

# Intravenous Anaesthetics

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## HISTORY

- intravenous anaesthesia as we know it today, dates from the introduction of **thiopentone** in 1934
- this was actually preceded by **hexobarbital** in 1932
- prior to this, the triad of anaesthesia, hypnosis, analgesia and muscle relaxation had been provided by a single inhalation agent, eg., ether or chloroform
- intravenous agents may be used for,
  - a. induction of anaesthesia
  - b. as a sole agent
  - c. to supplement general anaesthesia or regional anaesthesia
  - d. for sedation
- Sir Christopher Wren is usually given the credit for the first intravenous injection of fluids and drugs with anaesthetic properties
- in 1665 he reported to the Royal Society the injection of wine using a pig bladder and quill
- the hollow needle was perfected by Francis Rynd of Dublin (1845)
- the syringe was developed by Alexander Wood of Edinburgh (1855)
- both injected morphine to relieve pain
- the first GA was administered in 1846 but an inhalation anaesthetic agent was used
- ether & chloroform were used successfully as sole agents until the beginning of this century, though, some also added a N<sub>2</sub>O/O<sub>2</sub> mixture
- diluted ether and chloroform have also been administered intravenously but this has never gained popularity

## Barbiturates

- **barbituric acid**, a malonylurea devoid of hypnotic properties, was first prepared by Von Baeyer of Germany in 1864
- the first sedative barbiturate, diethyl barbituric acid or **barbitone** was described by Fischer and Von Mering in 1903 and enjoyed popularity as long lasting hypnotic sedative for many years
- **phenobarbitone** was discovered in 1912 is still used as anticonvulsant
- **somnifene**, a mixture of diethyl amines, diethyl and diallyl barbituric acids, was the first barbiturate used intravenously in 1921
- however **pernoston**, introduced by a German obstetrician, Bumm (1927), was the first barbiturate to gain widespread use as an intravenous anaesthetic
- **hexobarbitone**, introduced by Weese & Scharpff (1932) was popular in Europe
  - ~ 10 million anaesthetics in its first 10 years of use
- **thiopentone** was first administered by Lundy & Waters in 1934
- early use was associated with a large number of disasters due to the lack of knowledge of the drugs pharmacokinetics
- use of the drug for the induction and maintenance of anaesthesia for casualties in Pearl Harbour resulted in its description as "an ideal method of euthanasia"
- **methohexitone** used first by Stoelting (1957) is still used today

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## Non-Barbiturates

### ■ Eugenols

- there are chief constituent of oil of cloves, thus are insoluble in water
- *propanadid* was initially solubilized in Cremophor EL
- first used in Germany (1956), now withdrawn from the market due to hypersensitivity reactions to Cremophor

### ■ Steroids

- hydroxydione (1955) was never popular due to a high incidence of thrombophlebitis
- *althesin*, a mixture of alphaxolone and alphadolone in cremophor EL, provided a rapid onset and rapid recovery, however also had a high incidence of hypersensitivity reactions and was withdrawn from the market
- *minaxolone* (1978) produced a rapid onset with somewhat slower recovery than althesin
- toxicity in rats in some studies led to its withdrawal from clinical studies

### ■ Phencyclidine Derivatives

- *ketamine* "dissociative anaesthesia" was introduced in 1965

### ■ Propofol

- first clinical trials in 1977 by Kay and Rolly
- initially solubilized in Cremophor EL but later changed to intralipid

### ■ Benzodiazepines

- *diazepam* was first available in 1960 as a sedative
- water insoluble, therefore solubilised in propylene glycol but now also available in intralipid
- *midazolam* is water soluble and was introduced in 1978

### ■ Analgesic-Hypnotic Combinations

- a. neurolept analgesia, a state of indifference to pain
- b. neurolept anaesthesia
- c. narcotics as sole anaesthetic agents

### ■ Balanced Anaesthesia

- term first used by Lundy to describe combination of light general anaesthesia with nerve block
- later this was revised to include muscle relaxation, hypnosis and narcotic analgesia

## BARBITURATE INTRAVENOUS ANAESTHETICS

- barbituric acid, **2,4,6-trioxohexahydropyrimidine**, is the condensation of malonic acid and urea
- the carbonyl group at position 2 takes on acidic character because of lactam (keto) - lactim (enol) **tautomerization**
- the lactim form is favoured in alkaline solutions and substitution of  $\text{Na}^+$  for the H-atom of the lactim form results in water soluble and often unstable salts
- the barbituric acid derivatives are poorly water soluble but dissolve readily in nonpolar solvents
- barbituric acid itself lacks central depressant activity, but the presence of alkyl or aryl groups at position **C<sub>5</sub>** confers **sedative-hypnotic** activity
- the presence of a phenyl group at C<sub>5</sub>, or on one of the ring nitrogens confers **anticonvulsant** activity (eg. phenobarbital)
- increases in the length of one, or both the alkyl side chains at C<sub>5</sub> increases hypnotic potency up to 5-6 carbon atoms, above this potency is reduced and convulsant properties may result
- compounds possessing the C<sub>2</sub>=O are known as **oxybarbiturates**, those having a C<sub>2</sub>=S substitution as **thiobarbiturates**
- the thiobarbiturates have higher lipid solubilities than their corresponding oxybarbiturate
- in general, structural changes which increase **lipophilicity**,
  - a. decrease the latency of onset
  - b. decrease the duration of action
  - c. accelerate metabolic degradation
  - d. often increase hypnotic potency
- each of these subclasses may be methylated, giving rise to 4 groups
- methyl or ethyl substitution at the **N<sub>1</sub> position** increases lipid solubility and shortens duration of action
- subsequent demethylation may occur resulting in a longer acting metabolite
- these compound have a high incidence of **excitatory phenomena**
- pentobarbital, secobarbital, thiopental, thiamylal and methohexital all possess asymmetrical carbon atoms in their side chains
- the **l-isomers** are ~ 2x as potent, despite similar access to the CNS cf. the d-isomers
- **methohexital** has four stereoisomers due to an asymmetric centre at C<sub>5</sub>, the **b-l-isomer** being nearly 4 times as potent as the  $\alpha$ -l-isomer
- however, the former also produces excessive motor activity, and the marketed solution is a racemic mixture of the **a-isomers**

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**NB:** this specificity of action lead to the hypothesis that the barbiturates acted at some specific **CNS receptor**

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## Mechanisms of Action

- the **GABA receptor** complex is the most likely site of barbiturate action
- the mesencephalic ARAS is exquisitely sensitive to these agents
- of the various effects of the barbiturates seen at a cellular level, only their effects at the GABA receptor complex,
  1. occur at clinical concentrations
  2. correlate with their anaesthetic potency
  3. are stereospecific
- NB:** inhibition is postsynaptic in the cortical, diencephalic and cerebellar regions, and presynaptic in the spinal cord
- this occurs only at GABA-ergic sites, but the effect is not totally mediated by GABA
- that is, barbiturates both enhance and mimic the action of GABA, by binding to the receptor they,
  - a. decrease the rate of GABA dissociation
  - b. increase the duration of GABA activated Cl<sup>-</sup> channel opening
  - c. at higher concentrations directly activate Cl<sup>-</sup> channel
- consequently, in whatever neuraxis, these agents preferentially suppress **polysynaptic responses**,
  - a. they depress Ca<sup>++</sup> dependent AP's
  - b. decrease Ca<sup>++</sup> dependent release of neurotransmitters
  - c. enhance gCl<sup>-</sup> in the absence of GABA
- the barbiturate sedative-hypnotic activity probably relates to enhancement of GABA activity, whereas, barbiturate anaesthesia from their so-called "**GABA-mimetic action**"
- therefore, the action is probably at the GABA<sub>A</sub> receptor, as the GABA<sub>B</sub> subtype results in an increase in gK<sup>+</sup> and gNa<sup>+</sup>
- these effects have similarities with the **benzodiazepines**, but there are significant differences,
  - a. barbiturates → increase the **duration** of channel opening
  - b. benzodiazepines → increase the **frequency** of channel openings
- NB:** both lead to an increase in gCl<sup>-</sup> flux,  
however, the benzodiazepines act **only** in the presence of GABA

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## Classification

- traditionally classified according to their half-lives,

Group	Half-life	Example
Long Acting	24-96 hrs	phenobarbital
Medium Acting	21-42 hrs	<i>pentobarbital</i>
Short Acting	20-28 hrs	secobarbital
Ultra-Short Acting	≤ 10 hrs	<i>thiopentone</i> , methohexital

- the duration of action of the ultra-short acting compounds is due to rapid *redistribution*, however excretion may take much longer
- these agents are used principally as intravenous induction agents
- the medium acting agents have been essentially superseded for sedative-hypnotic use by the safer benzodiazepines
- the long acting agents are still useful in the management of epilepsy

## PHARMACOKINETICS

### Distribution

- the latency of onset for these agents is determined by the rapidity with which they cross the BBB
- this, in turn, is dependent upon their lipid solubility and degree of ionization
- as their MW's are all very similar, this factor can be ignored

#### ■ Degree of Ionization

- the barbiturates are *weak acids*, with  $pK_A$ 's slightly above 7.4
- thiopental (STP) has a  $pK_A \sim 7.6 \rightarrow \sim 40\%$  *ionised* at physiological pH
- methohexital (MOX) is  $\sim 25\%$  ionised at physiological pH
- phenobarbital, with a  $pK_A$  slightly below 7.4, is 60% ionised
- *acidosis* will therefore increase the non-ionised fraction and favour transfer of these agents into the brain (brain ECF pH = 7.36)
- in the stomach these agents exist almost entirely in the non-ionised form and are absorbed according to their lipid solubilities
- the degree of ionization also affects renal excretion
- back-diffusion will be less if the drug is highly ionised and this is the basis of forced alkaline diuresis in the management of overdose with *phenobarbitone*

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## ■ Lipid Solubility

- the rapidly acting agents are relatively unionised at plasma pH and are absorbed according to their lipid solubility
- thiopentone, being highly lipid soluble, equilibrates with the brain rapidly
- phenobarbital, with relatively low lipid solubility, may take over 15 mins to achieve unconsciousness when given IV

## ■ Protein Binding

- these agents are bound principally to plasma albumin
- binding for thiopentone varies between 65-85% and it may be competitively displaced by other drugs, eg. sulfisoxazole
- further, protein binding may be reduced in disease states where plasma albumin is altered, ie. renal and hepatic disease

## ■ Placental Transfer

- the factors determining access to the foetus are identical to those determining access to the brain
- thiopentone and the other highly lipid soluble agents readily cross the placenta
- maximum foetal blood thiopentone concentrations being seen within **3 mins** of IV administration of thiopentone

## Uptake & Redistribution

- the termination of action is the sum of redistribution, metabolism and renal excretion
- in the case of thiopentone, metabolism is too slow to account for its short duration of action and the return of consciousness is governed by two factors,
  1. mixing of the bolus with circulating blood volume
  2. redistribution from the brain (VRG)

Body Tissue Compartments			
Group	Blood Flow (% CO)	Size (% body weight)	Equilibrium (min)
V <sub>c</sub>	100%	~ 38%	~ 0.5
VRG	70-75%	10-15%	~ 1-3
MG	~ 20%	~ 50%	15-30
FG	~ 5%	15-20%	200-300 <sup>+</sup>

**NB:** the relative rates at which various tissue groups take up thiopentone will depend upon their blood flow and the tissue solubility (see W&W fig. 8-6)

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- this, and other compartmental models of the plasma concentration/time curve, have largely replaced physiological models, as these require extensive human data
- the  $V_c$  above is that for thiopentone, the  $V_c$  for methohexital ~ 35%
- these exceed intravascular space and combined with the rate of equilibration with brain suggests that **brain** should be considered as a part of  $V_c$
- cerebral blood flow ~ 1/6<sup>th</sup> of the cardiac output, therefore a large bolus of lipid soluble, unionised drug is presented to the brain within one arm-brain circulation time
- peak plasma concentrations of thiopentone ~ 175 mg/l, are achieved within 30 secs of IV administration of 350 mg
- internal jugular concentrations are much lower ~ 75 mg/l
- this equates to a **brain extraction ratio ~ 60%**
- the VRG includes the heart, liver, kidney and brain
- the high myocardial blood flow, ~ 70 ml/100g/min (~ 225 ml/min), accounting for the rapidity with which CVS depression follows administration of thiopentone
- blood flow to the muscles (20% of CO) is less and 15-30 mins are required for equilibration
- although thiopentone is highly soluble in fat, the poor blood supply to this tissue results in a prolonged equilibrium time

**NB:** thus, the redistribution of thiopentone within the first 30 mins after IV bolus is predominantly to the **muscle group**

## Metabolism

- most members have high lipid:water partition coefficients and are significantly protein bound, therefore,
  - a. they are **poorly filtered** at the glomerulus
  - b. they readily back-diffuse across the late tubular segments
  - c. excretion is largely dependent upon prior **metabolism** which occurs in the liver
- biotransformation is usually via oxidation of radicals at the ring C<sub>5</sub> to alcohols, ketones, phenols or carboxylic acids
- these are then conjugated with glucuronic acid and excreted
- other biotransformations occur, such as N-hydroxylation, N-dealkylation etc., however **side chain oxidation** is the most important
- Brodie calculated that ~ 10-15% of thiopentone was metabolised
- however, other workers have demonstrated a **hepatic extraction £ 50%**
- therefore, **metabolism** may play some part in the termination of activity of thiopentone

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## ■ Renal Excretion

- a few barbiturates have low lipid:water coefficients, such as aprobarbital and *phenobarbital*
- thus, these members are significant excreted unchanged in the urine, phenobarbital ~ 25%
- both *osmotic & alkaline* diuresis enhance excretion of these drugs
- impaired renal function may result in severe CNS and CVS depression with these agents, further decreasing renal elimination

## ■ Prolonged Administration

- data of the half-lives of these agents shows, that for the medium acting agents used for sedative-hypnotic effects, non of the drugs will be significantly excreted in 24 hours
- therefore, *all* of these agents will accumulate with repeated administration
- thiopentone has a half life considerably longer than its clinical effects
- therefore, with repeated doses or continuous infusion, the dose required progressively decreases

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## THIOPENTONE

Structure:	
Chemical name:	5-ethyl-5-(1-methyl-butyl)-2-thiobarbituric acid
Introduced:	1934                      Lundy & Waters
Lipid Solubility:	high
Acid dissociation K:	pK <sub>A</sub> = 7.6
Solution pH:	pH            = 10.6
Protein binding:	75-85 %
Pharmacokinetics:	Cl <sub>ss</sub> = 3.4 ± 0.5        ml/kg/min V <sub>dss</sub> = 2.5 ± 1.0        l/kg t <sub>1/2β</sub> = 11.6 ± 6.0       hrs ER            = 0.15

### Chemistry

- first used in clinical anaesthesia in mid 1934 by Lundy and Waters
- it is the sulphur analogue of *pentobarbitone*, ie. is a thiobarbiturate
- highly lipid soluble, with a **pK<sub>A</sub> = 7.6**
- presented as a sodium salt (STP) in order to ensure total solution of the drug,
  - a. pale yellow powder
  - b. mixed with anhydrous sodium carbonate 6%                      (*not* HCO<sub>3</sub><sup>-</sup>)
  - c. ampoule atmosphere is N<sub>2</sub> at 0.8 bar
  - d. **2.5%** solution has a **pH = 10.6**
- the solution not stable and should be used within 24-48 hrs
- Miller states the prepared solution may be kept up to a week if refrigerated

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## Pharmacokinetics

- thiopentone has rapid onset with a short duration of action from a single bolus dose
- the decline in plasma concentration follows a multi-compartment model, with short distribution *half-lives* a long elimination half-life,

- i.  $t_{1/2\alpha 1} \sim 2.8$  min
- ii.  $t_{1/2\alpha 2} \sim 48.7$  min
- iii.  $t_{1/2\beta} \sim 5-12$  hrs

- the rapid recovery is due to *redistribution* of the drug, principally to muscle & liver tissue
- this is due to the greater perfusion of muscle and liver tissues, despite the greater solubility of thiopentone in fat
- plasma *clearance*  $\sim 1.6-4.3$  ml/kg/min, is slow and almost entirely due to *hepatic metabolism*
  - *oxidation* to a pharmacologically inactive metabolite
- correspondingly, the *hepatic extraction ratio*  $\sim 0.1-0.2$  is low
- reversibly to albumin, high protein binding  $\sim 75-85\%$
- therefore the free fraction varies from 0.15 to 0.25
- steady state  $V_{\text{ass}} \sim 1.7-2.5$  l/kg, is greater than body volume, reflecting extensive tissue uptake
- the combination of low clearance and large volume of distribution results in the relatively long elimination half-life, ie. most of the drug is in the tissues rather than plasma and thus is not available for hepatic elimination
- with larger or repeated doses, recovery is slow as there is accumulation of the drug in the peripheral tissues
- some evidence suggests that with larger doses the behaviour of thiopentone changes from first-order to *zero-order kinetics*
- as such only a constant *mass* of drug is removed per unit time, and as the dose is increased the plasma concentration rises rapidly
- the pharmacokinetics of thiopentone are not affected by surgical stress, or the addition of either N<sub>2</sub>O or Enflurane (Ghonheim 1978)

## Effects of Physiological and Pathological States

### ■ Age

- there is a decreased requirement of thiopentone with increasing age
- the elimination half-life is prolonged in the elderly, however, this alone shouldn't alter the effects of a single dose
- in the *elderly*, for a given dose, the peak plasma levels of thiopentone are greater than those found in young adults
- this difference is explained by,
  - a. the volume of the *central compartment* is reduced
  - b. decreased albumin binding → 18-22% increase in *free fraction*
  - c. decreased rate of *redistribution* (reduced CO)
    - increased penetration of BBB (Muravchick & Mandel 1982)
- consequently, the induction dose should be decreased to prevent excessive depression of CNS and CVS function
- the elimination half-life is increased due to an increased  $V_{dss}$ , (b) above
  - techniques employing repeated boluses should be avoided
- *children* have a similar  $V_{dss}$ /kg to adults, while *clearance* ~ **2x** the adult value
  - thus the elimination half-life ~ ½ that of adults
- repeated dosage therefore leads to less accumulation in children
- higher  $MRO_2$  and CI leads to more rapid redistribution and faster awakening from a single dose

### ■ Pregnancy

- at term, the *clearance* ~ **1.5x** that of the non-pregnant
- probably due to increased hepatic metabolism, ? steroid hormone induction
- albumin binding is unchanged
- $V_{dss}$  <sup>3</sup> **2x** that of the non-pregnant, thus the elimination half-life is longer (~ 26 hrs)
- the volume of the central compartment is unchanged, therefore, at least theoretically the induction dose/kg should be the same as in the non-pregnant state
- repeated doses cause greater accumulation

### ■ Obesity

- due to high lipid solubility, the  $V_{dss}$  is increased
- albumin binding and clearance are unchanged, therefore the elimination half-life is prolonged
- the volume of the central compartment is greater in obese than lean patients
- this is due to a larger *blood volume*, myocardial hypertrophy and fatty infiltration of the liver
- however, when expressed in l/kg, it is similar to that of lean patients
- therefore, according to Hudson and Stanski, it would be logical to give the same induction dose/kg total body weight, in obese and lean individuals
- multiple injection techniques are not advisable due to the prolonged elimination time

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## ■ Renal Failure

- uraemia causes a decrease in albumin binding of thiopentone, with a consequent doubling in the plasma **free-fraction** and an increase in the unionised fraction
- more is available to cross the BBB with an increased depth of anaesthesia for a given dose
- there is also increased **CVS depression** (myocardial depression and hypotension), therefore the induction dose should be decreased (by 50%)
- however, **redistribution** is more rapid with a quicker recovery, thus there is a chance of inadequate anaesthesia at intubation
- the elimination half-life remains normal despite an increased  $V_{dSS}$  as the total **clearance** is increased, due to the increased free fraction increasing availability for metabolism
- therefore, the recommendations are,
  - a. use a slow rate of induction, or give in 2 or 3 doses, the total dose being unchanged
  - b. for maintenance with a repeated dose technique, decrease the individual doses by 50-75% and give more often

**NB:** recovery may be more rapid if the total dose is small

## ■ Hepatic Failure

- there is a decrease in **protein binding** of thiopentone in cirrhotics, directly related to decreased plasma albumin (~ 50%)
- therefore, cirrhotics behave similarly to those with renal failure and induction doses should be **reduced ~ 50-75%**
- $V_{dSS}$  is increased, clearance decreased, and the elimination half-life prolonged
- a standard induction dose of thiopentone will therefore have a prolonged recovery

## ■ Hypovolaemia

- the decreased **central compartment** leads to increased concentration of the drug reaching the brain and heart, with resulting severe respiratory and CVS depression
- there is also a decreased rate of **redistribution**

## Pharmacodynamics

### ■ Recommended Dosage

- a. healthy adults ~ 3.0 to 5.0 mg/kg (Stanley 1981)
- b. > 65 yrs ~ 1.8 to 2.5 mg/kg
- c. children (5-15) ~ 5.0 to 7.0 mg/kg (Cote *et al* 1981)

### ■ Concentration - Response

- the required total plasma [STP] for *surgical anaesthesia* ~ **40 µg/ml** (Becker 1978)
- the free fraction of thiopentone ~ 15%, equating to a free drug level of ~ 6 µg/ml
- plasma levels of ~ 30-50 µg/ml are required for total saturation of the metabolic pathway
  - *zero order kinetics*
- opioid premedication reduces thiopentone requirements by ~ 50%
- N<sub>2</sub>O/O<sub>2</sub> (67%) reduces the thiopentone anaesthetic concentration by 65-70%
- there are conflicting reports on *acute tolerance* but it is probably of little or no clinical significance
- the original reports (Brodie *et al.*, Toner *et al.*) used venous plasma levels, which were subsequently shown not to correlate well with internal jugular/brain venous levels

## Pharmacological Actions

### ■ CNS Effects

#### 1. Sleep

- injection of 3.5-4.0 mg/kg results in a smooth onset of sleep & unconsciousness
- usually unaccompanied by spontaneous movement or respiratory excitatory phenomena

#### 2. Analgesia

- the barbiturates are poor analgesics in subanaesthetic doses and **hyperaesthesia** to surgical stimuli may occur when given in low doses (25-150 mg of thiopentone)
- this may manifest as
  - i. tachycardia
  - ii. hypertension
  - iii. diaphoresis
  - iv. tearing
  - v. tachypnoea
  - vi. increased laryngeal & pharyngeal reflexes
  - vii. postoperative restlessness
- these features are more common in **children**

#### 3. Anaesthesia

- thiopentone usually produces short-lived surgical anaesthesia within 1-2 mins of injection, lasting from 5-8 minutes
- however, surgical stimulation at this time may lead to **laryngeal spasm**
- deeper levels of anaesthesia can be achieved which avoid this, however there may be significant CVS/CNS depression

#### 4. Cerebral Metabolism & Circulation

- there is a decrease of cerebral blood flow (CBF ~ 50%) and cerebral metabolism (CMRO<sub>2</sub> ~ 50%) with **anaesthetic** doses of thiopentone
- in patients with decreased intracranial compliance, or increased ICP, the barbiturates **increase** the cerebral perfusion pressure,

$$CPP = MAP - ICP$$

- this is due to their greater effect on decreasing ICP than arterial BP
- this profound cerebral vasoconstriction may be offset by increases in P<sub>aCO<sub>2</sub></sub>
- therefore, in the absence of controlled ventilation and normocapnia, thiopentone may increase CBF secondary to decreased respiration

#### 5. Other effects

- in common with other members, thiopentone possesses **anticonvulsant** activity

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## ■ CVS Effects

**NB:** *venous tone* consistently decreases with a resulting decrease in *venous return* and this is the predominant cardiovascular effect

- total peripheral resistance may either decrease or increase
- usually the initial decrease in CO & BP are compensated for by increased SNS tone
- when SNS tone is already high, such as in *hypovolaemia* from any cause, even small doses of thiopentone may result in profound decreases in CO & BP
- the vascular effects are due to a *central action* and to a lesser degree a direct action on venous smooth muscle
- thiopentone produces a dose related depression of *myocardial function*, however, this is less than that seen with the volatile agents
- usual clinical doses → 10 to 25% decrease in contractility, related to the speed of injection and the status of the patient
- there is a reflex increase in *HR* and myocardial *MRO<sub>2</sub>*, leading to a decrease in coronary vascular resistance and an increase in coronary blood flow
- the arteriocoronary venous O<sub>2</sub> difference remains unchanged, providing mean arterial pressure is not drastically lowered
- thus, if coronary perfusion is decreased due to lowered BP, ischaemia may result and thiopentone should be used cautiously in patients with heart disease
- particularly conditions where an *increase in HR* or *reduction in preload* may be detrimental, such as,
  - i. pericardial tamponade
  - ii. valvular heart disease
  - iii. CCF
  - iv. IHD
  - v. high degree AV block
- hypotension is greater in both treated and untreated *hypertension*
- this may result from blunting of the baroreceptor response, relative hypovolaemia or β-blockade

## ■ Respiratory Effects

- usual anaesthetic dose of thiopentone → 2 or 3 hyperpnoeic breaths followed by apnoea
- respiratory depression is *dose related*, with reduction in ventilatory responsiveness to CO<sub>2</sub> and hypoxia
- these effects are potentiated by opioid premedication
- the respiratory pattern rapidly returns to normal
- however the CO<sub>2</sub>/O<sub>2</sub> response curves remain depressed for some time
- *hypoxic pulmonary vasoconstriction* is unaffected by the intravenous agents in general
- there is a low incidence of laryngo & bronchospasm, unless the upper airways are stimulated by excess secretions, artificial airways or attempted intubation
- laryngeal reflexes are not depressed until deep levels of anaesthesia
- thiopentone is safe in asthmatic patients but *does not* cause bronchodilatation, as does ketamine

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## ■ Hepatic & Renal Effects

- there are no apparent significant effects on liver function, except that prolonged exposure may cause enzyme induction
- renal effects are 2° to RBF/GFR which are dependent on cardiac output and reflex SNS tone

## ■ Other Effects

- there is a clinically insignificant increase in the BSL and impairment of glucose tolerance
- plasma *insulin* levels are unchanged
- *heat loss* is increased from peripheral vasodilatation
- thiopentone decreases plasma *cortisol* levels but does not blunt the response to surgical stimulation, in contrast to etomidate which does both
- there is a dose related release of *histamine*, which is usually not significant
  
- thiopentone has no effects on the gravid uterus, although the drug crosses the placenta to foetus
- foetal levels are low when thiopentone is used as single dose in caesarian section, and are maximal at ~ 3 minutes after injection
- Kosakas *et al.* showed no significant foetal depression in 75-95% of infants in doses ranging from 4-7 mg/kg
- this was due to,
  - a. foetal hepatic extraction of the drug from umbilical venous blood
  - b. extensive shunting in the foetal circulation
  - c. the rapid decrease of maternal blood concentrations
  
- neurobehavioural studies do indicate more *neonatal sedation* following thiopentone than after ketamine induction or epidural anaesthesia
  
- STP has no effects or interactions at the NMJ, though, central effects may decrease muscular tone
- *intraocular pressure* is reduced ~ 40% after an induction dose
- subsequent administration of succinylcholine returns IOP to pre-induction values
- however, if  $\geq 2$  minutes is allowed to intervene, then IOP is raised above pre-induction values

## Clinical Use

- a. induction of anaesthesia
  - b. as sole anaesthetic
  - c. as supplementation to other drugs
  - d. in conjunction with regional anaesthesia
  - e. to treat status epilepticus
  - f. as a sedative
  - g. for cerebral protection with raised ICP
- normally given intravenously in a 2.5% solution
  - can also be given per rectum in a 5-10% solution
  - sleep is induced within 10-15 secs in normal individuals
  - the effects of a single dose last for 5-10 mins
- **Brain Protection**
- the principal protective effect of the barbiturates is a dose dependent reduction in  $CMRO_2$
  - this parallels the reduction in EEG activity until the EEG becomes *isoelectric*
  - after this point **no** further reduction is achieved
  - proposed that this effect would offer cerebral protection in injuries associated with raised ICP (Shapiro *et al.* 1973)
  - other protective effects may include,
    - a. inverse steal - vasoconstriction in healthy brain shunting blood to diseased areas
    - b. a reduction in ICP and increase in cerebral perfusion pressure
    - c. stabilisation of liposomal membranes
    - d. scavenging of free radicals
    - e. its anticonvulsant effects
- the data are somewhat variable, due to different models and different species
  - a number of randomised studies have shown **no improvement** in survival in the barbiturate treated group (global ischaemic injury)
  - thus, the addition of barbiturate coma **does not** seem warranted due to the risk of cardiovascular instability (Matjasko, Pitts & Katz 1986)
  - this contrasts models of **focal ischaemia**, where barbiturate administration reduces infarct volume
- the one exception to this is in young head injuries, where the initial response is a dramatic rise in ICP secondary to generalised hyperaemia
  - this is also a group where **mannitol** is contraindicated

# Intravenous Anaesthetics

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## Contraindications & Precautions

### ■ Contraindications

- a. proven allergy - rare but high fatality rate
- b. if airway is obstructed or in doubt - Ludwig's angina  
- tonsillar bleed  
- carotid bleed
- c. uncompensated heart disease - mitral stenosis  
- constrictive pericarditis  
- aortic stenosis
- d. severe shock or hypovolaemia - any cause, including Addison's
- e. status asthmaticus
- f. porphyria
- g. absence of IV access, or general anaesthetic equipment

### ■ Precautions

- a. cardiovascular disease - IHD, hypertension, valvular disease
- b. hypovolaemia - haemorrhage, burns, fluid depletion, dehydration
- c. uraemia
- d. septicaemia
- e. elderly

# Intravenous Anaesthetics

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## Porphyria

- an inborn error of metabolism with abnormal porphyrin metabolism
- **porphyrin** consists of 4 pyrrole rings linked by -CH- bridges
- found in haemoglobin, plus some of the cytochrome and peroxidase enzymes
- the rate limiting reaction for its synthesis is catalyzed by ***δ-aminolevulinic acid synthetase***
- this is responsible for the production of  $\delta$ -ALA from succinate & glycine within the mitochondria
- this enzyme is induced by the barbiturates and is increased in certain types of porphyria,
  - i. acute intermittent porphyria
  - ii. variagate porphyria
  - iii. coproporphyria **not** in porphyria cutanea tarda
- the clinical syndrome includes intermittent attacks of
  - i. nervous system dysfunction
  - ii. abdominal pain
  - iii. skin sensitivity to sunlight (not in AIP)
- administration of barbiturates to these patients may result in **paralysis** and death
- other drugs which may **exacerbate** the condition include,
  - i. barbiturates
  - ii. diazepam ? rest of benzodiazepines
  - iii. alcohol
  - iv. anticonvulsants
  - v. oestrogen
  - vi. other hormones
  - vii. hypoxia
- drugs that are **usually safe** in this condition include,
  - i. propofol
  - ii. opioids
  - iii. volatile anaesthetics
  - iv. N<sub>2</sub>O
  - v. succinylcholine
  - vi. atropine & neostigmine
  - vii. phenothiazines
  - viii. propranolol
- treatment of acute attacks includes,
  - a. infusion of **glucose** - negatively feeds-back against  $\delta$ ALA-synthetase activity
  - b. **haematin** - also acts at this step

# Intravenous Anaesthetics

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## Complications

### ■ Local

- subcutaneous administration causes pain, redness and swelling due to the high alkalinity
- this may be treated by infiltration of the area with 1% procaine and hyaluronidase
- ***intra-arterial injection*** may result in significant damage to the vessel,
  - a. vascular spasm & pain
  - b. loss of distal arterial pulses
  - c. ***gangrene*** and permanent nerve damage
- therefore, when giving thiopentone IV, a ***test dose*** of 2-4 ml should be given
- treatment includes,
  - a. leave the needle in the lumen of the artery
  - b. dilute with saline & give 0.5% procaine 10-20 ml
  - c. give papaverine 40-80 mg in 10-20 mls saline if possible, or give an alpha-blocker, or brachial plexus or stellate ganglion block
  - d. anticoagulants if necessary
- ***thrombophlebitis*** is uncommon with the 2.5% solution
- up to 5% of patients may have a painless thrombosis

### ■ General

- a. ***overdosage***, leading to respiratory, CVS and CNS depression
- b. ***allergic reactions*** are rare but usually severe (~ ***1:14,000***)
  - histamine release may occur, with the appearance of an urticarial type rash
- c. ***laryngeal spasm*** may occur, especially with light anaesthesia
- d. ***bronchospasm***, principally in asthmatics due to increased vagal reflexes but rarely severe
- e. ***excitatory phenomena***, these may occur but are less than with methohexital and may be reduced by opioid premedication

# Intravenous Anaesthetics

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## METHOHEXITONE

Structure:	
Chemical name:	<b>a-dl</b> -1-methyl-5-allyl-5-(1-methyl-2-pentynyl)-barbituric acid
Introduced:	1950's                  Stoelting
Lipid Solubility:	high                  (slightly < thiopentone)
Acid dissociation K:	pK <sub>A</sub> = 7.9
Solution pH:	pH                      = 10-11
Protein binding:	70-80 %
Pharmacokinetics:	Cl <sub>SS</sub> = 10.9 ± 3.0                  ml/kg/min V <sub>dSS</sub> = 2.2 ± 0.7                  l/kg t <sub>1/2β</sub> = 3.9 ± 2.1                  hrs ER                      = 0.5

### Chemistry

- introduced in the late 1950's (Stoelting) as an agent with a more rapid recovery than thiopentone
- methohexitone is an **oxybarbiturate** with a methyl group at the 1-Nitrogen
- methohexital has 2 asymmetrical C-atoms, thus has **4 isomers** which have been divided into 2 pairs → **a-dl & b-dl**
- the racemic mixture of all four is a potent agent, however results in excessive skeletal muscular activity and convulsions
- thus, the available solution is only the **a-dl** pair and is ~ 2-3x as potent as thiopentone
- it gives minor excitatory effects in ~ 33% of patients
- presented as a white powder mixed with 6% sodium carbonate to ensure stabilization and is stable for up to 6 weeks after preparation
- the prepared solution is **1%** with a **pH ~ 10-11**

# Intravenous Anaesthetics

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## Pharmacokinetics

- similar to thiopentone, methohexital is highly lipid soluble, is 75% unionised at pH = 7.4 and is 70-80% protein bound
- therefore, methohexital has similar pharmacokinetics to thiopentone, ie., redistribution from brain to peripheral tissues accounts for rapid recovery after a single dose
- methohexital is slightly less lipid soluble than thiopentone, thus has a smaller  $V_{\text{dss}} \sim 1.1-2.2 \text{ l/kg}$ , c.f. thiopentone  $\sim 1.7-2.5 \text{ l/kg}$  (W&W)
- the kinetics follow a 2-compartment model with a short distribution half life,  $t_{1/2\alpha} \sim 6.2 \text{ min}$
- elimination is almost entirely by the liver
- the *clearance*  $\sim 10-12 \text{ ml/kg/min}$ , is about 3x higher than that of thiopentone
- therefore after multiple doses, despite accumulation of methohexital in the peripheral tissues, recovery is more rapid than with thiopentone
- the elimination half-life,  $t_{1/2\beta} \sim 1.6-3.9 \text{ hours}$  (W&W = 97 min)

## Pharmacodynamics

- methohexital is about **2.5-3.5** times as potent a cerebral depressant as thiopentone
- it has a shorter duration of action than thiopentone, especially the time to full recovery

### ■ CNS

- a 1-1.5 mg/kg dose causes loss of consciousness in one arm/brain circulation time with recovery of consciousness after 2-3 minutes
- induction is frequently accompanied by transient twitching of skeletal musculature
- hiccup & *laryngospasm* occur in up to 45% of unpremedicated patients
- the incidence is reduced premedication with opiates or benzodiazepines
- it should not be used in patients with history of *epilepsy* as convulsions can be precipitated
- this is generally attributed to the ring N<sub>1</sub>-methyl group in its structure

### ■ Respiratory

- similarly to thiopentone, transient respiratory depression occurs with up to a 50% reduction of respiratory drive for a few minutes after administration
- methohexital *does not* cause bronchospasm in asthmatic patients

### ■ Cardiovascular

- causes less cardiovascular depression than thiopentone
- however, also acts on the sympathetic nervous system with resulting vasodilatation
- in clinical doses there appears to be little effect on arterial blood pressure

# Intravenous Anaesthetics

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## ■ Other Effects

- methohexitone is non-irritant with low incidence of venous thrombosis or tissue damage after perivenous injection
- after intra-arterial injection, thrombosis and gangrene may occur, depending on the dosage, concentration and volume injected
- the 1% solution is relatively safe
- treatment of intra-arterial injection is the same as for thiopentone

## Clinical Use

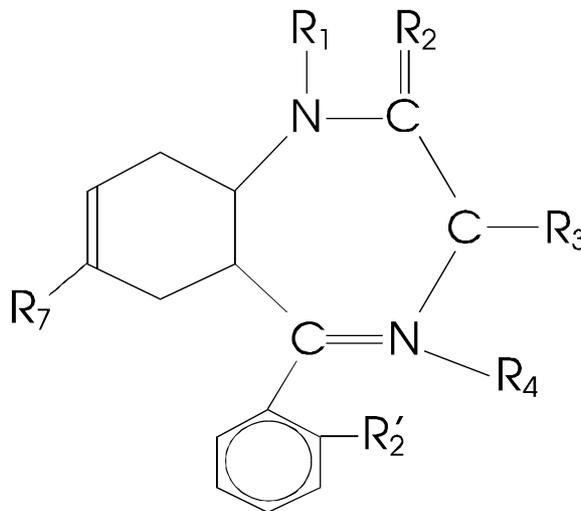
- similar indications to thiopentone but especially useful in the outpatient surgery when rapid recovery is desirable
- also used for *electropexy*
- can also be administered per rectum, 15-20 mg/kg

## ■ Precautions

- essentially the same precautions as for thiopentone, but also avoid usage in *epileptics*

## BENZODIAZEPINES

- the benzodiazepines were discovered accidentally
  - chlordiazepoxide (Librium) was synthesised by Sternbach in 1955 but discarded because it was presumed to be inert
  - the sedative hypnotic effects were discovered in mice in 1957 and it was released in 1960
  - **diazepam** was synthesised by Sternbach in 1959 and its metabolite, **oxazepam**, by Bell in 1961
  - the next major achievement was the synthesis of the water soluble **midazolam** by Fryer and Walser in 1976
  - the existence of a **benzodiazepine receptor** (BZR) was first discussed in Milan in 1971
  - isolation and receptor-ligand interaction were demonstrated in 1977
  - this has resulted in the generation of a number of new ligands and a specific antagonist
  
  - the term **benzodiazepine** refers to the portion of the structure composed of the following,
    - a. a benzene ring, fused to
    - b. a seven member diazepine ring
- NB:** however, since all of the important members of the group contain a 5-aryl substituent and a 1,4-diazepine ring, the term has come to refer to the **5-aryl-1,4-benzodiazepines**



- the 5-aryl ring greatly enhances potency
- from standpoint of anaesthesia diazepam, lorazepam and midazolam are of particular interest
- diazepam and lorazepam have quite similar structures, while midazolam contains an **imidazole ring** bridging R<sub>1</sub> and R<sub>2</sub> (see G&G. table 17-1)
- both diazepam and lorazepam are insoluble in water, therefore require solubilizing agents, while the imidazole ring renders midazolam water soluble

# Intravenous Anaesthetics

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## Pharmacological Properties

### ■ Mechanism of Action

- most, if not all, of the actions of these drugs are the result of potentiation of the neural inhibition mediated by *gaba-aminobutyric acid*
- the binding of the benzodiazepines to the receptor is of high affinity, saturable and stereospecific
- the rank order of *receptor affinity* is,

- a. diazepam x 1
- b. midazolam x 3-4
- c. lorazepam x 5

**NB:** this parallels their respective potencies

- possible actions which lead to an increased release of GABA cannot be excluded, but most of the action is due to potentiation of GABA induced increases in *chloride conductance*
- this accounts for the relative safety of this group, their effects requiring the central release of a neurotransmitter
- the barbiturates have similar effects in low doses, however, also inhibit the release of excitatory neurotransmitters at high doses
- dynamic pharmacokinetic models suggest that the different benzodiazepine effects correlate with different levels of receptor occupancy,

- a. anxiolysis ~ 20%
- b. sedation ~ 20-50%
- c. unconsciousness ~ 60%

- these neurones are regulated by both feedforward and feedback inhibitory pathways, composed of small GABAergic interneurons
- GABA induced increases in  $g_{Cl}$ , especially in the region of the *axon hillock*, effective shunt electrical currents which would otherwise depolarise the membrane
- the benzodiazepines decrease spontaneous and evoked electrical activity in major (large) neurones in all regions of the spinal cord and brain
- the specific binding sites are more concentrated in the brain and binding of benzodiazepines is increased by both  $Cl^-$  ions and GABA
- high concentrations are predominantly found in the,
  - a. limbic system - particularly the hippocampus and amygdala
  - b. cerebral cortex
  - c. cerebellum

- low concentrations are found in the brain stem and spinal cord
- there are two subtypes of GABA receptor, the benzodiazepine receptor appearing to be a part of the  $GABA_A$  complex, located on the subsynaptic membrane of the effector neurone

# Intravenous Anaesthetics

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## Benzodiazepine/GABA Receptor

- this receptor is a **tetramer** composed of two protein subunits with a central Cl<sup>-</sup> channel, in an  $\alpha_2\beta_2$  configuration
- these proteins contain the ligand binding sites for the benzodiazepines, barbiturates and GABA
- the benzodiazepine site is located on the  **$\alpha$ -subunit**, while that for GABA is on the  $\beta$ -subunit
- there are **three subclasses** of receptor ligands for the benzodiazepine portion of the GABA<sub>A</sub> receptor,

1. agonists - benzodiazepines & barbiturates
2. antagonists - flumazenil
3. inverse agonists - DMCM

- the benzodiazepines alter the conformation of the receptor such that the **affinity** for GABA is increased with a resultant increase in Cl<sup>-</sup> channel activation
- **antagonists** occupy the receptor but have no intrinsic activity, therefore they prevent the effects of both agonists and inverse agonists, ie. they **do not** affect the binding of GABA

**NB:** **inverse agonists** occupy the receptor and reduce the affinity for GABA, thus they result in CNS **stimulation**

## Central Nervous System

- the pharmacological effects of the benzodiazepines all result from actions in the CNS, and include,

- a. anxiolytic
- b. sedative
- c. hypnotic
- d. muscle relaxant
- e. amnesic
- f. anticonvulsant

- only one member, **alprazolam**, appears to have antidepressant activity
- only two effects appear to result from actions in the periphery,
  1. **coronary vasodilatation**, seen after IV injection of some agents
  2. neuromuscular blockade, only at very high doses

- the benzodiazepines are **not** general neuronal depressants, as are the barbiturates, and all members have a similar pharmacological profile
- the exception of the anticonvulsant and possibly analgesic effects of certain members
- in man, as the dose is increased, sedation progresses to hypnosis then stupor

# Intravenous Anaesthetics

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- the drugs **do not** cause true general anaesthesia, since awareness usually persists and relaxation sufficient for surgery cannot be achieved
- they do cause **anterograde amnesia** (following injection) which gives the illusion of anaesthesia
- some members induce **muscle hypotonia**, without interfering with locomotion, and may decrease decerebrate rigidity
- tolerance develops to both of these effects
- similarly, **tolerance** develops to their **anticonvulsant activity** and this limits their usefulness in the long-term management of epilepsy
- the effects on **sleep** are similar for most members,
  - i. decreased sleep latency
  - ii. diminished number of awakenings and time in stage 0
  - iii. time in **stage 2** (major non-REM component) is **increased**
  - iv. marked decrease in slow wave sleep (stages 3&4)\*
  - v. increase in REM latency (onset of spindle to 1st REM burst)
  - vi. decreased frequency of eye movement during REM sleep
  - vii. **decreased** time spent in **REM sleep**\* but increased number
  - viii. increased total sleep time

**NB:** \*with the exception of **temazepam**

- the amnesic effects are useful for preventing awareness during anaesthesia and the sedative effects are useful in ICU and during regional anaesthesia  
(this is **incorrect !!**, they prevent recall of awareness, anxiety & autonomic response still occur)
- benzodiazepines generally have **no analgesic** properties but they appear to potentiate the effects of both the narcotics and anaesthetics
- diazepam causes transient analgesia after IV administration but this has not been reported with any other agents
- unlike the barbiturates, they do not cause hyperalgesia
- the benzodiazepines produce a dose related reduction in  $CMRO_2$  and **cerebral blood flow**
- in human volunteers, midazolam 0.15 mg/kg induces sleep and reduces CBF ~ 34%, despite an increase in  $P_{aCO_2}$  from 34 to 39 mmHg
- EEG studies during the IV administration of midazolam show,
  - i. rhythmic  $\beta$ -activity ~ 22 Hz ~ 15-30 s
  - ii. a second  $\beta$ -rhythm ~ 15 Hz ~ 60 s
  - iii. reappearance of  $\alpha$ -rhythm ~ 30 minutes
- however, even after 60 minutes there was resistant rhythmic  $\beta$ -activity of 15-20  $\mu V$  amplitude
- similar EEG changes are seen with diazepam and are **not** generally consistent with light sleep, though, patients are such clinically
- thus, the effects on the waking EEG are similar to other sedative-hypnotic drugs,
  - i. alpha activity is decreased
  - ii. increase in low voltage, fast activity, especially beta
  - iii. the amplitude of somato-sensory EP's is reduced

**NB:** (b) & (c) correlate with the anxiolytic effects

# Intravenous Anaesthetics

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Common EEG Patterns		
Beta Rhythm	15-30 Hz	<ul style="list-style-type: none"><li>• alert, active patient</li><li>• lower voltage</li><li>• predominantly in the frontal regions</li><li>• possibly a harmonic of the <math>\alpha</math>-rhythm</li></ul>
Alpha Rhythm	8-12 Hz	<ul style="list-style-type: none"><li>• 50 <math>\mu</math>V</li><li>• maximal in the parieto-occipital area</li><li>• awake man, eyes closed, mind wandering</li></ul>
Theta Rhythm	4-7 Hz	<ul style="list-style-type: none"><li>• large, regular waves</li><li>• originate in the hippocampus</li><li>• seen in children</li><li>• present with onset of sleep</li><li>• anaesthetic induction</li></ul>
Delta Waves	$\leq 4$ Hz	<ul style="list-style-type: none"><li>• deepening anaesthesia</li></ul>

## Respiration

- the benzodiazepines have little effect on respiration, hypnotic doses are without effect in normal subjects
- the effects of *midazolam* may be greater in this area, though, comparative studies do not exist
- "pre-anaesthetic" doses do cause a decrease in alveolar ventilation and a respiratory acidosis
- the slopes of the ventilatory/ $\text{CO}_2$  response curves are flatter
- however, they are not shifted to the right, as occurs with the opioids
- the peak onset of ventilatory depression following midazolam is at ~ 3 minutes and lasts for ~ 15 minutes
- in patients with obstructive pulmonary disease they may result in significant respiratory depression,  $\text{CO}_2$  retention and narcosis
- diazepam may cause apnoea during anaesthesia, or when given in conjunction with the opioids
- other factors likely to increase the incidence of significant respiratory depression, or apnoea, include,
  - a. old age
  - b. debilitating disease
  - c. other respiratory depressant drugs

# Intravenous Anaesthetics

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## Cardiovascular

- the CVS effects are minor, except after severe intoxication
- in "pre-anaesthetic" doses they decrease the BP and increase the HR,
  - a. decrease peripheral resistance
    - flunitrazepam
    - midazolam
  - b. decrease LV work and cardiac output
    - diazepam
    - lorazepam
- **baroreceptor reflexes** generally remain intact, though, there is some depression
- the hypotensive effect is minimal and usually less than that seen with thiopentone
- the effect is possibly slightly greater with midazolam and is dose related
- in patients with elevated cardiac filling pressures, both midazolam and diazepam produce a "nitroglycerine like" effect, reducing **preload** and increasing cardiac output
- diazepam increases **coronary blood flow** in man, possibly by increasing interstitial concentrations of **adenosine**
- thus, diazepam may provide some protective function in patients with IHD
- used alone they do not provide protection against the stress of endotracheal intubation
- the addition of N<sub>2</sub>O has minimal haemodynamic effect
- however, when combined with opioids there is a synergistic effect, the combination producing greater decreases in BP than either agent alone

**NB:** there are few contraindications except for obstetric and perinatal anaesthesia

## Pharmacokinetics

- all members have high lipid:water partition coefficients in the non-ionised form
- however, lipophilicity varies over 50-fold according to the polarity of the ring substituents
- all members are essentially completely absorbed after oral administration, with the exception of cloazepate, which is converted to nordiazepam in the stomach, then absorbed
- after oral absorption, the time to peak plasma concentrations varies from 0.5 to 8 hrs
- with the exception of lorazepam, most members are erratically absorbed after IM injection
- the benzodiazepines, and their active metabolites, bind to plasma proteins in direct correlation with their lipid solubility
- ranging from alprazolam ~ 70% to diazepam ~ 99%
- the concentrations in CSF are approximately equal to the plasma free fraction
- competition with other protein bound drugs may occur, however there are no clinically significant examples
- **redistribution** is the major determinant of the onset and duration of effect after a single IV dose, not the rate of elimination
- most benzodiazepines exhibit patterns consistent with two or three-compartment models
- the kinetics of diazepam and the other highly lipid soluble agents are complicated by **enterohepatic circulation**
- with repeated dosages, the elimination half-life and plasma clearance remain determining factors

## Intravenous Anaesthetics

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- due to the slow onset of hypnosis, benzodiazepines are not generally good induction agents for routine anaesthesia, with the possible exception of midazolam
- they are useful when CVS stability is important and slow induction permissible
- the volumes of distribution are large and many are increased in the elderly
- these drugs readily cross the placenta and are excreted in the breast milk

Classification by Duration of Action		
Longer acting	$t_{1/2\beta} > 24$ hrs	<ul style="list-style-type: none"> <li>• diazepam ~ 40 hrs</li> <li>• nitrazepam</li> <li>• flunitrazepam</li> <li>• clorazepate</li> </ul>
Intermediate	$t_{1/2\beta} \sim 6-24$ hrs	<ul style="list-style-type: none"> <li>• lorazepam</li> <li>• temazepam</li> <li>• oxazepam</li> <li>• lormetazepam</li> </ul>
Shorter acting	$t_{1/2\beta} < 5$ hrs	<ul style="list-style-type: none"> <li>• midazolam ~ 2 hrs</li> <li>• triazolam</li> </ul>

- the longer acting agents are metabolised in the liver by *microsomal mixed function oxygenase* enzyme systems
- many of the metabolites (eg., desmethyldiazepam) are pharmacologically active, contributing to clinical effect of the drugs and extending the effective half-life (see G&G table 17-3)
- these agents cause *minimal enzyme induction*
- intermediate and short acting agents are inactivated by *glucuronidation* and then eliminated by renal excretion
- therefore, for the elderly and patients with hepatic disease, the intermediate and shorter acting agents are preferable
- *cimetidine* prolongs the effect of those agents susceptible to liver MFO systems
- ranitidine has no effect on metabolism of any benzodiazepines
- factors known to influence the pharmacokinetics of the benzodiazepines include,
  - i. age
  - ii. gender
  - iii. race
  - iv. enzyme induction
  - v. hepatic disease
  - vi. renal disease
- these drugs are all affected by *obesity*, the increased lipid stores increasing their respective volumes of distribution and elimination half lives
- therefore, induction doses need to be increased, whereas infusion rates are unaltered

# Intravenous Anaesthetics

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## Adverse Reactions & Precautions

- at peak plasma concentrations these agents will produce varying degrees of,
  - i. light-headedness
  - ii. lassitude
  - iii. slowed reaction time
  - iv. ataxia
  - v. confusion
  - vi. dysarthria
  - vii. anterograde amnesia
  - viii. impairment of cognitive function
  
- interactions with *ethanol* may be serious
- *psychotic ideation* rarely occurs but is more common in mentally ill patients
- *rebound anxiety*, "withdrawal type" syndromes occur after cessation of prolonged therapy and are probably more common than reported
- rebound *insomnia* also may occur after cessation
- with chronic use they may lead to abuse & dependence, though, this is far less than with the barbiturates

# Intravenous Anaesthetics

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## DIAZEPAM

- first synthesised in 1959 and later introduced in 1961
- insoluble in water, therefore prepared commercially in an organic solvent, each ml of solution containing,

- a. diazepam 5 mg
- b. propylene glycol 0.4 ml
- c. ethyl alcohol 0.1 ml
- d. benzyl alcohol 0.015 ml
- e. sodium benzoic acid to pH = 6.2-6.9

- now available also as an *intralipid* / water emulsion (Diazemuls)
- despite its high lipid solubility, the CNS effects (drowsiness and hypnosis) after intravenous administration have a slow or irregular onset and thus it is not very useful as an induction agent
- more commonly used as a sedative in premedication and during regional procedures
- premedication is usually given in oral form with peak plasma levels occurring between 30-60 minutes after oral administration
- the clearance of diazepam is dependent on phase I hepatic metabolism, being oxidised and reduced to form *active metabolites*,

- a. desmethyldiazepam - N-desmethylation
- b. 3-hydroxydiazepam - ring hydroxylation
- c. oxazepam - ring hydroxylation

**NB:** → these prolong the duration of CNS effects

- these undergo phase II reactions with conjugation to form inactive water soluble *glucuronides*

Pharmacokinetic Data - Diazepam	
$V_{dss}$	~ 0.7 - 1.7 l/kg
Clearance	~ 0.2 - 0.5 ml/kg/min
Hepatic extraction ratio	~ 0.01 - 0.025
Elimination half-life, $t_{1/2\beta}$	~ 20 - 50 hrs
Plasma free fraction	~ 1 - 2 %

# Intravenous Anaesthetics

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- plasma binding can be influenced by *age* and disease states
- other drugs can affect its clearance and thus its elimination half-life
- during *labour* diazepam accumulates in *foetal blood*, where its free fraction may be as high as 15% with marked effects on the new-born
- in *liver disease*  $V_{dss}$  is increased and together with a reduced capacity for metabolism
- thus the elimination half-life may be increased up to 2-fold
- chronic *renal failure* results in an increase of the unbound fraction
- this would increase clearance by 2-3 times, shortening its half-life, however, there is also an increase in  $V_{dss}$  counteracting this effect
- in the *elderly* the elimination half-life is increased due to changes in both tissue distribution and protein binding
- there is a great inter-individual variation with dose-effect

## Pharmacology

- no significant effects on CO or BP
- may increase heart rate and (?) decrease peripheral vascular resistance
- no effect on cerebral blood flow (G&G)
- dose dependent reduction in  $CMRO_2$  and reduction in CBF by  $\leq 30\%$  (Miller)
- decreases the MAC of inhalational anaesthetics (eg. Halothane  $\sim 30\%$ )
- there are slight but insignificant effects on breathing in clinical doses
- relieves muscle spasm and spasticity via a central effect
- probably no significant interaction with muscle relaxants though Feldman and Crawley (1970) found that diazepam potentiated non-depolarizing agents and prolonged the effects of suxamethonium
- the findings of this study have not been confirmed by others

# Intravenous Anaesthetics

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## MIDAZOLAM

- a water-soluble, short acting drug synthesised in **1976** by Fryer and Walser
- it displays ***pH dependent opening*** of the benzodiazepine ring below a **pH ~ 4.0**
- thus, at physiological pH the ring is closed and lipid solubility is increased, with increased penetration of the BBB
- useful in oral, IM and IV administration
- its water solubility minimizes the pain on injection and the incidence of venous thrombosis
- midazolam has about **3x** the sedative potency of diazepam
- anxiolytic, anticonvulsant, sleep inducing, "muscle relaxant" and anterograde amnesic actions are qualitatively similar to diazepam
- anterograde amnesia is shorter than that of lorazepam
- the induction dose for anaesthesia ~ 0.15-0.36 mg/kg, cf. sedation doses ~ 0.01-0.08 mg/kg
- the onset is slow ~ 2-3 mins and individual variability of response is wide
- recovery is rapid, making it a suitable agent for outpatient anaesthesia
- causes minimal changes in CVS function with a small increase in heart rate and a decrease in systemic vascular resistance
- therefore, midazolam is useful in patients with compromised cardiac function as the reduction in preload and afterload may improve the performance of the failing heart
- midazolam reduces the adrenergic, but not cortisol or renin, responses to surgical stress
- there is a decrease in blood flow to the liver and kidneys but no significant prolonged reduction in respective function
- cerebral and myocardial blood flow are reduced in proportion to respective reductions in  $\text{MRO}_2$

## Pharmacokinetics

Pharmacokinetic Data - Midazolam		
$V_{\text{dss}}$	~ 1.1 - 1.7	l/kg
Clearance	~ 6.4 - 11	ml/kg/min
Hepatic extraction ratio	~ 0.3 - 0.5	
Elimination half-life, $t_{1/2\beta}$	~ 1.7 - 2.6	hrs
Plasma free fraction	~ 3 - 4 %	

- after IV injection there is rapid distribution/redistribution
- oral doses of 10-40 mg produce peak plasma levels within 30 minutes
- the  $V_{\text{dss}} \sim 1.1-1.7$  l/kg and is ***increased*** in,
  - i. women
  - ii. obese individuals
  - iii. the elderly

# Intravenous Anaesthetics

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- there is extensive plasma protein binding ~ 96-97%
- has a high clearance = 6.4-11 ml/kg/min, being,
  - a. ~ 5 x that of lorazepam
  - b. ~ 10 x that of diazepam
- this more extensive hepatic metabolism is also due to the presence of the *imidazole ring*
- the extraction ratio ~ 0.3-0.5
- metabolism occurs by oxidation, conjugation to water soluble glucuronides and then excretion by the kidneys
- thus, its eliminated half-life,  $t_{1/2\beta}$  = 1.7-2.6 hrs, is shorter than any other benzodiazepine used in anaesthesia
- midazolam, therefore, is a useful drug,
  - a. in outpatient anaesthesia
  - b. for sedation in minor procedures and regional anaesthesia
  - c. for sedation in intensive care

## LORAZEPAM

- less lipid soluble than diazepam with slow entry into CNS and a slower onset of action
- therefore, it is not very useful as induction agent and thus its major use in anaesthesia is for premedication
- both oral and intramuscular administration results in reliable absorption
- clearance is dependent on hepatic metabolism, the drug being directly conjugated to glucuronides

Pharmacokinetic Data - Lorazepam		
$V_{dss}$	~ 0.8 - 1.3	l/kg
Clearance	~ 0.8 - 1.8	ml/kg/min
Hepatic extraction ratio	~ 0.3 - 0.5	
Elimination half-life, $t_{1/2\beta}$	~ 11 - 22	hrs
Plasma free fraction	~ 10 %	

- drug disposition is not significantly affected by age
- its elimination half-life is unaltered in renal disease
- hepatic disease causes an increase in the elimination half-life (protein binding and tissue distribution)

## Intravenous Anaesthetics

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Approximate Pharmacokinetic Data					
Drug	$V_{dSS}$		$t_{1/2\beta}$		Dose (70 kg)
Diazepam	1 - 1.5	1	20-40	hrs	10-20 mg
Midazolam	1 - 1.5	1	2-4	hrs	10-40 mg
Lorazepam	1 - 1.5	1	10-20	hrs	1-3 mg

### FLUMAZENIL

(ANEXATE)

- synthesised in 1979, this is the first benzodiazepine *antagonist* released for clinical use
- it is structurally similar to *midazolam*, except,
  - a. the 5-phenyl group is replaced by a *carbonyl* group
  - b. the benzene ring has an F substitution cf. the usual Cl
- it is a competitive ligand with minimal *intrinsic activity* and high receptor *affinity*
- thus, its actions are,
  - a. concentration dependent
  - b. reversible, and
  - c. surmountable
- the proportion of receptors occupied by agonist obeys the law of *mass action* and depends upon the respective receptor affinities and concentration of the two ligands
- being a *high affinity* ligand it will readily replace weak affinity agonists such as diazepam, providing a sufficient concentration is achieved
- flumazenil is, however, *rapidly cleared* and the potential for resedation exists
- this is less likely to occur with midazolam, both agents being cleared at a similar rate
- given alone it may produce *withdrawal* phenomena in humans or animals physically dependent upon benzodiazepines
- this is not a problem with acute reversal post-anaesthesia
- the onset of effect is rapid, reaching a maximum at ~ 1-3 minutes
- due to the different affinities of the respective agonists, different plasma levels of flumazenil are required for adequate reversal
- studies indicate it is devoid of the cardiovascular and respiratory effects of the agonist agents
- incremental doses up to 3.0 mg in patients with IHD had no effect on CVS variables
- administration to patients given agonists is also free of cardiovascular effects, unlike opioid reversal by naloxone
- the opioid reversal hyperdynamic response, believed to be due to catechol release, is not seen
- however, the rise in catecholamines seen with arousal is more rapid after flumazenil

## Intravenous Anaesthetics

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Usual Doses of Flumazenil	
Reversal of benzodiazepines	0.1 - 0.2 mg ≤ 3.0 mg maximum
Infusion rates	0.5 - 1.0 µg/kg/min
Diagnosis of Coma	0.5 mg ≤ 1.0 mg maximum <sup>1</sup>
<sup>1</sup> studies suggest there is no "safe" upper limit, however if coma is due to BZD overdose, then some reversal should be seen at this dose.	

### Pharmacokinetics

Pharmacokinetic Data - Flumazenil	
V <sub>dss</sub>	~ 0.6 - 1.6 l/kg
Clearance	~ 5 - 20 ml/kg/min
Hepatic extraction ratio	~ 0.25 - 0.9
Elimination half-life, t <sub>1/2β</sub>	~ <b>0.7 - 1.3</b> hrs
Plasma free fraction	~ 55-65 %

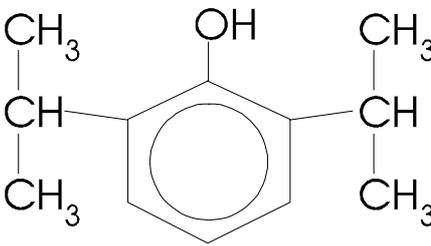
- undergoes hepatic metabolism to 3 metabolites, which are subsequently conjugated and excreted
- the activity of these species is unknown
- the clearance is the highest of any of these agents, partly due to the presence of the *imidazole ring* but also due to the high *free fraction*
- repeated administration or continuous infusion is required to maintain therapeutic levels
  
- there are no specific *contraindications* to its use
- large oral doses appear to be devoid of toxic local or systemic side effects
- ICU studies in the management of drug overdosage have used "massive doses" with relative clinical impunity
- the only potential hazard could be the occurrence of seizure activity in patients chronically addicted to benzodiazepines
- the major precaution is re-sedation due to the rapid elimination

# Intravenous Anaesthetics

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## PROPOFOL

(DIPRIVAN)

Structure:	
Chemical name:	2,6-di-isopropyl-phenol
Introduced:	1977 Kay and Rolly
Lipid Solubility:	high
Solution pH:	pH = 7.0
Protein binding:	~ 90 %
Pharmacokinetics:	$Cl_{SS}$ = 20-30 ml/kg/min $V_{dSS}$ = 2.0-10 l/kg $t_{1/2\beta}$ = 4-7 hrs ER > 1.0

- 2,6-diisopropyl-phenol, a member of the group of *hindered phenols*, an alkylphenol derivative
- first clinical trials in 1977 by Kay and Rolly
- propofol is insoluble in water and was first solubilised in cremophor EL
- this was withdrawn from the market due to anaphylactoid reactions
- it was subsequently reformulated in an emulsion with *intralipid*,
  - a. propofol 1% wt./vol.
  - b. soyabean oil 10%
  - c. glycerol 2.25%
  - d. purified egg phosphatide 1.2%
- the solution has a pH ~ 7.0 and is stable at room temperature and not sensitive to light
- it is compatible in 5% dextrose if dilution is required

# Intravenous Anaesthetics

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## Pharmacokinetics

Pharmacokinetic Data - Propofol				
	Adults		Children <sup>1</sup>	
$V_{d\text{init}}$	~ 0.2 - 0.6	l/kg	~ 0.3 - 0.7	l/kg
$V_{d\text{SS}}$	~ 1.1 - 1.7	l/kg	~ 2 - 24	l/kg
Clearance	~ 20 - 30	ml/kg/min	30 - 40	ml/kg/min
Hepatic extraction ratio <sup>2</sup>	≥ 1.0		≥ 1.0	
Distribution half-life $t_{1/2\alpha 1}$	~ 2 - 8	min	1 - 6.5	min
Distribution half-life $t_{1/2\alpha 2}$	~ 30 - 60	min	9 - 56	min
Elimination half-life $t_{1/2\beta}$	~ 240 - 420	min	210 - 735	min
Plasma free fraction	~ 2 - 10 %			
<sup>1</sup> data for children show wide variations, only a small number of studies, poorly controlled for age etc.				
<sup>2</sup> plasma clearance > hepatic blood flow, therefore either extrahepatic clearance, or simply measuring redistribution to lipid stores				

- IV administration of propofol results in rapid loss of consciousness, slightly slower than IV barbiturates, with a very rapid recovery following single dose or infusion
- the mean recovery time after a bolus dose of 2 mg/kg is ~ 4-5 mins
- as with other induction agents, redistribution causes the rapid recovery
- due to rapid metabolism there is minimal accumulation after repeated doses
- the  $V_{d\text{SS}} \sim 4.6$  l/kg is very high, representing a large tissue depot
- the clearance ~ 20-30 ml/kg/min, is greater than hepatic blood flow
- originally it was suggested there may be extrahepatic elimination of the drug
- this figure actually represents redistribution plus liver metabolism
- the majority of metabolism does occur in the liver
- the "effective" elimination half-life for single bolus injections, or small multiple boluses, therefore becomes,  $t_{1/2\alpha 2} \sim \mathbf{30-60 \text{ mins}}$
- only with prolonged administration does the true elimination half life become clinically significant,  $t_{1/2\beta} \sim 4-7 \text{ hr}$

## Intravenous Anaesthetics

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- the pharmacokinetics are altered by a number of factors,
  - a. the elderly
    - clearance is significantly decreased due to decreased hepatic blood flow
    - the initial volume of distribution is decreased
    - therefore, the dose should be decreased in elderly patients
  - b. women
    - higher volumes of distribution and clearance rates
    - the elimination half life is however similar
  - c. hepatic disease
    - both the central and steady state Vd are increased
    - clearance is unchanged
    - the elimination half life is slightly prolonged
  - d. renal disease
    - little effect on the pharmacokinetics of propofol
    - confirms the high capacity of the liver to metabolize the drug
  - e. fentanyl administration may decrease the clearance of propofol

Usual Doses of Propofol	
Induction of Anaesthesia	2.5-3.5 mg/kg (child) 1.0-2.5 mg/kg (adult) less if age > 50 yrs
Maintenance of Anaesthesia	50-150 $\mu\text{g/kg/min}^1$ $\pm \text{N}_2\text{O}$ $\pm \text{opiates}$
Sedation	25-75 $\mu\text{g/kg/min}$
<sup>1</sup> 1 ml/kg/hr = 10 mg/kg/hr = 166 $\mu\text{g/kg/min}$ ∴ start at ~ 1.0 ml/kg/hr and adjust to clinical effect	

## Pharmacodynamics

### ■ Central Nervous System

- propofol is primarily hypnotic
- unlike the barbiturates it is not analgesic but it has not been established if it has analgesic actions
- the average induction dose ~ 2-2.5 mg/kg results in unconsciousness in one arm-brain circulation time
- this should be decreased in patients who are heavily premedicated, in the elderly, or patients with debilitating disease → ~ 1.5-2 mg/kg
- for maintenance, intermittent doses or an infusion can be used at a rate of 6-12 mg/kg/h
- there is an increased incidence of *spontaneous movement*, though, less than that seen with methohexitone
- propofol displays hysteresis of its hypnotic effect
- lower doses can induce anaesthesia (1-1.5 mg/kg) but the time to onset is longer
- the duration of hypnosis is also dose dependent, generally lasting 5-15 minutes after a 2-2.5 mg/kg induction dose
- propofol alters mood less than thiopentone after short procedures and tends to produce a general state of well being
  
- initial studies in mice indicated it was neither anticonvulsant nor epileptogenic
- it does, however, result in a shorter duration of motor and EEG activity following ECT, as compared to thiopentone & methohexital
- there are isolated reports of it being used to treat seizures
- conversely, it has been associated with grand mal seizures and has been used for cortical mapping of epileptogenic foci
- there is a strong correlation between the log blood propofol level and percent EEG *α*activity and an inverse correlation with percent  $\beta$ -activity
  
- propofol will *decrease ICP* in patients with both normal and raised ICP
- in normals there is an associated small (~10%) decrease in *cerebral perfusion pressure*
- the addition of small doses of fentanyl, or supplemental doses of propofol are sufficient to blunt the rise in ICP associated with intubation
- normal vascular reactivity to  $P_{aCO_2}$  is retained
- in the presence of raised ICP, there may be a large fall in *CPP* (30-50%), which may clearly be detrimental
- there is a reduction in  $CMRO_2$  ~ 36%
  
- propofol acutely reduced *intraocular pressure* by 30-40%
- this effect is greater than seen with thiopentone, and following a supplemental dose is more effective in preventing the rise in IOP associated with succinylcholine or intubation

# Intravenous Anaesthetics

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## ■ Respiratory Effects

- there is a higher incidence of apnoea compared to other IV anaesthetics and the incidence is increased by,
  - a. opioid or other premedication
  - b. higher doses
  - c. the rate of injection
- a standard induction dose will produce **apnoea** in ~ 25-30%
- the major difference to other induction agents is that apnoea may be prolonged, lasting  $\geq 30$  secs
- following a 2.5 mg/kg induction dose,
  - a. the respiratory rate is significantly reduced for  $\geq 2$  minutes
  - b. tidal volume is significantly reduced for up to 4 minutes
- maintenance of propofol anaesthesia by infusion at 100  $\mu\text{g}/\text{kg}/\text{min}$  results in,
  - a. a decrease in tidal volume ~ 40%
  - b. an increase in respiratory frequency ~ 20%
  - c. unpredictable effects on minute volume
  - d. a similar reduction in the slope of the  $\text{CO}_2$ /ventilation response curve to that seen with 1 MAC halothane

**NB:** 100  $\mu\text{g}/\text{kg}/\text{min}$   $\rightarrow$  6 mg/hr/kg = 0.6 ml/kg/hr

- doubling the infusion rate to 200  $\mu\text{g}/\text{kg}/\text{min}$  produces only a small decrease in tidal volume and a minimal decrease in the  $\text{CO}_2$  response curve
- this is in contrast to the volatile agents, where a doubling of  $F_A$  will halve the  $\text{CO}_2$  response curve
- an induction dose of 1.5-2.5 mg/kg will cause a rise in  $P_{a\text{CO}_2}$  of 15-25%, with a corresponding decrease in arterial pH
- $P_{a\text{O}_2}$  does not usually alter

## ■ Cardiovascular

- the most prominent effect of propofol is a decrease in arterial BP during induction of anaesthesia
- 2-2.5 mg/kg results in a decrease of 25-40% in both systolic and diastolic blood pressures, while the heart rate remains stable
- this is associated with a decrease in CI, LVSWI, SVR, mean PAP, and PAOP
- the effect is maximal at ~ 2 mins after induction, and is due to,
  1. direct **myocardial depression**, plus
  2. decreased **peripheral resistance** and preload

**NB:** as HR is **unaltered**,  
it has been suggested that propofol "resets" the **baroreceptor reflex**

## Intravenous Anaesthetics

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- the *hypotensive effect* of propofol is potentiated by,
  - a. large doses of propofol
  - b. pre-existing CVS disease
  - c. hypovolaemia or CVS decompensation
  - d. advanced age
  - e. premedication with opiates
  - f. the concomitant use of N<sub>2</sub>O
- care should be practiced with patients who are hypovolaemic or have poor LV function
- both coronary blood flow and myocardial MRO<sub>2</sub> are reduced, implying that global myocardial supply-demand is maintained

### ■ Other Effects

- the most significant side effect is *pain on injection*, especially in small veins
- incidence can be decreased by using larger veins, or mixing the drug with lignocaine
- propofol can be administered by infusion to sedate ICU patients
- prolonged infusions must consider the effect of *volume* as well as *energy* provided by intralipid

**NB:** 3 mg/kg/hr provides ~ 555 kcal/24 hours

- this is equivalent to 25% of calorie requirements and 50% of lipid requirements per day
- the reports investigating C<sub>3</sub> complement, immunoglobulin or *histamine release* following intravenous propofol have not found any changes in the levels of these in healthy volunteers
- prolonged infusion does not impair *cortisol* synthesis or the response to ACTH
- preliminary studies indicate it does not trigger *malignant hyperpyrexia*
- case reports suggest its use is safe in *porphyria*

# Intravenous Anaesthetics

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## KETAMINE

Structure:	
Chemical name:	
Introduced:	1966                      Corssen & Domino
Lipid Solubility:	high      (> thiopentone)
Acid dissociation K:	$pK_A = 7.5$
Solution pH:	$pH = 3.5 - 5.5$
Protein binding:	45 - 50 %
Pharmacokinetics:	$Cl_{SS} = 12 - 20 \quad \text{ml/kg/min}$ $V_{dSS} = 2.3 - 3.1 \quad \text{l/kg}$ $t_{1/2\alpha} = 11 - 16 \quad \text{min}$ $t_{1/2\beta} = 120 - 180 \quad \text{min}$ $ER = 0.5 - 0.9$

- **phencyclidine** was the first drug of this class to be used in anaesthesia
- it was synthesised by Maddox and introduced into clinical use by Greifenstein in 1959
- although a useful anaesthetic, it had a high incidence of psychotomimetic side effects
- cyclohexamine, a congener of phencyclidine was trialed in 1959 but was less efficacious and had the same side effects
- ketamine was synthesised by Stevens in 1962 and first introduced to clinical anaesthesia by Corssen and Domino in 1966
- it was released for clinical use in 1970
- it is an **arylcyclohexylamine** structurally related to phencyclidine
- it contains an asymmetrical C-atom, hence has two isomers
- the **d-isomer** is more potent but the parenteral solution is a **racemic mixture**
- ketamine hydrochloride is a white crystalline solid, soluble in water
- supplied in 1, 5, and 10% solutions which are stable at room temperature
- benzethonium chloride is added as preservative
- the solution has a  $pH \sim 3.5$  to  $5.5$
- ketamine has a  $pK_A \sim 7.5$
- it has a lipid solubility  $\sim 5-10$  times that of thiopentone

# Intravenous Anaesthetics

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## Pharmacokinetics

- has similarities with STP
- ketamine is extremely soluble in fat, 5-10 times more soluble than STP
- however, plasma protein binding is limited 45-50%
- after intravenous injection, consciousness is lost within 1-2 minutes and the resultant anaesthesia lasts for ~ 20 minutes
- the distribution half-life is longer,  $t_{1/2\alpha} \sim 11-16$  mins and the elimination half-life  $t_{1/2\beta} \sim 2-3$  hrs (W&W = 2.5)
- termination of the anaesthetic action is due to **redistribution** from the central compartment, early metabolism playing a lesser part
- the  $V_{dss} \sim 2.3$  to  $3.1$  l/kg consistent with its high lipid solubility
- however, the clearance  $\sim 17.5-20$  ml/kg/min, is rapid resulting in the relatively short elimination half life
- this is due to both the high hepatic extraction ratio  $\sim 0.9$  and limited protein binding
- therefore, clearance will be sensitive to hepatic blood flow and agents such as halothane, which reduce this will decrease the clearance
- it can be administered IM with 93% bioavailability, but there is a delay of 20-25 mins prior to adequate anaesthetic levels
  
- the major pathway of metabolism is in the liver, with N-demethylation of the cyclohexylamine ring, forming **norketamine** (metabolite I)
- this is then hydroxylated to form hydroxy-norketamines, with up to 8 metabolites which may contribute to the undesirable side effects
- the activity of these metabolites has not been well studied, however, norketamine has  $\sim 20-30\%$  of the activity of ketamine
- these are subsequently conjugated and excreted in the urine

# Intravenous Anaesthetics

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## Pharmacodynamics

### ■ Central Nervous System

- causes a "dissociative anaesthetic state"
- this is a functional and electrophysiological dissociation between the *thalamocortical & limbic systems* (ie., blocks transmission between thalamus and cortex)
- this state is characterised by *cataplexy* in which eyes remain open with slow nystagmic gaze, while corneal and light reflexes remain *intact*
- when administered in subanaesthetic concentrations, ketamine produces good *analgesia* at plasma levels one-eighth those required for anaesthesia
- this may be related to its ability to suppress laminae specific spinal cord activity (opioid *k-receptors*, ? laminae II & III)
  
- ketamine induced psychotomimetic activity, *emergence reactions*, can be disturbing to physicians, nurses, other patients and the patient him/herself
- vivid dreams, hallucinations, and delirium are unpleasant for the patient and may occur in 5-30%
- a higher *incidence* of reactions is associated with,
  - a. age > 16 yrs
  - b. sex female > male
  - c. larger doses > 2mg/kg IV
  - d. rapid IV administration
  - e. subjects who normally dream during sleep
  - f. history of personality problems
  
- the incidence is not affected by covering eyes during emergence, nor by allowing the patient to emerge in a quiet room
- adverse reactions may be lessened by preoperative discussion with the patient
- *atropine & droperidol* may increase the incidence, while nitrous oxide supplementation decreases the dosage of ketamine and therefore the incidence of reactions
- *benzodiazepines* are the most effective drugs for attenuating the psychic reactions both preoperatively and for their treatment
- diazepam (0.15-0.3 mg/kg IV), lorazepam (2-4 mg PO or IV), or midazolam
  
- ketamine *increases* CMRO<sub>2</sub>, cerebral blood flow and intracranial pressure
- the excitatory CNS effects of ketamine can be detected by the development of theta-activity and "petit-mal like" seizure activity
- this is associated with an increased CMRO<sub>2</sub>, however, CBF increases to a greater degree
- this is probably due to cerebral vasodilatation and a rise in systemic blood pressure
- cerebrovascular responses to P<sub>aCO2</sub> remain intact
- however, due to these effects ketamine should be avoided in patients with potentially raised ICP

## ■ Cardiovascular Effects

- ketamine produces unique cardiovascular effects
  - there is an **increase** in mean arterial BP, HR, pulmonary arterial and central venous pressures
  - this is related to **sympathetic stimulation**, with increased circulating levels of adrenaline & noradrenaline, resulting in peripheral vasoconstriction and direct cardiac stimulation
  - the haemodynamic changes are **not** related to the dose of ketamine
  - there being no difference after administration of 0.5 or 1.5 mg/kg
  - further, subsequent doses do not produce the same effect and may even be associated with cardiovascular depression
  - the mechanism for this effect is uncertain
  - direct intrathecal administration is associated with an immediate increase in SNS outflow
  - this effect can be blocked by prior administration of barbiturates, droperidol and benzodiazepines
  - stimulation of the cardiovascular system is not always desirable and the benzodiazepines appear the most effective in attenuating this response
  - peripheral effects play an undetermined role
  - both inhibition of neuronal uptake of catecholamines, similar to cocaine, and inhibition of extraneuronal catecholamine uptake have been demonstrated
- 
- its **direct effects** are depressant on myocardium and dilatory on smooth muscle, but these are normally countered by the increased SNS activity
  - the effects on peripheral resistance are variable
  - ketamine abolishes adrenaline-induced arrhythmias by prolonging the relative refractory period
  - in congenital heart disease patients there is **no** significant change in **shunt** direction or fraction, or systemic oxygen flux after ketamine

**NB:** used in paediatric cardiac catheterisation with **less arrhythmias**

- in the normal heart, coronary blood flow increases secondary to the increased myocardial O<sub>2</sub> consumption and stroke work
- increases pulmonary vascular resistance, thus increasing pulmonary artery pressure and right ventricular stroke work
- therefore, the drug is a valuable induction agent for **poor risk** and **hypovolaemic patients**
- the (+)'ve chronotropic & inotropic effects are contraindicated in patients with IHD or minimal right ventricular reserve
- in patients with elevated pulmonary vascular pressures, ketamine appears to produce a more pronounced increase in PVR than in SVR

# Intravenous Anaesthetics

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## ■ Respiratory Effects

- respiratory depression is minimal with anaesthetic doses but may be depressed with large doses
- results in **bronchodilatation** and this is a useful agent for asthmatics or patients with CAO
- in patients with reactive airway disease, ketamine decreases airway resistance and bronchospasm  $\equiv^T$  to the volatile agents
- ketamine produces marked **salivation**, especially in children, therefore an antisialogogue should be administered prior to its use
- there are opposing views on its effectiveness in preserving pharyngeal reflexes and the patency of the upper airway → thus it is **not** a substitute for good airway management
- W&W states laryngeal & pharyngeal **reflexes** remain active and that aspiration is less likely but still possible (Miller holds the same view)

## ■ Other Effects

- there is a transient rise in intraocular pressure
- eye movements and nystagmus may occur
- nausea and vomiting are fairly common after sole administration

## Pharmacodynamics

Usual Doses of Ketamine	
Induction of Anaesthesia	<ul style="list-style-type: none"><li>• 0.5-2.0 mg/kg IV</li><li>• 4.0-6.0 mg/kg IM</li></ul>
Maintenance of Anaesthesia + N <sub>2</sub> O/O <sub>2</sub> or opiates	<ul style="list-style-type: none"><li>• 50-90 µg/kg/min</li><li>• 0.5-1.0 mg/kg IV prn or, 15-30 µg/kg/min</li></ul>
Sedation	<ul style="list-style-type: none"><li>• 0.2-0.8 mg/kg IV</li><li>• 2.0-4.0 mg/kg IM</li></ul>

# Intravenous Anaesthetics

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## ■ Induction

- especially poor risk patients,
  - a. ASA Class  $\geq$  IV
  - b. cardiac disorders
    - especially hypovolaemia, intrinsic myocardial disease, congenital heart disease, tamponade, restrictive pericarditis
    - \* with the exception of IHD
  - c. respiratory disorders
    - especially bronchospastic airways disease
  - d. otherwise healthy patients with trauma/hypovolaemia
- recommended IV induction dose ~ 1.0-2.0 mg/kg and unconsciousness usually lasts 5-15 mins
- incremental doses may be given if a longer duration is required
- combination of ketamine & midazolam by infusion is useful for valvular or IHD
- the addition of a BZD attenuates or eliminates the unwanted hyperdynamic response to ketamine

## ■ Anaesthesia

- produces *analgesia* without loss of consciousness at infusion rates ~ 50  $\mu$ g/kg/min
- may also be used in conjunction with N<sub>2</sub>O & muscle relaxants to provide sleep and analgesia at doses of 15-30  $\mu$ g/kg/min
- muscle relaxants are often necessary as ketamine increases *muscle tone*

## ■ Obstetrics

- reportedly used successfully as an induction agent in caesarean section but doses > 1.5 mg/kg IV may lead to foetal depression
- useful as a supplement to epidural insertion or LUSCS in low "analgesic" doses (0.2-0.3 mg/kg)

## ■ Day Surgery

- useful in children for short procedures as it may be given IV, IM, orally or rectally
- IM doses for children are ~ 5-10 mg/kg with an onset of surgical anaesthesia in 3-5 mins and a duration of 10-30 mins
- the use in children is more versatile as the incidence of emergence reactions is much lower
- lower dose may be used for diagnostic procedures such as cardiac catheterization, radiation therapy, dressing changes, or dental work
- may also be used in adults in conjunction with the benzodiazepines but these prolong recovery

## ■ Adjunct to Local and Regional Anaesthesia

- during performance of painful blocks ketamine produces analgesia, sedation and amnesia without CVS depression
- also used for sedation during regional anaesthesia in combination with benzodiazepines

# Intravenous Anaesthetics

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## ■ Burns Patients

- used extensively for dressing changes, debridements and skin grafting (1.5-2.5 mg/kg IM)
- however, tolerance appears to develop, necessitating increasing the dosage with time
- higher dosages (4-6 mg/kg) are adequate for eschar excision
- only 10%, in one study, were found to have mild emergence reactions

## ■ Miscellaneous

- successfully used in patients with MH susceptibility, myopathias, porphyria, etc.
- in acute hypovolaemia, the use of ketamine results in a more stable and better functioning cardiovascular system than with other induction agents

## Toxicity & Precautions

### ■ Disadvantages

1. the slow onset of action
2. increased muscle tone
3. spontaneous movements during induction & anaesthesia
4. CVS stimulation
5. slow recovery
6. emergence reactions
7. postoperative nausea & vomiting
8. elevated ICP & IOP
9. potent sialogogue, especially in children

### ■ Contraindications

1. poorly controlled hypertension
2. unstable angina or recent myocardial infarction
3. right or left heart failure
4. valvular heart disease - but may be useful in CHD
5. intracranial, thoracic or abdominal aneurysms
6. cerebrovascular disease
7. raised ICP
8. recent penetrating eye injury

# Intravenous Anaesthetics

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## ETOMIDATE

- an imidazole derivative synthesised in 1964 and introduced into clinical practice in 1973
- the structure is unrelated to any other IV anaesthetic
- it exists as two isomers, only the (+)-isomer being active
- presented in 10 ml ampoules containing 2 mg/ml dissolved in water with 35% propylene glycol
- the solution has a pH ~ 8.1 and an osmolality of 4,640 mosm/l

## Pharmacokinetics

Pharmacokinetic Data - Etomidate	
$V_{dss}$	~ 2.5 - 4.5 l/kg
Clearance	~ 18 - 25 ml/kg/min
Hepatic extraction ratio	~ 0.65 - 1.0
Distribution half-life $t_{1/2\alpha 1}$	~ 3 min
Distribution half-life $t_{1/2\alpha 2}$	~ 29 min
Elimination half-life $t_{1/2\beta}$	~ 2.9 - 5.3 hr
Plasma free fraction	~ 25 %

- the kinetics following an open 3 compartment model
- induction is rapid, sleep being produced within one arm-brain circulation time
- redistribution from the brain to peripheral tissues being responsible for the short duration of clinical action
- there is minimal accumulation following repeated doses
- highly lipid soluble and protein binding ~ 75%, therefore is susceptible to factors which later protein binding
- the clearance ~ 18-25 ml/kg/min, is 5-6x that of STP, and may be equal or above liver blood flow
- metabolism occurs rapidly by hepatic enzymes and plasma esterases to an inactive carboxylic acid metabolite
- the  $V_{dss}$  ~ 2.2-4.5 l/kg
- due to its large volume of distribution there is slow return of etomidate into blood, thus increasing its elimination half-life,  $t_{1/2\beta}$  ~ 2.5-4.5 hrs
- cirrhosis increases the volume of distribution and therefore the elimination half-life
- similar effects are seen in renal disease due to altered protein binding

# Intravenous Anaesthetics

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## ■ CNS Effects

- etomidate is primarily a hypnotic agent and the duration of CNS effects are dose dependent
- a usual induction dose ~ 0.3 mg/kg is effective in one arm-brain circulation and consciousness is regained in 5-8 mins (W&W: 7-14 mins)
- it has no intrinsic analgesia activity
- etomidate decreases the CMRO<sub>2</sub>, cerebral blood flow and ICP
- some studies suggest a possible protective action on the brain as mean arterial pressure is unaltered and **cerebral perfusion pressure** is increased
- etomidate has been associated with grand mal seizures and does increase epileptogenic activity in patients with seizure foci
- there is frequent myotonic activity during induction but this is not related to epileptiform discharges and may be decreased by opioid or benzodiazepine premedication
- the incidence of **nausea and vomiting** appears to be more common with etomidate than with other IV agents
- the incidence is decreased by droperidol from ~ 40% to 20%

## ■ CVS Effects

- minimal effects in both normal patients and those with cardiac disease
- clinical doses do cause a fall in arterial blood pressure, cardiac index and peripheral resistance but this is not significant (~ 10%)
- with 1-2 µg/kg fentanyl, 0.3 mg/kg etomidate blocks the CVS response to intubation
- there is a high incidence of pain at the site of injection (25 - 50%)

## ■ Respiratory Effects

- etomidate produces a dose related depression of respiratory rate and tidal volume, though, less than with STP
- induction often produces a brief period of hyperventilation, which is occasionally followed by apnoea
- it does not induce histamine release, nor increase bronchial reactivity

## ■ Endocrine Effects

- etomidate results in inhibition of adrenal corticoid synthesis by a concentration dependent, reversible block of **11-*b*-hydroxylase**
- this occurs after both induction doses and particularly when used as an infusion in ICU
- this results in inhibition of ascorbic acid resynthesis, required for steroid synthesis in humans
- vitamin C supplementation restores cortisol levels following the use of etomidate
- this inhibition is probably not significant when used as an induction agent

## ■ Clinical Uses

- as induction agent in patients with compromised cardiovascular function
- may be useful when rapid recovery is required as in outpatient anaesthesia

# Intravenous Anaesthetics

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## PROPANIDID

- first used in 1956 and is a eugenol derivative, chemically related to the constituents present in oil of cloves
- presented as a yellow oil, prepared as a 5% solution in Cremaphor EL

Pharmacokinetic Data - Propanidid	
$V_{dSS}$	~
Clearance	~
Hepatic extraction ratio	~
Distribution half-life $t_{1/2\alpha}$	~ 3 min
Elimination half-life $t_{1/2\beta}$	~ 10 min
Plasma free fraction	~ 60 %

- protein binding ~ 40%, therefore has a large free fraction
- more lipid soluble than STP, which accounts for its rapid onset of action
- its short duration of action is due to rapid **hydrolysis** by plasma and liver esterases to the main metabolite phenylacetic acid
- there is interaction between suxamethonium and propanidid due to common metabolism by **pseudocholinesterase**
- this explains the prolonged apnoea when these two are given concomitantly
- induction dose ~ 3-8 mg/kg, after which there is 2-5 mins of unconsciousness
- pharmacokinetic studies carried out on propanidid showed a distribution half-life,  $t_{1/2\alpha}$  ~ 3 mins and an elimination half-life,  $t_{1/2\beta}$  ~ 10 mins
- the elimination half-life is expected to be increased with plasma pseudocholinesterase deficiency
- there is no accumulation after repeated doses

### ■ CNS Effects

- sleep occurs within one arm-circulation time
- may cause unwanted muscular movements on induction, the incidence of which is related to the dose used, the rapidity of injection, and type of premedication, eg., narcotics decrease the incidence and anticholinergics increase the incidence
- the incidence is slightly higher than STP but much less than methohexital

### ■ Cardiovascular Effects

- there is a dose related depression of the cardiovascular system due to a negative inotropic action and a decrease in afterload
- this may result in a reflex tachycardia

## Intravenous Anaesthetics

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### ■ Respiratory

- there is often marked hyperpnoea after an induction dose followed by apnoea which marks onset of sleep
- there is a high incidence of coughing and hiccups

### ■ Neuromuscular Effects

- potentiates the effect of suxamethonium due to the common metabolic pathway

### ■ Adverse Effects

- there is a higher incidence of nausea and vomiting than with barbiturates
- problems with this drug are *cardiovascular depression* and *hypersensitivity reactions* to its solubilizing agent (Cremophor EL)

**NB:** Withdrawn from market!

## ALTHESIN

- a mixture of 2 water insoluble steroids,
  - a. alphaxalone 9 mg/ml, and
  - b. alphadolone 3 mg/ml
  - c. in 20% Cremaphor EL = propylene glycol + castor oil + parabenz
- *alphaxalone* is the major active component and alphadolone is added to increase solubility

## Pharmacokinetics

- althesin has a rapid onset of action and a high potency, both related to the free 3- $\alpha$ -OH group on the steroid molecule
- usual induction dose ~ 20-50  $\mu$ l/kg (or 0.3-0.6 mg/kg total steroid)
- plasma protein binding ~ 50% (albumin and  $\beta$ -lipoproteins)
- the rapid recovery from anaesthesia is due to redistribution and early metabolism of the drug, duration of action ~ 5-13 mins
- the  $V_{dss}$  ~ 0.7-0.9 l/kg and clearance ~ 17-21 ml/kg/min
- most of the drug being cleared after one passage through the liver, plasma clearance thus being dependent on hepatic blood flow
- the elimination half-life,  $t_{1/2\beta}$  ~ 0.5-1.0 hrs, thus there is no accumulation following repeated doses or infusion

### ■ CNS

- anaesthetic state achieved as rapidly as thiopentone
- cerebral blood flow, cerebral oxygen uptake and intracranial pressure are all decreased
- there is a high incidence muscle tremors and movements, though, less than with methohexitone

### ■ CVS

- has a negative inotropic effect with decreased peripheral resistance, decreased stroke volume and decreased blood pressure similar to the barbiturates
- this is seldom a problem clinically

### ■ Respiratory

- produces an initial hyperventilation followed by apnoea
- then dose dependent respiratory depression
- may cause hiccups, coughing and laryngospasm

### ■ Adverse Effects

- side effects and adverse effects occur with 1:1900 to 1:300 frequency and are characterised by flushing, skin rash, marked *complement* C<sub>3</sub> and massive *histamine* release

**NB:** Withdrawn from market!

# Intravenous Anaesthetics

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## MINAXOLONE

- is a water soluble steroid derived from alphaxolone
- given by bolus injection of 0.5 mg/kg it produces rapid induction of anaesthesia lasting ~ 20 mins
- there is a high incidence of side effects accompanying induction, ie., movement, hiccups and laryngeal spasm, the frequency being reduced by narcotic premedication and by slow injection of the drug

### Pharmacokinetics

- the  $V_{dSS} \sim 1.6-2.3$  l/kg and the clearance  $\sim 17-26$  ml/kg/min
- the distribution half-life,  $t_{1/2\alpha} \sim 2-8$  mins, and the elimination half-life,  $t_{1/2\beta} \sim 0.8-1.5$  hrs, which probably contributes to speed of recovery

**NB:** Before much more work was done on minaxolone it was withdrawn from clinical studies to evaluate reports of possible toxic effects on rats and despite these findings being unsubstantiated by further animal studies, it has not been re-introduced

## GAMMA HYDROXY BUTYRIC ACID

- first used in 1960 and supplied as a 20% solution
- a basal anaesthetic derived from GABA
- clinical effects are probably in the cortex rather than the midbrain
- has **slow onset** of action (10-15 mins) and therefore dose of 60-80 mg/kg is combined with STP 1 mg/kg for induction
- action lasts for 60-90 mins
- respiratory and cardiovascular effects not marked
- adverse effects include,
  - a. prolonged recovery
  - b. emergence delirium
  - c. extrapyramidal side-effects, clonic movements
  - d. venous irritation

### ■ Uses

- has been recommended for paediatric surgical procedures and as sedation for regional anaesthesia
- seldom used in Australia (or UK)

## NEUROLEPT ANALGESIA

**Def'n:** the state of neuroleptanalgesia, or neuroleptanaesthesia may be obtained using a combination of a *potent analgesic* and a *neuroleptic tranquiliser* drug

- this produces a state of *indifference* to pain, eg., droperidol and fentanyl (or phenoperidine)
- initially used to provide sedation for surgical procedures but now also used for procedures with general anaesthesia,

→ N<sub>2</sub>O/O<sub>2</sub> + droperidol + fentanyl + muscle relaxant

- first described by Delay (1959) in drug induced behaviour syndromes
- this syndrome includes,
  - a. inhibition of *purposeful movement* & conditioned behaviour
  - b. inhibition of amphetamine induced *arousal*
  - c. tendency to maintain an induced posture, *cataplexy*
  - d. marked inhibition of apomorphine induced *vomiting*
  - e. maintenance of corneal and light *reflexes*

- drugs with neurolept properties may also exhibit,

- a.  $\alpha$ -adrenergic blockade
- b. hypotension
- c. hypothermia
- d. sedation
- e. extrapyramidal effects
- f. anticholinergic properties

- a number of agents will induce this state, the two most common groups being,

- a. the phenothiazines - *chlorpromazine* is the prototype
- b. the butyrophenones - *droperidol & haloperidol*

**NB:** the mechanism of action of these agents is thought to be competitive antagonism at *dopaminergic receptors* in the brain

- these agents have a predilection for certain areas in the brain rich in DA-receptors, especially the CTZ and the extrapyramidal nigrostriatum

## DROPERIDOL

- first synthesised by Janssen, droperidol is a **butyrophenone**, a fluorinated derivative of the phenothiazines
- frequently used in conjunction with fentanyl
- it has a faster onset and shorter duration of action than haloperidol
- the elimination half-life,  $t_{1/2b}$  ~ **2-2.5 hrs**, is not dissimilar to that of fentanyl
- however, the effects frequently **outlast** those of fentanyl, possibly due to increased affinity for CNS receptors
- it has been postulated that the butyrophenones may occupy **GABA receptors** on the post-synaptic membrane, thereby reducing the build-up of dopamine in the synaptic cleft
- it is a potent **anti-emetic** and is effective against opioid induced vomiting
- it produces **extrapyramidal** side-effects
- respiratory effects are **minimal** and in general the CVS effects are small
- however, droperidol may cause a profound fall in peripheral resistance and BP in patients receiving vasodilator therapy and in those with a decreased circulating blood volume, due to both a CNS and peripheral  $\alpha$ -blocking effect
- cardiac arrhythmias are infrequent
- in combination with fentanyl, there is little effect, or a small reduction in cerebral blood flow
- it has **no analgesic** effect in man and the metabolic effects are minimal

### ■ Dosage & Administration

- droperidol is available for parenteral use as a 10 mg/2 ml solution
- was available in a fixed mixture with fentanyl, "Innovar", but no longer available in Australia
- for premedication, dose = 0.1-0.15 mg/kg IM, or 5-10 mg for an adult
- droperidol alone is unsatisfactory for surgery, being associated with increased anxiety, poor sedation and even refusal of surgery
- for induction, a dose ~ 10 mg, alone or in combination with fentanyl
- a neuroleptanaesthesia regimen would involve,
  - a. fentanyl 4  $\mu$ g/kg & droperidol 0.2 mg/kg
  - b. N<sub>2</sub>O/O<sub>2</sub>
  - c. a muscle relaxant
- with this technique, unless the total opioid dose is low, there will be profound respiratory depression and ventilation should be controlled

**NB:** \*\* droperidol should be avoided in patients with Parkinsonism

# Intravenous Anaesthetics

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## Ideal Intravenous Anaesthetic Agent

- the ideal intravenous anaesthetic, according to Dundee, should be,
  - a. **non-irritant** - IV or IA
  - b. **rapid induction** - sleep in one arm-brain circulation time
  - c. **short duration** of action - elimination by **metabolism**  
- no cumulative properties
  - d. good **analgesia**
  - e. **nontoxic** - with inactive, **nontoxic metabolites**
  - f. high **specificity** of action
    - i. minimal cardiorespiratory depression
    - ii. no increase in muscle tone
  - g. no hypersensitivity, or histamine release
  - h. physical properties
    - i. water soluble - therefore require no solvent
    - ii. stable in solution over long periods of time
    - iii. not adsorbed onto glass or plastic

## Adverse Reactions

**NB:** usefully described under four headings;

1. reactions on **induction**
  - pain on injection
  - muscle movements
  - cough & hiccup
  - cardiorespiratory depression
2. reactions on **recovery**
  - psychic problems
  - motor disturbances
  - pain
  - nausea & vomiting
  - prolonged somnolence
  - respiratory depression
3. tissue complications
  - local tissue damage
  - thrombophlebitis at the site of injection
4. hypersensitivity
  - anaphylactic reactions
  - anaphylactoid reactions
  - histamine release
  - skin rashes
  - bronchospasm

## Intravenous Anaesthetics

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Pharmacokinetic Data of the Intravenous Anaesthetics					
Drug	Dose mg/kg	V <sub>ass</sub> l/kg	t <sub>½β</sub> hr	Clearance <sup>1</sup> ml/kg/min	Protein Binding
<b>Thiopentone</b>	<b>4-7</b>	<b>1.7-2.5</b>	<b>5-12</b>	<b>1.6-4.3</b>	<b>75-85%</b>
Methohexitone	1-1.5	1.1-2.2	1.6-2.9	10-12	70-80%
<b>Propofol</b>	<b>2</b>	<b>2.0-10</b>	<b>4.0-7.0</b>	<b>20-30</b>	
Ketamine	1-2	2.3-3.1	2.5-2.8	17.5-20	45-50%
Diazepam	0.1-0.3	1-1.5	20-40	0.2-0.5	98-99%
Midazolam	0.15-0.36	0.8-1.5	1.7-2.6	6.4-11	96-97%
Droperidol	0.1-0.2	2	1.7-2.2	14	
Etomidate	0.3	2.2-4.5	2.0-5.3	15-26	75%

<sup>1</sup> **NB:** liver blood flow ~ 21.5 ml/kg/min