General Anaesthesia

General anaesthesia is a tetrad of amnesia (unconsciousness), analgesia, control of autonomic reflexes and muscle relaxation. Amnesia (unconsciousness) is usually induced by intra-venous anaesthetic agents and then maintained by using inhalational anaesthetic agents. Analgesia is provided by various analgesic drugs or by regional/peripheral nerve blocks. Muscle relaxation component of general anaesthesia is not required in all patients or surgical procedures. Muscle relaxants are used to facilitate tracheal intubation, mechanical ventilation or surgical procedure.

Amnesia or unconsciousness may be produced by various drugs, which depress the central nervous system (CNS). Commonly used anaesthetic agents (e.g. propofol, thiopentone,) produce unconsciousness in one arm-brain circulation time with transient depression of cardio-respiratory function. However, for some drugs the doses required to produce anaesthesia are so large that the cardiovascular and respiratory depression commonly occur, and recovery is delayed for hours and days e.g. benzodiazepines. Ideally intravenous anaesthetic agent should be able to produce rapid loss of consciousness and recovery from its effect should be quick without any hangover effects.

In patients with appropriate fasting, general anaesthesia is induced, usually, by administering short acting opioid analgesic agent (alfentanil or fentanyl) followed by slow injection of intravenous anaesthetic agent (propofol) with simultaneous assessment of verbal response or eyelash reflex of patient. When unconsciousness is induced, if needed muscle relaxant is administered. Patient’s airway is maintained using laryngeal mask airway (LMA) or endotracheal tube. General anaesthesia is commonly maintained by inhalational anaesthetic agent and ventilating the lungs with oxygen and nitrous oxide or air.

In ‘rapid sequence induction’ (RSI) of general anaesthesia, predetermined dose intravenous anaesthetic agent is administered. This is followed, immediately, by injecting faster acting muscle relaxant and tracheal intubation. This is performed in patients who are at increased risk of aspiration in to the lungs (e.g. full stomach, emergency patients). The pressure is applied on cricoid cartilage to occlude the oesophagus to avoid regurgitation of stomach contents into the oropharynx and subsequent aspiration.

Intravenous anaesthetic agents

Intra-venous anaesthetic agents can be classified in to different groups depending on their onset of action.

**Rapidly acting agents:** Barbiturates e.g. thiopental sodium, methohexitone
Imidazole e.g. etomidate
Hindred phenols e.g. propofol
Steroids e.g. pregnenolone

**Slower-acting agents:** Phencyclidine e.g. ketamine
Benzodiazepines e.g. midazolam

Warwick Medical School- Handbook of Anaesthesia 2006
Large dose of opioids: alfentanil, fentanyl, remifentanil

Drugs from these groups have been used in clinical anaesthetic practice. Some are not currently used because of adverse effects, allergic reactions or delayed onset of action and delayed recovery.

Intra-venous anaesthetic agents are used for following reasons:

- To induce general anaesthesia
- As a sole agent for anaesthesia for short operations
- To maintain anaesthesia after induction by giving intravenous infusion
- To provide sedation, e.g. in ITU and as an adjunct to regional anaesthesia
- To treat status epilepticus

**Thiopentone sodium:** It is an ultra short acting barbiturate available in powder form. It is dissolved in water that gives a solution with a pH of 10.5, this causes extreme irritation if injected extravascularly or intra-arterially. The dose of thiopentone is 4-7mg/kg. It produces rapid loss of consciousness and induction of anaesthesia is smooth & is rarely associated with involuntary movements or pain on injection. Recovery from amnesia usually occurs in 5-10 minutes after single dose. It decreases the cerebral metabolic rate and intracranial pressure. It is anticonvulsant and used in treatment of status epilepticus. Thiopentone has no analgesic affect. Thiopentone causes depression of myocardial contractility and peripheral vasodilatation. Arterial blood pressure decreases with reflex tachycardia. It causes dose-related depression of the respiratory centre. Apnoea is common. Laryngospasm may be precipitated by various stimuli in the oropharynx or larynx.

**Propofol:** It is phenol derivative, most commonly used intravenous anaesthetic agent because of its faster recovery profile and its antiemetic effect. Propofol is formulated in white aqueous emulsion containing soyabean oil & purified egg phosphatide. The dose is 1.5-2.5mg/kg for induction of anaesthesia. It induces anaesthesia very rapidly (20-40 seconds) and recovery of consciousness is quick (3-5 minutes) with minimal ‘hangover’ effect. Propofol frequently causes excitatory phenomenon on induction of anaesthesia. Because of occasional reports of convulsions & myoclonus following propofol administration, caution been exercised with using propofol in epileptic patients. Compared to thiopentone it causes greater hypotension, predominantly due to vasodilatation. Propofol causes apnoea more commonly and for a longer duration, than after thiopentone. The greater suppression of laryngeal reflexes enables the use of laryngeal mask airway (LMA) with low incidence of coughing or laryngospasm.

Propofol causes pain on injection. Propofol is most suitable of the agents currently available for use in total intravenous anaesthesia (TIVA) and sedation in ICU because of its significantly less cumulation on prolonged use.

**Etomidate:** It is imidazole compound. It is presented as clear aqueous solution. Etomidate has rapid onset (30-40 seconds) and short duration of action (3-5 minutes). An average dose is 0.3mg/kg. It causes pain on injection.

Etomidate causes minimal suppression of cardiovascular system and therefore its use is limited in patients with a compromised cardiovascular system. Etomidate depresses...
the synthesis of cortisol by the adrenal gland and impairs the response to adrenocorticotropic hormone. It causes nausea, vomiting and excitatory phenomenon.

**Ketamine:** It is a phencyclidine derivative. It produces ‘dissociative anaesthesia’ rather than generalised depression of CNS. Ketamine is presented as a solution in a vial. The dose is 1-2mg/kg. After i.v. injection, it induces anaesthesia in 30-60 seconds and last for 10-15 minutes. Ketamine is also effective within 3-4 minutes after i.m. injection and has duration of action of 15-25 minutes.

Ketamine is potent analgesic. Ketamine increases intracranial pressure and it should not be used in patients with intracranial pathology (e.g. - head injury). Recovery from ketamine anaesthesia may be associated with restlessness, agitation and disorientation. Unpleasant nightmares and hallucinations may occur during recovery and up to 24 hours. Ketamine causes tachycardia, rise in arterial blood pressure and cardiac output. The muscle tone increases with ketamine and this helps to maintain airway. The ventilation is well maintained and pharyngeal & laryngeal reflexes are preserved. Ketamine causes bronchodilatation. Ketamine currently used at the site of accident as an analgesic and anaesthetic. It’s also useful for induction of anaesthesia in hypotensive patients (e.g. trauma).

**Inhalational anaesthetic agents**

Inhalational and gaseous anaesthetic agents are mainly used for maintenance of general anaesthesia. Inhalational anaesthetic agent are sometime used for induction of anaesthesia (e.g. difficult i.v.access, difficult airway) Volatile anaesthetic agents are delivered through vaporiser, a equipment used to vaporise liquid volatile anaesthetic agent and deliver it to patient in controlled fashion. Vaporised anaesthetic agent is delivered through breathing circuit to lungs.

Minimum alveolar concentration (MAC) of inhalational agent is an index of its potency. MAC of volatile anaesthetic agent approximately equals brain concentration and this can be measured. Oil/gas solubility of inhalational agent determines the potency. Higher the oil/gas solubility of an agent, more potent the drug. Blood/gas solubility of volatile anaesthetic agent determines the onset & offset of action. Lower the blood/gas solubility of an agent, faster is the onset & offset of action.

Commonly used inhalational anaesthetic agents in UK are isoflurane, sevoflurane, desflurane. Most of the inhalational anaesthetic agents increase intracranial pressure and cause myocardial and respiratory depression. The degrees by which these effects occur vary with different agents and their concentration. All currently used inhalational anaesthetic agents cause malignant hyperpyrexia in susceptible patients. Use of halothane is reduced significantly in recent years because of rare occurrence of hepatotoxicity with its use.

**Isoflurane:** It is a colourless, volatile liquid with a slightly pungent odour. The pungency of the vapour causes coughing or breath holding on induction and therefore
Isoflurane is not used for induction of anaesthesia. The MAC of isoflurane is 1.15% in oxygen. Isoflurane causes dose dependent depression of ventilation. It increases the respiratory rate but depress the tidal volume. Isoflurane causes hypotension predominantly as a result of reduction in systemic vascular resistance. It is metabolised in liver, minimally, by oxidation.

**Sevoflurane:** It is a methyl propyl ether. It is non-flammable and has a pleasant smell. The blood/gas partition coefficient of sevoflurane (0.69) is about half of that of isoflurane (1.43). This lead to faster onset/offset of action as compared to isoflurane. The MAC of sevoflurane is about 2% in oxygen.

The pleasant smell, non-irritant to respiratory tract, low blood/gas partition coefficient – these properties makes sevoflurane a popular choice for the induction of anaesthesia. Sevoflurane causes dose dependent depression of ventilation. It relaxes bronchial smooth muscles. It decreases arterial blood pressure mainly by reducing the systemic vascular resistance, but cardiac output is well maintained over the normal anaesthetic concentration. It is more cardio-stable than isoflurane. Sevoflurane is metabolised in liver to an organic and inorganic fluoride ions. It is absorbed and degraded by soda lime. One of the breakdown product is ‘Compound A’. Normally concentration of ‘compound A’ produced is well below the toxic level.

**Desflurane:** It is relatively new volatile anaesthetic agent. It has ethereal, less pungent odour than isoflurane, and is irritant to the upper respiratory tract. It is therefore not recommended for gaseous induction of anaesthesia. Desflurane has a MAC of 6% in oxygen.

Desflurane has a boiling point of 23.5°C and has very high vapour pressure at room temperature. These properties demand use of special vaporizer (TEC 6) which requires a source of electric power to heat and pressurize it. Desflurane has a very low blood/gas partition coefficient (0.42). This, in theory, allows extremely rapid induction of anaesthesia but limited by a pungent odour and respiratory irritation. However, it is possible to alter the depth of anaesthesia rapidly and the recovery from anaesthesia is faster than that following any other inhalational anaesthetic agent. Desflurane is irritant to respiratory tract and causes coughing, breath holding and laryngospasm and therefore not preferred for induction of anaesthesia. It decreases myocardial contractility and systemic vascular resistance. Heart rate increases with higher concentration. Desflurane undergoes minimal biodegradation.

**Anaesthetic gases**

**Nitrous oxide:** It is a sweet smelling, non-irritant colourless gas. It is stored in compressed form as a liquid in cylinders. In the UK, the cylinders are painted blue. The cylinder of nitrous oxide contains liquid and vapour. Nitrous oxide is a good analgesic but a weak anaesthetic. Oxygen is highly soluble in blood. The use of 100% oxygen as the inspired gas may lead to absorption atelectasis in lung units distal to the site of airway closure. Therefore during general anaesthesia, oxygen is delivered along with nitrous oxide or air to achieve inspired oxygen concentration of about 33%.

Nitrous oxide has following disadvantages
Nitrous oxide diffuses 25 times faster than nitrogen. So it rapidly diffuses in to closed spaces. It increases in size of compliant spaces, e.g. pneumothorax, intestinal distension, air embolism. It increase the pressure in non compliant spaces e.g.: middle ear and intracranial space

- It contributes to post-operative nausea and vomiting
- On prolonged exposure can interact with vitamin B$_{12}$ and inhibit DNA synthesis, megaloblastic anaemia, fetotoxic effects and neuropathy
- Provides a potential room for error to administer hypoxic mixture through the anaesthetic machine.

**Analgesic drugs**

Analgesia is one of the components of general anaesthesia. There are various groups of analgesics used in clinical practice. They are broadly classified in following groups

- Simple analgesics
- Opioid analgesics
- Local anaesthetics drugs

**Simple analgesics**

Most of drugs from this group of analgesics also possess a variable degree of anti-inflammatory action and therefore are frequently referred as NSAIDs (non-steroidal anti-inflammatory drugs). Mainly administered through oral or rectal routes. They are principally used in the post-operative period for the treatment of mild or moderate pain associated with somatic structures. They may eliminate the need for opioid analgesia in minor surgery and may significantly reduce opioid requirement after major surgery.

- e.g. Paracetemol, Diclofenac, Ibuprofen

**Advantages:** lack of respiratory depression, low incidence of nausea/vomiting and simple to administer

**Disadvantages:** gastritis, exacerbation of asthma (in 5-10% of asthmatics), impairment of renal function in susceptible patients and increase bleeding tendency.

**Opioid Analgesics**

Opioid analgesics are used for the treatment of moderate or severe pain. They are used in the intra-operative as well as post-operative period. The commonly used opioid analgesics are alfentanil, fentanyl, morphine and remifentanil. They are administered mainly by intravenous route during intra-operative period. Remifentanil is ultra short acting analgesic administered as continuous infusion. It is an ideal intra-operative analgesic, however post-operative pain should be controlled with some other methods such as regional analgesia.

**Advantages:** They are very strong analgesics, can be used safely in patients with history gastric ulcer or asthma, no effect on platelet function.

**Disadvantages:** Side effects of opioids include nausea, vomiting, sedation, respiratory depression, tolerance, dependence.
Further details of simple analgesics and opioids are considered in chapter 7.

**Local Anaesthetics**

They are used to block peripheral nerves (e.g. brachial plexus block for upper arm surgery) or to block nerve conduction at spinal cord level (e.g. spinal or epidural block). They are also infiltrated at the site of incision for post-operative pain relief. e.g. lignocaine, bupivacaine, prilocaine

Advantages: very good quality pain relief, side effects associated with opioids or NSAIDs are absent.

Disadvantages: experience and skill is required to perform the nerve blocks, can be associated with motor block during postoperative period.

Further details on pharmacology of local anaesthetics are discussed in chapter 6.

**Muscle Relaxants**

Muscle relaxation is one of the three components of general anaesthesia. Muscle relaxation is not always required during general anaesthesia. Muscle relaxant is used during general anaesthesia if patient needs tracheal intubation, mechanical ventilation, or the nature of surgical procedure demands muscle relaxation. These drugs act at neuromuscular junction.

Muscle relaxants are classified as
- Depolarising muscle relaxant: suxamethonium
- Non-depolarising muscle relaxants: atracurium, rocuronium, vecuronium

**Depolarising muscle relaxant**

This group of muscle relaxant is similar in structure to acetylcholine and therefore causes depolarisation at neuromuscular junction. Only difference is that it acts for prolonged duration as compared to acetylcholine. Prolonged action leads to exhaustion of ion channel transmitting signal and muscle relaxation follows. Initial depolarisation causes muscle fasciculations which is a feature of depolarising block.

**Suxamethonium:** It is the only depolarising muscle relaxant used in current practice. Its use is limited for intubation in patients at increased risk of aspiration or in patients with anticipated difficult airway. Occasionally it is used for treatment of laryngospasm. Suxamethonium is presented in 2ml ampoule. The dose is 1-1.5mg/kg. It has fast onset of action (30-45 seconds) and its action last for 3-5 minutes. Because of the rapid onset and short duration of action, it is the muscle relaxant of choice for rapid sequence induction of anaesthesia.

Suxamethonium causes muscle fasciculations. Muscle fasciculations results in some degree of muscle tissue breakdown leading to rise in $K^+$ level and myalgia in the postoperative period.
Suxamethonium is metabolised by pseudocholinesterase enzyme. In presence of abnormal or deficient pseudocholinesterase enzyme, action of suxamethonium is prolonged for more than 30 minutes and this condition is called as suxamethonium apnoea. In susceptible patients, suxamethonium causes malignant hyperpyrexia.

Non-depolarising muscle relaxants

This group of muscle relaxants act by competing with acetylcholine at neuromuscular junction and thereby cause muscle paralysis. Nicotinic receptors are present at neuromuscular junction and have a role in transmission of impulse from nerve to muscle. Acetylcholine is a neurotransmitter at the neuro-muscular junction.

All non-depolarising muscle relaxants possess at least one quaternary ammonium group to bind to post-synaptic, nicotinic receptor at neuromuscular junction.

As term suggest, they do not cause depolarisation and so fasciculations are not seen with non-depolarising block. In absence of fasciculations, adverse effects like hyperkalemia or myalgia do not occur.

Non-depolarising agents are classified, depending on their duration of action.

- Short acting: mivacurium
- Intermediate acting: atracurium, vecuronium, rocuronium
- Long acting: pancuronium

Vecuronium: It is a monoquaternary amine. It is presented in powder form. An intubating dose is 0.1mg/kg. The onset of action is within 2-3 minutes and action last for about 30 minutes. Vecuronium, normally, does not produce histamine release, nor does it have any cardiovascular effects.

Rocuronium: Rocuronium is a monoquaternary amine with a very rapid onset of action for a non-depolarising muscle relaxant. It is presented in a vial as colourless solution. The dose is 0.6-0.9mg/kg. The onset of action is within 60-90 seconds. It is used as an alternative to suxamethonium (if no difficulty anticipated in intubation) in rapid sequence induction of anaesthesia. Its duration of action is about 30 minutes. In most other respects, rocuronium resembles vecuronium.

Atracurium: Atracurium is presented as colourless solution in ampoule and used in a dose of 0.5mg/kg. The onset of action is 2.0-2.5 minutes and it last for about 20 minutes. Atracurium is unique amongst muscle relaxant as it is metabolised in the body spontaneously by Hoffman degradation (pH & temperature dependent degradation) and ester hydrolysis. Its metabolism is not dependent on liver or kidney function. Atracurium is relaxant of choice in sick patients with impaired liver or kidney functions.

Atracurium may release histamine and may produce local wheal and flare around the injection site. This may be associated with slight fall in blood pressure. A metabolite of Hoffman degradation, laudanosine, has epileptogenic properties, although this complication has never been reported in humans.
**Cis-atracurium:** It is a specific isomer of atracurium developed to produce a drug with desired clinical actions but with reduced side effects. It is more potent than atracurium and has a slightly delayed onset & longer duration action.

Its main advantage is that it does not release histamine and therefore is more cardiostable. It also undergoes spontaneous degradation.

**Mivacurium:** This drug has shortest duration of action (~15 minutes) amongst non-depolarising muscle relaxants. So mivacurium is preferred in patients undergoing short duration surgical procedure. The dose is 0.15mg/kg. It is metabolised by plasma cholinesterase enzyme. In the presence of reduced plasma cholinesterase activity due to acquired or inherited factors, the duration of action of mivacurium, similar to that of suxamethonium, may be increased. It also produces histamine release.

**Anticholiesterase Drugs**

These drugs inhibit the action of acetylcholinesterase at the neuromuscular junction. Acetylcholinesterase is an enzyme responsible for metabolising and thereby terminating the action of acetylcholine. By inhibiting acetylcholinesterase at neuromuscular junction and they prolong the half-life of acetylcholine. Thus, increased concentration of acetylcholine, competitively antagonise the action of non-depolarising agents.

Anticholiesterase drugs are used at the end of surgery to reverse the residual neuromuscular block. The most commonly used anticholinesterase during anaesthesia is neostigmine, but endrophonium and pyridostigmine are also available. Anticholinesterases are also used in treatment of Myasthenia gravis.

**Neostigmine:** Neostigmine is commonly used anticholinesterase to reverse the residual effect of non-depolarising muscle relaxant at the end of surgical procedure. Neostigmine potentiates the action of acetylcholine. Action of acetylcholine at nicotonic receptor helps to antagonise the effects of muscle relaxant. Acetylcholine by its action on muscaranic receptors produces undesirable effects like bradycardia, salivation, sweating, bronchospasm, increased intestinal motility and blurred vision. These undesirable effects are reduced by the simultaneous administration of an anticholinergic agent such as glycopyrrolate or atropine.

**Total intravenous anaesthesia (TIVA)**

Anaesthesia is induced with intravenous anaesthetic agent and then maintained with continuous infusion of an intravenous anaesthetic agent instead of volatile anaesthetic agent. All the components of general anaesthesia is provided by selecting specific intravenous agents. Syringe pumps (figure 3.1) programmed with pharmacokinetics of specific intravenous agents are now available. A combination of propofol and remifentanil has been commonly used. It avoids hazards associated with volatile anaesthetic agents (respiratory irritation, operating room pollution, malignant hyperpyrexia). TIVA using propofol is also associated with reduced incidence of postoperative nausea and vomiting.
Figure 3.1 Intravenous infusion pump

Anaesthetic machine

It safely delivers oxygen, anaesthetic gases and volatile agents at a desired concentration as controlled by the operator to the patient’s lungs through breathing system. It provides a supply of anaesthetic gases, regulates the pressure of anaesthetic gases and oxygen, allows mixing of gases and anaesthetic agents. A basic anaesthetic machine consists of following components.

- Rigid metal frame work with compressed gas source
- Pressure regulators: regulates the pressure of oxygen, air and nitrous oxide
- Pressure gauges: Measures the pressure of oxygen, air and nitrous oxide both in cylinder and pipelines.
- Flow meters: Reads the flow of oxygen, air and nitrous oxide
- Back bar system with vaporisor attachment
- Antihypoxic device: ensures a minimum concentration of oxygen at least 25%.
- High pressure release valve: protects the anaesthetic machine from high pressure due to downstream obstruction.
- Oxygen flush: enables to deliver high flow of oxygen at a rate of 35 L/min.
- Common gas outlet: final mixture of gases and volatile agents leaves the anaesthetic machine and enters the breathing system.
Figure 3.2 A modern anaesthetic machine

Anaesthetic machines should be regularly checked according to the guidelines published by Association of Anaesthetists of Great Britain and Ireland. A breathing system delivers the mixture of anaesthetic gases from the machine to patient. Circle breathing system, Bain system, Magill system and modified T piece system are commonly used. All the waste anaesthetic gases (exhaled from patient and spilled over from anaesthetic machine) are scavenged using specific scavenging system. Modern anaesthetic machine also incorporates with a ventilator, monitor and several safety mechanisms that enables early warning of any problems and possible critical incidents.

Further reading

