Remifentanil and tramadol

D. J. R. DUTHIE

Remifentanil (Ultiva, Glaxo Wellcome) and tramadol (Zydol, Searle; Tramake, Galen; Zamadol, ASTA Medica) represent two contrasting approaches by pharmaceutical companies to improve the clinical treatment of pain. Remifentanil has the same mode of action as existing pure \( \mu \) opioid analgesic drugs, but because of its rapid esterase metabolism it has an ultrashort duration of action. The drug has therefore to be given by continuous i.v. infusion, but any drug effects can be rapidly controlled. Tramadol and its active metabolite have low affinities for the \( \mu \) opioid receptor, but inhibit reuptake of norepinephrine and enhance secretion of serotonin, achieving modulation of pain in the central nervous system. Clinicians are offered the chance to take advantage of new pharmacokinetics and new pharmacodynamics to treat pain in clinical practice.

Remifentanil

Remifentanil (fig. 1) is the hydrochloride salt of 3-[4-methoxyxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine] propanoic acid, methyl ester. It is a short-acting, synthetic, esterase-metabolized opioid, with a side branch susceptible to rapid hydrolysis by non-specific blood and tissue esterases to an acid, GR90291. It is presented as a lyophilized powder for reconstitution with water. The preparation is a white crystalline powder, readily soluble in water with a \( \text{pK}_a \) of 7.07. The aqueous solution has a \( \text{pH} \) of 4.5. The vials contain hydrochloric acid and glycine USP 15 mg vial\(^{-1}\). Glycine is an inhibitory neurotransmitter, which renders the preparation unsuitable for extradural or subarachnoid injection. Once reconstituted in water then diluted with dextrose 5% down to concentrations of 20 \( \mu \)g ml\(^{-1}\), the solutions remain stable at room temperature for up to 24 h.

MODE OF ACTION

Remifentanil is an effective agonist at the \( \mu \) opioid receptor and produces profound analgesia. This effect is antagonized effectively by naloxone. The drug differs from existing highly effective opioid agonists in its rapid metabolism by nonspecific red-cell and tissue esterases, rather than in any novel properties at the opioid receptor.

INDICATIONS AND CONTRAINDICATIONS

Remifentanil is indicated for use as a supplement to general anaesthesia during induction and as an analgesic during maintenance of anaesthesia. It is effective in blunting haemodynamic responses to stimuli during anaesthesia. Clinical studies have compared heart rate and systemic arterial blood pressure in groups of patients given remifentanil or alfentanil as the opioid, in part of an anaesthetic technique balanced by muscle relaxant and inhalation or i.v. anaesthetic agent; there are consistently fewer responses to remifentanil in the doses used. Responses to intubation and skin incision measured by rises in heart rate and blood pressure occurred in 15% and 8% of patients given remifentanil 1.0 then 0.5 \( \mu \)g kg\(^{-1}\) min\(^{-1}\), and 28% and 17% with alfentanil. During outpatient laparoscopic surgery, 11% of patients given remifentanil 1.0 then 0.5 \( \mu \)g kg\(^{-1}\) min\(^{-1}\) responded to insertion of the trochar compared with 32% of patients given alfentanil. Responses at any time during surgery were demonstrated by 53% of patients given remifentanil compared with 71% in the alfentanil group.

Obtunding haemodynamic response is dose related until 1.0 \( \mu \)g kg\(^{-1}\) min\(^{-1}\). At intubation, heart rate and blood pressure were significantly lower in patients given remifentanil 1.0 \( \mu \)g kg\(^{-1}\) min\(^{-1}\), 75.2 (20.4 (SD)) mm Hg, than in those given remifentanil 0.5 \( \mu \)g kg\(^{-1}\) min\(^{-1}\), 85.0 (14.8) mm Hg, and 125.2 (34.3) mm Hg, although the differences were not significant clinically. Before cardiac surgery 93% of patients suffered no haemodynamic response to sternotomy and maximal sternal spread when given remifentanil 1.0 \( \mu \)g kg\(^{-1}\) min\(^{-1}\) and propofol 50 \( \mu \)g kg\(^{-1}\) min\(^{-1}\). There was no improvement on increasing the dose to 1.5 and 2.0 \( \mu \)g kg\(^{-1}\) min\(^{-1}\), when responses to sternotomy and maximal sternal spread were 89% and 91% respectively.9 There is the customary opioid effect on spectral edge (\( \text{SE}_{95} \)), where the frequency of the EEG spectral edge, falls with increasing effect-site concentration in a sigmoid relationship. However, remifentanil does not reliably produce loss of consciousness. Over a dose range of 2–20 \( \mu \)g kg\(^{-1}\) the \( \text{ED}_{50} \) of 12 \( \mu \)g kg\(^{-1}\) and \( \text{EC}_{50} \) of 53.8 ng ml\(^{-1}\) for loss of consciousness were far in excess of doses used clinically and were associated with severe muscle rigidity. Remifentanil is not recommended as a sole anaesthetic agent and should be given in association with an inhalation or i.v. anaesthetic agent. Similarly, for sedation during surgical procedures under local anaesthesia, better...
results were obtained using remifentanil with midazolam 2 mg i.v. than with remifentanil alone. When infusing remifentanil and titrating infusion rate to effect, introducing midazolam reduced the rate of remifentanil required from 0.12 (0.05) to 0.07 (0.03) μg kg⁻¹ min⁻¹ and resulted in less nausea. Equally, when infusing remifentanil and titrating it to effect with placebo or midazolam 2, 4, or 6 mg i.v., remifentanil alone was found to be less satisfactory than remifentanil 0.05–0.1 μg kg⁻¹ min⁻¹ with midazolam 2 mg i.v.²

The amount of anaesthetic supplement required to achieve anaesthesia is considerably reduced by remifentanil. Using computer-controlled infusions to achieve target remifentanil concentrations of 0–32 ng ml⁻¹, remifentanil 1.37 ng ml⁻¹ achieved a 50% reduction in minimum alveolar concentration (MAC) of isoflurane required to prevent movement on skin incision from 1.3% without remifentanil. Remifentanil 2–4 ng ml⁻¹ achieved a 70% reduction in MAC and remifentanil 32 ng ml⁻¹ a 91% reduction. Even at very high concentrations, remifentanil without isoflurane did not provide adequate anaesthesia. Blood remifentanil clearances of 28–35 ml min⁻¹ kg⁻¹ were calculated. At steady state, when infusion rate = concentration at steady state × blood clearance, remifentanil 0.038–0.048 μg kg⁻¹ min⁻¹ would be required to achieve a 50% reduction in MAC for isoflurane. This is at the lower end of the dose range recommended for clinical anaesthesia. The use of remifentanil as the mainstay of an anaesthetic technique, with doses of anaesthetic agent much lower than those required when using small opioid supplement, forms the basis of anaesthesia based on “esterase metabolized opioid” advocated by Glaxo Wellcome. The effect of excessive inhalation or i.v. agents in the presence of remifentanil at times of minimal surgical stimulation may be responsible for episodes of hypotension, reversed promptly by simple measures, seen during remifentanil infusion.⁴⁹

Remifentanil is an effective opioid supplement but, because of its rapid offset, patients will experience immediate pain after emergence from anaesthesia unless there is an effective strategy to treat pain after operation. Following abdominal surgery under remifentanil/propofol total i.v. anaesthesia, 86% of patients experienced no or mild pain in the recovery room with a continuous infusion of remifentanil reduced to 0.086 μg kg⁻¹ min⁻¹. Patients were then changed to postoperative extradural analgesia or patient-controlled morphine i.v. Subsequently, in the surgical ward, patients receiving extradural analgesia achieved better pain scores than did those using patient-controlled analgesia.５ Remifentanil infusion 0.05–0.23 μg kg⁻¹ min⁻¹ provided better analgesia after abdominal surgery under total i.v. anaesthesia, when 58% of patients experienced no or mild pain compared with 33% of those receiving intermittent morphine i.v. However, moderate or severe pain was experienced in 74% of patients after removal of the tracheal tube, and the effects of remifentanil dissipated promptly after discontinuation of the infusion.⁶⁸ After abdominal surgery initial infusions of remifentanil 0.1 μg kg⁻¹ min⁻¹ provided better anaesthesia than 0.05 μg kg⁻¹ min⁻¹. Once the drug was titrated to effect, 71% of patients reported no or mild pain with an adequate rate of spontaneous ventilation.⁵⁰

**ADVERSE EFFECTS OF REMIFENTANIL.**

The familiar adverse effects of an opioid—respiratory depression, sedation, nausea and vomiting, muscle rigidity, bradycardia and pruritus—are demonstrated. Like the analgesic effects of remifentanil, the adverse effects are short-lived and antagonized by naloxone.¹ Remifentanil has not been associated with histamine release. In patients breathing spontaneously, the onset of life-threatening muscle rigidity and apnoea can be alarmingly rapid. Injection of 0.5 μg kg⁻¹ doses in less than 10 s and large infusion rate increases within 2 min of a previous increase were more likely to be followed by muscle rigidity and apnoea. These effects dissipated rapidly when the drug was withheld and may be avoided by spreading injection of single doses over 30 s and changing remifentanil infusion rates no more frequently than at 10-min intervals. During operation, bradycardia was more likely during abdominal surgery in patients given remifentanil than alfentanil,⁵⁰ and in children undergoing strabismus surgery the oculocardiac response was more marked with remifentanil than alfentanil.⁵⁰ There was little change in heart rate in patients who received remifentanil during cardiac surgery in the presence of the vagolytic muscle relaxant, pancuronium.⁴⁹

**DOSE**

Remifentanil is recommended for induction of anaesthesia as an infusion of 0.5–1 μg kg⁻¹ min⁻¹ with or without 1 μg kg⁻¹ injected i.v. over 30 s. During maintenance of anaesthesia an analgesic infusion of 0.05–2 μg kg⁻¹ min⁻¹ is given, with supplemental doses as required should light anaesthesia be suspected. When patients are breathing spontaneously an initial infusion of 40 ng kg⁻¹ min⁻¹ is then adjusted, usually to within the range 25–10 ng kg⁻¹ min⁻¹. Early clinical experience of remifentanil has been obtained within sponsored drug trials undertaken to gather data for regulatory authority approval. Subsequent experience in routine clinical practice may well limit the 40-fold dose range for analgesic supplement and demonstrate reduced requirements for concurrent inhalation and i.v. anaesthetic agents.

**PHARMACOKINETICS**

Remifentanil arose from a deliberate attempt to develop a 4-anilido piperidine compound with opti-
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oid effects and a very short duration of action.18
Within the molecule is an ester side branch (fig. 1) that is crucial to its opioid activity and susceptible to hydrolysis. The distinctive pharmacokinetics of remifentanil are a result of the drug being rapidly metabolized by non-specific red blood cell and tissue esterases, like the beta-adrenoceptor antagonist esmolol57 and calcium antagonist clevidipine.43 This rapid esterase metabolism distinguishes remifentanil from other opioids and will determine its place in clinical practice.

Extensive metabolism occurs in blood cells and muscle that is unaffected by isolated organ failure. The pharmacokinetics and respiratory effects of remifentanil are unchanged in patients with end-stage hepatic15 and renal disease.9,26 The major metabolite GR90291 is itself a μ opioid agonist and is excreted by the kidney. The metabolite accumulates in renal failure, but its activity is only 1/4600 that of the parent compound; only if there was substantial accumulation could the metabolite exert a clinically important opioid effect.25 In the liver, in the same way that fentanyl is metabolized, there is a minor pathway of N-demethylation for remifentanil. The lung does not clear remifentanil from the circulation.14

The esterase metabolism suffered by remifentanil is not related to pseudo-cholinesterase (butyrylcholinesterase), which terminates the action of suxamethonium. Remifentanil is not a substrate for pseudo-cholinesterase and patients who are deficient in pseudo-cholinesterase and therefore susceptible to suxamethonium apnoea, metabolize remifentanil normally.54

Remifentanil is 70% bound to α-1-acid glycoprotein. Its in vitro metabolism is significantly reduced by dilution with albumin, which may bind to remifentanil and prevent metabolism by red-cell esterases.11 The high protein binding contributes to its volume of distribution at a steady state of 0.3–0.4 litre kg−1, which is smaller than that of other opioids. Because of this, and its rapid metabolism and large clearance of 2.9 (0.4) litre min−1 or 174 (24) litre h−1,1531 the terminal elimination half-life of remifentanil is extremely short, with a mean of 9.52 (3.95) min.19 Consequently, remifentanil must be delivered by continuous infusion i.v. or without a loading dose to be useful clinically. It is possible to dilute any opioid for injection i.v. and deliver it by continuous infusion, but remifentanil, of all the available opioids, best satisfies by far the five requirements of a drug necessary to make rate-controlled delivery worthwhile: short elimination half-life; no active metabolites; offset by metabolism or excretion and not redistribution; a concentration–effect relationship; and a narrow therapeutic index.44

Another distinction between remifentanil and other opioids is the behaviour of the drug after prolonged infusion. Early safety studies of single doses of a drug in healthy volunteers generated pharmacokinetic data summarized by variables such as elimination half-life, rate constants, clearance and volume of distribution. Far from being immutable, these variables may change markedly with larger doses, repeated doses or continuous delivery, and may vary with the duration of therapy. The consistency of the pharmacokinetics of remifentanil with prolonged infusion contrasts markedly with changes in pharma-

The pharmacokinetics of remifentanil make blood concentrations predictable. Remifentanil blood concentrations obtained by infusions of 1.0–2.0 μg kg−1 min−1 were related linearly to the rate of infusion and pharmacokinetic values obtained with other opioids after prolonged administration.

Of the main pharmacokinetic variables, half-life is easiest to comprehend, because time is a familiar unit of measurement. However, half-life alone gives little information about the behaviour of a drug in a single-compartment model and predicts less of the behaviour of a drug better described by two- or three-compartment models.52 A more useful descriptor, “context-sensitive half-time” has been proposed, where “context” refers to the duration of infusion and the “half-time” is the time required for the drug concentration in the central compartment to decline by half after a particular duration of infusion.27

The difference between single injection and prolonged infusion arises when distribution from central to peripheral compartments is responsible for a considerable part of the offset of action of a drug. After prolonged infusion, the peripheral-compartment drug concentration tends to equilibrate with the central-compartment concentration. When the infusion is stopped there is no opportunity for offset of drug action by distribution from central to peripheral compartment and the offset of action is delayed relative to the offset after single injection. By declaring the context of duration of infusion, subsequent central-compartment half-times of different drugs may be calculated and compared.

However much of an improvement context-sensitive half-time may be, it remains a pharmacokinetic variable of use in predicting only drug concentrations, albeit in the central compartment. If these concentrations are to be used to derive a prediction of drug effect, it is necessary to take into account the influence of delay caused by a drug equilibrating between the central compartment and site of action. This may be calculated by considering the site of action as an effect compartment with a rate constant ke0 between central and effect compartments. The equilibration half-life, τeq/ke0, is calculated from the ratio of ln(2)/ke0. For drugs like remifentanil, whose ke0 is large, the difference between pharmacokinetic and pharmacodynamic context-sensitive half-times will be small.

For drugs whose concentration–effect relationship is described by a sigmoid curve, the central portion may demonstrate a linear relationship between drug concentration at the effect site and clinical response. Even then, the ability of the calculated central-compartment concentration to predict drug effect is hindered by the equilibration time between central compartment and effect site. For remifentanil this equilibration time is very short. The τeq/ke0 was 1.3 min for effect on minute volume of ventilation.

The change in minute volume% followed closely the same time course as blood concentrations.10 Modelling changes in spectral edge on the EEG, τeq/ke0 was 1.34 min.38 These rate constants are dependent on age. In the elderly, modelling of pharmacokinetic and EEG data suggest that single doses of remifentanil should be halved and infusions run at a third of the rate compared with doses intended for healthy adults.39

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unrelated to the duration of infusion, unlike those of fentanyl and alfentanil, which demonstrate accumulation.

SUMMARY

Remifentanil is a highly effective opioid analgesic with a short half life, predictable pharmacokinetics and a close concentration–effect relationship. It offers the best available opportunity to control opioid effects. However, care must be taken to ensure that infusion rates are set appropriately to control pain and responses to surgical stimuli without inducing life-threatening respiratory depression and muscle rigidity, the onset of which can be rapid.

Tramadol

Tramadol (fig. 2), (±)-cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-cyclohexanol hydrochloride, is presented as a racemic mixture of two enantiomers. It is available as capsules and soluble tablets of 50 mg and as a solution of 50 mg ml⁻¹ for i.v. or i.m. injection.

MODE OF ACTION

The analgesic mode of action of tramadol is not fully understood. It has demonstrable analgesic properties, but its effects are distinct from those of the pure μ opioid agonists available in clinical practice. Initially considered an opioid analgesic, it has a weak affinity for μ opioid receptors. In the mouse tail-flick test, the antinociceptive activity of tramadol was completely antagonized by naloxone and both tramadol and morphine have failed to demonstrate antinociceptive activity after intracerebroventricular injection in CXBK mice. The (+)-M1 metabolite, O-desmethyltramadol, has a higher affinity than tramadol for opioid receptors. This demethylation is blocked by quinidine, a potent CYP2D6 inhibitor. The opioid activity of tramadol may well be consequent to metabolism of the parent drug to the active demethylated metabolite by the polymorphic cytochrome P450 enzyme, debrisoquine-4-hydroxylase (CYP2D6).

Tramadol was discovered subsequently to inhibit reuptake of norepinephrine and promote release of serotonin. The contribution of enhanced monoaminergic transmission to the analgesic actions of tramadol is supported by the blocking of antinociceptive effects of intrathecal tramadol, but not those of morphine, by yohimbine and ritanserin. The reversal of the antinociceptive effects of tramadol by these α2- adrenoceptor antagonists suggests that tramadol achieves monoaminergic spinal modulation of pain through indirect activation of postsynaptic α2- adrenoceptors, blocking impulses reaching the brain. The synergy of monoaminergic and opioid activity achieves analgesic effects.

Tramadol is a racemic mixture. Each enantiomer has different opioid binding affinities and they differ in their inhibition of monoaminergic re-uptake inhibition.

INDICATIONS AND CONTRAINDICATIONS

Tramadol is indicated for moderate to severe pain in adults. It has the same analgesic potency as pethidine, 1/5 of that of nalbuphine, 1/1000 that of fentanyl and 1/10 that of morphine i.v. Tramadol 50–150 mg i.v. was equivalent to morphine 5–15 mg i.v., but a preservative-free preparation had only 1/13 of the potency of morphine extradurally.

Despite being relatively less potent than pure opioids, tramadol has achieved efficacy when used to treat moderate pain after surgery. In treating pain after thoracotomy, tramadol 150 mg i.v. was no different in effect to morphine 2 mg extradurally combined with an extradural infusion of 0.2 mg h⁻¹, but in the first 24 h after surgery patients required mean rescue doses of morphine 27.2 (16.9 (SD)) mg i.v. and 34.2 (15.7) mg i.v. respectively by patient-controlled analgesia. After hysterectomy, tramadol 50 mg i.v. was as effective as morphine 5 mg i.v. in treating pain described as moderate; pain assessment was by serial changes in verbal rating scores after analgesic administration. By the same assessment, tramadol was less effective than morphine in relieving pain described as severe. Because of its efficacy as an analgesic, tramadol is considered to be effective in step two of the World Health Organisation guidelines for the treatment of patients with cancer pain.

As tramadol enhances monoaminergic transmission, the drug is contraindicated in patients receiving monoamine oxidase inhibitors and caution is advised in patients with epilepsy. It is not recommended for children.

ADVERSE EFFECTS OF TRAMADOL

There have been reports of dizziness, nausea, sedation, dry mouth and sweating, but this particular pattern of adverse effects may offer advantages in patients for whom opioids and non-steroidal anti-inflammatory drugs are not suitable.

Respiratory depression with tramadol is less than with morphine, and has features that differ clinically from those of opioid respiratory depression. Patients breathing spontaneously under halothane anaesthesia had a transient fall in respiratory rate without change in end-tidal carbon dioxide concentration after tramadol 0.5–2.0 mg kg⁻¹ i.v., but demonstrated apnoea or considerable respiratory depression after morphine sulphate 0.143 mg kg⁻¹ i.v. It was concluded that tramadol had no clinically relevant respiratory depression. In patients breathing spontaneously after major abdominal surgery, with analgesia provided by extradural lidocaine in combination with extradural tramadol 100 mg or morphine 4 mg, morphine but not tramadol produced a fall in arterial oxygen tensions when patients breathed air. Neither drug was associated with a rise in arterial carbon dioxide tensions and the incidence of itching, nausea and vomiting was no different between the two. After tramadol 50 mg or morphine 5 mg i.v. in patients after gynaecological surgery, peripheral
haemoglobin oxygen saturation did not fall below 86% in patients given tramadol, but did fall below this value in 13.3% of patients given morphine i.v. 86%. After lateral thoracotomy in patients given tramadol 150 mg i.v. or morphine 2 mg and 0.2 mg h⁻¹ extradurally, measurements of arterial oxygen tension were higher and those of carbon dioxide tension were lower at 2 and 4 h after surgery in patients who received tramadol. Respiratory depression is unusual in recommended doses and was not found in neonates whose mothers had been given tramadol. The advantage of tramadol over opioids with respect to reduced respiratory depression is limited by the lack of efficacy of tramadol in severe pain, where opioids are more effective.

Unlike non-steroidal anti-inflammatory drugs, tramadol does not inhibit prostaglandin synthesis. Patients with peptic ulceration, renal impairment and asthma may avoid drug-induced exacerbations of these diseases by substituting tramadol for non-steroidal anti-inflammatory drugs. Unlike morphine, tramadol does not elicit histamine release and so does not cause skin flushing and idiosyncratic hypotension.

Although tramadol is substantially haemodynamically stable, transient haemodynamic effects have been recorded after injection i.v. During anaesthesia,ystolic arterial pressures rose 14–16 mm Hg and diastolic pressures rose 10–12 mm Hg for 4–6 min, returning to baseline within 15 min. Postoperatively the blood pressure rise was only 6–9 mm Hg after 1.5 mg kg⁻¹ tramadol i.v. Associated with the changes in systemic arterial pressures, peripheral vascular resistance rose 25% at 2–10 min after injection and there was an increase of 15–20% in the work of the heart over the same period. No clinically significant change in heart rate was demonstrated during postoperative infusion i.v.

Reported gastrointestinal effects of tramadol include nausea, vomiting and constipation, but to a lesser extent than with opioids. There was no increase in the baseline pressure or duration, frequency and amplitude of contractions of the bile duct sphincter when tramadol was given i.v. to patients during endoscopic retrograde cholangiopancreatography (ERCP).

Tramadol has not been recommended for use as an analgesic supplement during-light planes of general anaesthesia because of increased postoperative recall. The anaesthetic technique used involved fentanyl, droperidol and atropine premedication, methohexitone induction and maintenance by nitrous oxide 79% in oxygen. Enflurane was delivered when indicated clinically and patients received either tramadol or saline by infusion. There was no difference between tramadol and placebo patients in the duration or dose of enflurane used, but 65% of patients receiving tramadol and none receiving placebo could recall the music played to them under anaesthesia. As a supplement to anaesthesia including diazepam premedication, propofol and suxamethonium induction and mechanical end-expired concentrations of nitrous oxide 66% and isoflurane 0.7% in oxygen, tramadol 100 mg and 200 mg i.v. obtained minor electroencephalogram changes, no movement to skin incision and no spontaneous conscious recall. The lightening of anaesthesia and increased postoperative recall found with tramadol during anaesthesia with nitrous oxide in oxygen was not reproduced using a technique that included an inhalation anaesthetic agent throughout maintenance of anaesthesia.

Tramadol has a low potential for abuse i.v. in clinical doses and is a prescription-only medicine rather than a drug controlled by the Misuse of Drugs Act. In contrast to morphine in doses of 15 and 30 mg i.m., which was recognized as an opioid by non-dependent opioid abusers and produced subjective effects and miosis, tramadol in doses 75 and 150 mg i.m. was not recognized as an opioid. Tramadol 300 mg was recognized as an opioid, but produced no other morphine-like effects or miosis. Whereas nalbuphine, buprenorphine and morphine elicit tolerance and cross-tolerance, this was not observed with tramadol in arthritic-induced rats after repeated administration of tramadol twice daily for 4 days.

**DOSE**

Tramadol is recommended in a dose of 50–100 mg orally every 4 hours. A total of more than 400 mg per day by mouth is not usually required. Postoperatively, an initial dose of 100 mg i.v. then 50 mg every 10–20 min up to a maximum of 250 mg in the first hour and 600 mg in 24 h (BNF) may be given.

**PHARMACOKINETICS**

Oral tramadol is rapidly absorbed and has a bioavailability of 68% after a single dose and 90–100% after multiple doses. Tramadol begins to appear in plasma after 15–45 min and reaches peak plasma concentrations at 2–4 h. Regular dosing will achieve steady state within 2 days. It has a high tissue affinity with a volume of distribution of 306 and 203 litres after oral and i.v. administration. There is 1% placental transfer. Tramadol is 20% bound to plasma protein with an elimination half life of 5.1 (0.8) h. Liver metabolism accounts for 86% of the absorbed dose by N- or O-demethylation with subsequent sulphation or glucuronidation. The (+)-M1 metabolite O-desmethyl-tramadol is an agonist at the opioid receptor with a higher affinity than the parent compound and a half life of 9 h. Ninety per cent of an oral dose is excreted via the kidneys, the remainder in faeces.

In patients with chronic renal failure and a creatinine clearance of < 30 ml min⁻¹, the dose of tramadol should be reduced to a maximum of 200 mg per day in 12-hly divided doses. With hepatic cirrhosis, the elimination half life is doubled and the maximum dose of tramadol should be further reduced to 50 mg every 12 h. When induction of hepatic enzymes with, for example, carbamazepine 400 mg twice daily occurs, the dose of tramadol can be doubled to compensate for the enhanced hepatic clearance. There has been no correlation demonstrated between plasma tramadol and analgesic effect.

**SUMMARY**

The lack of analgesic efficacy limits tramadol as a sole agent to treat severe pain after surgery. However, it has a relative lack of respiratory depressant and
constituting effects compared with morphine and codeine, and does not share the propensity of non-steroidal anti-inflammatory drugs to provoke asthma, gastrointestinal mucosal damage and renal impairment. It may well have a place in the management of pain after surgery, in combination with another drug, such as paracetamol, or after control of the worst of pain after surgery by a regional local anaesthetic technique.

References


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