

Drug differences

Table 5.1 Differences between atropine and hyoscine

	<i>Atropine</i>	<i>Hyoscine</i>
Source:	Atropa belladonna and Datura stramonium	Hyoscyamus niger and Scopolia canolica
Chemistry:	Ester of tropic acid and tropine	Ester of tropic acid and scopine
Mechanism of action:	Antimuscarinic, competitive antagonist of acetylcholine	Antimuscarinic, competitive antagonist of acetylcholine
Duration of action:	Prolong	Short
Peripheral antimuscarinic action:	More prominent on heart, GIT and bronchial muscle	More prominent on eyes, salivary and bronchial secretion and sweat
Action on CNS:	Stimulation, followed by depression	Depression from the beginning (in the presence of pain, there may be excitement)
Loss of memory:	Not seen	It causes amnesia to recent events. It is thus more commonly used as a pre-anaesthetic medication as compared to atropine
Motion sickness and Parkinsonism:	Less useful	More useful
Toxicity:	Restlessness, excitement, mania and delirium	Drowsiness
Dose:	0.25–2 mg	0.3–0.6 mg

Table 5.2 Differences between non-opioids (NSAIDs) and opioids

	Non-opioids (NSAIDs)	Opioids
Source:	Synthetic	Natural opium alkaloids/semi-synthetic/synthetic morphine substitutes
Structure:	Heterogeneous	Phenanthrene compounds, benzyl-isoquinoline compounds
Type of pain relieved:	Somatic pain arising from musculoskeletal structures	Deep visceral pain
Mechanism of action:	<ul style="list-style-type: none"> • Inhibition of prostaglandin synthesis by inhibiting the cyclooxygenase enzyme • Inhibits generation of nociception by inhibiting the peripheral nociceptors • No action on specific opioid receptors (μ, κ, δ, ϵ, σ) 	<ul style="list-style-type: none"> • Decreased nociception input, decreased processing and integration, decreased transmission, decreased perception and decreased emotional reaction to pain. Decreased release of neurotransmitters (especially excitatory neurotransmitters like glutamic acid). By causing hyper-polarisation due to increase in potassium efflux • Acts on opioid receptors (μ, κ, δ, ϵ, σ)
CNS depression:	Do not depress CNS	Depress CNS

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Table 5.2 Differences between non-opioids (NSAIDs) and opioids (continued)

	Non-opioids (NSAIDs)	Opioids
Pharmacological actions and effects:	<ul style="list-style-type: none"> • Acts as analgesics, antipyretic, anti-inflammatory, antiplatelet (at low doses) and uricosuric (at high doses) • No antispasmodic effect on GIT smooth muscles (unlike morphine which commonly causes constipation, NSAIDs do not cause constipation) 	<ul style="list-style-type: none"> • Acts only as analgesics. Also produce euphoria, sedation, hypnosis and cough suppression. No antipyretic and anti-inflammatory effects • Morphine-like alkaloids produce constipation through decreased intestinal peristalsis which is mediated by effects on opioids receptors in the enteric nervous system. Hence clinically used as antidiarrhoeal agents • Also opioids alone produce contraction of sphincter pupillae (→ miosis), truncal rigidity, contraction of biliary smooth muscle (→ biliary colic), contraction of sphincter of Oddi (reflux of biliary and pancreatic secretion) and relaxation of uterine smooth muscle (→ prolongation of labour)
Tolerance and dependence:	Do not produce tolerance/dependence	Produce tolerance/dependence
Withdrawal syndrome:	Do not produce withdrawal syndrome	Produce withdrawal syndrome
Side effects:	Mainly due to inhibition of prostaglandin synthesis like peptic ulceration, upper GI bleed, bleeding tendency, precipitation of an acute attack of asthma (due to ↑ synthesis of leukotrienes), Reye's syndrome (hepatic fatty degeneration and encephalopathy), ARF, interstitial nephritis, respiratory alkalosis (at high doses) and metabolic acidosis (at toxic doses)	Mainly due to CNS depression. Most serious is depression of the respiratory centre; others include ↑ ICP, postural hypotension, urinary retention, constipation, itching around nose and urticaria

Table 5.3 Differences between morphine and pethidine

	<i>Morphine</i>	<i>Pethidine</i>
Source:	Natural	Synthetic
Chemistry:	Phenanthrene derivative	Phenylpiperidine derivative
Pharmacokinetics:	<ul style="list-style-type: none"> • Route of administration: S/C, I/M, I/V, epidural, intrathecal and per-rectal • Bioavailability: 25% • Plasma protein binding: 33% • Onset of action: slow • Duration of action: longer (3–5hrs) 	<ul style="list-style-type: none"> • Route of administration: Oral, S/C, I/M • Bioavailability: 50% • Plasma protein binding: 60% • Onset of action: quick • Duration of action: short (2–4hrs)
Metabolism:	Glucuronidation in liver	Demethylation in liver
Metabolites:	Morphine-3-glucuronide and Morphine-6-glucuronide. Both metabolites are active	Normepidine (→ CNS stimulation; but no analgesic property)
Pharmacodynamics:	<ul style="list-style-type: none"> • Receptors: μ predominantly • Potency: more as analgesic • Sedation: more marked • Miosis: present • Corneal anaesthesia and loss of corneal reflex: absent • Bronchoconstriction: present • Cough suppression: present • Effect on heart rate: bradycardia • Antimuscarinic effects: absent • Spasmogenic effect: present • Urinary retention: present • Constipation: more marked • Pregnancy and lactation: contraindicated because morphine delays labour • Withdrawal syndrome: long-lived (8–10 days) 	<ul style="list-style-type: none"> • Receptors: κ predominantly • Potency: 1/10th as analgesic • Sedation: less marked • Miosis: absent • Corneal anaesthesia and loss of corneal reflex: present (on parenteral administration) • Bronchoconstriction: absent • Cough suppression: absent • Effect on heart rate: tachycardia • Antimuscarinic effects: present • Spasmogenic effect: absent • Urinary retention: absent • Constipation: less marked • Pregnancy and lactation: can be given (no effect on labour) • Withdrawal syndrome: short-lived (4–6 days)
Therapeutic uses:	Analgesic, LVF with massive pulmonary oedema, pre-anaesthetic medication and anxiety	Analgesic (for short procedures like upper/lower GI endoscopy, cystoscopy, I/V ascending pyelography)
Excretion:	Not affected by acidification of urine	Acidification of urine increases excretion

Table 5.4 Differences between heparin and warfarin

	<i>Heparin</i>	<i>Warfarin</i>
Source:	Bovine lungs, porcine intestinal mucosa	Semi-synthetic
Chemistry:	Mucopolysaccharide	Coumarin derivative
Structure:	Large polymer, acidic	Small, lipid-soluble
Route of administration:	Parenteral (S/C, I/V)	Oral
Site of action:	Blood	Liver
Mechanism of action:	It binds to antithrombin-III (ATIII) forming a heparin-ATIII complex. This complex binds and irreversibly inactivates thrombin (activated factor II), factors IXa, Xa, XIa, XIIa, and XIIIa. In the presence of heparin, ATIII proteolyzes clotting factors 1000-fold faster than in its absence	Warfarin inhibits Vit-K dependent synthesis of factors X, VII, IX and X in the liver by inhibiting the enzyme Vit-K epoxide reductase
Onset of action:	Quick (in seconds). Since heparin acts by inactivating the pre-formed clotting factors, it produces its therapeutic effect immediately	Slow (36–48hrs). Since warfarin acts by inhibiting the synthesis of clotting factors, its therapeutic effect is produced only when the pre-formed clotting factors having $t_{1/2}$ of 8–60hrs are eliminated from the circulation. Also, whereas effect of warfarin can be reversed by giving Vit-K, it only occurs when Vit-K causes the synthesis of new clotting factors – a process that takes 6–24hrs. More rapid reversal requires transfusion of fresh frozen plasma (FFP) that contains normal clotting factors
Effect on vascular tone:	Vasodilatation	Nil
Duration of action:	Short (10–15 min)	Long (4–7 days)
Protein binding:	Nil	Extensive
Metabolites:	Uroheparin	S-warfarin-7-hydroxy warfarin; R-warfarin-warfarin alcohol
Half-life:	40–90 min	15–70hrs

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	<i>Heparin</i>	<i>Warfarin</i>
Therapeutic uses:	Used when anticoagulation is needed immediately, i.e. on starting anticoagulant therapy, heparin is given first, followed 24hrs later by warfarin. Important therapeutic indications include DVT, pulmonary embolism, acute MI (in combination with thrombolytics for revascularisation), atrial fibrillation, coronary angioplasty and placement of coronary stents (in combination with glycoprotein IIb/IIIa inhibitors), CVA, haemodialysis/peritoneal dialysis, anticoagulation during pregnancy and to preserve blood in vitro	Warfarin is used for chronic anticoagulation (starting 24hrs after commencement of heparin therapy) in all of the clinical situations described for heparin (except during pregnancy). Heparin-warfarin combination therapy is continued for 4–5 days, followed by warfarin monotherapy for months or may be more depending upon the indication
Pregnancy and lactation:	Safe	Contraindicated (teratogenic: causes bone defects and multiple haemorrhages in the developing fetus)
Adverse effects:	Bleeding (commonest side effect), thrombocytopenia, osteoporosis, transient alopecia, allergic reactions (like asthma, urticaria and anaphylactic shock)	Bleeding (commonest side effect), teratogenicity, decreased production of Protein C (→ development of a period of hypercoagulability; heparin is thus always started before warfarin therapy to avoid the development of hypercoagulability)
Drug interactions:	Nil	Cytochrome P450-inducing drugs → ↑ warfarin clearance → ↓ anticoagulant effect. Cytochrome P450-inhibiting drugs → ↓ warfarin clearance → ↑ anticoagulant effect
Antidote:	Protamine sulphate 1% I/V is the antidote for unfractionated heparin; it only partially reverses the effects of LMW heparins	Vit K (phytomenadione) I/V

Table 5.5 Differences between cimetidine and ranitidine

	<i>Cimetidine</i>	<i>Ranitidine</i>
Chemistry:	Imidazole derivative	Furan derivative
Duration of action:	Short (4–6hrs)	Long (8–12hrs)
Bioavailability:	60%	50%
Plasma protein binding:	20%	15%
Binding with cytochrome P450:	Present	Negligible
Increase in cell-mediated immunity:	Yes	No
Hepatic blood flow:	Decreased	Decreased
Crossing of blood brain barrier (BBB):	Poor	Very poor
Potency:	Less	5–10 times more potent
Elimination $t_{1/2}$:	2–3hrs	2–3hrs
Drug interactions:	Interferes with hepatic metabolism of drugs like digoxin, warfarin, benzodiazepines, beta-blockers, etc.	Negligible
Toxicity:	CNS: lethargy, hallucinations, convulsions Endocrine: Unlike ranitidine, cimetidine causes hyperprolactinemia (→ gynecomastia in males and galactorrhea in females) Hepatotoxicity: As compared to ranitidine, cimetidine is a potent inhibitor of hepatic drug metabolising enzyme (CYP450)	Endocrine: Doesn't cause hyperprolactinemia. Hepatotoxicity: Less potent inhibitor of hepatic drug metabolising enzyme (CYP450)
Dose:	800 mg/day in divided doses	300 mg/day in divided doses

Table 5.6 Differences between adrenaline and noradrenaline

	<i>Adrenaline</i>	<i>Noradrenaline</i>
Source:	Adrenal medulla	Postganglionic sympathetic nerve endings
Chemistry:	Catecholamine (contains methyl group)	Catecholamine (does not contain methyl group)
Receptors stimulated:	$\alpha 1, \alpha 2, \beta 1, \beta 2, \beta 3$	$\alpha 1, \alpha 2, \beta 1$
Effects on the cardiovascular system:	Rate: \uparrow <ul style="list-style-type: none"> • Force of contraction: \uparrow • Excitability and conductivity: much increased • Coronary blood flow: \uparrow • Cardiac output: \uparrow • Arteriolar tone in the skeletal muscles: vasodilatation • Arteriolar tone in skin and viscera: vasoconstriction • Total peripheral resistance: \downarrow • Systolic blood pressure: \uparrow • Diastolic blood pressure: \downarrow 	Rate: \downarrow <ul style="list-style-type: none"> • Force of contraction: little effect • Excitability and conductivity: increased • Coronary blood flow: \uparrow • Cardiac output: no change or \downarrow • Arteriolar tone in the skeletal muscles: vasoconstriction • Arteriolar tone in skin and viscera: vasoconstriction • Total peripheral resistance: \uparrow • Systolic blood pressure: \uparrow • Diastolic blood pressure: \uparrow
Effects on smooth muscles:	<ul style="list-style-type: none"> • Intestine and bladder: relax • Bronchi: relax • Sphincter: constrict • Uterus: inhibition of uterine contraction • Eye: mydriasis 	<ul style="list-style-type: none"> • Intestine and bladder: relax • Bronchi: little effect • Sphincter: constrict • Uterus: stimulation of uterine contraction • Eye: mydriasis
Metabolism (glycogenolysis and O_2 consumption):	\uparrow	Insignificant effect

Table 5.7 Differences between methyl dopa and clonidine

	<i>Methyldopa</i>	<i>Clonidine</i>
Structure:	Structural analogue to levodopa	2-imidazole derivative
Mechanism of action:	It is a pro-drug. After having being converted to alpha-methyl-norepinephrine, it acts as an agonist on the postsynaptic α_2 -receptors in the CNS \rightarrow \downarrow sympathetic outflow from the centre to periphery	It is an active drug that acts as an agonist on the postsynaptic α_2 -receptors in the CNS \rightarrow \downarrow sympathetic outflow from the centre to periphery
Pharmacokinetics:	On oral administration, absorption is incomplete and slow with extensive first-pass metabolism. Elimination is mainly through liver metabolism and some through renal excretion	Being lipid-soluble, GI absorption of clonidine is rapid. Elimination is mainly through renal excretion
Route of administration:	Oral, sometimes I/V in emergencies	Oral and transdermal (in the form of patch), but never I/V
$T_{1/2}$	2hrs	8–12hrs
Bioavailability:	25%	95%
Dose-response curve:	Increasing doses are not more effective	Increasing doses are more effective (and also more toxic)
Reduction in dosage required in moderate renal insufficiency:	No	Yes
Pharmacologic effects:	It reduces blood pressure chiefly by reducing peripheral vascular resistance	It reduces blood pressure both by reducing heart rate (and thus cardiac output) and peripheral vascular resistance
Therapeutic uses:	Mild to moderate cases of hypertension, hypertensive crisis and carcinoid syndrome	Mild to moderate cases of hypertension, diabetic diarrhoea ($\rightarrow \uparrow \text{Na}^+$ and H_2O reabsorption and \downarrow secretion of HCO_3^-) and alcohol/tobacco/opioid withdrawal syndrome. It is contraindicated in hypertensive crisis

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	<i>Methyldopa</i>	<i>Clonidine</i>
Toxicity:	Causes sedation (commonest side effect), extrapyramidal signs (Parkinsonism), ↑ prolactin secretion (→ lactation), positive Coomb's test, hemolytic anaemia, hepatitis and drug fever	Common side effects include sedation and dry mouth. It also causes depression. In case depression develops during the course of the therapy, clonidine should be withdrawn. If withdrawn suddenly after protracted use, clonidine can precipitate hypertensive crisis. It should, therefore, be withdrawn gradually. In case hypertensive crisis develops, it is treated by reinstitution of clonidine or administration of α - and β -blockers