Review Article

A Comprehensive Review on Structure Elucidation of General Anaesthetics and Opioid Analgesics as an Element of Modern Pharmaceutical Sciences

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ABSTRACT

Anaesthetics are the drugs used to promote unconsciousness during surgical purpose. It is an important part in medical science. Nowadays a surgery without anaesthetics is impossible. Usually anaesthetics, classified as general anaesthetic and local anaesthetic, are used to block the transmission of pain. General anaesthetics are classified into two types depending upon their mode of administration, Inhalation anaesthetics and Intravenous anaesthetics. Local anaesthetics are classified as Topical anaesthetics, Infiltration anaesthetics, Nerve block anaesthetics, Spinal anaesthetics, Epidural anaesthetics and Caudal anaesthetics.

Keywords: Sevoflurane, Ketamine, Propofol, Benzodiazepines, General Anaesthesia, Opioid Anaesthesia.

INTRODUCTION

Pain is an uncomfortable sensation in human body which is classified into two categories including acute pain and chronic pain[1,2]. Anaesthetics help to temporarily block the pain signals from nerves to the centre in the brain[3]. Anaesthetics are group of drugs used to produce loss of sensation and consciousness. Anaesthetics are generally classified as General anaesthetics and local anaesthetics.

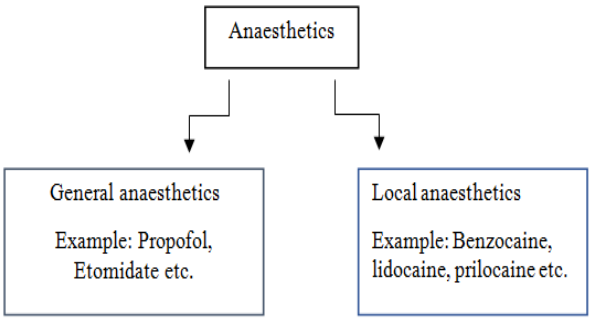


Figure 1: Classification of Anaesthetics

General anaesthetics:

General anaesthetics (GAs) are the drugs used to dropping consciousness by descending depression of central nervous system. General anaesthetics made people totally unconscious but loss of sensation and consciousness is reversible and often used in surgical purpose during serious operations.

Local anaesthetics:

Local anaesthetics act by inhibit excitation of nerve endings or by blocking the nerve impulses. Local anaesthetics are used to stupor a particular part of the body but not losing consciousness.

In 1844, a Hartford dentist, Horace Wells first denotes the use of nitrous oxide (N_2O) as effective anaesthetics in surgical purpose. Then in 1860, a Boston dentist William Morton shows the action of diethyl ether as anaesthetics[4].

Stages of general anaesthesia[5]:

- **Analgesia (Stage I)**: In this state patient is conscious and can experience sensation, can see and hear. Respiration remain normal is this stage. Variable levels of analgesia and amnesia are observed in this phase. This stage of anaesthesia used during minor surgery.
- **Delirium or excitement (stage II)**: Loss of consciousness begins from this stage. Heart rate and respiration is typically irregular in this stage. Muscle tone increases, BP and heart rate rises.
- **Surgical anaesthesia (stage III):** In this stage unconsciousness fully occupied. Blood pressure is maintained. Surgical procedures are carried out through this stage. There are four planes in this stage.

  Plane 1**:** Nomadic eyeballs. When eye become fixed this plane ends.

  Plane 2**:** Loss of corneal reflexes occurred.

  Plane 3**:** Pupil dilates and light reflex lost.

  Plane 4**:** Dilated pupil, intercostals paralysis.

  Heart rate increases, BP falls at phase.
- **Impending death or medullary paralysis (stage IV)**: Failures of respiration and circulations occur as a result of depression in vital centres of the medulla and brain stem occurs.

Table 1: Stages of anaesthesia

Stage		Respiration	Pupil size	Blood pressure
I. Analgesia				Normal
II. Delirium				Increases
III. Surgical anaesthesia	Plane 1.			Maintained normal
	2.			
	3.			
	4.			
IV. Medullary paralysis				Low

Pharmacological classification [5]:

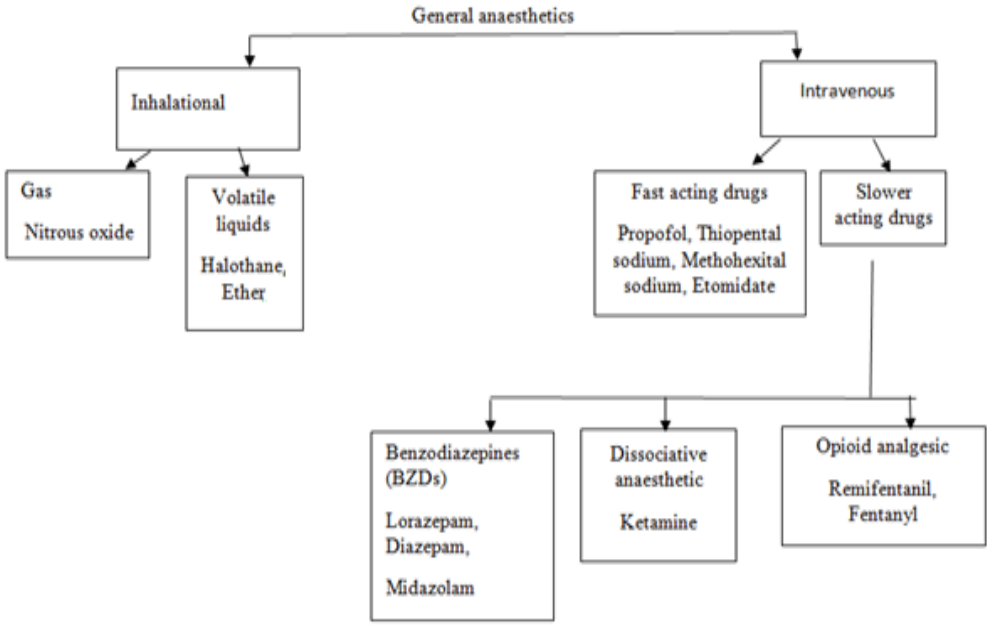


Figure 2: Pharmacological classification of general anaesthetics

Chemical classification [6]:

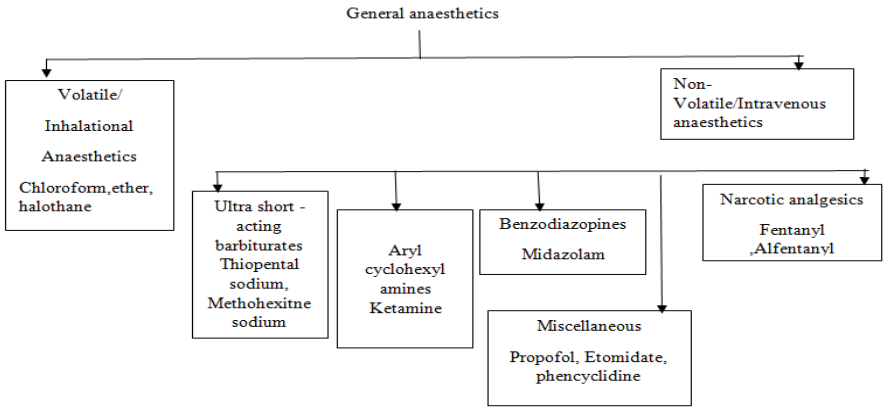


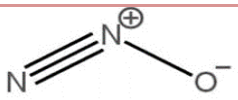
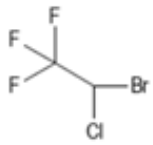
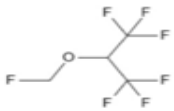
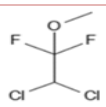
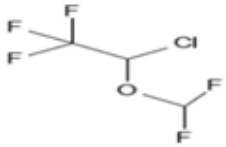
Figure 3: Chemical classification of general anaesthetics

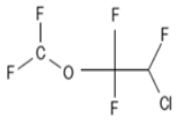
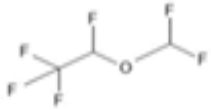
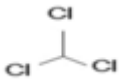
Mechanism of Action of general anaesthetics [5,6]:

The mechanism of action of GAs is not accurately known. But some recent study demonstrated that the general anaesthetics target the ligand gated ion channel and bring about anaesthetic action. The $GABA_A$ receptor gated chloride ion channel is most important site for these. Some anaesthetics like propofol, barbiturates interact with its own biding sites on the $GABA_A$ receptor's Cl^- channel. Ketamine, nitrous oxide is selectively inhibiting the excitatory NMDA type of glutamate receptor which belongs to calcium gated channel in the neurones. But they do not affect GABA gated Cl^- channel.

A. Inhalational anaesthetics [4,5,6]:

Table 2: Structure & Properties of Inhalation anaesthetics

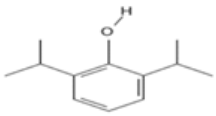
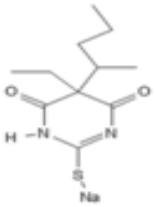
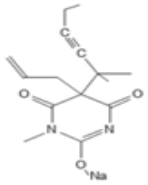
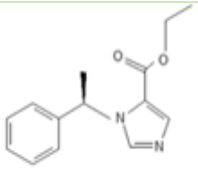
Sl. No.	Name of Anaesthetic	Structure	Properties
1.	Nitrous oxide		Colourless gas, sweet odour weak general anaesthetic Minimum alveolar concentration=104%
2.	Halothane		Colourless liquid, Sweet smell Unstable in light. Boiling point:50°C Minimum alveolar concentration, =0.75% Blood: gas partition coefficient =2.4 Potent anaesthetic
4.	Sevoflurane		Colourless liquid, Mildly unpleasant odour. Administered with O_2 and NO_2 Boiling point:58.9°C Minimum alveolar concentration, =2.1% Blood: gas partition coefficient=0.65 Mild irritant of mucous membrane.
5.	Cyclopropane		Highly inflammable gas with a sweet odour. When combined with O_2 gave onset action .High cost. Boiling point: -33°c
6.	Methoxyflurane		Colourless liquid with fruity aroma Boiling point:105°c Produce nephro - toxicity
7.	Isoflurane		Volatile liquid Boiling point:48.5°C Minimum alveolar concentration =1.15 Blood: gas partition coefficient=1.43 Mild respiratory irritant

8.	Enflurane		Volatile liquid Boiling point:56.9°C Minimum alveolar concentration =1.68% Blood: gas partition coefficient=1.8. Increase heart rate
9.	Desflurane		Highly volatile, colourless liquid. Amber-colour vials used for packaging. Boiling point:22.8°C Minimum alveolar concentration =7.3% Blood: Gas partition coefficient=0.42
10.	Chloroform		Dense liquid, Colourless ,sweet smelling Boiling point:61°c Discarded due to toxicity

B. Intravenous anaesthetics

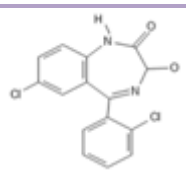
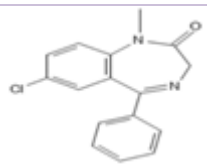
i. Fast acting drugs

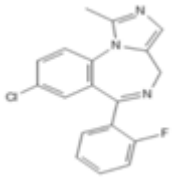
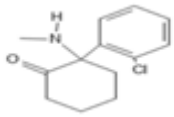
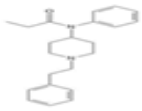
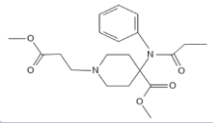
Table 3: Structure & Properties of Intravenous fast acting anaesthetics

Serial No.	Name of Anaesthetic	Structure	Properties
1.	Propofol		Oil in water emulsion, Octanol /water partition coefficient =6761:1 Rapid distribution (t ½ 2-4 min Elimination t ½ is 100 min.
2.	Thiopental sodium		Highly water soluble Distribute very rapidly, t ½ =2.5 min. Elimination t ½ is 8-12 hr.
3.	Methohexital sodium		Quick acting Metabolized rapid t ½is 4hr.
4.	Etomidate		Not soluble in water More potent Effect cardiac output

ii. Slower acting drugs

Table 4: Structure & Properties of Intravenous slower acting anaesthetics

Serial No.	Class	Name of Anaesthetic	Structure	Properties
1.	a. Benzodiazepines	Lorazepam		Slow acting mild irritant
2.		Diazepam		Poor water soluble, produce irritation

3.		Midazolam		Water soluble, non-irritant
4.	b. Dissociative anaesthetics	Ketamine		Highly lipid soluble Not suitable for hypertensives
5.	c. Opioid analgesic	Fentanyl		Short acting Highly lipophilic Heart rate decreases
6.		Remifentanil		Synthetic ultra-short acting

A. Inhalational anaesthetics:

These anaesthetics introduced through inhalation process.

Structure activity relationship [4]:

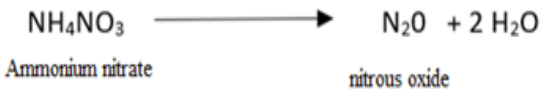
- Halogenations of hydrocarbons increase the anaesthetics potency.
- Asymmetric halogenated carbon is the reason behind better anaesthetic action.
- Fluorination increases the stability.
- Double bond increases the chemical reactivity and also the toxicity.

1. Nitrous oxide:

Synthesis [7]:

Ammonium nitrate breaks down at high temperature (about 250°) and produce nitrous oxide and water. It is an exothermic reaction.

Reaction:



Mechanism of Action [8]:

It acts as antagonist of NMDA receptor. The non-selective ion channel and glutamate binding of NMDA receptor involves in it. Central sympathetic gives stimulation activity of nitrous oxide support to control cardiac output, blood pressure.

Pharmacokinetics [8, 9, 10]:

- **Absorption:** Absorbed quickly through alveoli. Show action within 2-5 min.
- **Distribution:** As it diffuses more rapidly across alveolar basement membrane it may produce the second gas effect. The remaining gases of alveoli get concentrated rapidly as a result of rapid exit of nitrous oxide. Thus, uptake of nitrous oxide increases in blood and onset anaesthetic activity happened.MAC of nitrous oxide is 105%.
- **Metabolism:** Nitrous oxide mainly metabolized by reduction by the help of anaerobic bacteria in stomach.
- **Excretion:** Nitrous oxide almost eliminated through the lungs.

Adverse effects [11, 12, 13]:

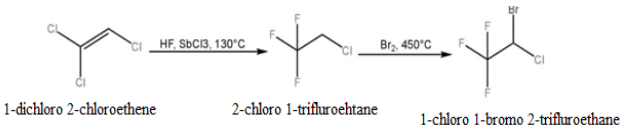
- Diffusion hypoxia
- Post operative nausea and vomiting
- Respiratory disorder
- Hyperhomocysteinemia

2. Halothane

Synthesis [6]:

Trichloroethylene reacts with hydrogen fluoride (HF) presence of antimony trichloride at 130°c to produce 2-chloro-1,1,1-trifluoroethane. This reacts with bromine (Br) at temperature 450°c and form halothane.

Reaction:



Mechanism of Action [4, 6]:

Halothane show its action on multiple ion channels as a result nerves became depressed. Mainly it binds with potassium ion channel in cholinergic neurons. It also interacts with NMDA and calcium ion channels which causing hyperpolarisation.

Pharmacokinetics [14, 15]:

- **Absorption:** Rate of absorption is about 12-18 g during 1 to 2 hr of anaesthesia.

- **Distribution:** within 30 minutes after administration halothane distributed throughout the body and small quantity of it absorbed by tissue fats.
- **Metabolism:** It metabolized in liver with the help of some metabolites like CYP2E1, CYP3A4, CYP2A6.
- **Excretion:** Mainly 60 to 80% eliminated by lungs and it may continue for 24 -48 hr after administration.

Adverse effects [15, 16]:

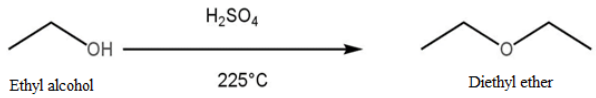
- Cardiac arrhythmia
- Kidney problem
- Malignant hyperthermia
- Oxygen level decreased in blood
- Increases tachycardia pressure
- Malignant hyperthermia, hepatitis, less urine formation occurs rarely[5].

3. Diethyl ether

Synthesis [17]

Alcohol reacts with sulphuric acid to produce diethyl ether.

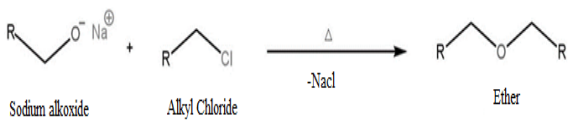
Reaction:



Synthesis:

Diethyl ether can also be prepared by Williamson ether synthesis in which an alkoxide react with alkyl halide (nucleophilic substitution).

Reaction:



Mechanism of Action [18]:

The exact mode of action and site of action of diethyl ether is not well known but its effect in central nervous system is mainly due to interactions with ion channels, neuronal membrane and chemical agents.

Pharmacokinetics [18, 19]:

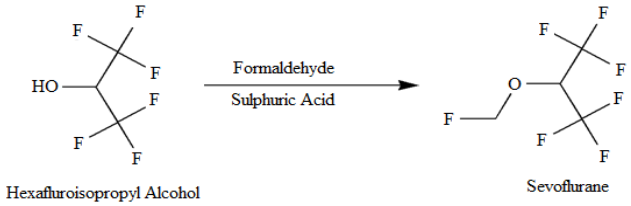
- **Absorption:** After administration it rapidly transfers to blood from alveoli.
- **Distribution:** Diethyl ether is highly soluble in blood and having blood/gas distribution coefficient of 12.1. Due to high solubility the distribution rate is also high.
- **Metabolism:** About 10% of absorbed ether metabolized in the body by the help of hepatic enzyme cytochrome-p450.
- **Excretion:** The major amount of diethyl ether eliminated through lungs.

Adverse effects [19]:

- Breathing problem
- May affect kidney
- Drowsiness
- Vomiting

4. Sevoflurane:

Reaction:



Mechanism of Action [21, 22]:

Sevoflurane leading anaesthetic activity by binding to ligand gated ion channels and blocking central nervous system neurotransmission. It has effect on several ionic currents like the T-Type and L-Type Ca^2+currents, hyperpolarisation activated cation current and Na^+/Ca^{2+} exchange current.

Pharmacokinetics [22, 23]:

- Absorption: it rapidly absorbed through lungs.
- Distribution: The total volume of distribution is approximately 1748 ml/kg.
- Metabolism: Metabolism occurred in liver. Metabolised by CYP2E1 and metabolized to
- Hexafluoroisopropanol and biotransformation occur through cytochrome P450 (CYP) 2E1.
- Excretion: About 98% is rapidly eliminated through lungs and about 4% does appear in urine.

Adverse effects [23]:

- Hypertension
- Tachycardia
- Sheering

B. Intravenous anaesthetics: Intravenous anaesthetics administered through parenteral route.

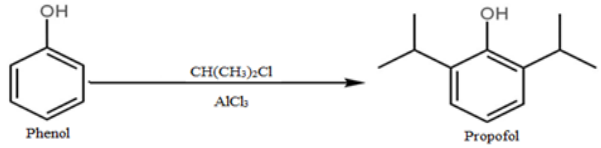
i. Fast acting drugs

1. Propofol

Synthesis [6, 24]:

Phenol undergoes friedel craft's alkylation using propylene gas presence of Lewis acid catalysts.

Reaction:



Mechanism of Action [24, 25]:

Propofol interacts with GABA (gamma aminobutyric acid).It is the prime inhibitory neurotransmitter in central nervous system. The rate of dissociation of GABA from the receptor decreased by propofol so the duration of GABA activated opening of chloride channel increases. As a result, hyperpolarisation of cell membrane occurred.

Pharmacokinetics [25, 26]:

- **Absorption:** This drug only suitable for intravenous route. Rapid distribution happened from plasma to CNS and unconsciousness occurred within 30 seconds.
- **Distribution:** After administration propofol majorly bound with plasma proteins and erythrocytes. Propofol is able to cross blood brain barrier and show rapid action.
- **Metabolism:** Metabolism mainly occurred in the liver by glucuronidation at the C1 hydroxyl. Hydroxylation also occurred via CVP2B6 and 2C9 with subsequent conjugation to gluconic acid or sulphuric acid.
- **Excretion:** Mainly eliminated by hepatic conjugation and excreted by kidney.

Adverse effects [27, 28]:

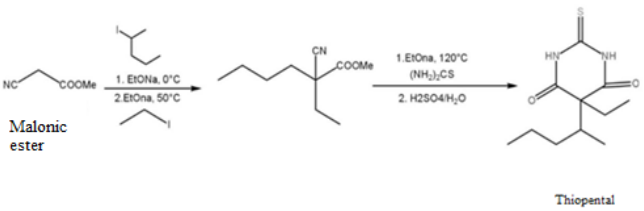
- Myoclonus
- Discolour urine
- Pain in site if injection
- Hypotension

2. Thiopental sodium:

Synthesis[29]:

From Alkylation of malonic ester

Reaction:



Mechanism of Action[5]:

Thiopental sodium can bind to an entire superfamily of ligand gated ion channels. $GABA_A$ receptor channel is one of the representatives of this superfamily. Some receptors are nAChR receptor, the 5-HT3 receptor, glycine receptor etc. that are included in superfamily of ligand gated ion channels. Thiopental sodium interact to Cl^- ionophore site of $GABA_A$ receptor therefore increasing the inhibitory action of $GABA_A$ in thalamus, as a result neuronal excitement decrease and anaesthetic activity initiated.

Structure activity relationship [29,30]:

- In aqueous solution tri keto form is stable and 4,6-dialcoholic tautomeric form is least stable.
- Lipophilicity of the drug increases by increasing the number of carbons at R_2 carbon.
- Analgesic activity increases and hypnotic properties decreases to the esterification of the 5th position substituents.
- If the 2nd position oxygen modifies with sulphur atom then it yields thiobarbiturate derivatives with high lipophilicity, shorter duration of action.
- Lack of anticonvulsive activity yields if the polar functional group introduced at 5th position.
- Anticonvulsive activity retained with the substitution of 1,3-diazine nitrogen with aliphatic carbons.

Pharmacokinetics [30,31,32]:

- **Absorption:** Show onset of action within 10 to 30 seconds.
- **Distribution:** Thiopental sodium quickly distributed such organs like liver, brain, kidney and redistributed to peripheral organs.
- **Metabolism:** primarily metabolized in liver and small amount of administered dose eliminated through urine. Pentobarbital is an active metabolite which oxidized thiopental sodium to its carboxylic acid and it is the major product which excreted renally.
- **Excretion:** Eliminated through hepatic metabolism.

Adverse effects [5]:

- Laryngospasm
- Respiratory depression
- Hypotension
- Somnolence

ii. Slower acting drugs:

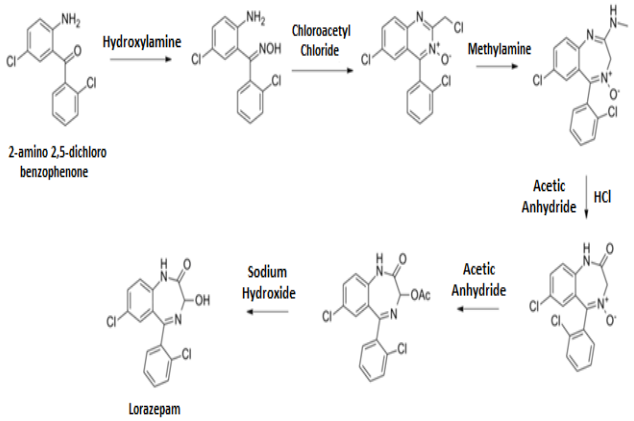
1. Benzodiazepines:

Lorazepam

Synthesis[33]:

From 2-amino-2, 5-dichlorobemzophenone

Reaction:



Mechanism of Action [33]:

Lorazepam binds with the receptor benzodiazepine. It is present in $GABA_A$ ligand gated chloride channel in different sites of CNS and as a result GABA inhibitory effect increases which is translated as an increase flow of chloride ions into the cell causing hyperpolarisation and stabilize plasma membrane. Lorazepam binds in cerebral cortex which helps in seizure disorder and binding in amygdala helps in anxiety disorder.

Structure activity relationship [33]:

- Functional anxiolytic activity increases with substitution of an electronegative group at 7 position of ring A.
- Functional anxiolytic activity decreases if introduced electronegative group at 6, 8 or 9 position on ring A.
- Drug show poor pharmacological activity if heterocyclic ring used as ring A.
- Maximum activity is noticed when a proton accepting group present on the 2 position of ring B and is coplanar with ring A.
- When methylene 3 positions or imine nitrogen of ring B is substituted then the antagonist activity reduced.
- Nitrogen at 4 positions is no essential for anxiolytic activity.
- If 1,2 bond of C ring modifies by the addition of electron rich ring such as imidazole, affinity to the benzodiazepines enlarged.

Pharmacokinetics [34,35]:

- **Absorption:** when a dose of 4 mg administered intramuscularly it is absorbed rapidly and completely.
- **Distribution:** The volume of distribution is about1.3 L/kg. It is not redistributed as fast in the brain due to lipophilicity.
- **Metabolism:** It is metabolized by an isoenzyme CYP450 and widely conjugated to the 3-0-phenolic glucuronide [(31)] which is an inactive metabolite.
- **Excretion:** When given orally, large volume of administrated dose eliminated by urine about 88% and about 7% is by faeces.

Adverse effects [36,37,38]:

- Amnesia
- Urinary retention
- Dysarthria
- Respiratory depression
- Rarely cause acute liver injury

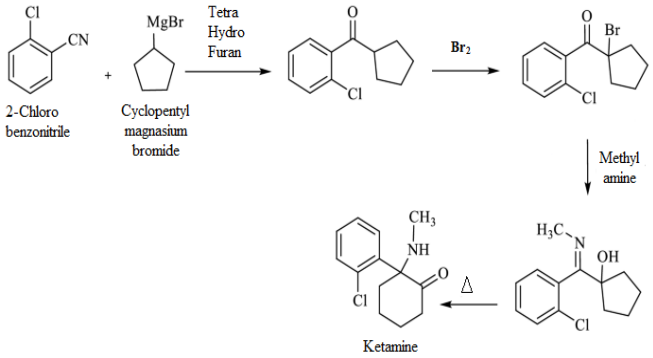
2. Dissociative anaesthetics

❖ Ketamine:

Synthesis [39]:

From 2-Chloro benzonitrile.

Reaction:



Mechanism of Action [40,41]:

Ketamine mainly interacts with NMDA (N-methyl-D-aspartate) which is an excitatory type amino acid receptor in the brain, like other anaesthetics ketamine does not have affinity on $GABA_A$ receptor.

Structure activity relationship [40,41]:

- N-Aliphatic ester analogues of non-opioid ketamine increase the effectiveness as anaesthetic.
- The effect of ester analogues depends upon several factors like polarity, length and cross section of aliphatic chain.
- Weak anaesthetic activity will result with substitution with More stable amide and ethylsulfone analogues.

Pharmacokinetics [40,41,42]:

- **Absorption:** It absorbed very quickly and the bioavailability is around 93%.
- **Distribution:** After absorption ketamine distributed into brain and other tissues. Approximately 371.3ml/kg is the volume of distribution of central compartment.

- **Metabolism:** ketamine mainly metabolized in liver presence of metabolites such as norketamine, dehydronorketamine, hydroxynorketamine.
- **Excretion:** The elimination half -life is about 3 hr. About 90 to 95% of administrated dose is eliminated through urine. It also eliminated through bile and faeces.

Adverse effects [43]:

- Insomnia
- Blurry vision
- Vomiting

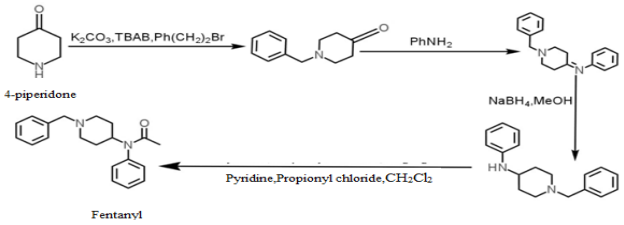
3. Opioid analgesic

❖ Fentanyl

Synthesis [44]:

Fentanyl can be synthesized from 4-piperidone.

Reaction:



Mechanism of Action [44]:

Fentanyl binds with an opioid receptor specially with the mu opioid receptor which are coupled to G-proteins as a result of activation of opioid receptors causes GTP to be exchanged for GDP on the G-protein which reduce the regulates adenylate cyclase and concentration of cAMP. Reduction of cAMP affects the cAMP dependant reflux of calcium ions in the cell. Due to exchange of GTP for GDP hyperpolarisation of cells occurred and nerve activity decreased.

Structure activity relationship [44]:

- Replacement of methyl group from tertiary nitrogen by hydrogen atom will decrease the anaesthetic activity.
- If methyl group from tertiary nitrogen replaced with N-allyl or N-propyl group, the compound acts as morphine antagonist.
- When alcoholic hydroxyl group replaced by -OCH_3, it makes the compound more active.
- If N-CH_3 is replaced by NCH_2CH_2Ph, activity increases.
- The group in 3rd position of piperidine ring which are larger than methyl group decreased the potency.

Pharmacokinetics [44,45]:

- **Absorption:** Different form of fentanyl has different bioavailability. Bioavailability of buccal tablet is about 65%, sublingual spray is 76%, and nasal spray is 20%.
- **Distribution:** The intravenous volume of distribution of fentanyl is about 3-8L/Kg and Oral volume is about 25L/Kg. Fentanyl is able to cross blood brain barrier.
- **Metabolism:** Fentanyl metabolised in liver primarily by Cytochrome P450 3A4.
- **Excretion:** About 75% of administrated dose is excreted by urine and 8 to 9 % by faeces.

Adverse effects [46]:

- Euphoria
- Respiratory depression
- Urinary retention
- Anorexia
- Hypotension

CONCLUSION

Anaesthesia is one of the great inventions of medical science. Nowadays anaesthetics no only use for surgical purposes but also used in diagnostic procedures. Though several studies show some negative effects of several anaesthetics on human health but a wide range of anaesthetics are safely administrated to the patients of different ages every year.

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