Pharm-04B4 Write short notes on tramadol.

**Background**

Tramadol is a partial opioid receptor agonist, commonly used for its analgesic properties in the management of both acute and chronic pain.

**Physicochemical and Pharmaceutical**

![Chemical structures](image)

LEFT = (1R,2R)-tramadol; RIGHT = morphine

Cyclohexanol derivative (synthetic 1977 but found to ∃ nature in 2013!)

Exists as racemic mixture:
- 1S,2S (+) enantiomer = SSRI and MOP agonist
- 1R,2R (–) enantiomer = SNRI

100 mg in 2 mL tramadol hydrochloride as clear colourless solution for injection tablet/capsule/sachet of various strengths ranging from 50 to 400 mg

Typical dose 3 mg/kg, up to 400 mg per day in divided doses

**Pharmacokinetics**

**Absorption**

Available in IV, IM, PO

Oral bioavailability 70% (can increase to 90% with repeated doses)

Short acting and sustained release preparations available

**Distribution**

Vd = 4 L/kg

20% protein bound

Crosses placenta (80%)

pKa 9.4 → 1% unionised at pH 7.4

**Metabolism**

Hepatic metabolism (demethylation) via CYP 2D6, 3A4 and 2B6 → main metabolite is O-desmethytramadol (200× potency of tramadol at MOP) → contributes to observed analgesic property

Exist CYP 2D6 polymorphism → fast and slow metabolisers

**Slow metabolisers** have **reduced activation** of tramadol and need dose increase

Approximately 10% UK population and 30% Hong Kong Chinese population carry CYP2D6 polymorphism ∴ slow metabolisers
Elimination
Metabolites are glucuronidated by liver → renally excreted.
∴ may accumulate in renal impairment and require dose reduction

$t_{1/2}^\beta$ of tramadol = 5 ~ 6 hrs
$t_{1/2}^\beta$ of O-desmethyltramadol = 9 hrs

Pharmacodynamics

Mechanisms of action
Tramadol’s analgesic properties derive from the synergism between:
(1) direct opioid receptor agonist activity
(2) spinal descending inhibitory pathway activation via SSRI, SNRI and stimulation of presynaptic 5HT release

Note: naloxone only reverses approx 30% of analgesic effect of tramadol (in healthy volunteers; Collart, Luthy et al 1993)

MOP binding > KOP and DOP

Potency
1/10 potency of morphine
Comparable potency to pethidine

CNS
Analgesia → dual mechanism, analgesic effect diminished with 5HT antagonists (e.g. ondansetron)
Sedation → less than morphine at equianalgesic doses
Nausea + vomiting → both via MOP activation and 5HT release at CTZ
Seizures → either direct or via interaction with other medications

Partial MOP agonist → has ceiling effect + less conducive of tolerance/dependence/abuse + opioid induced hyperalgesia

May precipitate serotonin syndrome → constellation of (1) autonomic (SNS surge, hyperthermia); (2) musculoskeletal (rigidity) and (3) neurological (agitation, seizures) instabilities

Some suggestion that tramadol may ↑ risk of awareness under GA (? via SNRI)

RESP
Less respiratory depression vs morphine at equianalgesic doses

CVS
Minimal effect
Possible serotonin syndrome → tachycardia, hypertension

GIT
Less constipation and gastric emptying slowing vs morphine at equianalgesic doses
**Examiner’s Comments** - 50% of candidates passed this question.

Many candidates handled this question well. A complete answer was helped by organising the essay around sub-headings such as pharmacodynamics, pharmacokinetics, adverse effects and so on.

While most answers recognised that tramadol is presented as a **racemic mixture**, only a proportion went on to say that **each isomer had specific effects** contributing to the analgesic effect of the drug. Likewise, while the majority of answers noted that the drug has **actions on opioid and non-opioid sites**, nobody mentioned that the drug’s **analgesic effect is as a result of this somewhat peculiar synergistic activity**.

As an analgesic, it is useful to compare it to a standard opioid such as morphine and most did so, noting its reduced potential for the development of tolerance and dependence and respiratory depression. Pharmacokinetic aspects were less well handled with many failing to note that **tramadol is highly metabolised** and that one metabolite (M1 or O-desmethyl tramadol) has considerable activity at the opioid receptor and may **contribute to the drugs activity**.

As with codeine, a proportion of patients **deficient in the P450 cytochrome CYP2D6 enzyme will fail to form this product and may exhibit reduced analgesia**.

Some candidates noted other interesting features of the drug such as an improvement in **oral bioavailability with multiple dosing**; the suggestion that **tramadol might increase the risk of awareness under general anaesthesia** and that **tramadol’s analgesic effect might be antagonised by 5HT 3 antagonists**.