 10 : 1 for tramadol:morphine, it was concluded that tramadol had less effect on the respiratory centre than morphine.[14]

In addition, the effects of intravenous tramadol 0.6 mg/kg on the inspiratory-expiratory oxygen

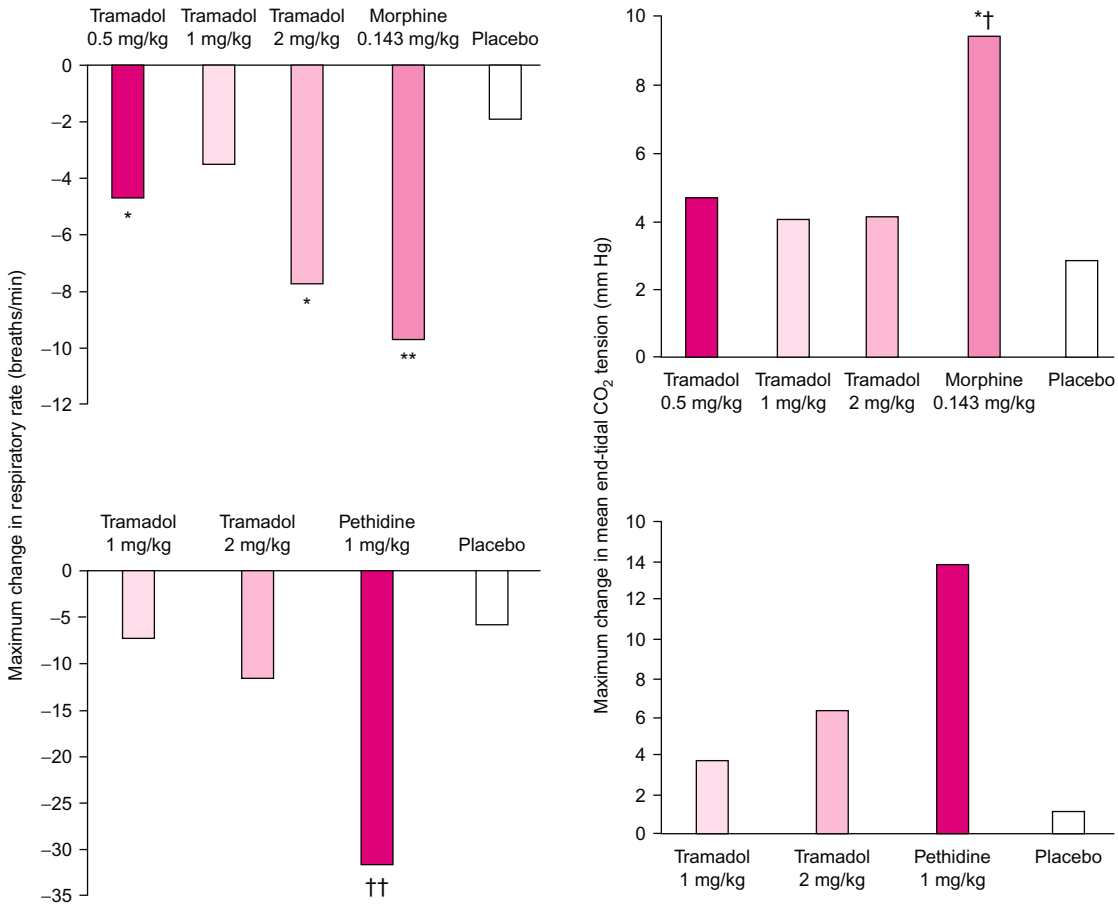


Fig. 2. Comparative effect of tramadol on the respiratory rate and end-tidal CO_2 tension in adults[14] and children (aged 2 to 10 years)[16] in 2 randomised double-blind studies. (**Top**) 30 adult patients aged 18 to 60 years received intravenous tramadol 0.5, 1 or 2 mg/kg or morphine 0.143 mg/kg during stable halothane anaesthesia.[14] (**Bottom**) 88 children received intravenous tramadol 1 or 2 mg/kg, pethidine 1 mg/kg or placebo during stable halothane anaesthesia for inguinal surgery.[16] There was a significant difference in the mean maximum change in the respiratory rate with tramadol 1 mg/kg compared with tramadol 2 mg/kg ($p < 0.003$). Values for the end-tidal CO_2 tension were estimated from a graph.[16] * $p < 0.05$, ** $p < 0.001$ *vs* placebo; † $p < 0.05$, †† $p < 0.005$ *vs* comparators.

difference, end-tidal CO_2 concentration, minute volume and respiratory rate were similar to those observed with placebo, whereas intravenous oxycodone 0.04 mg/kg caused significant depression of respiration in 36 spontaneously breathing anaesthetised patients.[13] The inspiratory-expiratory oxygen difference was significantly higher with oxycodone treatment from the 3-minute time point onwards ($p < 0.05$ *vs* tramadol or placebo), although pulse oximetric saturation remained stable (mean 97% mm Hg) in all treatment groups for the 30-minute study period. In addition, the mean respiratory rate (25 *vs* 11 breaths/minute; $p < 0.05$) and mean minute volume of respiration (7.1 *vs* 4.5 L/min) decreased significantly from baseline in the oxycodone group, whereas these values remained constant throughout the 30-minute study period in both the tramadol and placebo groups. Similarly, although there was no change in the mean end-tidal CO_2 concentration in the tramadol and placebo groups, with oxycodone treatment there was a significant increase in this parameter from baseline ($p < 0.05$).[13]

Intravenous tramadol 0.6 mg/kg also proved superior to equianalgesic doses of intravenous pethidine (0.6 mg/kg) with respect to respiratory depression.[12] Hence, with pethidine treatment there was a significant increase in fractional inspiratory-expiratory oxygen difference ($p < 0.001$) and end-tidal CO_2 concentration ($p < 0.01$) and a decrease in minute volume ($p < 0.001$) and respiratory rate ($p < 0.001$) from baseline values, whereas these parameters remained stable in the placebo and tramadol groups.[12]

The respiratory effects of intravenous tramadol have also been investigated in a 2 randomised, double-blind, placebo-controlled, comparative studies in children.[15,16] In the largest study in 88 children aged 2 to 10 years undergoing inguinal hernia surgery, intravenous tramadol 1 or 2 mg/kg caused significantly less respiratory depression than intravenous pethidine 1 mg/kg (fig. 2).[16] The mean maximum decrease in the respiratory rate with tramadol 1 or 2 mg/kg, pethidine 1 mg/kg or placebo was 7.3, 11.4, 31.4 and 1.7 breaths/minute, respectively ($p < 0.001$ for pethidine *vs* all other treatment groups; $p < 0.003$ for tramadol 1 mg/kg *vs* 2 mg/kg). Prolonged apnoea occurred in the pethidine group only, with 90.9% of patients in this group requiring manual ventilatory support compared with 13.6, 22.7 and 13.6% of those in tramadol 1 and 2 mg/kg and placebo groups, respectively.[16] Recovery in all drug treatment groups was slower than in the placebo group according to the Aldrete score, with pethidine-treated patients having the slowest recovery.[16] In 60 children aged 1 to 9 years, intramuscular tramadol 0.75 to 1 mg/kg caused significantly less respiratory depression than intramuscular nalbuphine 0.15 to 0.2 mg/kg, with a more marked decrease in respiratory rate 90 minutes after administration with nalbuphine-treatment (7.5 *vs* 3.6 breaths/minute; $p < 0.05$).[15]

Tramadol had no clinically relevant effects on blood gases in surgical patients.[11,16] A study in 150 patients undergoing gynaecological surgery indicated that intravenous tramadol 50 to 150mg provided analgesia equivalent to that of morphine 5 to 15mg.[11] However, the average minimum transcutaneous pulse oxygen saturation (t-SaO_2) values were significantly higher in the tramadol group than in morphine recipients 32 to 60 minutes after the initial dose (94 *vs* 93%; $p < 0.05$) and remained higher 62 to 90 minutes after administration (95 *vs* 92%; $p < 0.001$).[11] Furthermore, t-SaO_2 values decreased to ≤86% in 13.3% of morphine-treated patients, but no tramadol recipients showed a decrease of this magnitude.[11] In addition, no clinically significant changes in oxygen saturation were reported in a study involving 88 children aged 2 to 10 years receiving intravenous tramadol 1 or 2 mg/kg, pethidine 1 mg/kg or placebo.[16]

2.4 Other Effects

Parenteral tramadol appeared to have no clinically relevant effects on heart rate or blood pressure in adults and children.[13-15] Both intravenous tramadol 0.6 mg/kg and oxycodone 0.04 mg/kg had no significant effects on systolic arterial pressure

and heart rate during the 30-minute study period prior to minor surgery in 36 spontaneously breathing anaesthetised patients.[13] However, postoperative intramuscular tramadol 0.75 to 1.5 mg/kg or nalbuphine 0.15 to 0.2 mg/kg decreased both heart rate and diastolic blood pressure in 60 children during the first 4 hours, although there were no effects on systolic blood pressure.[15] The effects on respiratory rate were more marked with nalbuphine treatment than with tramadol.[15] In contrast, a study in 30 adult patients indicated that both the mean systolic and diastolic blood pressure levels in the tramadol group increased by 3.8mm Hg compared with a mean decrease of 7.5 and 2mm Hg, respectively, in the pethidine group.[14] These differences were not thought to be clinically relevant, but were statistically significant for both systolic and diastolic pressures ($p < 0.05$).[14] In this study, postoperative patients received tramadol or pethidine for 24 hours using PCA with a demand dose of 20mg and a lockout time of 5 minutes for the first hour and 10 minutes thereafter.

In general, opioids, centrally acting α_2-agonists, and volatile and intravenous anaesthetics have been shown to act on autonomic thermoregulatory systems to increase the sweating threshold while decreasing vasoconstriction and shivering thresholds.[17] In contrast to other opioids, oral tramadol 125 or 250mg decreased the sweating threshold by 1.03 °C/mg/L in 8 healthy volunteers.[17] The effects on other thermoregulatory parameters were similar to those observed with most opioids, with the vasoconstriction threshold reduced by 3.0 °C/mg/L and the shivering threshold by 4.2 °C/mg/L.[17] Furthermore, the addition of naloxone 3.5 mg/L only partially reversed these thermoregulatory effects of tramadol 250mg.[17] It was concluded that tramadol, like midazolam, reduced the 'setpoint' for thermoregulatory control rather than causing an overall inhibition. Importantly, clinical studies in patients undergoing surgery indicated that tramadol reduced postoperative shivering (see section 4.1.1).

A study in mice demonstrated that tramadol had anticonvulsant effects in a maximal electroshock seizure test.[38] Intraperitoneal tramadol (10 to 50 mg/kg) resulted in a dose-dependent decrease in the duration of the hind limb extensor phase (anticonvulsant), with tramadol 50 mg/kg providing the maximum effect (ED_{50} 33 mg/kg).[38] Moreover, this effect was antagonised by specific κ-receptor antagonists but not by the μ-receptor antagonist naloxone, suggesting κ-receptor-mediated anticonvulsant effects.[38] The clinical relevance of this finding requires clarification, as tramadol has been shown to cause idiopathic seizures in clinical use, although the incidence is low (<1%; see section 5).[39,40]

Although agents acting at μ-receptors, such as morphine, have previously been shown to impair gastrointestinal function, tramadol generally had no significant effects on this. Effects of tramadol on gastrointestinal function have been investigated in healthy volunteers in small randomised, double-blind, crossover, placebo-controlled studies[18-21] and in patients following abdominal surgery in a randomised, double-blind study.[22] In this latter study, patients received a continuous intravenous infusion of tramadol or morphine for 48 hours after abdominal surgery. Tramadol recipients received a loading bolus dose of 2 mg/kg, followed by an infusion of 0.5 mg/kg/h for the first 24 hours, then 0.25 mg/kg/h for the duration of the study. Morphine recipients received a bolus dose of 0.1 mg/kg, with an infusion rate of 0.05 mg/kg/h for the first 24 hours and then 0.025 mg/kg/h for the subsequent 24 hours.[22] There was a significant increase in orocaecal and colonic transit times compared with baseline in both morphine and tramadol recipients ($p < 0.005$), although gastric emptying was prolonged only with morphine treatment ($p < 0.05$ *vs* baseline).[22]

Studies in healthy volunteers also indicated that tramadol had minimal effects on the gastric emptying rate.[19-21] For example, after a liquid meal, intravenous tramadol 1.25 mg/kg had a measurable but nonsignificant effect on the gastric emptying rate compared with placebo, whereas intravenous morphine 0.125 mg/kg significantly decreased the gastric emptying rate ($p < 0.05$ *vs* tramadol or

placebo; measured using a paracetamol absorption test).[21] In addition, in a short term study (10 days' duration), the median orocaecal transit time in volunteers receiving oral dosages of tramadol 50mg 4 times daily was similar to that in the placebo group (90 minutes for each treatment), although there was a trend to an increase in the total colonic transit time with tramadol (58.8 *vs* 46.5 hours).[18]

3. Pharmacokinetic Profile

The pharmacokinetic properties of tramadol have been investigated in small studies in children undergoing surgery, in young and elderly adult healthy volunteers, and in patients with hepatic or renal impairment. The pharmacokinetic properties of tramadol and its M1 metabolite in healthy volunteers are summarised in table III. Some of the data discussed in this section have been reviewed previously in *Drugs*.[1]

Quantitative determination of tramadol in human serum was performed using capillary gas chromatography with nitrogen-selective detection and by gas chromatography coupled with mass spectrophotometry. High performance liquid chromatography has also been used to quantify tramadol and its major metabolites extracted from tissue samples.

3.1 Absorption and Distribution

Tramadol was rapidly absorbed after administration of single and multiple oral 100mg doses in adult volunteers.[4,43-45] After administration of a single oral 100mg dose, the mean absolute bioavailability of tramadol was 67.9% and increased to >90% with multiple 100mg doses.[1,4,42] It is suggested that the increased bioavailability of the drug with multiple oral doses may be due to saturated first-pass hepatic metabolism.[1,4,42] Administration of tramadol with food also increased the bioavailability of the drug. In volunteers who received a single oral dose of tramadol 100mg, the mean peak plasma concentration (C_{max}) was 16.7% higher ($p < 0.001$) and the area under the AUC was 10% higher ($p < 0.001$) than corresponding values in fasted volunteers.[46,47] However, this increase in absolute bioavailability was not considered clinically relevant.[46,47] In addition, the mean absolute bioavailability of tramadol increased with age;[1,3] and with intramuscular administration, the mean absolute bioavailability of tramadol increased to ≈100%.[1,41] According to the manufacturer's prescribing information, after a single oral dose of tramadol, females had a 12% higher C_{max} and a 35% increase in AUC compared with males, although the clinical relevance of this is still to be determined.[48]

Table III. Summary of pharmacokinetic properties of tramadol and its M1 metabolite (*O*-desmethyl tramadol) after single and multiple oral doses, and of tramadol after single intravenous or intramuscular doses in healthy adult volunteers[41,42]

Parameter	Oral[42] (n = 18)				Intravenous[a][41] (n = 12)	Intramuscular[41] (n = 12)
	single 100mg dose		multiple 100mg doses[b]		single 50mg dose	single 50mg dose
	tramadol	M1 metabolite	tramadol	M1 metabolite		
C_{max} (μg/L)	308	55	592	110	347.4	193
t_{max} (h)	1.6	2.97	2.25	2.43	NR	0.75
AUC_{∞} (μg/L • h)	2649	722	3679	835	1556	1582
$t_{½\beta}$ (h)	5.64	6.69	6.71	6.98	5.5	5.5
CL_T (L/h)	NR	NR	NR	NR	34.8	35.7
CL_R (L/h)	6.6	11.3	4.38	8.04	NR	NR
Vd (L)	NR	NR	NR	NR	262	261

a Administered as an intravenous infusion over 30 minutes.

b Tramadol 100mg 4 times daily for 1 week.

AUC_{∞} = area under the plasma concentration-time curve from zero to infinity; **C_{max}** = maximum plasma concentration; **CL_T** = total clearance; **CL_R** = renal clearance; **NR** = not reported; **t_{max}** = time to reach C_{max}; **$t_{½\beta}$** = terminal elimination half-life; **Vd** = volume of distribution.

After administration of single oral 100mg doses of tramadol to healthy adult volunteers, a C_{max} of 308 μg/L was reached in 1.6 hours (t_{max}).[1,41] C_{max} values were 193 μg/L (t_{max} 0.75 hours) after a single intramuscular 50mg dose of the drug and 374.4 μg/L after a single intravenous 50mg dose (table III). In 18 healthy adult volunteers receiving oral tramadol 100mg 4 times daily for 7 days, the C_{max} value was markedly higher than that observed with a single dose (592 *vs* 308 μg/L) and it took longer to reach these values (2.25 *vs* 1.6 hours).[42] Similarly, C_{max} and t_{max} values for the M1 metabolite were higher in volunteers who received multiple doses than after a single dose of the drug (table III).[42]

Tramadol has a large volume of distribution following parenteral administration (≈260L), confirming the high tissue affinity of this drug.[1,41,43] Although ≈20% is bound to plasma proteins, saturation of binding sites does not occur in the therapeutic dose range.[4,46] Tramadol crosses the placental barrier, with umbilical venous serum concentrations being 80% of maternal concentrations.[1] Low concentrations (0.1% of the original dose) of racemic tramadol and its M1 metabolite have been detected in breast milk within 16 hours after administration.[48-50]

3.2 Metabolism and Elimination

Tramadol undergoes extensive first-pass metabolism in the liver via 2 main metabolic pathways involving isoenzymes CYP3A and CYP2D6 (see section 2.2), with CYP2D6 being pivotal in the metabolism of this drug.[43,51,52] The level of CYP2D6 sparteine-oxygenase in the liver determines which metabolic route tramadol undergoes. In the presence of high concentrations of this enzyme, tramadol is demethylated at the phenolic oxygen site to yield the active M1 metabolite, whereas with low enzyme concentrations demethylation occurs at the amino nitrogen site to yield inactive *N*-desmethyl tramadol.[27] Hence, in a study in 104 healthy adult volunteers, poor metabolisers of sparteine (an *in vivo* probe for CYP2D6 enzyme activity) exhibited significantly higher mean metabolic ratios of tramadol *O*-demethylation than extensive metabolisers (4.4 *vs* 0.8; $p < 0.0001$; see section 2.2).[52] These *O*- and *N*-demethylated compounds (phase I reactions) may undergo further sulphation or glucuronidation in phase II reactions.[43,51]

Approximately 10 to 30% of the parent drug was excreted unmetabolised in the urine.[1,48,53] Mass spectrophotometry identified ≈23 metabolites in the urine, including 11 phase I products and 12 phase II conjugates.[53] Only one of these metabolites, the M1 metabolite, is pharmacologically active.[1,3,53]

The elimination kinetics of tramadol are best described as a 2-compartmental model, with a terminal elimination half-life ($t_{½β}$) after a single oral 100mg or parenteral 50mg dose of ≈5.5 hours.[1,4,41] The $t_{½β}$ values for the M1 metabolite following single and multiple oral 100mg doses were 6.69 and 6.98 hours, respectively.[42] Tramadol and its metabolites are primarily excreted via the kidneys (90%), with the remaining 10% eliminated in the faeces.[1,3,4,51]

3.3 In Special Populations

Pharmacokinetic properties of tramadol in healthy volunteers of various ages, children undergoing surgery and patients with renal or hepatic impairment are summarised in table IV.[1,42,54,55] Results of these studies showed that pharmacokinetic parameters are not generally age dependent (table IV). Hence, pharmacokinetic properties in 14 children (aged 1 to 12 years) receiving intravenous or caudal tramadol 2 mg/kg were similar to those in adults.[54] Furthermore, there were no clinically relevant differences in pharmacokinetic properties between healthy adult volunteers aged <65 years and volunteers aged >65 to 75 years. However, in healthy volunteers over 75 years of age, the $t_{½β}$ of tramadol was longer (7 hours) than in younger volunteers (5.6 and 6.1 hours; table IV).[1,42,55] In addition, there was a trend to increased absolute bioavailability with age.[1,42,55]

Since tramadol is eliminated both metabolically and renally, $t_{½β}$ was prolonged in patients with

Table IV. Summary of pharmacokinetic properties of tramadol after a single oral or parenteral 100mg dose in healthy adult volunteers[42] compared with healthy elderly volunteers,[1] children[54] and patients with hepatic or renal impairment[a] [1]

	Adult volunteers (aged <65y; n = 18)	Elderly volunteers (aged 65-75y; n = 12)	Elderly volunteers (aged >75y; n = 8)	Children[b] (aged 1-12y; n = 14)		Patients with renal insufficiency (n = 10)	Patients with hepatic impairment[c] (n = 12)
Route	PO	PO	PO	IV[d]	caudal[d]	IV	PO
C_{max} (μg/L)	308	324	415	1079	709	894	433
t_{max} (h)	1.6	2.0	2.1	0.19	0.55	NR	1.9
AUC (μg/L • h)	2649	2508	3854	5738	4774	7832	7848
$t_{½β}$ (h)	5.64	6.1	7.0	6.4	3.7	10.8	13.3
CL_T (L/h)	NR	47.6	29.5	0.37[e]	0.40[e]	16.8	16.3
Vd (L)	NR	NR	NR	3.1[f]	2[f]	NR	NR

a Creatinine clearance 0.3 to 4.8 L/h.

b Children undergoing elective limb or thoracic surgery.

c Level of hepatic impairment not reported.

d 2 mg/kg dose administered.

e Units reported as L/kg/h.

f Units reported as L/kg.

AUC = area under the plasma concentration-time curve; **C_{max}** = maximum plasma drug concentration; **CL_T** = total clearance; **IV** = intravenous; **NR** = not reported; **PO** = oral; **$t_{½β}$** = terminal elimination half-life; **t_{max}** = time taken to reach maximum plasma concentration; **Vd** = volume of distribution.

impaired renal (creatinine clearance 0.3 to 4.8 L/h) or hepatic function (10.8 and 13.3h, respectively; table IV).[1,42] Moreover, there was an increase in renal excretion of unmetabolised drug in these patients (30%) compared with healthy volunteers (≈10%).[43,48] Hence, in patients with renal (creatinine clearance <1.8 L/h) or severe hepatic impairment the dosage interval should be adjusted (see section 6).[46,48,55] Only 7% of orally administered tramadol is removed by haemodialysis.[51]

3.4 Drug Interactions

Tramadol is extensively metabolised in the liver via CYP3A and CYP2D6 (see section 3.2) and thus, drugs acting on these and other liver enzymes may affect the pharmacokinetic properties of tramadol. Concomitant administration of tramadol with carbamazepine, an inducer of hepatic enzymes, resulted in a 50% reduction in tramadol $t_{½β}$, possibly through induction of the metabolism of tramadol.[1,3] Furthermore, there was an increase in $t_{½β}$ values of tramadol and M1 during concomitant administration with cimetidine 400mg twice daily, although these changes were not considered clinically relevant.[1] In addition, according to the manufacturer's prescribing information, concomitant administration with quinidine (a selective inhibitor of CYP2D6) resulted in elevated serum concentrations of tramadol and decreased M1 concentrations, although the clinical relevance of these changes has not been determined.[48] Moreover, *in vitro* studies using human liver microsomes indicate that the metabolism of tramadol may be inhibited when administered with fluoxetine or amitriptyline as these 2 drugs are also inhibitors of CYP2D6.[48]

Concomitant administration of tramadol with phenprocoumon (a coumarin anticoagulant) prob-

ably has no clinically relevant effect on the International Normalised Ratio (INR). In a double-blind, placebo-controlled, crossover study in 19 patients who had been in a stable hypothrombinaemic state for ≥3 months with phenprocoumon treatment, the addition of oral tramadol 50mg 3 times daily for 7 days had no significant effect on the INR compared with placebo (3.94 *vs* 4).[56] However, 2 case reports indicated that co-administered tramadol and phenprocoumon increased the INR.[57] It was suggested that effects on the INR observed in these 2 patients[57] may be attributable to concomitant paracetamol, a drug which has been shown to interact with coumarin anticoagulants, and/or that they were in the early stages of anticoagulant therapy, when fluctuations in INR are known to occur.[58]

According to the manufacturer's prescribing information, postmarketing surveillance studies have reported rare instances of digoxin toxicity, and alteration of warfarin effects including elevation of prothrombin times.[48,59,60] For instance, in a 76-year-old man receiving concomitant warfarin 5mg once daily and tramadol 50mg 3 times daily as required for ≈3 months, both the prothrombin time (27.8 seconds; control = 11.5 seconds) and INR (3.5 prior to concomitant therapy *vs* 7.31 when concomitant therapy with tramadol was discontinued) showed clinically relevant increases.[59]

4. Clinical Efficacy

The perioperative use of parenteral (intravenous or intramuscular) and oral tramadol has been evaluated in several randomised, double-blind, parallel-group studies in surgical patients. The analgesic efficacy of tramadol was evaluated after intra- and postoperative administration, and in both inpatients and day surgery patients. In general, only studies of reasonable size (≥45 patients evaluated) are tabulated and discussed. However, in certain sections, in which limited data are available, smaller studies have been included. Most trials evaluated the analgesic efficacy of tramadol in adult patients (aged 18 to 84 years), with a limited number assessing the efficacy of the drug in children. Patients in each study were well matched in terms of the severity of pain and other baseline characteristics (e.g. age, weight, and the type and duration of surgery).

Quantitative assessment of analgesic efficacy is difficult, since pain is inherently subjective in nature, with the severity of pain being affected by emotional factors.[61,62] Thus, there are currently no objective measures available for assessing pain intensity.[61,62] In addition, the high and variable placebo response rate associated with randomised controlled clinical trials of analgesic agents exacerbates the difficulties of evaluating these agents.[61,63] In the absence of any truly objective measures, the patient's assessment of pain using categorical verbal response (VRS) or visual analogue (VAS) scales are accepted as standard subjective measures of analgesic efficacy.[62,64-68] These efficacy measures have been extensively validated, with modified versions of these scales available for assessing pain in paediatric patients and special populations.[62,64,69] Where appropriate, only studies that used these efficacy measures and where baseline pain is reported as moderate to severe are discussed in this review. However, in certain sections, where only limited and/or preliminary data are available, adherence to these criteria is not possible.

4.1 Postoperative Pain

The primary efficacy measure used to evaluate analgesic efficacy in acute pain trials reviewed in this section is change in pain intensity according to a 100mm or 100-point VAS scale or a 4- or 5-point VRS scale. Other criteria used to evaluate analgesic efficacy in this section include:

- the percentage of patients responding at 90 minutes (those who had no or slight pain or those who were asleep)
- the mean cumulative dose of drug (from which the potency ratio is derived)
- the percentage of patients requiring rescue medication
- quality of sleep assessed on a 5-point VRS scale

Table V. Therapeutic efficacy of tramadol (T) in adults (aged 18 to 84 years) in nurse-administered analgesia of moderate to severe[a] postoperative pain: summary of comparative, randomised multiple dose trials. Only studies with ≥45 patients are included

Reference	Surgery; trial design (duration of trial)	Treatment regimen (no. of patients evaluated)	Mean cumulative dose (mg)	Results					
				mean VAS score[b] (% reduction from baseline)				patients requiring rescue medication (%)	overall efficacy
				baseline	30-90 min	4-6h	24h		
Comparison with opioids									
Gritti et al.[70]	Abdominal; nb, mc (24h)	T 100mg IM initial dose then 100mg IM prn [maximum dose 600 mg/day] (35)	253	85.3	54.4* (36.3)	36.2 (57.4)		45.7	T≡M
		M 10mg IM initial dose then 10mg IM prn [maximum dose 60 mg/day] (35)	22	82.3	40.3 (51.0)	24.9 (69.8)		31.4	
Kupers et al.[76]	Intervertebral disc repair; db, mc (6h)	T 50mg PO prn [maximum dose 200mg] (79)	119	75	54* (28.0)	38 (49.3)		7.6	T≡P
		P 50mg PO prn [maximum dose 200mg] (79)	108	76	47 (38.2)	37 (51.3)		10.1	
Magrini et al.[75]	Various (72h)	T 100mg tid IM (25)	NR	94[c]	6[c]* (93.6)	50[c]* (46.8)	20[c]* (78.7)	NR	T>P for 1 to 24h, then T≡P for 24 to 72h
		P 30mg tid IM (25)	NR	90[c]	14[c] (84.5)	67[c] (25.6)	28[c] (68.9)	NR	
Manji et al.[73][d]	Coronary artery bypass (72h)	T 100mg IV initial dose then prn IV inf [maximum dose 600 mg/day] (29)	NR	NR	NR	23[e]	33[e]	10.3	T≡A
		A 12.5 μg/kg/h IV inf (27)	NR	NR	NR	24[e]	36[e]	25.9	
Sellin et al.[74][d]	Cardiac (30h)	T 360 mg/day IV inf and 50mg bolus prn when VAS >40 [maximum dose 600 mg/day]; concomitant PP 2g qid (50)	NR	NR	NR	30	28*	64[f]; 14[g]	T≡M[h]
		M 24 mg/day IV inf and 2mg bolus prn when VAS >40; concomitant PP 2g qid (50)	NR	NR		23	21	72[f]; 14[g]	
Comparison with nonsteroidal anti-inflammatory drugs									
Colletti et al.[71]	Nasal; nb, mc (72h)	T 100mg IM prn [maximum dose 400 mg/day] (39)	382	2.8[c,i]	0.6[c,i] (78.6)	NR	NR	NR	T≡K
		K 30mg IM prn [maximum dose 90 mg/day] (38)	116	2.6[c,i]	0.5[c,i] (80.8)	NR	NR	NR	
Lanzetta et al.[72]	Orthopaedic; nb, mc (72h)	T 100mg IM prn [maximum dose 400 mg/day] (24)	242[j]	84.6	49.3 (41.7)	39.3 (53.5)	NR	NR	T≡K
		K 30mg IM prn [maximum dose 90mg/day] (24)	90[j]	83.7	55.3 (33.9)	47.4 (43.4)	NR	NR	

Table V. Contd

a VAS score >60 on a VAS 100mm or 100–point scale or rated moderate to severe on a VRS.
b Assessed using a 100mm or 100-point VAS.
c Values estimated from graph.
d Abstract; no data on trial design or baseline VAS score provided.
e Median value.
f Percentage of patients receiving 0 or 1 bolus.
g Percentage of patients receiving >3 bolus injections.
h No significant differences between groups at 6 and 30 hours. Overall efficacy similar.
i Assessed using a 5-point VRS scale: 0 = no pain, 1 = mild, 2 = moderate, 3 = strong and 4 = unbearable pain.
j Mean daily dose.

A = alfentanil; **db** = double-blind; **IM** = intramuscular; **inf** = infusion; **IV** = intravenous; **K** = ketorolac; **M** = morphine; **mc** = multicentre; **nb** = nonblind; **NR** = not reported; **P** = pentazocine; **PO** = oral; **PP** = propacetamol; **prn** = as required; **qid** = 4 times daily; **tid** = 3 times daily; **VAS** = visual analogue scale; **VRS** = verbal response scale; ≡ indicates similar efficacy based on VAS scores; **>** indicates greater efficacy based on VAS scores $p < 0.05$ *vs* comparator; **<** indicates less efficacy based on VAS scores $p < 0.05$ *vs* comparator; ***** $p < 0.05$ *vs* comparator.

- the number of doses of drug administered
- patient and physician global assessments.

Earlier studies investigating the analgesic efficacy of oral or parenteral (intravenous, intramuscular or epidural) tramadol in the management of postoperative pain have been reviewed previously in *Drugs*.[1] As discussed in this review, intravenous tramadol 50 to 150mg was equivalent in analgesic efficacy to morphine 5 to 15mg in the treatment of moderate, but not severe pain. In addition, intramuscular tramadol achieved analgesia similar to that of pentazocine 30mg, nefopam 20mg and dipyrone 1500mg, but was less effective than nicomorphine 10mg or buprenorphine 0.3mg. With intramuscular tramadol, the peak analgesic effect occurred within 1 to 2 hours and analgesia persisted for 5 to 6 hours. After surgery in paediatric patients, intramuscular tramadol provided analgesia similar to that of equipotent doses of nalbuphine.

4.1.1 In Adults

Nurse-Administered Analgesia

The clinical efficacy of tramadol in the treatment of moderate to severe postoperative pain in adults has been investigated in several studies using nurse-administered analgesia. These studies have compared the analgesic efficacy of tramadol with that of several opioid agents (including morphine, which is the gold standard opioid comparator) and nonsteroidal anti-inflammatory drugs (NSAIDs). All patients in these studies had moderate to severe pain (VAS score ≥60 on 100mm or 100-point scale or rated moderate to severe on a 4- or 5-point VRS scale). However, some studies, particularly those involving NSAIDs, were nonblind.[70-72] Two recent studies in patients who underwent cardiothoracic surgery were available as abstracts only, with limited trial design data reported.[73,74] A further fully published study also reported limited trial design data.[75] Exclusion criteria for patients in some studies included concomitant treatment with other analgesic or anti-inflammatory drugs.[71,72,75] Perioperative opioid agents, which were used in some studies, may have confounded results by lowering pain perception.[71,73,74] Relevant comparative randomised studies in ≥45 patients, which met the criteria described, are summarised in table V.

Studies excluded from discussions in this section include those where baseline pain intensity was not clearly stated and/or analgesic efficacy was not assessed using the previously stated criteria.[11,22,77-81] A meta-analysis of 9 randomised, double-blind, placebo-controlled trials (mainly unpublished) in 1594 postoperative patients was also excluded, since no VRS scores were provided [the main efficacy criterion was the percentage of patients achieving >50% of the maximum area under the pain-relief-time curve (TOTPAR)].[82] In this study, analgesic efficacy with tramadol 75 to 100mg was reported to be significantly superior to

that of placebo (statistical value not reported) and similar to that of codeine 60mg, and combinations of aspirin 650mg plus codeine 60mg and paracetamol (acetaminophen) 650mg plus dextropropoxyphene 100mg.[82]

Tramadol (dose titrated to response) effectively relieved moderate to severe postoperative pain associated with several types of surgery (including abdominal, orthopaedic and cardiac surgery; table V).[70-76] In these patients, tramadol reduced pain intensity by 46.8 to 57.6% after 4 to 6 hours compared with a 69.8% reduction with morphine and a 25.6 to 51.3% reduction with pentazocine (table V).[70-76] Analgesic efficacy with tramadol was maintained for the duration of these studies (6 to 72 hours; fig. 3).[74,75]

With nurse-controlled analgesia, the overall analgesic efficacy with tramadol (over a 24- to 72-hour period) was comparable to that achieved using equipotent doses of parenteral morphine[70,74] or alfentanil (table V).[73] However, at individual time points, there were significant differences in the analgesic efficacy of tramadol and morphine (fig. 3).[70,74] In 1 study, although intramuscular morphine 10mg (maximum dose 60 mg/day) provided better analgesia 3 hours after the first dose than intramuscular tramadol 100mg (maximum dose 600 mg/day), subsequent doses of both drugs provided similar pain relief.[70] After the first dose of tramadol, 31.5% of patients rated pain intensity as absent or mild and 22.8% rated it as severe compared with 58.5 and 5.8%, respectively, in the morphine group ($p < 0.05$ both comparisons).[70] In another study, although there were no significant differences in analgesic efficacy between tramadol 360 mg/day and morphine 24 mg/day (each administered as an intravenous infusion) at 6 and 30 hours in patients who had undergone cardiac surgery, morphine provided superior pain relief at 24 hours ($p < 0.05$; fig. 3).[74]

According to a preliminary report of a study in 60 patients who underwent lower abdominal or lower limb surgery, the time to onset of action of intravenous tramadol 100mg or morphine 10mg boluses was comparable (13 and 10 minutes, respectively; drugs administered as required).[83] There was also no difference in the time between the first and second dose or between subsequent doses with these 2 agents, which confirms results from previous studies.[1,70,79,83] Furthermore, for the first 24 hours after surgery, intramuscular tramadol 300 mg/day was significantly more effective than intramuscular pentazocine (an opioid agonist/antagonist) 90 mg/day in providing analgesia ($p < 0.05$; fig. 3).[75] Both treatments provided similar analgesia for the subsequent 48 hours. However, another large study (158 patients evaluated) indicated that tramadol provided efficacy similar to pentazocine during the first 6 hours.[76]

Secondary efficacy parameters also indicated that tramadol had analgesic efficacy similar to that of other opioid agents. There were no significant differences in the percentage of patients requiring rescue medication with tramadol treatment compared with morphine in 2 trials (table V).[70,74] A preliminary report in patients who had undergone cardiac surgery indicated that fewer patients receiving a tramadol infusion of ≤600 mg/day (10.3%) required rescue medication than recipients of alfentanil 12.5 μg/kg/h (25.9%; statistical significance not reported; table V).[73] Furthermore, the quality of sleep was generally similar in patients receiving tramadol compared with those receiving morphine (67.6% of tramadol treated patients rated quality of sleep as good to excellent *vs* 58.8% with morphine).[70] In addition, intramuscular tramadol 300 mg/day was significantly more effective at improving the quality of sleep during the first 24 hours than intramuscular pentazocine 90 mg/day ($p < 0.01$).[75]

According to both patient and physician global assessments, analgesic efficacy with tramadol was similar to that of other opioid agents.[70,76] For example, in a nonblind study, analgesic efficacy was rated as good or excellent by 31.4% of tramadol recipients undergoing abdominal surgery, compared with 20% of patients receiving morphine. Physicians rated the response as good or excellent in 77 and 88.5% of patients, respectively.[70]

Very few comparative studies have investigated postoperative analgesia with tramadol in comparison with an NSAID (table V, see section 4.3). Improvements in postoperative analgesia and quality of sleep were similar with intramuscular tramadol or ketorolac.[71,72] Following orthopaedic surgery, 50% of patients assessed their quality of sleep as good or restful in the tramadol group versus 34.8% of patients in the ketorolac group.[72] Tramadol provided longer mean pain-free intervals between doses than those observed in ketorolac-treated patients. Mean pain-free intervals between the first and second doses were 19.3 and 15.2 hours, respectively. Corresponding times between the second and third doses were 18.7 and 13.8 hours ($p < 0.05$) and 21.3 and 16.3 hours between the third and fourth doses.[72] Investigators judged the analgesic efficacy of tramadol as excellent in 79.2% of patients, compared with 58.3% in the ketorolac group; both tramadol and ketorolac were considered to provide excellent analgesic efficacy by 79.2% of patients.[72]

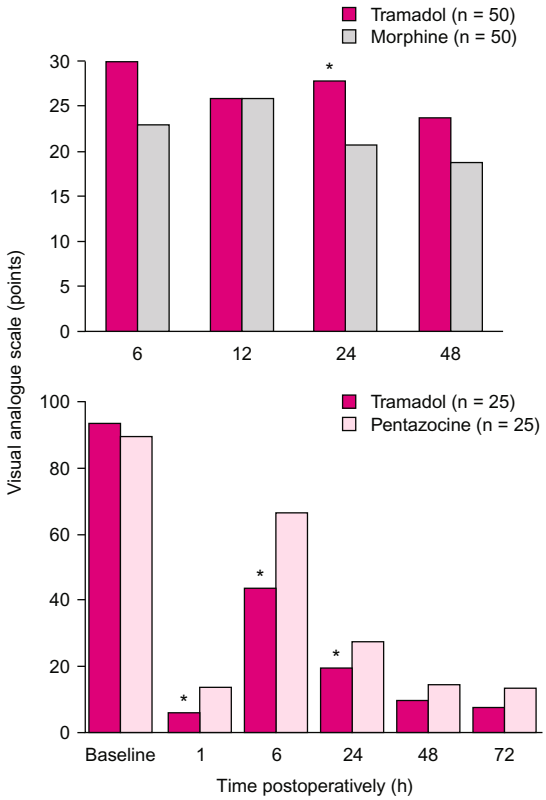


Fig. 3. Comparative analgesic efficacy of tramadol in 2 randomised studies in postoperative patients (assessed using a 100 point visual analogue scale; limited trial design data reported).[74,75] (**Top**) Adult patients received an infusion of tramadol (360 mg/24h) or morphine (24 mg/24h) following cardiac surgery, with a bolus intravenous dose of 50 or 2mg, respectively, as required (abstract).[74] All patients received concomitant propacetamol 2g every 6 hours. (**Bottom**) Adult patients received intramuscular tramadol 100mg or pentazocine 30mg 3 times daily for 3 days following haemorrhoidectomy, or traumatological or abdominal surgery.[75] * $p < 0.05$ *vs* comparator.

In the majority of investigations conducted in patients with postoperative pain, tramadol was administered either by intravenous or intramuscular routes, with very few studies of oral or epidural tramadol being reported. In comparative multiple dose studies in patients with postoperative pain, there appeared to be no difference in the analgesic efficacy of parenteral or oral tramadol (table V).[70-76]

Continuous intravenous infusion provides similar analgesia to that of intermittent intravenous bolus doses, the most frequent method of administration in postoperative pain therapy.[84] In 2 double-blind comparative studies (n >100 enrolled patients), continuous intravenous infusions of tramadol (12 mg/h) showed analgesic efficacy similar to that of intermittent intravenous bolus doses of tramadol 50mg (assessed using VAS scores).[84,85] However, patients who received tramadol (12 mg/h) administered as a continuous infusion also had a significantly increased requirement for on-demand intravenous tramadol (100mg bolus) compared with those receiving a placebo infusion with bolus doses of tramadol ($p \leq 0.05$).[84,85] Furthermore, the mean total consumption of tramadol after 6 to 8 hours was ≈30% higher with a continuous infusion than with intermittent bolus doses (223.5 *vs* 176.6mg; $p \leq 0.05$), and after 24 hours, it was approximately twice that observed with intermittent bolus doses (449.5 *vs* 201.6mg; $p \leq 0.001$).[84] Importantly, this increased consumption of tramadol with continuous infusion

was not associated with an increased incidence of adverse events.[84,85]

Since tramadol has been shown to reduce the 'set point' for thermoregulatory control (see section 2.4), the effects of the drug on postanaesthetic shivering have been investigated in randomised, double-blind, placebo-controlled trials.[73,86-88] In these studies, tramadol reduced the severity and prevalence of postanaesthetic shivering in a dose-dependent manner.[73,86-88] Two of these studies are currently available in abstract form only.[73,88] In the largest trial (100 patients), tramadol decreased the intensity of shivering in 98% of patients compared with a decrease in 16% of patients receiving placebo (no statistical data reported in abstract).[88] Tramadol 0.7 to 1 mg/kg reduced shivering completely in 68% of these patients, whereas doses of 2 to 2.5 mg/kg effectively abolished shivering in all patients.[88] Furthermore, following cardiac bypass graft surgery, significantly fewer recipients of tramadol experienced shivering (6.8%) compared with alfentanil recipients (48.1%; $p < 0.0004$).[73]

Patient-Controlled Analgesia

PCA permits self-titration of an analgesic agent and, thus, allows for the individual variations in postoperative pain that occur in patients.[89] The effective dose of an intravenous analgesic drug and its potency relative to other pain-relieving agents can be estimated by comparison of administered doses in identical groups of patients, since this method of analgesia ensures optimum doses and near-optimum analgesic efficacy.[1,89] Drugs are usually administered intravenously with PCA, although other routes, particularly epidural, may also be used.[89]

Comparative, randomised, double-blind trials involving ≥50 patients that assess the analgesic efficacy of tramadol using PCA are summarised in table VI. These trials have compared the analgesic efficacy of tramadol with that of opioid agents (morphine and oxycodone) and NSAIDs (ketorolac, clonixin and lysine acetylsalicylate). All drugs were administered intravenously in these trials. Some of these studies are currently only available as abstracts.[91,93,95,98]

Tramadol provided effective analgesia over a 24- to 48-hour period using PCA for moderate to severe postoperative pain (table VI). Analgesic efficacy with tramadol was similar to that observed with morphine[90-94] and oxycodone,[95] and superior to that observed with placebo ($p < 0.05$).[94] For instance, in a placebo-controlled study, the overall responder rates in patients after 48 hours in the tramadol, morphine and placebo groups were 66.7, 75 and 18.3%, respectively ($p < 0.001$ *vs* placebo for each treatment group).[94] In this study, responders were defined as patients in whom the VAS score decreased by ≥20 during the first 90 minutes after drug administration and who judged their analgesia as sufficient during the subsequent 48 hours.

Opioid μ-receptor agonists, such as morphine and fentanyl, are the most commonly used drugs for PCA.[89] Thus, very few studies of PCA have investigated the analgesic efficacy of tramadol in comparison with NSAIDs (table VI).[96] In a large study (160 enrolled patients), there was a trend to improved analgesic efficacy with a continuous infusion of tramadol 15 mg/h compared with ketorolac 5 mg/h, clonixin 15 mg/h or dipyrone 330 mg/h, although this improvement achieved statistical significance in comparison with clonixin only ($p < 0.05$).[96] According to patient global assessment, 71.8% of patients in the tramadol group assessed analgesia as excellent or very good, compared with 57.5% of those in the ketorolac group, 50% with clonixin ($p < 0.05$ *vs* tramadol) and 55% of those in the dipyrone group. Physicians rated analgesia as excellent or very good in 79.5, 57.5, 50 and 57.5% of patients, respectively ($p < 0.05$ *vs* tramadol for each of the treatment groups).[96] In addition, fewer patients required rescue analgesia in the tramadol group (2.5%) than in the ketorolac (27.5%; $p < 0.001$ *vs* tramadol), clonixin (27.5%; $p < 0.001$) or dipyrone (12.5%) groups.

A limited number of studies have investigated the concomitant use of tramadol with other analgesic agents for use with PCA (table VI). Tramadol with concomitant dipyrone provided significantly better analgesia than piritramide (an opioid agent;

Table VI. Therapeutic efficacy of intravenous tramadol (T) in patient-controlled analgesia (PCA) of postoperative pain; summary of randomised, double-blind, comparative trials. Only studies with ≥50 patients are included

Reference	Surgery (duration of trial)	Intravenous regimen				Mean cumulative dose (mg)	Mean no. of bolus doses	Mean baseline VAS[a]	Overall efficacy (relative potency of T)[b]
		loading dose (mg) [no. of patients]	infusion (mg/h)	demand dose (mg)	lockout time (min)				
Comparison with opioids									
Naguib et al.[90]	Laparoscopy (24h)	T 100 [50]	NR	16	5	248	NR	NR	T≡M (1:12.6)
		M 10 [50]	NR	1.6	5	19.7	NR	NR	
Pang et al.[91]c	Orthopaedic (48h)	T 3 mg/kg [30]	5	30	10	1188.5	NR	NR	T≡M≡L/T (1:14.8)[d]
		M 0.1 mg/kg [30]	0.4	1	10	80.4	NR	NR	
		L 27/T 1.5 mg/kg [30]	45/2.5	270/15	10	17 865/982.5	NR	NR	
Pang et al.[92]	Orthopaedic (48h)	T 284.9[e] [40]	None	30	10	868.3	28.9*	NR	T≡M (1:19)
		M 13.1[e] [40]	None	1	10	45.7	42.7	NR	
Silvasti et al.[93]c	Breast (42h)	T 137[e] [27]	NR	450 μg/kg	5	628	NR	NR	T≡M (1:10.6)
		M 10[e] [27]	NR	45 μg/kg	5	59	NR	NR	
Stamer et al.[94]	Abdominal or gynaecological (48h)	T 144.9[e] [60]	NR	20	5	714.6		62.6	T≡M>PL (1:12)
		M 12.3[e] [60]	NR	2	5	59.7		64.9	
		PL 1[ef] [60]	NR	1[f]	5	108.6[f]		61.0	
Tarkkila et al.[95]c	Maxillofacial (24h)	T 10 [27]	NR	0.3 mg/kg	5	202			T≡O (1:7.8)
		O 1 [27]	NR	0.03 mg/kg	5	26			
Comparison with nonsteroidal anti-inflammatory drugs									
Rodriguez et al.[96]	Abdominal hysterectomy (24h)	T 30 [40]	15	15	NR	NR	1.6*		T≡K≡D>CL
		K 10 [40]	5	5	NR	NR	4.5		
		CL 30 [40]	15	15	NR	NR	5.3		
		D 660 [40]	330	330	NR	NR	4.4		
Combination analgesia									
Likar et al.[97]	Orthopaedic or traumatological (24h)	T 164[e]/D 1090[e] [18]	NR	10/50	6	267/1335	26.7	56[g]	High and low dose T/D > high and low dose PT
		T 72[e]/ D 482[e] [19]	NR	5/25	6	256/1275	51	64[g]	
		PT 7.5[e] [21]	NR	1.5	6	43.5	29	61[g]	
		PT 4.5[e] [20]	NR	0.75	6	37.2	49.6	52[g]	
Migliorini et al.[98]c	Orthopaedic (24h)	T[h] [35]	10	50	15	489**	18.7**	62.6	T+P>T
		T[h]+PP 2g qid [35]	10	50	15	426	13	63.5	

a VAS score assessed using a 100mm or 100-point scale.

b Potency ratio for opioids based on the mean cumulative dose.

c Abstract.

d Potency ratio for tramadol:morphine.

e Dose titrated according to pain intensity.

f Dose reported in millilitres.

g Values estimated from graph.

h No loading dose was reported.

CL = clonixin; **D** = dipyrone; **K** = ketorolac; **L** = lysine acetylsalicylate; **M** = morphine; **NR** = not reported; **O** =oxycodone; **PL** = placebo; **PP** = propacetamol; **PT** = piritramide; **qid** = 4 times daily; **VAS** = visual analog scale; ≡ indicates similar efficacy over 24 hours based on VAS scores; **>** indicates greater efficacy over 24 hours based on VAS scores; * $p < 0.05$, ** $p < 0.001$ *vs* comparator(s).

$p < 0.05$; table VI).[97] Superior analgesic efficacy was shown with both high (tramadol 10mg plus dipyrone 50mg) and low (tramadol 5mg plus dipyrone 25mg) bolus dosages of concomitant therapy compared with bolus doses of piritramide 0.75 or 1.5mg (assessed using VAS scores; $p < 0.05$).[97] In addition, a continuous intravenous infusion of tramadol 10 mg/h with concomitant intravenous propacetamol 2g 4 times daily provided analgesia superior to that of tramadol monotherapy in 70 patients with moderate to severe postoperative pain (no VAS data were presented in the abstract; table VI).[98] In this study, with concomitant propacetamol there were significant reductions in the number of bolus doses of tramadol administered versus tramadol monotherapy (13 *vs* 18.7; $p < 0.001$) and in the 24-hour consumption of tramadol (426 *vs* 489mg; $p < 0.001$).[98]

4.1.2 In Children

The analgesic efficacy of tramadol in children with moderate to severe postoperative pain following surgery (including dental, lower abdominal and hypospadia) has been evaluated in several studies.[15,16,99-102] The majority of these studies were randomised, double-blind trials,[15,99-101] with 2 studies also being placebo-controlled.[16,99] A non-blind study has also been reported.[102] All participants in these studies were aged 1 to 12 years. There were no significant differences in patient characteristics (including age, weight, type and duration of surgery) between treatment groups in these studies.[15,16,99-102] In the majority of instances, pain intensity was assessed by investigators and/or nursing staff using modified VAS scores [such as the Hannallah objective pain scale, the Oucher six faces pain scale and a modified toddlers preschooler postoperative pain scale (TPPPS)].

Oral tramadol 1.5 mg/kg (drops) with concomitant oral midazolam 0.5 mg/kg (an anxiolytic; maximum dose 7.5mg) provided postoperative analgesia superior to that of placebo ($p < 0.05$) in 60 children undergoing extraction of 6 or more teeth (assessed using the Hannallah objective pain scale and the Oucher six faces pain scale).[99] In these patients, significantly fewer patients required rescue analgesia (paracetamol 120mg) in the tramadol group (19.4%) compared with the placebo group (82.8%; $p < 0.05$). There was no significant difference in the time to awake recovery in these two groups (48.8 *vs* 36.4 minutes).

Intramuscular tramadol 2 mg/kg as required provided analgesic efficacy similar to that of intramuscular pethidine 1 mg/kg or nalbuphine 0.1 mg/kg in 75 children with moderate to severe postoperative pain following lower abdominal surgery (no statistical analysis was performed on data in this trial).[102] Within 60 minutes of the initial dose, 92 to 100% of patients experienced no or slight pain. This level of analgesia was effectively maintained in the tramadol and pethidine groups for the duration of the study (24 hours), but moderate pain was experienced at 60 minutes in 1 child and after 6 hours in 2 children receiving nalbuphine. The mean total drug consumption in patients in the tramadol group was 55mg compared with 31.6 and 3.4mg in the pethidine and nalbuphine groups, respectively.[102] Furthermore, fewer patients in the tramadol group required 2 or more additional bolus doses (4%) compared with those in the pethidine (28%) or nalbuphine (40%) groups. These results confirm previous results from a smaller study in 30 children who underwent various surgical procedures.[15] In this study, intramuscular tramadol 0.75 to 1 mg/kg as required showed analgesic efficacy similar to that of intramuscular nalbuphine 0.15 to 0.2 mg/kg (assessed using a 100mm VAS scale by investigators/nursing staff).[15]

Two recent studies have investigated the analgesic efficacy of caudal tramadol in children after hypospadia day surgery (fig. 4).[100,101] In the larger study (90 children aged 1 to 4 years), a single caudal injection of tramadol 2 mg/kg provided analgesia (3 to 12 hours postoperatively) similar to that of caudal bupivacaine 2 mg/kg or tramadol 2 mg/kg with concomitant bupivacaine 2 mg/kg (a local anaesthetic) [assessed using a modified TPPPS].[100] However, at the 3-hour time point, pain scores were significantly higher in patients in the tramadol group than those documented for the

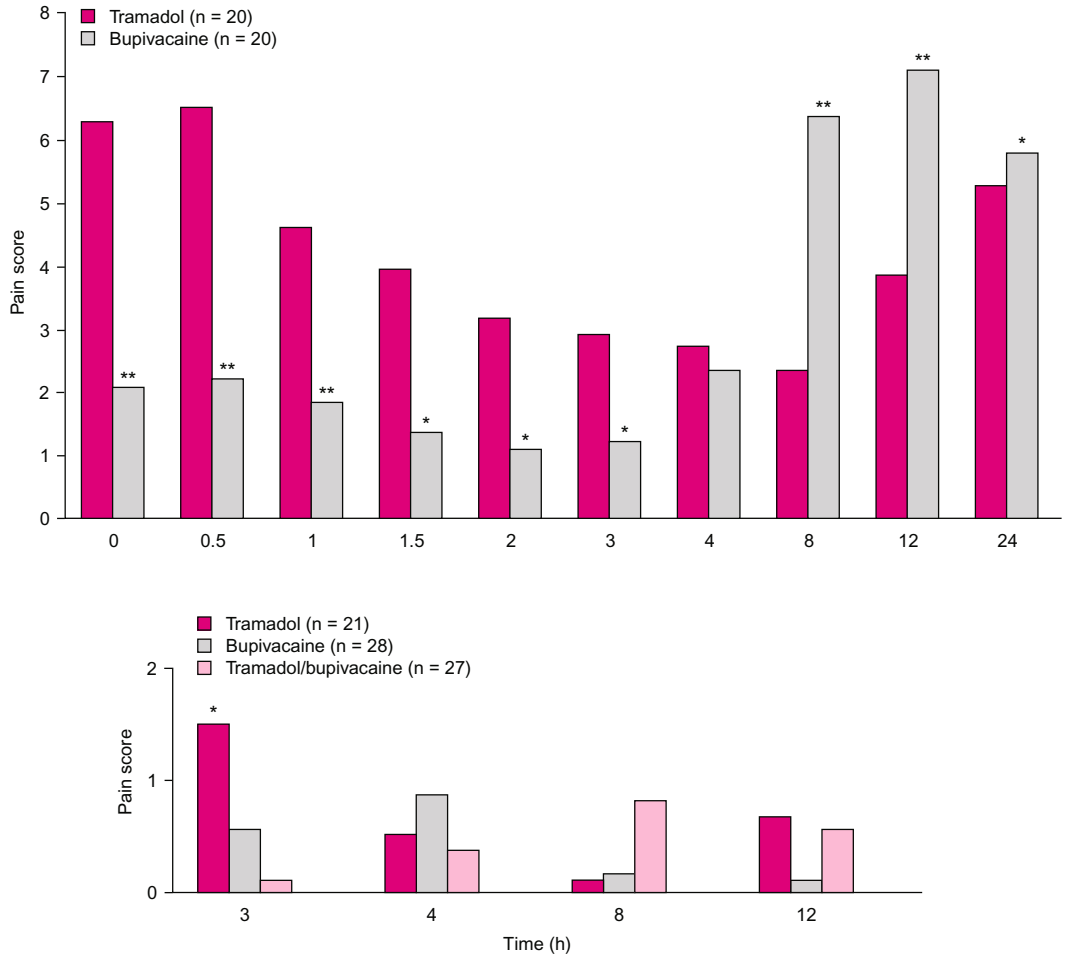


Fig. 4. Comparative analgesic efficacy of intraoperative caudal tramadol for hypospadia surgery in children aged 1 to 8 years in 2 randomised, nonblind trials (assessed using modified Hannallah pain or toddler-preschooler postoperative scales).[100,101] Anaesthesia was induced with thiopentone 4 to 5 mg/kg and maintained with halothane 1 to 5% and 70% nitrous oxide in oxygen. (**Top**) Children aged 4 to 8 years received intraoperative caudal tramadol 1 mg/kg or 0.025% bupivacaine 0.5 ml/kg after induction of anaesthesia.[101] (**Bottom**) Children aged 1 to 4 years received caudal tramadol 2 mg/kg, bupivacaine 2 mg/kg or concomitant tramadol 2 mg/kg with bupivacaine 2 mg/kg intraoperatively.[100] * $p < 0.05$, ** $p < 0.001$ *vs* comparators.

other 2 treatment groups ($p < 0.05$; fig. 4).[100] In addition, significantly more patients in the tramadol group (30%) required rescue analgesia than in the bupivacaine (6.7%; $p < 0.05$) or tramadol/bupivacaine groups (10%; $p < 0.05$).[100] It was concluded that the concomitant use of tramadol with bupivacaine did not significantly prolong the action of bupivacaine.[100] In the smaller study (n = 40), although 0.025% bupivacaine 0.5 ml/kg was more effective than tramadol during the first 3 hours after surgery, tramadol provided better analgesia during the subsequent 21 hours of the study (assessed using a modified Hannallah's pain score; fig. 4).[101] However, the total consumption

Table VII. Therapeutic efficacy of tramadol (T) following intraoperative administration in adults; summary of randomised, double-blind, comparative trials

Reference	Surgery (duration of trial)	Anaesthesia	Treatment regimen (no. of patients enrolled)	Results	
				analgesic efficacy[a]	measures for lightening of anaesthesia and recall
Coetzee et al.[106]	Abdominal hysterectomy (1.5h)	Induction with F 4 µg/kg+PR 1.5-2 mg/kg+V 0.08 mg/kg; then maintained using E+60%NO	T 3 mg/kg IV (20) M 0.2 mg/kg IV (20)	No differences in VAS[b] scores between the treatment groups up to 90 minutes postoperatively	15 min postoperatively, all patients in both groups were unable to perform a p-deletion test[c]; by 30 min ≈50% of patients in both groups were able to perform the test
de Witte et al.[107]	Laparoscopy (24h)	Induction with S 0.2 µg/kg+PR 2.5-3 mg/kg+AT 0.5 mg/kg; then maintained using 66%NO+I	T 3 mg/kg IV (20) PL (20)	VAS score significantly lower in the T group on arrival in recovery room (0 *vs* 20; $p < 0.05$). Lower retrospective pain score with T for the 24-hour postoperative period ($p < 0.05$)	Extubation time was similar in both treatment groups, indicating there was no clear awakening effect of T
James et al.[108]	Thoracotomy (24h)	Induction with F 1.5 µg/kg+TH+PA; then maintained using 5-10ml 0.25% bupivacaine EPI	T 150mg IV (20) M 2mg EPI (19)	No difference in VAS and observer pain scores between treatment groups over 24-hour study period. No patient in either treatment group had persistent pain after the first 4 hours postoperatively	Not reported
Lauretti et al.[109]	Abdominal (6h)	Induction with T 1.5 mg/kg+PR 2.5-3 mg/kg+AT 0.5 mg/kg; then maintained with PR 6-12 mg/kg/h and inf of one of the treatment regimens	T 1.2 mg/kg/h inf (12) BCP[d] inf (12) T+BCP[d] 1.2 mg/k/h inf (12) PL (12)	PR consumption in the T, BCP, T+BCP and PL groups was 8.4, 9.4, 6.9 and 10.6 mg/kg/h, respectively ($p < 0.001$ T or T+BCP *vs* PL). PR consumption was higher in the T ($p < 0.001$) and BCP ($p < 0.01$) groups than T+BCP	One patient in the T+BCP group could recall the electrocautery but not the music or conversations that occurred during surgery. No patients in the other treatment groups showed intraoperative recall
Naguib et al.[90]	Laparoscopy (1.5h)	Induction with TH 5 mg/kg+AT 0.5 mg/kg; then maintained using 70%NO+I	T 100mg IV 10 minutes prior to induction of anaesthesia, then prn ≤200mg (50) M 10mg IV 10 minutes prior to induction of anaesthesia, then prn ≤20mg (50)	Intraoperative mean cumulative dose with T was 137mg and with M 12.2mg. Significantly higher consumption in the T group at 10 and 30 minutes after induction ($p < 0.01$), whereas with M it was significantly higher than T at 45 minutes ($p < 0.05$)	No intraoperative recall reported, either spontaneously or on enquiry

Table VII. Contd

Raff[110]	Orthopaedic, traumatology, major vascular surgery (6h)	Induction with PR 2 mg/kg +V 0.1 mg/kg; then maintained using 0.8%E+70%NO	T 1 mg/kg IV, then continuous inf 2.5 mg/ml at 15 ml/h (25) M 0.1 mg/kg IV, then continuous inf 0.25 mg/ml at 15 ml/h (25)	44% in T group had no pain *vs* 48% M group; no differences in pain scores between treatment groups; mean dose of rescue analgesia was 45 mg/h in the T group *vs* 2.87 mg/h with M	Not reported

a Evaluated for the study period.
b VAS score assessed using a 100mm or 0-10 scale.
c Cognitive function was assessed using a p-deletion test.
d Dose not reported.

AT = atracurium; **BCP** = piroxicam β-cyclodextrin; **E** = enflurane; **EPI** = epidural; **F** = fentanyl; **I** = isoflurane; **inf** = infusion **IV** = intravenous; **M** = morphine; **NO** = nitrous oxide in oxygen; **PA** = pancuronium; **PL** = placebo; **PR** = propofol; **prn** = as required; **S** = sufentanil; **TH** = thiopental; **V** = vecuronium; **VAS** = visual analogue scale.

of rescue analgesia (oral paracetamol) over the 24-hour study period was significantly lower with tramadol treatment than with bupivacaine (mean 368 *vs* 984mg; $p < 0.001$).[101] The investigators suggested that the delay in onset of action of tramadol analgesia observed in these 2 studies may reflect the slow absorption of this agent across the dura and slow uptake of tramadol from the epidural space into the systemic circulation.[100,101]

4.2 Intraoperative Analgesia

Early studies of the intraoperative use of tramadol were controversial. Although some of the studies reviewed previously indicated that intraoperative tramadol provided good balanced anaesthesia,[1] a double-blind randomised study in 40 patients indicated that 65% of those receiving tramadol were aware of intraoperative music whereas patients in the placebo group were amnesiac.[103] In this study, patients received nitrous oxide anaesthesia supplemented by intermittent administration of low concentrations of enflurane.[103] It was concluded that insufficient sedation was provided by tramadol and it should not be recommended as the sole agent for intraoperative use.[1,103] However, several recent studies using tramadol in combination with continuous potent volatile or intravenous anaesthetics, in both inpatients and in day surgery patients (section 4.3), have not shown any clinically significant lightening of anaesthetic depth sufficient to cause accidental awareness while undergoing surgery.[34,104,105]

Double-blind, randomised, comparative studies in patients anaesthetised with volatile or intravenous anaesthetics are summarised in table VII.[90,106-110] In these fully published studies involving ≥40 enrolled patients, intravenous tramadol was compared with intravenous morphine,[90,108,110,111] piroxicam β-cyclodextrin (an NSAID)[109] or placebo.[107] The primary endpoints assessed in these studies were the effects of the drug on analgesic efficacy, on the depth of anaesthesia and on postoperative shivering (see section 2.3 and 4.1.1).

Intraoperative tramadol provided analgesia similar to that of equipotent doses of morphine,[106,108,110] but superior to that of placebo ($p < 0.05$; table VII).[107] The potency ratio was similar to that reported in PCA studies (see section 4.1.1), with a mean cumulative dose of intraoperatively administered tramadol of 137mg compared with 12.2mg of morphine (ratio morphine to tramadol of 1:11.23).[90] However, tramadol consumption was significantly higher than that of morphine 10 and 30 minutes after induction of anaesthesia ($p < 0.01$), whereas morphine consumption was significantly higher than tramadol at 45 minutes ($p < 0.05$).[90]

Tramadol showed no clinically significant effects on the depth of anaesthesia (table

VII).[90,105-110,112] Although systolic blood pressure ($p < 0.001$) and heart rate ($p < 0.001$) showed significant dose-related increases with intravenous tramadol 100 or 200mg compared with placebo (indicating a clinically relevant dose had been used), no effect on the depth of anaesthesia was observed (assessed using auditory evoked responses) in 29 patients undergoing routine surgery.[112] In 51 patients who were anaesthetised with propofol and suxamethonium, with anaesthesia maintained by 0.7% isoflurane and 66% nitrous oxide in oxygen, intravenous tramadol 100 or 200mg increased EEG frequencies compared with placebo.[105] However, these changes did not reach levels associated with near awakening and were not considered to indicate clinically significant lightening of anaesthesia.[105] In addition, these patients did not show signs of movement on skin incision and during the early stages of operative procedures (an indication of depth of anaesthesia), and there was no evidence of either spontaneous or investigator-reported intraoperative recall.[105]

Interestingly, although no incidences of intraoperative recall were reported in studies comparing tramadol with morphine, 1 case of possible intraoperative recall was reported when a continuous infusion of tramadol 1.2 mg/kg/h with concomitant piroxicam β-cyclodextrin was used.[109] This patient recalled the sound of the electrocautery machine, but not the music or conversations that occurred during surgery. There were no reports of recall in the tramadol, piroxicam β-cyclodextrin or placebo groups in this study.[109]

4.3 Day Surgery

The lack of sedative and respiratory depressant effects (see section 2.3) of tramadol may make it a suitable analgesic agent for use in patients undergoing day surgery. Currently only a few comparative studies, summarised in table VIII, have investigated the analgesic efficacy of tramadol in patients undergoing day surgery.[104,113-116] All of these studies were randomised, double-blind trials involving ≥40 enrolled patients. One recent study is available only as an abstract.[104] Efficacy criteria included assessment of pain intensity using a 100mm VAS or 0 to 10 score, the number of patients requiring rescue analgesia, the total consumption of the drug and the quality of sleep. Analgesic agents were generally administered intravenously at the time of anaesthesia, followed by oral administration postoperatively.[104,113-115] Moreover, the majority of studies investigating the analgesic efficacy of tramadol following day surgery have involved complex treatment regimens, with the concomitant administration (pre-, intra- and/or post-operatively) of several other analgesic agents (both opioids and NSAIDs). This may have confounded the interpretation of results.

In these studies, perioperative tramadol provided better analgesia than fentanyl plus codeine/paracetamol or ketorolac, but similar pain relief to that of naproxen sodium. In a large multicentre study, pre-, intra- and postoperative intravenous tramadol 100mg (oral tramadol 100mg after discharge; maximum 400 mg/day) provided analgesia (during the first 24 hours) superior to that of a combination of intraoperative intravenous fentanyl 100μg and postoperative codeine 16mg/paracetamol 1000mg (≡2 tablets; maximum 8 tablets/day) [$p < 0.05$; odds ratio 1.99 (range 1.04 to 3.79)].[104] Furthermore, the percentage of tramadol recipients requiring rescue analgesia was almost half that reported in the fentanyl plus codeine/paracetamol group (4.5 *vs* 8.5%; no statistical data reported; table VIII).[104]

In addition, intravenous tramadol 1.5 mg/kg provided better pain relief than ketorolac 10mg in the recovery room, (VAS score of 30.5 *vs* 53; $p = 0.007$) and at the time of hospital discharge (13 *vs* 17; $p < 0.05$) in 60 patients after laparoscopic surgery (table VIII).[114] Pain scores in the tramadol group remained lower than those in the ketorolac group over the subsequent 2 hours in the recovery room, although these differences were not statistically significant. The lack of statistical significance during this period may be a reflection of a significant difference in the percentage of patients receiving rescue analgesia with intramuscular

Table VIII. Therapeutic efficacy of tramadol (T) in adults after day case surgery; summary of randomised, double-blind, comparative trials. Only studies in ≥45 patients are included.

Reference	Surgery; trial design (duration of trial)	Treatment regimen (no. of patients evaluated)	Results				
			mean VAS score[a]			% of patients requiring rescue analgesia	overall efficacy
			baseline	4h	24h		
Comparison with opioids							
Bamigbade et al.[104]b	Groin; mc (72h)	T 100mg IV at induction of anaesthesia, then T ≤100mg IV intraoperatively, then T 100mg IV or PO postoperative, and after discharge T 100mg (2 tablets) PO q4h prn for up to 72h [maximum 8 tablets/day] (111) F 100µg IV at induction of anaesthesia, then F ≤100µg IV intraoperative, then F 100µg IV or C 16mg/P 1000mg (2 tablets) PO postoperative, and after discharge C 16mg/P 1000mg PO q4h prn for up to 72h [maximum 8 tablets/day] (117)	T provided analgesic efficacy superior to that of F/C+P for the first 24h [odds ratio 1.99 (1.04, 3.79)][c*]			4.5	T>F + C/P
Comparison with nonsteroidal anti-inflammatory drugs							
Peters et al.[113]	Hysterosalpinography; mc (24h)	T 100mg PO 30 min preoperative; then 50-100 mg/day PO prn postoperative (24)	56	16	6	NR	T≡N
		N 500mg PO 30 min preoperative, then 250-500 mg/day prn postoperative (25)	45	22	8	NR	
	Aspiration curettage; mc (24h)	T 100mg PO 30 min preoperative, then 50-100 mg/day prn postoperative (20)	41	18	9	NR	T≡N
		N 500mg PO 30 min preoperative, then 250-500 mg/day prn postoperative (22)	38	11	9	NR	
Putland et al.[114]	Laparoscopy (2h)	T 1.5 mg/kg IV 30 min preoperative (30)	30.5[d**]	17.5[e]	13[f*]	33[*]	T>K
		K 10mg IV 30 min preoperative (30)	53[d]	28[e]	17[f]	63	
Comparison with combination analgesia							
Broome et al.[115]	Third molar tooth extraction (24h)	T 100mg+ME 10mg IV after induction of anaesthesia[g] (25)	27.8			72	T+ME≡F+ME ≡ T+O≡F+O
		F 100µg+ME 10mg IV after induction of anaesthesia[g] (28)	26			82	
		T 100mg+O 4mg IV after induction of anaesthesia[g] (25)	29.9			73	
		F 100µg+O 4mg IV after induction of anaesthesia[g] (30)	29.1			80	
Crighton et al.[116]	Laparoscopy (24h)	T 50mg PO 1-2 tablets q4-6h prn [maximum 8 tablets/day][h] (21)	46[d]	30[f]	22[i]	4.2[j]	T≡P/C≡P/D
		P 500mg/C 30mg PO 1-2 tablets q4-6h prn [maximum 8 tablets/day][h] (25)	43[d]	36[f]	25[i]	3.1[j]	
		P 325mg/D 32.5mg PO 1-2 tablets q4-6h prn [maximum 8 tablets/day][h] (22)	34[d]	27[f]	22[i]	3.5[j]	

a Assessed using a 100mm or 0-10 VAS. Values reported on a 0-10 scale were multiplied by 10 to fit a 0-100 scale.
b Abstract; limited data available with no verbal response scale scores reported.
c Odds ratio (range) determined using verbal response scores based on a 4-point verbal response scale.
d Median value in recovery room.
e Median value at 2h.
f Median value at the time of discharge from hospital.
g Diclofenac 75mg PO 1 hour preoperatively; all patients received postoperative oral dextropropoxyphene 32.5mg/paracetamol 325mg (×2 tablets) with concomitant ibuprofen 400mg prn and intramuscular prochloperazine 12.5mg (an antiemetic) every 8 hours prn.
h Intravenous morphine 0.1 mg/kg plus ketorolac 10mg intraoperatively.
i Median value during the first 24h after discharge from hospital.
j Mean number of tablets taken.

C = codeine; **D** = dextropropoxyphene; **DI** = diclofenac; **F** = fentanyl; **IV** = intravenous; **K** = ketorolac; **M** = morphine; **mc** = multicentre; **ME** = metoclopramide; **N** = naproxen sodium; **O** = ondansetron; **P** = paracetamol; **PO** = oral; **prn** = as required; **q4h** = every 4 hours; **q4-6h** = every 4 to 6 hours; **VAS** = visual analogue scale; ≡ indicates similar efficacy based on VAS scores; **>** indicates greater efficacy $p < 0.05$ *vs* comparator based on VAS scores; * $p < 0.05$, ** $p = 0.007$ *vs* comparator.

morphine 10mg in these groups (33 *vs* 63%; $p < 0.05$).[114]

Oral tramadol 100mg (administered pre- and postoperatively) provided similar analgesic efficacy compared with oral naproxen sodium 500mg in patients after gynaecological surgery (table VIII).[113] In those who underwent aspiration curettage, the patients' assessment of well-being showed a significant improvement with tramadol treatment compared with naproxen sodium treatment at both 4 (VAS well-being scores of 44 *vs* 23 points; $p < 0.005$) and 8 hours (37 *vs* 21; $p < 0.05$).[113] Similarly, in patients who underwent hysterosalpinography, well-being improved significantly in the tramadol group compared with those in the naproxen sodium group at 8 hours (38 *vs* 22 points; $p = 0.005$).[113]

Postoperative administration of tramadol 50 to 100mg every 4 to 6 hours provided efficacy similar to that of combinations of paracetamol 500mg/codeine 30mg or paracetamol 325mg/dextropropoxyphene 32.5mg during the first 24 hours in 68 patients who underwent laparoscopic surgery (table VIII).[116] 35% of tramadol recipients reported disturbed sleep attributable to pain compared with 27.3 and 28%, respectively, in the paracetamol/dextropropoxyphene and paracetamol/codeine groups. All participants in this study received intraoperative intravenous morphine 0.1 mg/kg and concomitant ketorolac 10mg.

Combining intraoperative intravenous tramadol 100mg with preoperative oral diclofenac 75mg (an NSAID) did not improve analgesic efficacy 2 hours after surgery compared with preoperative diclofenac 75mg and intraoperative intravenous fentanyl 4 μg/kg in patients undergoing third molar tooth extraction (assessed using VAS scores; table VIII).[115]

5. Tolerability

5.1 General Tolerability

In several well designed clinical trials, perioperative tramadol has been generally well tolerated in patients undergoing various surgical procedures.[70-73,75,76,90-94,96-98,104,107-110,113-116] In addition, a previous review in Drugs has summarised the tolerability profile of tramadol in more than 21 000 patients from several phase II to IV clinical trials and postmarketing surveillance studies.[117] Importantly, in addition to patients with postoperative pain, the phase IV and postmarketing surveillance studies discussed in the previous review included patients (the majority of whom were outpatients) with other acute and chronic pain conditions.[117] Furthermore, in these studies, tramadol was administered rectally or subcutaneously in some recipients, whereas these routes of administration were not used in clinical trials discussed in this review of the perioperative use of tramadol.

As reviewed previously, the most common adverse events reported in clinical and postmarketing surveillance studies with single and multiple doses of oral or parenteral (mainly intravenous and intramuscular) tramadol doses were nausea (6.1% of patients), dizziness (4.6), drowsiness (2.4), tiredness (2.3), sweating (1.9), vomiting (1.7) and dry mouth (1.6).[117] Less frequent adverse events (incidence 0.5 to 1%) were nausea/vomiting (0.9%), sedation (0.7), headache (0.6), postural hypotension (0.6), hot flushes (0.6) and digestive problems (0.6).[117]

The incidence of the most common adverse events following oral or parenteral administration of single or multiple tramadol doses over a maximum 24-hour period in clinical and postmarketing surveillance studies in 6011 patients are summarised in figure 5.[117] Although there were no qualitative differences in the adverse events profile between phase II and phase IV clinical trials compared with those observed in postmarketing surveillance studies, there were quantitative differences in the incidence of individual events (fig. 5).[117] For example, the incidence of nausea and vomiting in postmarketing studies following intravenous or intramuscular tramadol was 4.2 and 0.5%, respectively, whereas in clinical trials the incidence was markedly higher with intravenous (16.2 and 6.2%) and intramuscular tramadol (17.8 and 7%).[117] These differences possibly reflect

population differences between those involved in clinical trials and those surveyed in postmarketing surveillance studies.[117] All of the postmarketing studies included outpatients whereas the majority of participants in the clinical studies were hospitalised.[117]

Importantly both in clinical studies reviewed previously (fig. 5)[117] and in individual clinical trials in surgical patients (fig. 6),[76,90] the incidence of nausea and vomiting was markedly greater with parenteral (intravenous or intramuscular) than with oral administration. All clinical studies discussed in this review have used oral, intravenous or intramuscular routes of administration, with the majority having used parenteral administration of tramadol.

Comparative studies discussed in sections 2 and 4 indicated that the tolerability profile of perioperative tramadol appeared to be generally similar to that of other opioid agents.[11-13,15,16,70,76,90,92,94,95] The most common adverse events following oral or intravenous administration of tramadol, morphine or pentazocine in surgical patients in 2 large, randomised, double-blind, parallel-group studies are presented in figure 6.[76,90] In general, there were no differences in the incidence of nausea and vomiting in tramadol recipients compared with other opiate therapies (fig. 6).[70,73,75,76,90,93,94,104,108,110] Although the adverse event profile with tramadol treatment was generally similar to that of other opioids, several individual studies reported differences in the incidence of individual adverse events (fig. 6).[76,92,118] For example, in 158 postoperative patients receiving oral tramadol 50mg or pentazocine 50mg as required (maximum dose 200 mg/6h), adverse events occurred in fewer tramadol than pentazocine recipients (16.5 vs 27.8%).[76] Nausea, vomiting, sweating, dry mouth and fatigue occurred with a similar frequency in both groups, whereas severe dysphoria occurred in 3% of pentazocine recipients compared with 0% in the tramadol group (fig. 6).[76]

Of particular significance, tramadol caused significantly less respiratory depression than morphine, oxycodone, pethidine or nalbuphine in

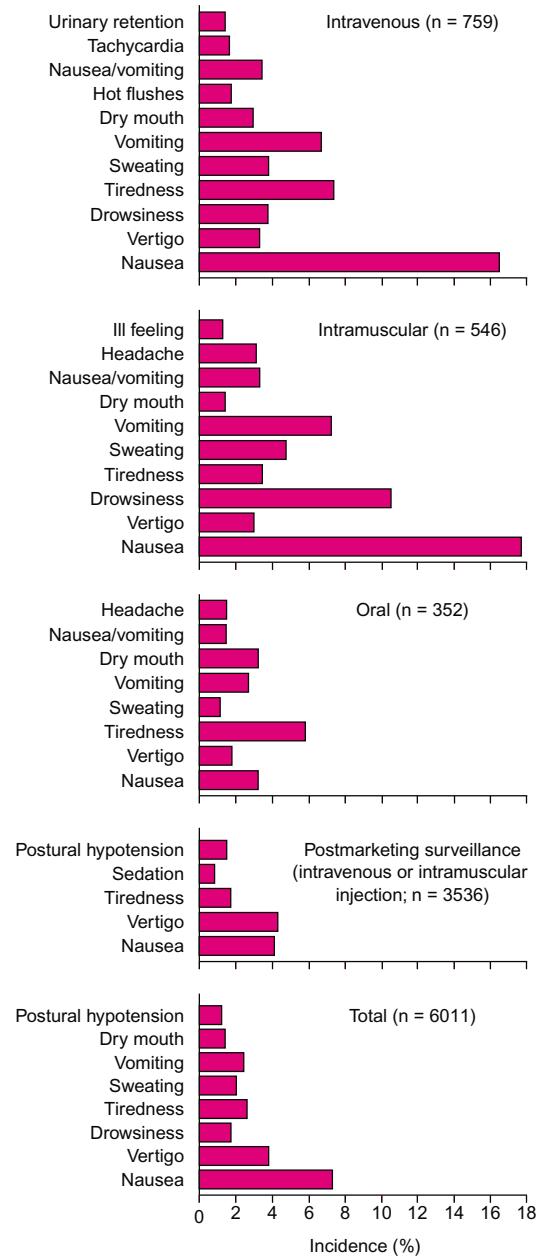


Fig. 5. Comparative incidence of adverse events reported in clinical trials and postmarketing surveillance studies after parenteral administration of single or multiple doses (based on an average dosage of 200 mg/day) of tramadol over a maximum 24-hour period.[117] A single dose in these studies corresponded to a 50mg capsule, a 50 or 100mg ampoule, a 100mg suppository or 20 drops containing 50mg of tramadol. Only adverse events occurring in ≥1% of patients are presented.

clinical studies in adults and children (see section 2.3).[11-16]

The tolerability profile of tramadol has also been compared with that of several NSAIDs in clinical studies.[71,72,91,96,113,114] The incidence of adverse events was similar with ketorolac and tramadol treatments.[71,72,114] For example, the incidence of nausea and vomiting were similar in 60 patients who received intravenous tramadol 1.5 mg/kg or ketorolac 10mg 30 minutes prior to gynaecological day case surgery.[114] In this study, dry mouth was the only adverse event reported more frequently in tramadol than ketorolac recipients (60 *vs* 27% of patients; $p < 0.01$).[114] In addition, there were no significant differences in the incidence of nausea or vomiting in patients receiving tramadol or NSAIDs (dipyrone, ketorolac or clonixin) using PCA, but the requirement for antiemetics was significantly lower in the tramadol and clonixin groups than with dipyrone or ketorolac ($p < 0.05$).[96] However, in 91 patients who underwent gynaecological day surgery, adverse events occurred in significantly more patients receiving tramadol (100 to 200 mg/day) than in naproxen sodium recipients (500 to 1000 mg/day) according to both investigator (36.4 *vs* 10.6%; $p = 0.004$) and spontaneous reports (67 *vs* 22%; $p < 0.01$).[113] There were significantly higher incidences of dizziness (34 *vs* 1%; $p < 0.01$) and nausea (25 *vs* 1%; $p < 0.01$) in the tramadol group.

The incidence of seizures in patients receiving tramadol is estimated to be <1%.[39] Postmarketing

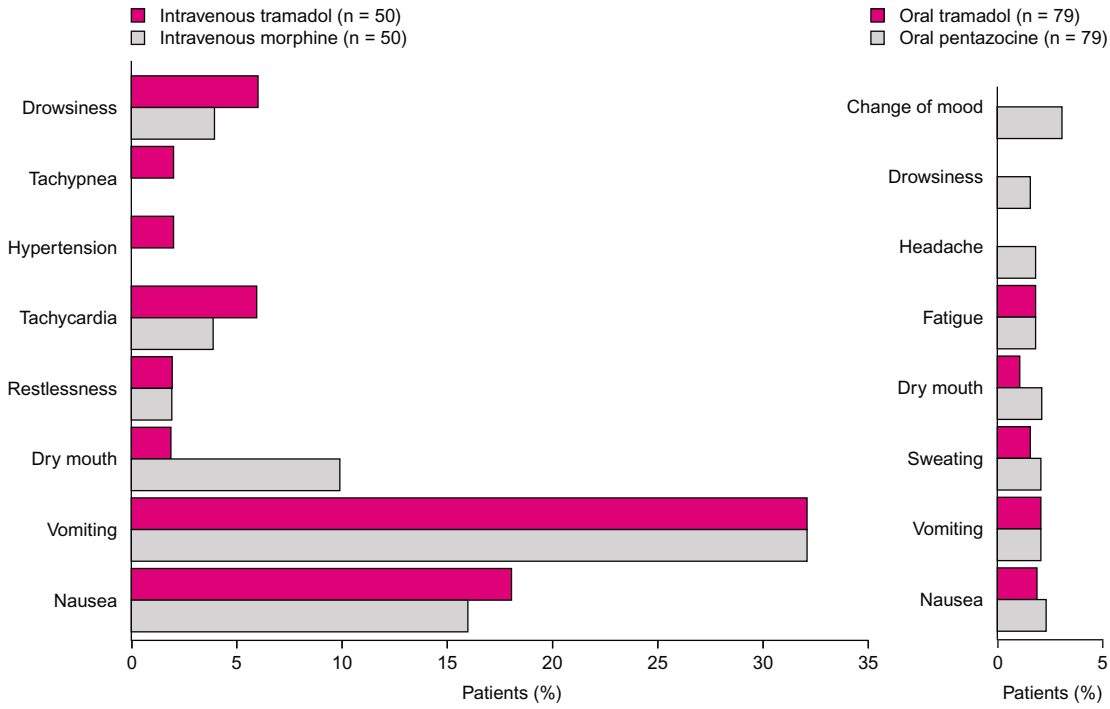


Fig. 6. Comparison of the most common adverse events following oral or intravenous administration of tramadol, morphine or pentazocine in 2 randomised, double-blind, parallel-group studies. (Left) Patients undergoing laparoscopic surgery received intraoperative intravenous tramadol 100mg or morphine 10mg (maximum intraoperative dose of 200mg or 20mg, respectively).[90] Postoperatively patients received tramadol or morphine using patient-controlled analgesia with a demand dose of tramadol 16mg or morphine 1.6mg (maximum dose 400 and 40 mg/4h, respectively) and a lockout time of 5 minutes. (Right) In a multicentre study, patients received oral tramadol 50mg or pentazocine 50mg postoperatively after intervertebral disc repair.[76] The average consumption of tramadol or pentazocine during the 6-hour study period was 119 and 108mg, respectively.

surveillance studies indicate that the risk may be increased with multiple doses, but seizures have occurred following a single dose.[39] In cases reported spontaneously to the US Food and Drug Administration, 58% of patients had at least one predisposing risk factor for seizures.[39] However, data from the General Practice Research Database in the UK for the period 1994 to 1996 indicated that there was no increase in the incidence of idiopathic seizures associated with exposure to tramadol monotherapy, with most cases reported involving concomitant opioid therapy.[40]

5.2 In Children

Although pooled results of phase IV and postmarketing surveillance studies discussed previously included data from studies in children[117,119-121] very few studies have specifically reported on the tolerability profile of tramadol in children.[16,99-102] In a comparative, randomised study in 40 children aged 4 to 8 years, there were no differences in oxygen saturation during the 24-hour postoperative period after caudal tramadol 1 mg/kg compared with caudal 0.025% bupivacaine 0.5 ml/kg (see section 2).[101] However, vomiting occurred in significantly more patients in the tramadol group than with bupivacaine treatment (31.5 *vs* 5%; $p < 0.05$), with no other adverse events reported.[101] Furthermore, in 90 children aged 1 to 4.5 years, there were no significant differences in the sedation score or ventilatory frequency with caudal tramadol 2 mg/kg compared with bupivacaine 2 mg/kg or with concomitant tramadol 2 mg/kg and bupivacaine 2 mg/kg.[100] In addition, there were no significant differences in vomiting (28.6, 10.7 and 18.8%, respectively), pruritus (4.8, 3.6 and 3.7%), flushing (33.3, 32.1 and 33.3%) or numbness (0, 3.6 and 3.7%) between these treatment groups.[100] Vomiting was the only adverse event reported in a nonblind, comparative, randomised study in 75 children aged 2 to 12 years receiving tramadol 2 mg/kg, pethidine 1 mg/kg or nalbuphine 0.1 mg/kg, and occurred in 4, 0 and 0% of patients, respectively.[102] There were no significant effects on haemodynamic or respiratory parameters in any of these treatment groups.[102] The incidence of perioperative bleeding following tonsillectomy was similar in 60 children (age not reported) receiving preoperative tramadol 2 mg/kg compared with those receiving concomitant diclofenac 1 mg/kg plus propacetamol 30 mg/kg.[122]

5.3 Overdose and Abuse

An overdose with tramadol may produce significant neurological toxicity, including seizures, coma and respiratory failure, and mild tachycardia and hypertension.[36] Importantly, the risk of overdose in the perioperative setting is probably small. Prospective data from 7 poisons centres in the US indicated that the most common symptoms associated with an overdose were lethargy (30% of patients), nausea (14%), tachycardia (13%), agitation (10%), seizures (8%), coma (5%), hypertension (5%) and respiratory depression (2%).[36] All seizures were brief, with tramadol 500mg being the lowest dose associated with seizure. Naloxone treatment reversed sedation and apnoea in 50% of patients. No serious cardiotoxicity was observed on tramadol overdose.[36] The majority of adverse effects appeared to be attributable to inhibition of monamine reuptake rather than opioid effects.[36] Overdose may produce a mild serotonin syndrome including symptoms such as agitation, confusion, tachycardia and hypertension, although a limited number of individual cases have been reported.[36,123-125] All of these patients were being treated for chronic pain and were receiving concomitant medications.[123-125]

The risk of dependence or abuse with tramadol is low. In patients receiving this agent for the treatment of moderate to severe postoperative pain, this risk is probably decreased, since administration is mainly in the hospital setting and of short duration. In the period from April 1995 to June 1997 in the US, there were 1.55 cases of abuse per 100 000 individuals exposed to tramadol reported.[126] This rate declined to 0.7 cases per 100 000 in the next 2 quarters, with 97% of individuals who abused

tramadol having a previous history of substance abuse.[126]

6. Dosage and Administration

Tramadol is recommended for the management of acute (including perioperative pain) or chronic moderate to severe pain.[48,50,55,127,128] It may be administered orally, rectally or parenterally (intravenous, intramuscular and subcutaneous), although only an oral formulation is available in the US.[48] In this review of the perioperative use of tramadol, parenteral administration involved intravenous or intramuscular routes only. The dosage should be titrated according to the intensity of pain and the response of the individual patient.

Recommended dosages of oral or parenteral (intravenous and intramuscular) tramadol in various populations are summarised in table IX. The usual recommended dosage in adults <75 years of age for oral or parenteral tramadol is 50 to 100mg every 4 to 6 hours as required (maximum dosage of 400 mg/day; table IX).[48,50,55,127,128] Recommendations for the use of tramadol in paediatric patients vary between individual countries; for example, tramadol is not recommended for use in children <12 years of age in the UK or in those <16 years of age in the US, whereas in Germany some formulations are approved for use in children aged ≥1 year.[48,50,55,127,128]

Tramadol is contraindicated in patients who have previously demonstrated hypersensitivity to it and in cases of acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic drugs.[48,50,55,127,128] It is not recommended in patients who are receiving monoamine oxidase inhibitors or within 2 weeks of their withdrawal.[48,50,55,127,128] Tramadol is also not recommended for use during pregnancy or in lactating mothers in the US and UK, although a single dose may be used during pregnancy or in lactating mothers in Germany.[48,50,55,127,128]

Although the risk of seizure with tramadol use is low (see section 5.3), this risk may be enhanced in patients receiving monoamine oxidase inhibitors, neuroleptics, other drugs that reduce the seizure threshold, patients with epilepsy or patients otherwise at risk of seizure.[48,50,55] Care should be taken when administering tramadol to these patients.[48,50,55] Since pupillary changes occurring in patients receiving tramadol may obscure the extent, existence or course of intracranial pathology, this agent should be used with caution in patients with increased intracranial pressure.[48,50,55] Tramadol should also be used with caution when treating patients with respiratory depression or if concomitant central nervous system depressant agents are being administered.[48,50,55,127,128]

Concomitant administration of tramadol with carbamazepine causes a significant increase in tramadol metabolism and thus patients receiving long term carbamazepine therapy may require increased doses of tramadol (see section 3.4).[48,50,55] No dosage adjustment is necessary when used with concomitant cimetidine.[48,50,55] Quinidine is a selective inhibitor of the CYP2D6 enzyme and concomitant administration with tramadol increases plasma concentrations of tramadol and reduces plasma concentrations of M1.[48] The clinical relevance of this interaction has not been fully investigated.[48]

Mutagenicity tests in animal studies indicate that tramadol does not have genotoxic potential in humans.[48] There were also no effects on fertility with oral tramadol doses of up to 50 mg/kg in animal studies.[48]

7. Place of Tramadol in the Management of Perioperative Pain

The management of perioperative pain is important, not only for the patients' well-being, but also because it may play an important role in reducing the duration of hospitalisation and in preventing long term complications, including pneumonia.[129,130] Recent evidence from preclinical studies indicates that the expression of genes associated with neuronal remodelling and sensitisation occurs within 20 minutes of injury.[129] Moreover, acute pain may rapidly evolve into chronic pain.[129] Hence, the effective management of pain

Table IX. Dosage and administration of tramadol[48,50,55,127,128]

	Intravenous or intramuscular formulations[a,b]	Oral formulations
Recommended dosage[c]	50 to 100mg q4-6h prn in those ≥14 years of age in Germany and ≥12 years of age in the UK. The maximum recommended daily dosage is 400 mg/day	50 to 100mg q4-6h prn in patients ≥16 years of age in the US, ≥14 years of age in Germany and ≥12 years of age in the UK. The maximum recommended daily dosage is 400 mg/day
Postoperative/PCA[d]	Use in the UK: tramadol solution for parenteral administration (intramuscular, slow intravenous injection over 2 to 3 minutes or dilute solution for PCA): bolus 100mg with further doses of 50mg every 10 to 20 minutes prn up to a total dose of 250mg; subsequent doses should be 50 to 100mg q4-6h prn up to a maximum dose of 600 mg/day	
PCA[d]	Use in Germany: initial individual loading doses, with subsequent boluses of 20mg and a lockout time of 5 minutes	
Intraoperative[d]	Use in Germany: tramadol ≤500 mg/4h, although higher dosages may be necessary with a tramadol infusion Use in the UK: tramadol may be used intraoperatively provided continuous, potent volatile or intravenous anaesthetics are used rather than a nitrous oxide/opioid anaesthetic technique	Not applicable
Special populations		
Children[d]	Not recommended for use in patients <12 years of age in the UK	Not recommended for use in patients <16 years of age in the US or in patients <12 years of age in the UK
	Recommended for use in children ≥1 year of age in Germany; the recommended dose in these patients is 1 to 2 mg/kg	In Germany, some formulations (drops for oral administration) are recommended for use in children ≥1 year of age. The recommended dose in these patients is 1 to 2 mg/kg
Elderly	No dosage adjustment required in those <75 years of age. In patients >75 years of age, the elimination half-life is increased and dosage adjustments may be required. In the US (only available as an oral formulation), the maximum recommended daily dosage in patients >75 years of age is 300 mg/day, with the dose divided equally as per the usual regimen	
Hepatic impairment	Elimination of tramadol may be prolonged. The usual dosage should be used but in severe hepatic impairment the dosage interval should be increased to 12 hours. In the US (only available as an oral formulation), dosage adjustment is recommended in patients with cirrhosis, although no regimen is specified	
Renal impairment	The elimination of tramadol may be prolonged. For patients with a creatinine clearance of <1.8L/h (30 ml/min), the dosage interval should be increased to 12 hours. Not recommended for patients with a creatinine clearance <0.6L/h (10 ml/min). Since only 7% of the administered dose is removed by haemodialysis, no further dosage adjustments are necessary in these patients	

a Tramadol is also available as a subcutaneous injection and as suppositories; however, these formulations were not used in clinical trials discussed in this review.
b An oral formulation only is available in the US.
c Adolescent and adult dosage unless indicated otherwise.
d Recommendations for use may vary between countries; these guidelines are provided as examples.
PCA = patient-controlled analgesia; **prn** = as required; **q4-6h** = every 4 to 6 hours.

may improve the clinical outcome in many patients.[22,129,130]

Postoperative pain is characterised by variable initial pain intensity which progressively diminishes with time.[131] The most common therapeutic approach for the management of acute postoperative pain, especially moderate to severe pain, usually involves treatment with pharmacological agents.[132,133] Other therapeutic options include psychological therapy, physiotherapy and regional anaesthesia.[132,133]

Moderate to severe perioperative pain has traditionally been managed using opioid analgesics, with morphine being the standard reference drug.[130,133,134] These agents act, in part, through the modulation of descending inhibitory pathways in the CNS, resulting in the modulation of secondary neurons in the spinal cord. However, although

morphine provides excellent analgesia, its use is limited, particularly by its respiratory depressant effects and dependence potential. Furthermore, although opioids have no ceiling effects, clinicians are often reluctant to prescribe efficacious doses because of concerns of addiction and possible serious adverse events, such as sedation and respiratory and cardiovascular depression, particularly in high-risk patients, such as those with poor cardiopulmonary reserves.[81,131]

With its unique dual mechanism of action (weak opioid agonist, and a weak noradrenaline and 5-HT reuptake inhibitor), tramadol offers an alternative to other opioids, as these 2 complementary, synergistic actions enhance its analgesic effects and improve its tolerability profile. Most importantly, unlike other opioid agents, this weak opioid agonist shows no clinically relevant effects on cardiovascular and respiratory parameters and has a low potential for abuse and dependence.[11-14,37,79,129] In addition, tramadol is not a controlled substance, although along with its low potential for abuse, this factor is probably less relevant in the management of postoperative pain than with long term administration. Furthermore, intravenous tramadol has been shown to provide similar analgesia to that of epidural morphine, but has considerable cost advantages.[135]

Anaesthesia and surgical procedures, particularly of the thorax and upper abdomen, cause important changes in respiratory function, including decreased residual reserve.[129] These changes in respiratory function are most marked in the elderly, the obese, smokers and those with pre-existing cardiopulmonary disease.[129] Furthermore, as a consequence of age-related changes in cardiovascular and respiratory functions which lower the overall pulmonary reserve, the elderly are less able to cope with changes in respiratory function that follow major surgery.[129] Thus, tramadol, with its lack of respiratory effects, may prove particularly beneficial in this group of patients.

Several well designed comparative clinical studies have demonstrated the analgesic efficacy of oral and parenteral (intramuscular or intravenous) tramadol in the management of moderate to severe perioperative pain (see section 4). In the majority of these studies, tramadol was administered intramuscularly or intravenously. Tramadol provided similar analgesic efficacy to that of morphine or alfentanil and superior analgesia to that of pentazocine. In addition, tramadol demonstrated similar analgesia to that of several NSAIDs, including ketorolac, naproxen sodium, dipyrone and clonixin. Tramadol may prove particularly beneficial in patients in whom NSAIDs are not recommended or need to be used with caution, including patients with peptic ulcers or those predisposed to them, those with haemorrhagic disorders or hypertension, and in patients with impaired renal, hepatic or cardiac function.[136]

Clinical studies have evaluated the perioperative use of tramadol in both nurse-administered and patient-controlled analgesia in patients undergoing several types of surgical procedures, including abdominal, orthopaedic and cardiac surgery (see section 4.1.1). In a few recent studies (available as abstracts only) in patients who had undergone cardiac surgery, tramadol infusions provided analgesia similar to that of morphine or alfentanil.[73,74] In addition, a few studies have indicated that parenteral tramadol provides effective analgesia in paediatric patients, although its use in this group is not recommended currently in some countries (e.g. the US).

In day surgery patients, good perioperative pain management requires the use of pharmacological agents that provide effective analgesia, without the adverse sequelae that may delay or prevent discharge from hospital. Thus, tramadol, with its lack of sedative and respiratory effects (see section 2.3), may prove a suitable analgesic agent for use in these patients. In a recent study, tramadol provided analgesia equivalent to that of morphine in day surgery patients (see section 4.1.1).[115] In addition, intravenous and oral tramadol provided better analgesia than intravenous fentanyl plus oral codeine and paracetamol,[104] or ketorolac.[114]

Although in earlier studies the intraoperative use of tramadol as part of balanced anaesthesia was

associated with an increase in the incidence of intraoperative awareness, further studies have suggested that this increased incidence of recall may be a reflection of the anaesthetic technique (see section 4.2). Several recent studies in both inpatients and day surgery patients anaesthetised with potent volatile or intravenous anaesthetics indicated that intraoperative tramadol provided effective analgesia without causing any clinically significant lightening of anaesthetic depth.[90,106-110]

Perioperative oral or parenteral tramadol has been generally well tolerated in surgical patients, with a tolerability profile that appeared to be similar to that of other opioid agents. However, unlike other opioids, tramadol had no clinically relevant effects on cardiovascular or respiratory parameters. The most common adverse events were nausea and vomiting, although there were generally no differences in the incidence of these events compared with other opioid agents. Furthermore, tramadol has a low potential for abuse and dependence, unlike some other opioids. In addition, tramadol appeared to be as well tolerated as several NSAIDs, including ketorolac, dipyrone and clonixin.[96,114] However, in patients who underwent gynaecological day surgery, adverse events occurred in significantly more tramadol recipients than naproxen sodium recipients, with a significantly higher incidence of dizziness and nausea in tramadol recipients.[113]

In summary, the efficacy of tramadol for the management of moderate to severe pain has been demonstrated in both inpatients and day surgery patients. Most importantly, unlike other opioids, tramadol has no clinically relevant effects on respiratory or cardiovascular parameters. Tramadol may prove particularly useful in patients with poor cardiopulmonary function, including the elderly, the obese and smokers, in patients with impaired hepatic or renal function, and in patients in whom NSAIDs are not recommended or need to be used with caution. Parenteral (intravenous or intramuscular) or oral tramadol has proved to be an effective and well tolerated analgesic agent in the perioperative setting.

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