

Pentazocine

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INTRODUCTION

In 1967 pentazocine became the first opioid agonist-antagonist to be introduced into clinical practice as an analgesic. It was hoped that pentazocine would prove to be a powerful analgesic, free of the side-effects of opioid narcotics, particularly avoiding drug dependency. In practice pentazocine has proved to be less effective than hoped, but it is still used widely in resource-poor countries.

CHEMISTRY

Pentazocine is a benzomorphan which is chemically related to morphine. It is a white or cream, odourless, crystalline powder. It consists of a racemic mixture of dextro- (d) and laevo- (l) isomers which is soluble in acidic aqueous solutions. Pentazocine hydrochloride is used for oral use and the lactate form is used for parenteral and rectal administration.

Molecular weight (free base).....	321.9
pKa.....	8.7
Solubility in water	1 in 30
Chemical structure.....	C ₁₉ H ₂₇ NO.HCl

PHARMACODYNAMICS

The action of pentazocine is mainly due to its l-isomer and it is a potent analgesic with both an agonist and antagonist action at opioid receptors. It differs from morphine in that it is a weak antagonist at OP3 (μ) opioid receptors, with its analgesic action due to an agonist action on OP2 (κ) receptors which interrupts pain pathways in the spinal cord. It also has some agonist action at other receptors which may result in dysphoric side-effects. It has no anti-inflammatory or anti-pyretic function.

Given intravenously, estimates of its potency vary from one third to one quarter the strength of morphine. This ratio is similar with intramuscular

use with 30 - 40 mg of pentazocine equivalent to 10 mg morphine. When given by mouth, the analgesic action of pentazocine is much weaker than morphine and is thought to lie somewhere between that of peripherally acting analgesics such as paracetamol and weak opioids such as codeine.

Other actions of pentazocine mirror those of other opioids including respiratory depression, cough suppression, miosis, decreased gastric emptying and constipation and increased smooth muscle tone in the uterus and bladder. However in normal use these effects are usually of little clinical significance.

In contrast to other strong opioid analgesics however, there is a dose-related systemic and pulmonary hypertension, increased left ventricular end-diastolic pressure and a rise in central venous pressure, probably as a result of a rise in plasma catecholamine concentrations. Pentazocine also increases renal plasma flow but no change in glomerular filtration rate is seen.

PHARMACOKINETICS

Absorption

Pentazocine is completely absorbed after oral administration with peak plasma concentration at about 1-3 hours and a mean plasma half-life of about 2 hours. However blood levels show considerable variation both within and between subjects due to extensive but variable pre-systemic (hepatic) elimination.

Oral bioavailability ranges from 11 to 32% in subjects with normal hepatic function. Regardless of route of administration, pain relief lasts 2-3 hours as a maximum.

Animal studies show rapid and widespread distribution in the liver, lungs, kidneys, muscle and brain following IV or IM administration.

Summary

This article describes the pharmacology and clinical uses of the opioid agonist-antagonist pentazocine. Pentazocine is widely used around the world despite its considerable side-effects and tendency to cause dependency. It still has a useful function to play in the management of moderate to severe pain when used intravenously or intramuscularly, but should not replace morphine or pethidine if available.

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Low levels are detected in organs other than the liver after oral administration due to pre-systemic elimination.

The apparent volume of distribution varies but indicates significant drug accumulation in some tissues. Plasma protein binding is also variable, but up to 50 % may be present in red blood cells. Placental transfer occurs, with mean cord blood levels in the region of 60-70 % of those in maternal blood.

Table 1. Peak plasma concentrations

Route of administration	Time to peak plasma concentration (minutes)
Intravenous	2-3
Intramuscular/ subcutaneous	15-30
Oral	60-90

As a result of extensive hepatic metabolism, less than 10 % of an oral dose appears unchanged in the urine, although in patients with cirrhosis a significant reduction in body clearance and a marked increase in bioavailability are seen.

Metabolism and elimination

Up to 10 % is excreted unchanged in the urine with 1-2 % in the faeces as a result of enterohepatic circulation. Both are independent of the route of administration. The remainder

undergoes extensive hepatic metabolism, including conjugation with glucuronic acid and oxidation of the terminal methyl groups of the dimethylallyl side chain. The two principle metabolites found in the urine are the cis-alcohol metabolite (11 %) and the trans-carboxylic acid metabolite (40 %). Both are inactive.

An increased rate of metabolism due to enzyme induction has been reported in smokers and following nitrous oxide administration.

PHARMACEUTICAL PREPARATIONS

Trade names of pentazocine include Fortral, Talwin, Fortralgesic, Fortralin, Sosegon, Sosenyl, Pentgin and Liticon. Pentazocine is also available in combination with aspirin and paracetamol (acetaminophen).

DOSE AND PATIENT RESTRICTIONS

As with analgesics in general there is no consistent relationship between analgesic activity and plasma concentrations of pentazocine. However normal doses are set out in Table 3.

Adults

Oral administration is usually started at 50-100 mg every 3-4 hours; titrating dose and frequency of administration to pain relief with the total daily dose not exceeding 600 mg.

Starting treatment at night, and using frequent smaller doses in preference to less frequent large doses, helps to reduce the incidence of side effects. Rectal administration may give more prolonged analgesia than equivalent oral doses.

Table 2. Pharmaceutical preparations of pentazocine

Parenteral forms:	
1. Talwin injection (USA):	30mg/ml in 1 or 2ml ampoules, sterile cartridge needle units, 10ml multiple dose vials. Mixed in an aqueous solution of pH4-5 as pentazocine lactate. For IV, IM and subcutaneous injection.
2. Fortral injection (UK):	30mg/ml in 1 or 2 ml ampoules for IV, IM or subcutaneous use
Oral forms:	
1. Talwin-Nx (USA)	50mg pentazocine with 500mcg naloxone
2. Fortral tablets (UK)	25mg and 50mg pentazocine hydrochloride tablets
3. Talwin Compound	12.5mg pentazocine with 325mg aspirin (2 tablets three-four times daily)
4. Talacen (acetaminophen)	25mg pentazocine with 650mg paracetamol (1 tablet four hourly)
Rectal forms:	
1. Fortral suppositories	50mg pentazocine lactate
Generally preparations should be stored at room temperature and protected from light and freezing	

Table 3. Dosing of pentazocine

Route of administration	Dose	Interval	Total dose in 24 hour
Intravenous - inject undiluted by slow bolus	0.5 mg/kg or 30-40mg	3-4 hourly	not to exceed 360mg
Intramuscular - inject deep into well developed tissue	1.0 mg/kg or 30-60mg	3-4 hourly	not to exceed 360mg
Oral	50-100mg	3-4 hourly	not to exceed 600mg

Use subcutaneous injection only when necessary: severe tissue damage is possible at injection sites

Children

Oral administration under the age of 6 years is not recommended. Some sources recommended avoiding pentazocine for children of 6-12 years, although other studies suggest 25 mg every 3-4 hours as a suitable dose. Children over 12 years may receive an adult dose.

Use in pregnancy

Safety has not been unequivocally established and pentazocine should be used with caution. Neonatal dependency has been reported in women who have taken 50-300 mg daily throughout pregnancy.

Pentazocine has not been demonstrated to pass into breast milk although monitoring is recommended if high doses are prescribed.

Use in the elderly

Although no specific problems have been identified, care is required with impairment of hepatic or renal function as it may predispose to increased toxicity.

THERAPEUTIC USE

Postoperative pain

Pentazocine is a controlled drug in the UK and is prescribed parenterally for moderate to severe acute postoperative pain. In these circumstances 30-60 mg by IM or SC injection has a similar analgesic action to 10 mg morphine or 100 mg pethidine (meperidine).

In comparison to morphine or pethidine, the duration of action of pentazocine is slightly shorter. It has been claimed that pentazocine produces a lower incidence of side-effects in postoperative patients compared with morphine and pethidine, in particular nausea and vomiting, sedation and hypotension. However the side-effects of pentazocine are dose-related and overall the incidence and severity of side-effects at equivalent analgesic doses are similar with all three drugs.

Oral pentazocine is not a strong analgesic. While some comparisons show it to be as effective as codeine or dihydrocodeine, other studies have shown aspirin to have a

greater analgesic effect than pentazocine. It is clear that the duration of analgesia produced by pentazocine is about 3 hours.

Chronic Pain

The usefulness of oral pentazocine in chronic pain is limited by its weak and unpredictable analgesic activity, dose-related (particularly psychomimetic) side-effects and its ability to antagonise the effects of pure opioid agonists if used concurrently.

Obstetrics

Pentazocine appears to be an effective analgesic during labour. There is some evidence that uterine activity may be increased and, compared with pethidine, the second stage of labour may be shortened. However there is no advantage with regard to side-effects; respiratory depression is comparable to pethidine in both the mother and the neonate.

Renal and biliary colic

Pentazocine may be used for the relief of acute pain of renal or biliary colic and has been shown to cause less smooth muscle contraction in renal and biliary tracts than morphine. However another study has shown a significant rise in intrabiliary pressure so that its use may be best avoided if other drugs are available.

Myocardial infarction

Pentazocine is an effective analgesic post myocardial infarction and may cause a rise in systolic blood pressure in contrast to the hypotensive effect of other opioids. However the associated rise in pulmonary artery pressure, left ventricular end-diastolic pressure and left ventricular minute work is potentially hazardous as it may lead to an increase in myocardial oxygen demand and extension of the infarcted area. An alternative opioid analgesic is generally preferred.

Intravenous anaesthesia and premedication

There have been attempts to use pentazocine for intravenous anaesthesia and as a premedicant prior to general anaesthesia. However it confers no advantage over standard drugs and is generally only used when other drugs are not available.

CONTRAINDICATIONS

1. Respiratory depression
2. Raised intracranial pressure
3. Arterial or pulmonary hypertension
4. Pre-existing opioid dependency
5. Porphyria

Respiratory depression

This is mainly found with the l-isomer and in equipotent doses to that seen with morphine. Care is required in patients with impaired respiratory drive. Transient apnoea may occur in the neonate following its use in labour.

Raised intracranial pressure

Pentazocine increases intracranial fluid pressure in patients with an acute brain injury or when ICP is already increased due to a space-occupying lesion. However these changes are not seen in normal patients or in patients ventilated after a head injury, suggesting that mild respiratory depression with an associated intracranial vasodilatation from a rise in PaCO₂ may be the underlying cause.

Arterial or pulmonary hypertension

Pentazocine increases both heart rate and systolic blood pressure to a variable and unpredictable degree and should be avoided in patients with hypertension. IV doses of 30-60mg may cause an increase in pulmonary artery pressure with an associated increase in left ventricular end-diastolic pressure and their use should also be avoided. An increase in central venous pressure has also been reported but little consistent effect on systemic vascular resistance, cardiac output, stroke volume or coronary perfusion has been found.

Pre-existing opioid dependency

Withdrawal effects may occur in patients with opioid dependency due to its opioid antagonistic action.

Porphyria

Pentazocine has been found to be porphyrogenic in rats and on this basis is not recommended for use in patients with porphyria.

ADVERSE REACTIONS

Despite hopes that pentazocine would have less severe side-effects than pure μ -receptor agonists, this has not been the case in practice.

Life threatening adverse effects

Respiratory depression - when used as an adjuvant to anaesthesia in patients with chronic respiratory insufficiency.

Agranulocytosis - latency of 4-24 weeks from exposure to the drug. Although fatalities have been reported most cases are reversible on withdrawing the drug.

Severe or irreversible adverse effects

Epileptic seizures - rare and most often associated with high dose IV use during anaesthesia, or if there is an underlying intracranial pathology.

Addiction - although not considered addictive when first introduced, its potential for abuse has been increasingly recognised, particularly for the IV formulation which has resulted in greater control over its prescribing. As a consequence pentazocine-only tablets have been withdrawn in the USA in favour of one in combination with naloxone. Although naloxone is ineffective when given orally it is effective when injected IV.

Withdrawal symptoms are usually mild and include anxiety, dysphoria, tremor, sweating and musculoskeletal pains.

Pruritis - stinging, flushing when given IV. Repeated IM injections may cause soft tissue induration, fibrosis or ulceration, hyperpigmentation and a myopathy which, if severe, may impair movement resulting in contractures (more often associated with drug abuse rather than therapeutic use).

Symptomatic adverse effects

They are often dose-related, mild and self-limiting but can be severe:

- Psychotomimetic effects in 20% of patients. Includes disturbed dreams, auditory or visual hallucinations, euphoria and depersonalisation. Naloxone may be effective.
- Sedation, light headedness, vertigo
- Nausea and vomiting
- Other opioid side-effects include sweating, hot flushes, dry mouth, urinary retention
- Blurred vision, nystagmus, diplopia, miosis
- Headaches, chills and fever.

ACUTE OVERDOSE

Deaths due to pentazocine alone are rare. The main clinical features are respiratory depression, tachycardia and hypertension. Status epilepticus, coma, acidosis, respiratory depression, profound hypotension and ventricular arrhythmias can also be found.

Treatment is IV naloxone, a competitive antagonist at the opioid receptors, mediating the respiratory depression and maintaining respiration. Dose given is 0.1 mg repeated at 2-minute intervals according to the clinical state of the patient. 0.4-2 mg is sufficient in most cases although higher doses of 15-20 mg have been known to be required. An infusion of naloxone may be required.

OTHER EFFECTS

No significant biochemical effects have been recognised. No interference with clinical pathology tests. IM injections may increase creatine kinase levels.

DRUG INTERACTIONS

- **Halothane** - increases respiratory depression and hypotensive effects.
- **Anticoagulants** - may increase anticoagulant effect of both heparin and oral coumarins (e.g. warfarin).
- **Lignocaine** - prior administration enhances respiratory depressant effect of pentazocine.
- **CNS depressants** - increased sedation.
- **Opioid analgesics** - withdrawal effects if opioid dependency.
- **Monoamine oxidase inhibitors** - increased toxicity in mice although not demonstrated in humans.
- **Barbiturates** - do not mix in the same syringe as precipitation will occur.

CONCLUSION

Pentazocine was introduced in the hope that it would provide pain relief for moderate to severe pain without the side-effects of morphine. Unfortunately the reality has been disappointing. Although 30 mg of IM or IV pentazocine is comparable to 10 mg morphine, it has a more variable efficacy than morphine and its side-effects are still considerable, particularly the

potential for dependency. This almost certainly accounts for the decrease in its use in the United Kingdom. Despite its removal from the WHO guide of essential drugs, it is still widely used in some poorly-resourced countries.

In summary, pentazocine still has a useful function to play in the management of moderate to severe pain when used intravenously or intramuscularly but should not replace morphine or indeed pethidine if available.

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