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Research Article

OVERVIEW- TRAMADOL: A REFINED OPIOID ANALGESIC

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ABSTRACT
Clinicians and patient alike have long desired a therapeutic agent capable of providing the high level of pain relief for which the opioid are unrivaled, without the cost of potentially life threatening and at least unpleasant adverse effects of commonly associated with drugs such as morphine and pethidine. A synthetic opioid agent 'tramadol' may advances towards achieving this goal.
Tramadol hydrochloride is a centrally acting opioid analgesic with activity similar to that of morphine. The benign side effect profile of tramadol despite good analgesic activity is thought to result from a novel mode of action involving a combination of opioid and non-opioid receptor mechanism. It has excellent therapeutic potential in acute and chronic pain status, but the freedom from respiratory and adverse cardiovascular effects offered by tramadol are particularly advantageous in the post operative situation. μ opiate receptors mediates analgesia and respiratory depression, while *k* receptor mediate analgesia and sedation. The analgesic effects of tramadol are mediated by an opioid, as well as non-opioid mechanism of action. In addition, the drug inhibits nor-adrenaline uptake and stimulates serotonin release; one of the foremost advantages of tramadol is its low addiction liability compared with traditional opioid agents such as morphine. Hence, we can redefine as- Tramadol: a refined opioid analgesic.

Key Words: *Opioids, Analgesia, Hemodynamic Effects, Sphincter of Oddi, Bioavailability*

INTRODUCTION
Despite the importance of post operative pain control, fear of respiratory depression or hypotension with traditional opioid agents may result in some withholding of opioid administration by medical or nursing staff, often aggravating the patient's pain. Clinicians and patient alike have long desired a therapeutic agent capable of providing the high level of pain relief for which the opioid are unrivaled, without the cost of potentially life threatening and at least unpleasant adverse effects of commonly associated with drugs such as morphine and pethidine. A synthetic opioid agent 'tramadol' may advances towards achieving this goal.
Tramadol hydrochloride is a centrally acting opioid analgesic with activity similar to that of morphine. However, unlike other potent analgesics tramadol does not induces respiratory depression or cardiovascular effects of clinical significance when administered at therapeutic dosages. Furthermore, its euphoric effects are slight relative to traditional opioids and its dependence potential is low. As a result, tramadol is not a controlled drug in most countries in which it is marketed, it has definite advantages over alternative opioid such as morphine and pethidine in treatment of severe pain.
The benign side effect profile of tramadol despite good analgesic activity is thought to result from a novel mode of action involving a combination of opioid and non-opioid receptor mechanism. It has excellent therapeutic potential in acute and chronic pain status, but the freedom from respiratory and adverse cardiovascular effects offered by tramadol are particularly advantageous in the post operative situation, when many of the patients for analgesia have disorders in these systems.
The following sections present a pharmacological overview of tramadol:

Pharmacological Profile
Tramadol is a synthetic opioid. Its chemical formula is ±-*trans*-2- [(di-methyl amino) methyl]-1-(m-methoxyphenyl) cyclohexanol hydrochloride. Tramadol is orally and parenterally active, inducing opiate-like analgesia in experimental animals and humans.

Haemodynamic Effects (Muller and Wilsmann, 1984; Vogel et al., 1978; Paravicini et al., 1982)

A benign profile regard to cardiac and haemodynamic effects is highly desirable for centrally acting analgesics in particular, because they are extensively used in patients with cardiovascular disorder.

The effects on blood pressure and heart rate in anaesthetized rabbits were clearly less pronounced with tramadol than with pentazocine. In addition, the negative inotropic action in catecholamine-depleted papillary muscle was considerably less pronounced with tramadol and, in contrast to Pentazocine, in untreated preparation this effect was at least offset by alterations in catecholamine activation.

These results are consistent with clinical experience, where analgesic dose of tramadol 1-2 mg/kg intravenously did not significantly influence arterial pressure, heart rate or left ventricular contractility.

Effects on Respiration (Vickers et al., 1992)

Numerous investigations have shown that tramadol does not produce respiratory depression of the type that occurs with clinical dosage of alternative opioid agents such as morphine and pethidine. The comparative effects of morphine and tramadol on respiration were investigated in 30 patients scheduled to undergo elective surgery under halothane anaesthesia.

They were randomized to receive morphine 0.14mg/kg, tramadol in 1 of 3 dose levels: 0.5, 1 or 2 mg/kg or saline, given intravenously over 30 seconds. And they noticed that, morphine caused greater depression of respiration than all the doses of tramadol. The maximal reduction in respiratory rate was significantly greater with morphine than with tramadol. In addition, morphine rapidly produced a considerable increase in end tidal carbon di-oxide tension, an effect which continued throughout the 30 minute measurement period, whereas the effects of tramadol were short-lived and similar to placebo. Tramadol thus demonstrated clear advantages over morphine: an equi-analgesic dose has much less effect on the respiratory center than morphine, indicating a higher therapeutic ratio.

Mechanism of Action (Hennies et al., 1988; Dhasmana et al., 1989)

μ opiate receptors mediates analgesia and respiratory depression, while *k* receptor mediate analgesia and sedation. The analgesic effects of tramadol are mediated by an opioid, as well as non-opioid mechanism of action. Tramadol is a weak agonist at all types of opioid receptors, with some selectivity for μ receptors. In addition, the drug inhibits nor-adrenaline uptake and stimulates serotonin release; these neurotransmitters in the descending pathways enhances the analgesic response without inducing adverse effects on the cardiovascular and respiratory systems.

Effects on Bile Duct Sphincter (Staritz et al., 1986; Coelhu et al., 1986)

Disturbance of motility of gastrointestinal tract and spasm of the sphincter of Oddi with a secondary increase in biliary pressure is a well known side effect of traditional opioid analgesics. Because analgesics are commonly used as pre medication for endoscopic procedures involving the bile duct sphincter (sphincter of Oddi), their effects on this structure are relevant to clinical practice.

The effects of intravenous opioid analgesics on the sphincter of Oddi were investigated by use of endoscopic retrograde cholangiopancreatography manometry in small groups of patients. Within 10 minutes of Pentazocine injection, increases were noted in the duration of contractions (8.2 *vs* 6.2 seconds) and in the baseline pressure of the sphincter of Oddi (8.8 *vs* 5.1 mmHg). Tramadol along with buprenorphine produced no effects on these variables. In the light of these findings, the author counseled against the use of Pentazocine in endoscopic procedures involving the sphincter of Oddi. It should also be avoided in patients with pancreatic and biliary disorders (Coelhu *et al.,* 1986).

Pharmacokinetic Properties (Lintz et al., 1986; Flick et al., 1978; Lintz et al., 1981; Friderichs et al., 1978)

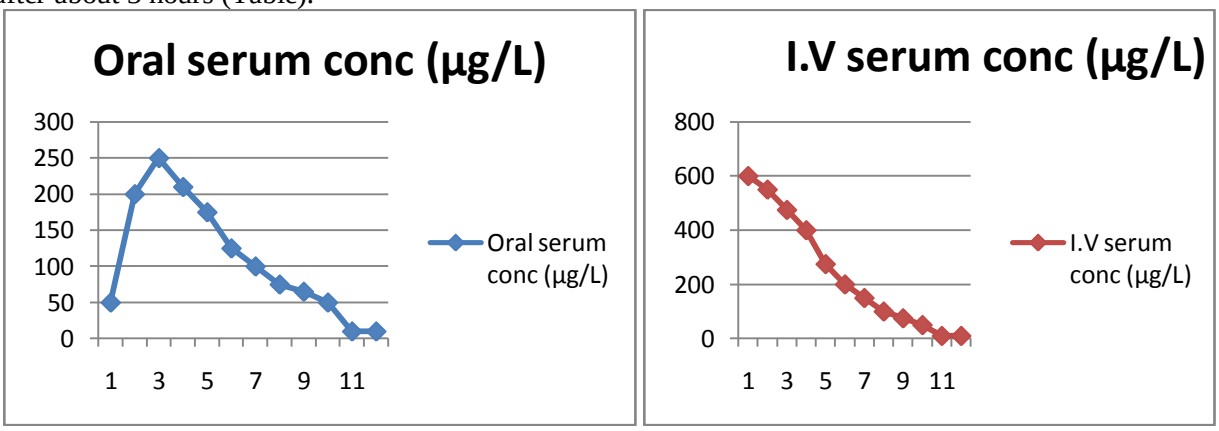
Tramadol is highly effective when given by the intravenous intramuscular or epidural routes and also offers excellent oral absorption (Table).

Route	t1/2 (hrs)	Cmax(mg/L)	Tmax(hrs)	Vd (L)	Cl tot (ml/min)	AUC(mg.h/L)
Intravenous	5.2	-	-	203	467	3709
Oral	5.1	290	1.9	306	710	3488

Abbreviations: Cmax=maximum serum concentration, Tmax= time of maximum serum concentration, Cl tot= total systemic clearance, AUC= area under the plasma concentration-time curve

Absorption

Individual serum concentration profiles for tramadol after oral administration showed very little variation. Oral absorption is quite rapid after a short lag time (Figure), with maximum concentrations occurring after about 3 hours (Table).



The absorption of a weak base such as tramadol would be expected to commence in the duodenum, where the non-ionized tramadol fraction is 10-100 times higher than in the stomach.

The onset of action after oral administration estimated as the time taken to reach a serum tramadol concentration of 100 mg/L was 0.67 hours, indicating that analgesic activity should be evident 40 minutes after 100g oral dose. Based on similar assumptions, the mean duration of action of 100 mg dose is approximately 9 hours with oral administration. With a 50 mg oral dose, the duration of action after oral and intravenous administration was calculated to be 4 hours, and 5 hours, respectively.

If the same duration of action is to be obtained with oral administration as with as with intravenous injection, the oral dose must be increased by a factor of 1.25, or the dosage interval reduced. In view of its relatively long half-life and high bioavailability, oral tramadol is likely to produce a longer duration of analgesia than equi-analgesic doses of agents such as Pentazocine or codeine.

Oral Bioavailability

The oral bioavailability of tramadol administered in a capsule formulation was determined in 10 volunteers. In a balanced crossover design, tramadol 100 mg was administered by the intravenous and oral routes on 2 different occasions separated by at least a week. The subjects fasted for 12 hours before the experiments and received a standard breakfast 2 hours after drug administration. Blood samples (10 ml) were taken from the cubital vein 0.25 hours before and 0.25 (after intravenous injection only), 0.5, 1, 2, 4, 6, 8, 10, 12, 14, and 24 hours after administration.

Serum tramadol concentrations were determined by gas chromatography-mass spectrometry and bioavailability was ascertained by calculation of the areas under plasma concentration-time curves (AUCs). The absolute bioavailability of tramadol in capsule formulation was 68±13% with a range of 41 to 84% and a 95% confidence interval of 55.0 to 79.2%. Relatively little inter-individual variation in the bioavailability of tramadol was found, despite extensive metabolism. This level of bioavailability is the highest reported among centrally acting analgesics. Results approaching the figure obtained for tramadol have only been obtained with pethidine.

Distribution

After intravenous administration, tramadol serum concentration-time curves show the characteristics of 2- or 3-compartment elimination. A distribution phase is not always evident. The volumes of distribution obtained after oral or intravenous administration of tramadol (table) confirm the high tissue affinity of the drug.

Elimination

Tramadol is mainly eliminated by hepatic metabolism, and the So-called 'first-pass' effect reduces the amount of systemically available drug from that absorbed by the gastrointestinal tract. The main biotransformation pathways ate 0- and N-demetheylation. 0-Demethyltramadol has been shown to be 1 to 5 times more potent an analgesic than the patent drug depending on the test, species and route of administration. In humans tramadol metabolism appears to be rather slow, and relatively high amounts are excreted unchanged in the urine. Thus, first-pass extraction in humans is about 20%, which explains the high oral bioavailability.

The terminal-phase elimination half-life of tramadol was very similar after intravenous and oral administration, at about 5 hours. Moreover, the individual values for elimination half-life did not show large variation and ranged from 4.1 to 6.7 Hours.

Addiction Liability

Development of dependence has always been a problem during treatment with opioid analgesics and, depending on the clinical application, may restrict their usefulness. One of the foremost advantages of tramadol is its low addiction liability compared with traditional opioid agents such as morphine. Investigations in rats and mice showed that the development of dependence was less pronounced with tramadol compared with codeine, Pentazocine and morphine. In substitution studies in morphine-dependent monkeys, tramadol did not suppress withdrawal symptoms. In addition, self-administration experiments with monkeys showed no increase in drug requirement.

In volunteers, studies of the psychotropic effects of tramadol have shown no consistent euphoric or dysphoric effects with short term administration Thus, tramadol does not seem to produce psychic dependence. In patients receiving long term intramuscular treatment with tramadol, it was hardly possible to produce even marginal withdrawal symptoms by the application of naloxone. Similar findings have been reported in patients receiving long term oral tramadol therapy. In a multicentre study, 153 in and outpatients received oral tramadol in dosages of up to 400 mg/day for severe pain of various causes. After 3 weeks, 109 of the 121 patients still receiving tramadol were given naloxone 1.6 mg or saline intramuscularly in randomized double-blind fashion (precipitation test), in order to evaluate the risk of dependency. Development of tolerance was not observed, as evident from the relatively constant daily tramadol dosage associated with constant analgesia. The median net withdrawal scores were equivalent in the naloxone and saline-treated groups, indicating an absence of dependence.

Conclusion

- No clinically significant adverse effect on respiration or cardiovascular function at therapeutic dosages
- Novel mode of action involving opioid and non-opioid mechanisms
- No disturbance of motility of gastrointestinal tract or spasm of bile duct sphincter
- Highest bioavailability among opioids (70%)
- Half life consistent- 4 to 7 hours
- Very low abuse/dependence potential
- Virtually free of addiction liability

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