SECTION 7

DRUGS ACTING ON CENTRAL NERVOUS SYSTEM

Chapter 27 General Anaesthetics

General anaesthetics (GAs) are drugs which produce reversible loss of all sensation and consciousness. The cardinal features of general anaesthesia are:

- Loss of all sensation, especially pain
- Sleep (unconsciousness) and amnesia
- Immobility and muscle relaxation
- Abolition of somatic and autonomic reflexes.

In the modern practice of balanced anaesthesia, these modalities are achieved by using combination of inhaled and i.v. drugs, each drug for a specific purpose. Anaesthesia has developed as a highly specialized science in itself.

History Before the middle of 19th century a number of agents like alcohol, opium, cannabis, or even concussion and asphyxia were used to obtund surgical pain, but operations were horrible ordeals. Horace Wells, a dentist, picked up the idea of using *nitrous oxide* (N_2O) from a demonstration of laughing gas in 1844. However, he often failed to relieve dental pain completely and the use of N_2O had to wait till other advances were made. Morton, a dentist and medical student at Boston, after experimenting on animals, gave a demonstration of *ether* anaesthesia in 1846, and it soon became very popular. *Chloroform* was used by Simpson in Britain for obstetrical purpose in 1847, and despite its toxic potential, it became a very popular surgical anaesthetic. *Cyclopropane* was introduced in 1929, but the new generation of anaesthetics was heralded by *halothane* in 1956. The first i.v. anaesthetic *thiopentone* was introduced in 1935.

MECHANISM OF GENERAL ANAESTHESIA

The mechanism of action of GAs is not precisely known. A wide variety of chemical agents produce general anaesthesia. Therefore, GA action had been related to some common physicochemical property of the drugs. Mayer and Overton (1901) pointed out a direct parallelism between lipid/water partition coefficient of the GAs and their anaesthetic potency.

Minimal alveolar concentration (MAC) is the lowest concentration of the anaesthetic in pulmonary alveoli needed to produce immobility in response to a painful stimulus (surgical incision) in 50% individuals. It is accepted as a valid measure of potency of inhalational GAs, because it remains fairly constant for most young adults. The MAC of all inhalational anaesthetics declines progressively as age advances beyond 50 years.

The MAC of a number of GAs shows excellent correlation with their oil/gas partition coefficient. However, this only reflects capacity of the anaesthetic to enter into CNS and attain sufficient concentration in the neuronal membrane, but not the mechanism by which

anaesthesia is produced. The *'unitary hypothesis'* that some single common molecular mechanism (like membrane expansion/perturbation/fluidization) is responsible for the action of all inhalational anaesthetics has now been replaced by the *'agent specific theory'* according to which different GAs produce anaesthesia by different mechanisms.

Recent evidence favours a direct interaction of the GA molecules with hydrophobic domains of membrane proteins or the lipid-protein interface.

Not only different anaesthetics appear to act by different molecular mechanisms, they also may exhibit stereospecific effects, and that various components of the anaesthetic state may involve action at discrete loci in the cerebrospinal axis. The principal locus of causation of unconsciousness appears to be in the thalamus or reticular activating system, amnesia may result from action in cerebral cortex and hippocampus, while spinal cord is the likely seat of immobility on surgical stimulation.

Recent findings show that ligand gated ion channels (but not voltage sensitive ion channels) are the major targets of anaesthetic action. The $GABA_A$ receptor gated Cl^- channel is the most important of these. Many inhalational anaesthetics, barbiturates, benzodiazepines and propofol potentiate the action of inhibitory transmitter GABA to open Cl^- channels. Each of the above anaesthetics appears to interact with its own specific binding site on the $GABA_A$ receptor-Cl^- channel complex, but none binds to the GABA binding site as such; though some inhaled anaesthetics and barbiturates (but not benzodiazepines) can directly activate Cl^- channels. Action of glycine (another inhibitory transmitter which also activates Cl^- channels) in the spinal cord and medulla is augmented by barbiturates, propofol and many inhalational anaesthetics. This action may block responsiveness to painful stimuli resulting in immobility of the anaesthetic state. Certain fluorinated anaesthetics and barbiturates, in addition, inhibit the neuronal cation channel gated by nicotinic cholinergic receptor which may mediate analgesia and amnesia.

On the other hand, N_2O and ketamine do not affect GABA or glycine gated Cl^- channels. Rather they selectively inhibit the excitatory NMDA type of glutamate receptor. This receptor gates mainly Ca^{2+} selective cation channels in the neurones, inhibition of which appears to be the primary mechanism of anaesthetic action of ketamine as well as N_2O. The volatile anaesthetics have little action on this receptor.

Neuronal hyperpolarization caused by GAs has been ascribed to activation of a specific type of K^+ channels called 'two-pore domain' channels. This may cause inhibition of presynaptic transmitter release as well as postsynaptic activation. Inhibition of transmitter release from presynaptic neurones has also been related to interaction with certain critical synaptic proteins. Thus, different facets of anaesthetic action may have distinct neuronal basis, as opposed to the earlier belief of a global neuronal depression.

Unlike local anaesthetics which act primarily by blocking axonal conduction, the GAs appear to act by depressing synaptic transmission.

STAGES OF ANAESTHESIA

GAs cause an irregularly descending depression of the CNS, i.e. the higher functions are lost first and progressively lower areas of the brain are involved, but in the spinal cord lower segments are affected somewhat earlier than the higher segments. The vital centres located in the medulla are paralysed the last as the depth of anaesthesia increases. Guedel (1920) described four stages with *ether* anaesthesia, dividing the III stage into 4 planes. These clear-cut stages are not seen now-a-days with the use of faster acting GAs, premedication and employment of many drugs together. The precise sequence of events differs somewhat with anaesthetics other than ether. However, ether continues to be used in resource poor remote areas, and description of these stages still serves to define the effects of light and deep anaesthesia. Important features of different stages are depicted in Fig. 27.1.

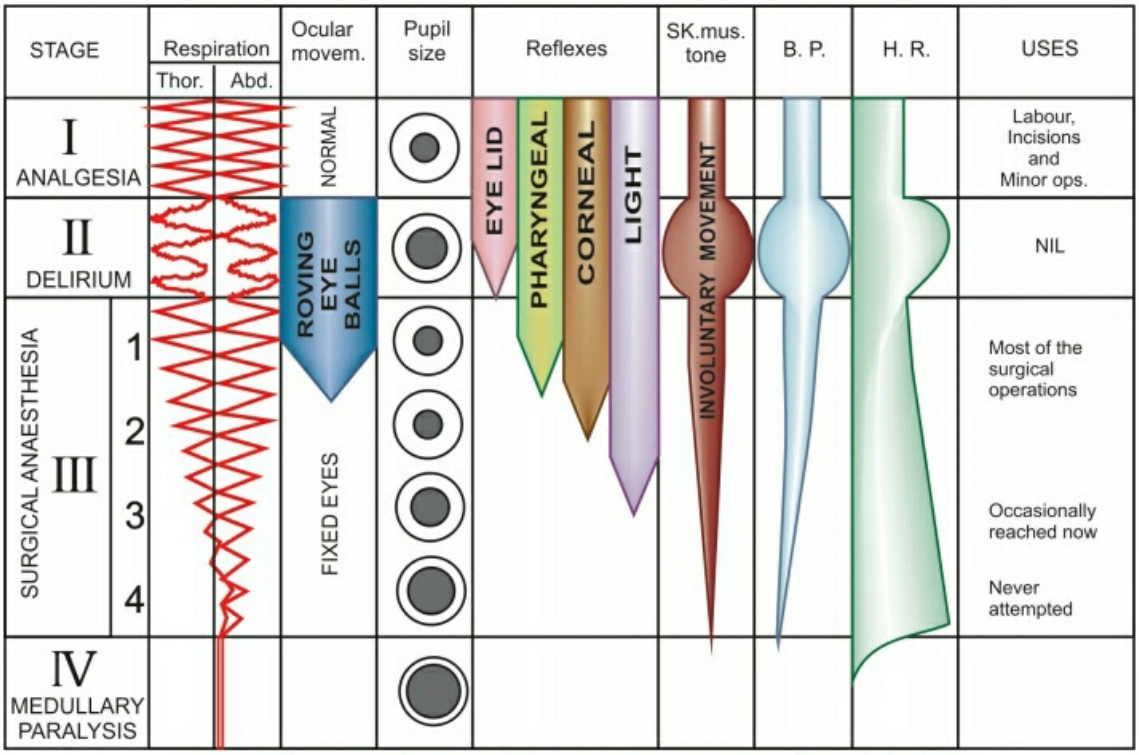


Fig. 27.1: Physiological changes during stages of general anaesthesia (with ether)

I. Stage of analgesia Starts from beginning of anaesthetic inhalation and lasts upto the loss of consciousness. Pain is progressively abolished. Patient remains conscious, can hear and see, and feels a dream like state; amnesia develops by the end of this stage. Reflexes and respiration remain normal.

Though some minor operations can be carried out during this stage, it is rather difficult to maintain—use is limited to short procedures.

II. Stage of delirium From loss of consciousness to beginning of regular respiration. Apparent excitement is seen—patient may shout, struggle and hold his breath; muscle tone increases, jaws are tightly closed, breathing is jerky; vomiting, involuntary micturition or defecation may occur. Heart rate and BP may rise and pupils dilate due to sympathetic stimulation.

No stimulus should be applied or operative procedure carried out during this stage. This stage is inconspicuous in modern anaesthesia.

III. Surgical anaesthesia Extends from onset of regular respiration to cessation of spontaneous breathing. This has been divided into 4 planes which may be distinguished as:

Plane 1 Roving eyeballs. This plane ends when eyes become fixed.

Plane 2 Loss of corneal and laryngeal reflexes.

Plane 3 Pupil starts dilating and light reflex is lost.

Plane 4 Intercostal paralysis, shallow abdominal respiration, dilated pupil.

As anaesthesia passes to deeper planes, progressively—muscle tone decreases, BP falls, HR increases with weak pulse, respiration decreases in depth and later in frequency also. Thoracic respiration lags behind abdominal respiration.

IV. Medullary paralysis Cessation of breathing to failure of circulation and death. Pupil is widely dilated, muscles are totally flabby, pulse is thready or imperceptible and BP is very low.

Many of the above indices of anaesthesia have been robbed by the use of atropine (pupillary, heart rate), morphine (respiration, pupillary), muscle relaxants (muscle tone, respiration, eye movements, reflexes), etc. and the modern anaesthetist has to depend on several other observations to gauge the depth of anaesthesia.

- If eyelash reflex is present and patient is making swallowing movements—stage II has not been reached.
- Loss of response to painful stimulus (e.g. pressure on the upper nasal border of orbit) — stage III has been reached.

- Incision of the skin causes reflex increase in respiration, BP rise or other effects; insertion of endotracheal tube is resisted and induces coughing, vomiting, laryngospasm; tears appear in eye; passive inflation of lungs is resisted—anaesthesia is light.
- Fall in BP, cardiac and respiratory depression are signs of deep anaesthesia.

In the present day practice, anaesthesia is generally kept light; adequate analgesia, amnesia and muscle relaxation are produced by the use of intravenous drugs. Premedication with CNS depressants and opioids or their concurrent use lowers MAC of the inhaled anaesthetic. When a combination of two inhalational anaesthetics (e.g. N_2O + isoflurane) is used, their MACs are additive: lower concentration of each is required, e.g. 0.5 MAC of N_2O (53%) and 0.5 MAC of isoflurane (0.6%) produce CNS depression equivalent to 1 MAC of isoflurane alone. The dose-response relationship of inhaled anaesthetics is very steep; just 30% higher concentration (1.3 MAC) immobilizes 95% subjects. Concentrations of inhalational anaesthetics exceeding 1.5 MAC are rarely used, and 2–3 MAC is often lethal. Anaesthetized subjects generally wake up when anaesthetic concentration falls to 0.4 MAC.

PHARMACOKINETICS OF INHALATIONAL ANAESTHETICS

Inhalational anaesthetics are gases or vapours that diffuse rapidly across pulmonary alveoli and tissue barriers. The depth of anaesthesia depends on the potency of the agent (MAC is an index of potency) and its partial pressure (PP) in the brain, while induction and recovery depend on the rate of change of PP in the brain. Transfer of the anaesthetic between lung and brain depends on a series of tension gradients which may be summarized as—

Alveoli ⇌ Blood ⇌ Brain

Factors affecting the PP of anaesthetic attained in the brain are—

1. *PP of anaesthetic in the inspired gas* This is proportional to its concentration in the inspired gas mixture. Higher the inspired tension more anaesthetic will be transferred to the blood. Thus, induction can be hastened by administering the GA at high concentration in the beginning.

2. *Pulmonary ventilation* It governs delivery of the GA to the alveoli. Hyperventilation will bring in more anaesthetic per minute and respiratory depression will have the opposite effect. Influence of minute volume on the rate of induction is greatest in the case of agents which have high blood solubility because their PP in blood takes a long time to approach the PP in alveoli. However, it does not affect the terminal depth of anaesthesia attained at any given concentration of a GA.

3. *Alveolar exchange* The GAs diffuse freely across alveoli, but if alveolar ventilation and perfusion are mismatched (as occurs in emphysema and other lung diseases) the attainment of equilibrium between alveoli and blood is delayed: well perfused alveoli may not be well ventilated—blood draining these alveoli carries less anaesthetic and dilutes the blood coming from well ventilated alveoli. Induction and recovery both are slowed.

4. *Solubility of anaesthetic in blood* This is the most important property determining induction and recovery. Large amount of an anaesthetic that is highly soluble in blood (ether) must dissolve before its PP is raised. The rise as well as fall of PP in blood and consequently induction as well as recovery are slow. Drugs with low blood solubility, e.g. N_2O, sevoflurane, desflurane induce quickly.

Blood: gas partition coefficient (λ) given by the ratio of the concentration of the anaesthetic in blood to that in the gas phase at equilibrium is the index of solubility of the GA in blood.

5. *Solubility of anaesthetic in tissues* Relative solubility of the anaesthetic in blood and tissue determines its concentration in that tissue at equilibrium. Most of the GAs are

equally soluble in lean tissues as in blood, but more soluble in fatty tissue. Anaesthetics with higher lipid solubility (halothane) continue to enter adipose tissue for hours and also leave it slowly. The concentration of these agents is much higher in white matter than in grey matter.

6. *Cerebral blood flow* Brain is a highly perfused organ; as such GAs are quickly delivered to it. This can be hastened by CO_2 inhalation which causes cerebral vasodilatation—induction and recovery are accelerated. Carbon dioxide stimulates respiration and this also speeds up the transport.

Elimination When anaesthetic inhalation is discontinued, gradients are reversed and the channel of absorption (pulmonary epithelium) becomes the channel of elimination. All inhaled anaesthetics are eliminated mainly through lungs. The same factors which govern induction also govern recovery. Anaesthetics, in general, continue to enter and persist for long periods in adipose tissue because of their high lipid solubility and low blood flow to fatty tissues. Muscles occupy an intermediate position between brain and adipose tissue. Most GAs are eliminated unchanged. Metabolism is significant only for halothane which is >20% metabolized in liver. Others are practically not metabolized. Recovery may be delayed after prolonged anaesthesia, especially in case of more lipid-soluble anaesthetics (halothane, isoflurane), because large quantities of the anaesthetic have entered the muscle and fat, from which it is released slowly into blood.

Second gas effect and diffusion hypoxia

In the initial part of induction, diffusion gradient from alveoli to blood is high and larger quantity of anaesthetic is entering blood. If the inhaled concentration of anaesthetic is high, substantial loss of alveolar gas volume will occur and the gas mixture will be sucked in, independent of ventilatory exchange—gas flow will be higher than tidal volume. This is significant only with N_2O, since it is given at 70–80% concentration; though it has low solubility in blood, about 1 litre/min of N_2O enters blood in the first few minutes. As such, gas flow is 1 litre/min higher than minute volume. If another potent anaesthetic, e.g. halothane (1–2%) is being given at the same time, it also will be delivered to blood at a rate 1 litre/min higher than minute volume and induction will be faster. This is called *'second gas effect'*.

The reverse occurs when N_2O is discontinued after prolonged anaesthesia; N_2O having low blood solubility rapidly diffuses into alveoli and dilutes the alveolar air, and PP of oxygen in alveoli is reduced. The resulting hypoxia, called *diffusion hypoxia*, is not of much consequence if cardiopulmonary reserve is normal, but may be dangerous if it is low. Diffusion hypoxia can be prevented by continuing 100% O_2 inhalation for a few minutes after discontinuing N_2O, instead of straight away switching over to air. Diffusion hypoxia is not significant with other anaesthetics, because they are administered at low concentrations (0.2–4%) and cannot dilute alveolar air by more than 1–2% in any case.

TECHNIQUES OF INHALATION OF ANAESTHETICS

Different techniques are used according to facility available, agent used, condition of the patient, type and duration of operation.

1. Open drop method Liquid anaesthetic is poured over a mask with gauze and its vapour is inhaled with air. A lot of anaesthetic vapour escapes in the surroundings and the concentration of anaesthetic breathed by the patient cannot be determined. It is wasteful—can be used only for a cheap anaesthetic. However, it is simple and requires no special apparatus. Use now is limited to peripheral areas. Either is the only agent administered by this method, especially in children.

2. Through anaesthetic machines Use is made of gas cylinders, specialized graduated vaporisers, flow meters, unidirectional valves, corrugated rubber tubing and reservoir bag.

The gases are delivered to the patient through a tightly fitting face mask or endotracheal tube. Administration of the anaesthetic can be more precisely controlled and in many situations its concentration estimated. Respiration can be controlled and assisted by the anaesthetist.

(a) *Open system* The exhaled gases are allowed to escape through a valve and fresh anaesthetic mixture is drawn in each time. No rebreathing is allowed—flow rates are high—more drug is consumed. However, predetermined O_2 and anaesthetic concentration can be accurately delivered.

(b) *Closed system* The patient rebreaths the exhaled gas mixture after it has circulated through sodalime which absorbs CO_2. Only as much O_2 and anaesthetic as have been taken up by the patient are added to the circuit. Flow rates are low. This is especially useful for expensive and explosive agents (little anaesthetic escapes in the surrounding air). Halothane, isoflurane, desflurane can be used through closed system. However, control of inhaled anaesthetic concentration is imprecise.

(c) *Semiclosed system* Partial rebreathing is allowed through a partially closed valve. Conditions are intermediate with moderate flow rates.

Properties of an ideal anaesthetic

A. *For the patient* It should be pleasant, non-irritating, should not cause nausea or vomiting. Induction and recovery should be fast with no after effects.

B. *For the surgeon* It should provide adequate analgesia, immobility and muscle relaxation. It should be noninflammable and nonexplosive so that cautery may be used.

C. *For the anaesthetist* Its administration should be easy, controllable and versatile.

- Margin of safety should be wide—no fall in BP.
- Heart, liver and other organs should not be affected.
- It should be potent so that low concentrations are needed and oxygenation of the patient does not suffer.
- Rapid adjustments in depth of anaesthesia should be possible.
- It should be cheap, stable and easily stored.
- It should not react with rubber tubing or soda lime.

The important physical and anaesthetic properties of inhalational anaesthetics are presented in Table 27.1.

CLASSIFICATION

Inhalational

Gas	*Volatile liquids*
Nitrous oxide	Ether
	Halothane
	Isoflurane
	Desflurane
	Sevoflurane

TABLE 27.1 Physical and anaesthetic properties of inhalational anaesthetics

Anaesthetic	*Boiling point (°C)*	*Inflammability*	*Irritancy (odour)*	*Oil: Gas partition coefficient**	*Blood: Gas partition coefficient**	*MAC (%)*	*Induction*	*Muscle relaxation*
1. Ether	35	Infl. + Explo.	+++ (Pungent)	65	12.1	1.9	Slow	V. good
2. Halothane	50	Noninfl.	– (Pleasant)	224	2.3	0.75	Interm.	Fair
3. Isoflurane	48	Noninfl.	± (Unpleasant)	99	1.4	1.2	Interm.	Good
4. Desflurane	24	Noninfl.	+ (Unpleasant)	19	0.42	6.0	Fast	Good
5. Sevoflurane	59	Noninfl.	– (Pleasant)	50	0.68	2.0	Fast	Good
6. Nitrous oxide	Gas	Noninfl.	–	1.4	0.47	105	Fast	Poor

*At 37°C; Oil: gas and blood: gas partition coefficients are measures of solubility of the anaesthetic in lipid and blood respectively.

MAC—Minimal alveolar concentration; Infl.—Inflammable; Explo.—Explosive; Interm.—Intermediate

Intravenous

Fast acting drugs	*Slower acting drugs*
Thiopentone sod.	*Benzodiazepines*
Methohexitone sod.	Diazepam
Propofol	Lorazepam
Etomidate	Midazolam
	Dissociative anaesthesia
	Ketamine
	Opioid analgesia
	Fentanyl

Cyclopropane, trichloroethylene, methoxyflurane and enflurane are no longer used.

INHALATIONAL ANAESTHETICS

1. Nitrous oxide (N_2O) It is a colourless, odourless, heavier than air, noninflammable gas supplied under pressure in steel cylinders. It is nonirritating, but low potency anaesthetic; unconsciousness cannot be produced in all individuals without concomitant hypoxia; MAC is 105% implying that even pure N_2O cannot produce adequate anaesthesia at 1 atmosphere pressure. Patients maintained on 70% N_2O + 30% O_2 along with muscle relaxants often recall the events during anaesthesia, but some lose awareness completely.

Nitrous oxide is a good analgesic; even 20% produces analgesia equivalent to that produced by conventional doses of morphine. Muscle relaxation is minimal. Neuromuscular blockers are mostly required. Onset of N_2O action is quick and smooth (but thiopentone is often used for induction), recovery is rapid, because of its low blood solubility. Second gas effect and diffusion hypoxia occur with N_2O only. Post-anaesthetic nausea is not marked. It tends to increase sympathetic tone which counteracts weak direct depressant action on heart and circulation.

Nitrous oxide is generally used as a carrier and adjuvant to other anaesthetics. A mixture of 70% N_2O + 25–30% O_2 + 0.2–2% another potent anaesthetic is employed for most surgical procedures. In this way concentration of the other anaesthetic can be reduced to 1/3 for the same level of anaesthesia. Because N_2O has little effect on respiration, heart and BP: breathing and circulation are better maintained with the mixture than with the potent anaesthetic given alone in full doses. However, N_2O can expand pneumothorax and other abnormal air pockets in the body. It increases cerebral blood flow and tends to elevate intracranial pressure.

As the sole agent, N_2O (50%) has been used with O_2 for dental and obstetric analgesia. It is nontoxic to liver, kidney and brain. However, prolonged N_2O anaesthesia has the potential to depress bone marrow and cause peripheral neuropathy. Metabolism of N_2O does not occur; it is quickly removed from the body by lungs. It is cheap and commonly used.

2. Ether (Diethyl ether) It is a highly volatile liquid, produces irritating vapours which are inflammable and explosive.

$$(C_2H_5 — O — C_2H_5)$$

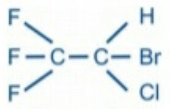
Ether is a potent anaesthetic, produces good analgesia and marked muscle relaxation by reducing ACh output from motor nerve endings. The dose of competitive neuromuscular blockers should be reduced to about 1/3.

It is highly soluble in blood. Induction is prolonged and unpleasant with struggling, breath-holding, salivation and marked respiratory secretions (atropine must be given as premedication to prevent the patient from drowning in his own secretions). Recovery is slow; post-anaesthetic nausea, vomiting and retching are marked.

Respiration and BP are generally well maintained because of reflex stimulation and high sympathetic tone. It does not sensitize the heart to Adr, and is not hepatotoxic.

Ether is not used now in developed countries because of its unpleasant and inflammable properties. However, it is still used in developing countries, particularly in peripheral areas because it is—cheap, can be given by open drop method (though congestion of eye, soreness of trachea and ether burns on face can occur) without the need for any equipment, and is relatively safe even in inexperienced hands.

3. Halothane (FLUOTHANE) It is a volatile liquid with sweet odour, nonirritant and noninflammable. Solubility in blood is intermediate—induction is reasonably quick and pleasant.



HALOTHANE

It is a potent anaesthetic—precise control of administered concentration is essential. For induction 2–4% and for maintenance 0.5–1% is delivered by the use of a special vaporizer. It is not a good analgesic or muscle relaxant, but it potentiates competitive neuromuscular blockers.

Halothane causes direct depression of myocardial contractility by reducing intracellular Ca^{2+} concentration. Moreover, sympathetic activity fails to increase reflexly. Cardiac output is reduced with deepening anaesthesia. BP starts falling early and parallels the depth. A 20–30 mm Hg drop in BP is common. Many vascular beds dilate but total peripheral resistance is not significantly reduced. Heart rate is reduced by vagal stimulation, direct depression of SA nodal automaticity and absence of baroreceptor activation even when BP falls. It tends to sensitize the heart to the arrhythmogenic action of Adr. The electrophysiological effects are conducive to reentry—tachyarrhythmias occur occasionally.

Halothane causes relatively greater depression of respiration; breathing is shallow and rapid—PP of CO_2 in blood rises if respiration is not assisted. Cerebral blood flow increases. Ventilatory support with added oxygen is frequently required. It tends to accentuate perfusion-ventilation mismatch in the lungs by causing vasodilatation in hypoxic alveoli.

Pharyngeal and laryngeal reflexes are abolished early and coughing is suppressed while bronchi dilate. As such, halothane is preferred for asthmatics. It inhibits intestinal and uterine contractions. This property is utilized for facilitating external or internal version during late pregnancy. However, its use during labour can prolong delivery and increase postpartal blood loss.

Urine formation is decreased during halothane anaesthesia—primarily due to low g.f.r. as a result of fall in BP.

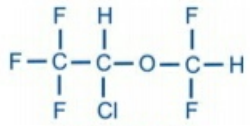
Hepatitis occurs in rare susceptible individuals (1 in 35000 to 1 in 10,000) especially after repeated use and in those with familial predisposition. A metabolite of halothane is probably involved—causes chemical or immunological injury.

A genetically determined reaction *malignant hyperthermia* occurs rarely. Many susceptible subjects have an abnormal RyR1 (Ryanodine receptor) calcium channel at the sarcoplasmic reticulum of skeletal muscles. This channel is triggered by halothane to release massive amounts of Ca^{2+} intracellularly causing persistent muscle contraction and increased heat production. Succinylcholine accentuates the condition (*see* Ch. 25). Rapid external cooling, bicarbonate infusion, 100% O_2 inhalation and i.v. dantrolene (*see* p. 356) are used to treat malignant hyperthermia.

About 20% of halothane that enters blood is metabolized in the liver, the rest is exhaled out. Elimination may continue for 24–48 hours after prolonged administration due to accumulation in fatty and other tissues. Recovery from halothane anaesthesia is smooth and reasonably quick; shivering may occur but nausea and vomiting are rare. Psychomotor performance and mental ability remain depressed for several hours after regaining consciousness.

Halothane is a popular anaesthetic in developing countries, because it is relatively cheap and nonirritant, noninflammable, pleasant with relatively rapid action. It is particularly suitable for use in children, both for induction as well as maintenance. In adults, it is mainly used as a maintenance anaesthetic after i.v. induction. Halothane toxicity is less frequent in children. However, in affluent countries it has been largely replaced by the newer agents which are costlier. Its deficiencies in terms of poor analgesia and muscle relaxation are compensated by concomitant use of N_2O or opioids and neuromuscular blockers.

4. Isoflurane (SOFANE, FORANE, ISORANE) This fluorinated anaesthetic introduced in 1981 is currently the routinely used anaesthetic all over. It has totally replaced its earlier introduced isomer enflurane. Isoflurane is somewhat less potent and less soluble in blood as well as in fat than halothane, but equally volatile. Compared to halothane, it produces relatively rapid induction and recovery, and is administered through a special vaporizer; 1.5–3% induces anaesthesia in 7–10 min, and 1–2% is used for maintenance.



ISOFLURANE

Magnitude of fall in BP is similar to halothane, but unlike halothane, this is primarily due to vasodilatation, while cardiac output is well maintained. Heart rate is increased. These cardiovascular effects probably result from stimulation of β adrenergic receptors, but it does not sensitize the heart to adrenergic arrhythmias. Isoflurane dilates coronaries. Though not encountered clinically, possibility of 'coronary steal' has been apprehended in coronary artery disease patients on theoretical grounds. Respiratory depression is prominent and assistance is usually needed to avoid hypercarbia. Secretions are slightly increased.

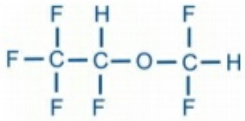
Uterine and skeletal muscle relaxation is similar to halothane. Potentiation of neuromuscular blockers is greater than that with halothane.

Metabolism of isoflurane is negligible. Renal and hepatic toxicity has not been encountered. Postanaesthetic nausea and vomiting is low.

Pupils do not dilate and light reflex is not lost even at deeper levels.

Though mildly pungent, isoflurane has many advantages, i.e. better adjustment of depth of anaesthesia and low toxicity. It is a good maintenance anaesthetic, but not preferred for induction because of ether like odour which is not liked by conscious patients, especially children. In contrast to enflurane, it does not provoke seizures and is particularly suitable for neurosurgery.

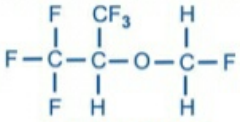
5. Desflurane It is a newer all fluorinated congener of isoflurane which has gained popularity as an anaesthetic for out patient surgery. Though it is highly volatile, a thermostatically heated special vapourizer is used to deliver a precise concentration of pure desflurane vapour in the carrier gas ($N_2O + O_2$) mixture. Its distinctive properties are lower lipid solubility as well as very low solubility in blood and tissues, because of which induction and recovery are very fast. Depth of anaesthesia changes rapidly with change in inhaled concentration giving the anaesthetist better control. Postanaesthetic cognitive and motor impairment is shortlived, so that patient can be discharged a few hours after surgery.



DESFLURANE

Desflurane is 5 times less potent than isoflurane; higher concentration has to be used for induction which irritates air passage and may induce coughing, breath-holding and laryngospasm. A somewhat pungent odour makes it unsuitable for induction. Rapid induction sometimes causes brief sympathetic stimulation and tachycardia which may be risky in those with cardiovascular disease. Degree of respiratory depression, muscle relaxation, vasodilatation and fall in BP are similar to isoflurane. Cardiac contractility and coronary blood flow are maintained. Lack of seizure provoking potential arrhythmogenicity and absence of liver as well as kidney toxicity are also similar to isoflurane. It is rapidly exhaled unchanged. As such, desflurane can serve as a good alternative to isoflurane for routine surgery as well, especially prolonged operations. If closed circuit is used, soda lime should be fresh and well hydrated.

6. Sevoflurane (SEVORANE) This new polyfluorinated anaesthetic has properties intermediate between isoflurane and desflurane. Solubility in blood and tissues as well as potency are less than isoflurane but more than desflurane.



SEVOFLURANE

Induction and emergence from anaesthesia are fast so that rapid changes in depth can be achieved. Absence of pungency makes it pleasant and administrable through a face mask. Unlike desflurane, it poses no problem in induction and is frequently selected for this purpose. Acceptability is good even by pediatric patients. Recovery is smooth; orientation, cognitive and motor functions are regained almost as quickly as with desflurane. Sevoflurane is suitable both for outpatient as well as inpatient surgery, induction as well as maintenance, but its high cost and need for high-flow open or semiclosed system makes it very expensive to use. In India, only high-end hospitals are using it.

Sevoflurane does not cause sympathetic stimulation and airway irritation even during rapid induction. Fall in BP is due to vasodilatation as well as modest cardiac depression. Respiratory depression, and absence of seizure or arrhythmia precipitating propensity are similar to isoflurane. About 3% of absorbed sevoflurane is metabolized, but the amount of fluoride liberated is safe for kidney and liver. However, it reacts with sodalime—not recommended for use in fully closed circuit.

INTRAVENOUS ANAESTHETICS

FAST ACTING DRUGS

These are drugs which on i.v. injection produce loss of consciousness in one arm-brain circulation time (~11 sec). They are generally used for induction because of rapidity of onset of action. Anaesthesia is then usually maintained by an inhalational agent. They also serve to reduce the amount of maintenance anaesthetic. Supplemented with analgesics and muscle relaxants, they can also be used as the sole anaesthetic.

1. Thiopentone sod. It is an ultrashort acting thiobarbiturate, highly soluble in water yielding a very alkaline solution, which must be prepared freshly before injection. Extravasation of the solution or inadvertent intraarterial injection produces intense pain; necrosis and gangrene can occur.

Injected i.v. (3–5 mg/kg) as a 2.5% solution, it produces unconsciousness in 15–20 sec. Its undissociated form has high lipid solubility—enters brain almost instantaneously. Initial distribution depends on organ blood flow—brain gets large amounts. However, as other less vascular tissues (muscle, fat) gradually take up the drug, blood concentration falls and it back diffuses from the brain: consciousness is regained in 6–10 min ($t_{½}$ of distribution phase is 3 min).

On repeated injection, the extracerebral sites are gradually filled up—lower doses produce anaesthesia which lasts longer. Its ultimate disposal occurs mainly by hepatic metabolism (elimination $t_{½}$ is 8–12 hr), but this is irrelevant for termination of action of a single dose. Residual CNS depression may persist for > 12 hr. The patient should not be allowed to leave the hospital without an attendant before this time.

Thiopentone is a poor analgesic. Painful procedures should not be carried out under its influence unless an opioid or N_2O has been given; otherwise, the patient may struggle, shout and show reflex changes in BP and respiration.

It is a weak muscle relaxant; does not irritate air passages. Respiratory depression with inducing doses of thiopentone is generally marked but transient. With large doses it can be severe. BP falls immediately after injection mainly due to vasodilatation, but recovers rapidly. Cardiovascular collapse may occur if hypovolemia, shock or sepsis are present. Reflex tachycardia occurs, but thiopentone does not sensitize the heart to Adr, arrhythmias are rare.

TABLE 27.2 Effects of intravenous anaesthetics on vital functions

Anaesthetic drug	*HR*	*BP*	*Resp.*	*CBF*
1. Thiopentone	↑↑	↓↓	↓↓	↓↓↓
2. Propofol	–, ↓	↓↓↓	↓↓↓	↓↓↓
3. Etomidate	–	↓	↓	↓↓↓
4. Diazepan	–, ↑	↓	↓↓	↓↓
5. Ketamine	↑↑	↑↑	↓, –	↑↑↑
6. Fentanyl	↓	↓	↓↓↓	↓

HR—Heart rate; BP—Systemic arterial blood pressure; Resp.—Respiratory drive; CBF—Cerebral blood flow. (Changes in intracranial pressure parallel CBF).

Cerebral blood flow is reduced, both due to fall in BP as well as constriction of cerebral vessels. However, cerebral oxygenation does not suffer, because there is greater decrease in cerebral O_2 consumption and cerebral perfusion is maintained. A comparative summary of effects of i.v. anaesthetics is presented in Table 27.2.

Thiopentone is a commonly used inducing agent. It can be employed as the sole anaesthetic for short operations that are not painful.

Adverse effects Laryngospasm occurs generally when respiratory secretions or other irritants are present, or when intubation is attempted while anaesthesia is light. This can be prevented by atropine premedication and administration of succinylcholine immediately after thiopentone. Succinylcholine and thiopentone react chemically—should not be mixed in the same syringe.

Shivering and delirium may occur during recovery. Pain in the postoperative period is likely to induce restlessness; adequate analgesia should be provided. Postanaesthetic nausea and vomiting are uncommon.

It can precipitate acute intermittent porphyria in susceptible individuals, therefore contraindicated.

Other uses Occasionally used for rapid control of convulsions.

Gradual i.v. infusion of subanaesthetic doses can be used to facilitate verbal communication with psychiatric patients and for 'narcoanalysis' of criminals; acts by knocking off guarding.

PENTOTHAL, INTRAVAL SODIUM 0.5, 1 g powder for making fresh injectable solution.

2. Methohexitone sod. It is similar to thiopentone, 3 times more potent, has a quicker and briefer (5–8 min) action. Excitement during induction and recovery is more common. It is more rapidly metabolized (t½ 4 hr) than thiopentone: patient may be roadworthy more quickly.

3. Propofol Currently, propofol has superseded thiopentone as an i.v. anaesthetic, both for induction as well as maintenance. It is an oily liquid employed as a 1% emulsion. Unconsciousness after propofol injection occurs in 15–45 sec and lasts 5–10 min. Propofol distributes rapidly (distribution t½ 2–4 min). Elimination t½ (100 min) is much shorter than that of thiopentone due to rapid metabolism.

Intermittent injection or continuous infusion of propofol is frequently used for total i.v. anaesthesia when supplemented by fentanyl. It lacks airway irritancy and is not likely to induce bronchospasm: preferred in asthmatics. It is particularly suited for outpatient surgery, because residual impairment is less marked and shorter-lasting. Incidence of postoperative nausea and vomiting is low; patient acceptability is very good. Excitatory effects and involuntary movements are noted in few patients. Induction apnoea lasting ~1 min is common. Fall in BP due primarily to vasodilatation with less marked cardiac depression occurs consistently, and is occasionally severe, but short lasting. Baroreflex is suppressed; heart rate remains unchanged or may decrease. Maintenance anaesthesia with

propofol produces dose-dependent respiratory depression which is more marked than with thiopentone. Effect of cerebral blood flow and O_2 consumption is similar to thiopentone. Pain during injection is frequent; can be minimized by combining with lidocaine.

Dose: 2 mg/kg bolus i.v. for induction; 100–200 µg/kg/min for maintenance.

PROPOVAN 10 mg/ml and 20 mg/ml in 10, 20 ml vials.

In subanaesthetic doses (25–50 µg/kg/min) it is the drug of choice for sedating intubated patients in intensive care units. However, it is not approved for such use in children; prolonged sedation with higher doses has caused severe metabolic acidosis, lipaemia and heart failure even in adults.

4. Etomidate It is another induction anaesthetic (0.2–0.5 mg/kg) which has a briefer duration of action (4–8 min) than thiopentone; produces little cardiovascular and respiratory depression, but motor restlessness and rigidity is more prominent as are pain on injection or nausea and vomiting on recovery. It is a poor analgesic and has not found much favour.

SLOWER ACTING DRUGS

1. Benzodiazepines (BZDs) In addition to preanaesthetic medication, BZDs are now frequently used for inducing, maintaining and supplementing anaesthesia as well as for 'conscious sedation'. Relatively large doses (diazepam 0.2–0.3 mg/kg or equivalent) injected i.v. produce sedation, amnesia and then unconsciousness in 5–10 min. If no other anaesthetic or opioid is given, the patient becomes responsive in 1 hr or so due to redistribution of the drug (distribution t½ of diazepam is 15 min), but amnesia persists for 2–3 hr and sedation for 6 hr or more. Recovery is further delayed if larger doses are given. BZDs are poor analgesics : an opioid or N_2O is usually added if the procedure is painful.

By themselves, BZDs donot markedly depress respiration, cardiac contractility or BP, but when opioids are also given these functions are considerably compromised. BZDs decrease muscle tone by central action, but require neuromuscular blocking drugs for muscle relaxation of surgical grade. They do not provoke postoperative nausea or vomiting. Involuntary movements are not stimulated.

BZDs are now the preferred drugs for endoscopies, cardiac catheterization, angiographies, conscious sedation during local/regional anaesthesia, fracture setting, ECT, etc. They are a frequent component of balanced anaesthesia employing several drugs. The anaesthetic action of BZDs can be rapidly reversed by flumazenil 0.5–2 mg i.v.

Diazepam 0.2–0.5 mg/kg by slow undiluted injection in a running i.v. drip: this technique reduces the burning sensation in the vein and incidence of thrombophlebitis.

VALIUM, CALMPOSE 10 mg/2 ml inj.

Lorazepam Three times more potent, slower acting and less irritating than diazepam. It distributes more gradually—awakening may be delayed. Amnesia is more profound.

Dose: 2–4 mg (0.04 mg/kg) i.v. CALMESE 4 mg/2 ml inj.

Midazolam This BZD is water soluble, non-irritating to veins, faster and shorter acting (t½ 2 hours) and 3 times more potent than diazepam. Fall in BP is somewhat greater than with diazepam. It is being preferred over diazepam for anaesthetic use: 1–2.5 mg i.v. followed by 1/4th supplemental doses. Also used for sedation of intubated and mechanically ventilated patients and in other critical care anaesthesia as 0.02–0.1 mg/kg/hr continuous i.v. infusion.

FULSED, MEZOLAM, SHORTAL 1 mg/ml, 5 mg/ml inj.

2. Ketamine This unique anaesthetic is pharmacologically related to the hallucinogen phencyclidine. It induces a so called '*dissociative anaesthesia*' characterized by profound analgesia, immobility, amnesia with light sleep. The patient appears to be conscious, i.e. opens his eyes, makes swallowing movements and his muscles are stift, but he is unable to process sensory stimuli and does not reeact to them. Thus, the patient appears to be dissociated from his body and surroundings. The primary site of action is in the cortex and

subcortical areas; not in the reticular activating system, which is the site of action of barbiturates.

Respiration is not depressed, bronchi dilate, airway reflexes are maintained, muscle tone increases. Non-purposive limb movements occur. Heart rate, cardiac output and BP are elevated due to sympathetic stimulation. A dose of 1–2 (average 1.5) mg/kg i.v. or 3–5 mg/kg i.m. produces the above effects within a minute, and recovery starts after 10–15 min, but patient remains amnesic for 1–2 hr. Emergence delirium, hallucinations and involuntary movements occur in upto 50% patients during recovery; but the injection is not painful. Children tolerate the drug better. Ketamine is rapidly metabolized in the liver and has an elimination t½ of 2–4 hr.

Ketamine has been used for operations on the head and neck, in patients who have bled, in asthmatics (relieves bronchospasm), in those who do not want to lose consciousness and for short operations. It is good for repeated use; particularly suitable for burn dressing. Combined with diazepam, it has found use in angiographies, cardiac catheterization and trauma surgery. It may be dangerous for hypertensives, in ischaemic heart disease (increases cardiac work), in congestive heart failure and in those with raised intracranial pressure (ketamine increases cerebral blood flow and O_2 consumption), but is good for hypovolemic patients.

KETMIN, KETAMAX, ANEKET 50 mg/ml in 2 ml amp, 10 ml vial.

Clandestinely mixed in drinks, ketamine has been misused as rape drug.

3. Fentanyl This highly lipophilic, short acting (30–50 min) potent opioid analgesic related to pethidine (*see* Ch. 34) is generally given i.v. at the beginning of painful surgical procedures. Reflex effects of painful stimuli are abolished. It is frequently used to supplement anaesthetics in balanced anaesthesia. This permits use of lower anaesthetic concentrations with better haemodynamic stability. Combined with BZDs, it can obviate the need for inhaled anaesthetics for diagnostic, endoscopic, angiographic and other minor procedures in poor risk patients, as well as for burn dressing. Anaesthetic awareness with dreadful recall is a risk.

After i.v. fentanyl (2–4 µg/kg) the patient remains drowsy but conscious and his cooperation can be commanded. Respiratory depression is marked, but predictable; the patient may be encouraged to breathe and assistance may be provided. Tone of chest muscles and masseters may increase with rapid fentanyl injection: a muscle relaxant is then required to facilitate mechanical ventilation. Heart rate decreases, because fentanyl stimulates vagus. Fall in BP is slight and heart is not sensitized to Adr. Cerebral blood flow and O_2 consumption are slightly decreased. Supplemental doses of fentanyl are needed every 30 min or so, but recovery is prolonged after repeated doses.

Nausea, vomiting and itching often occurs during recovery. The opioid antagonist naloxone can be used to counteract persisting respiratory depression and mental clouding. Fentanyl is also employed as adjunct to spinal and nerve block anaesthesia, and to relieve postoperative pain.

TROFENTYL, FENDOP, FENT 50 µg/ml in 2 ml amp, 10 ml vial.

Alfentanil, *Sufentanil* and *remifentanil* are still shorter acting analogues which can be used in place of fentanyl.

4. Dexmedetomidine Activation of central α_2 adrenergic receptors has been known to cause sedation and analgesia. Clonidine (a selective α_2 agonist antihypertensive) given before surgery reduces anaesthetic requirement. Dexmedetomidine is a centrally active selective α_{2A} agonist that has been introduced for sedating critically ill/ventilated patients in intensive care units. It is also being used as an adjunct to anaesthesia. Analgesia and sedation are produced with little respiratory depression, amnesia or anaesthesia. Sympathetic response to stress and noxious stimulus is blunted. It is administered by i.v. infusion. Side effects are similar to those with clonidine, *viz.* hypotension, bradycardia and dry mouth. It has been recently approved for use in India as well.

CONSCIOUS SEDATION

'Conscious sedation' is a monitored state of altered consciousness that can be employed (supplemented with local/regional anaesthesia), to carryout diagnostic/short therapeutic/dental procedures in apprehensive subjects or medically compromised patients, in place of general anaesthesia. It allows the operative procedure to be performed with minimal physiologic and psychologic stress. In conscious

sedation, drugs are used to produce a state of CNS depression (but not unconsciousness), sufficient to withstand the trespass of the procedure, while maintaining communication with the patient, who at the same time responds to commands and is able to maintain a patent airway. The difference between conscious sedation and anaesthesia is one of degree. The protective airway and other reflexes are not lost, making it safer. Drugs used for conscious sedation are:

1. *Diazepam* It is injected i.v. in small (1–2 mg) repeated doses or by slow infusion until the desired level of sedation is produced indicated by relaxation, indifference, slurring of speech, ptosis, etc. Further injection is stopped, after which this state lasts for about 1 hour and psychomotor impairment persists for 6–24 hours; an escort is needed to take the patient back to home. Flumazenil can be used to reverse the sedation, but repeated doses are needed.

   Midazolam (i.v.) is a shorter acting alternative to diazepam. Oral diazepam administered 1 hr before is also used with the limitation that level of sedation cannot be titrated. The patient remains sedated (not roadworthy) for several hours.

2. *Propofol* Because of brief action, it has to be administered as continuous i.v. infusion throughout the procedure by using a regulated infusion pump. Advantage is that level of sedation can be altered during the procedure and recovery is relatively quick, permitting early discharge of the patient.

3. *Nitrous oxide* The patient is made to breathe 100% oxygen through a nose piece or hood and N_2O is added in 10% increments (to a maximum of 50%, rarely 70%) till the desired level of sedation assessed by constant verbal contact is obtained. This is maintained till the procedure is performed. Thereafter, N_2O is switched off, but 100% O_2 is continued for next 5 min. The patient is generally roadworthy in 30–60 min.

4. *Fentanyl* Injected i.v. (1–2 µg/kg every 15–30 min), it can be used alone or in combination with midazolam/propofol.

COMPLICATIONS OF GENERAL ANAESTHESIA

A. *During anaesthesia*

1. Respiratory depression and hypercarbia.
2. Salivation, respiratory secretions. This is less problematic now as nonirritant anaesthetics are mostly used.
3. Cardiac arrhythmias, asystole.
4. Fall in BP.
5. Aspiration of gastric contents: acid pneumonitis.
6. Laryngospasm and asphyxia.
7. Awareness: dreadful perception and recall of events during surgery. This may occur due to use of light anaesthesia + analgesics and muscle relaxants.
8. Delirium, convulsions and other excitatory effects are generally seen with i.v. anaesthetics; especially if phenothiazines or hyoscine have been given in premedication. These are suppressed by opioids.
9. Fire and explosion. This is rare now due to use of non-inflammable anaesthetics.

B. *After anaesthesia*

1. Nausea and vomiting.
2. Persisting sedation: impaired psychomotor function.
3. Pneumonia, atelectasis.
4. Organ toxicities: liver, kidney damage.
5. Nerve palsies—due to faulty positioning.
6. Emergence delirium.
7. Cognitive defects: prolonged excess cognitive decline has been observed in some patients, especially the elderly, who have undergone general anaesthesia, particularly of long duration.

DRUG INTERACTIONS

1. Patients on antihypertensives given general anaesthetics—BP may fall markedly.
2. Neuroleptics, opioids, clonidine and monoamine oxidase inhibitors potentiate anaesthetics.
3. Halothane sensitizes the heart to Adr.
4. If a patient on corticosteroids is to be anaesthetized, give 100 mg hydrocortisone intraoperatively because anaesthesia is a stressful state—can precipitate adrenal insufficiency and cardiovascular collapse.
5. Insulin need of a diabetic is increased during GA: switch over to plain insulin even if the patient is on oral hypoglycaemics.

PREANAESTHETIC MEDICATION

Preanaesthetic medication refers to the use of drugs before anaesthesia to make it more pleasant and safe. The aims are:

1. Relief of anxiety and apprehension preoperatively and to facilitate smooth induction.
2. Amnesia for pre- and postoperative events.
3. Supplement analgesic action of anaesthetics and potentiate them so that less anaesthetic is needed.
4. Decrease secretions and vagal stimulation that may be caused by the anaesthetic.
5. Antiemetic effect extending to the postoperative period.
6. Decrease acidity and volume of gastric juice so that it is less damaging if aspirated.

Different drugs achieve different purposes. One or more drugs may be used in a patient depending on the needs.

1. Sedative-antianxiety drugs Benzodiazepines like diazepam (5–10 mg oral) or lorazepam (2 mg oral or 0.05 mg/kg i.m. 1 hour before) have become popular drugs for preanaesthetic medication because they produce tranquility and smoothen induction; there is loss of recall of perioperative events (especially with lorazepam) with little respiratory depression or accentuation of postoperative vomiting. They counteract CNS toxicity of local anaesthetics and are being used along with pethidine/fentanyl for a variety of minor surgical and endoscopic procedures.

Midazolam is a good amnesic with potent and shorter lasting action; it is also better suited for i.v. injection, due to water solubility.

Promethazine (50 mg i.m.) is an antihistaminic with sedative, antiemetic and anticholinergic properties. It causes little respiratory depression.

2. Opioids Morphine (10 mg) or pethidine (50–100 mg), i.m. allay anxiety and apprehension of the operation, produce pre- and postoperative analgesia, smoothen induction, reduce the dose of anaesthetic required and supplement poor analgesics (thiopentone, halothane) or weak anaesthetics (N_2O). Postoperative restlessness is also reduced.

Disadvantages They depress respiration, interfere with pupillary signs of anaesthesia, may cause fall in BP during anaesthesia, can precipitate asthma and tend to delay recovery. Other disadvantages are lack of amnesia, flushing, delayed gastric emptying and biliary spasm. Some patients experience dysphoria. Morphine particularly contributes to postoperative constipation, vomiting and urinary retention. Tachycardia sometimes occurs when pethidine has been used.

Use of opioids is now mostly restricted to those having preoperative pain. When indicated, fentanyl is mostly injected i.v. just before induction.

3. Anticholinergics (*see* Ch. 8) Atropine or hyoscine (0.6 mg or 10–20 µg/kg i.m./i.v.) or glycopyrrolate (0.2–0.3 mg or 5–10 µg/kg i.m./i.v.) have been used, primarily to reduce salivary and bronchial secretions. This need is infrequent now due to use of non-irritant anaesthetics. However, they must be given beforehand when ether is used. The main aim of their use now is to prevent vagal bradycardia and hypotension (which occur reflexly due to certain surgical procedures), and prophylaxis of laryngospasm which is precipitated by respiratory secretions.

Hyoscine, in addition, produces amnesia and antiemetic effect, but tends to delay recovery. Some patients get disoriented; emergence delirium is more common. Moreover, antibradycardiac effect of hyoscine is less marked. Therefore, it is infrequently selected for use during anaesthesia.

Glycopyrrolate is twice as potent and longer acting quaternary antimuscarinic which does not produce central effects. Antisecretory action is more marked than atropine, while tachycardia is less marked, especially after i.m. injection. It acts rapidly when given i.v. and is the preferred antimuscarinic in anaesthetic practice.

Action	*Atropine*	*Glycopyrrolate*
1. Antisecretory	++	+++
2. Tachycardia	+++	++
3. CNS effects	+	–
4. Bronchodilatation	++	++

Antimuscarinics facilitate assisted ventilation by reducing airway resistance, but tend to increase the anatomic dead space. They dilate pupils, abolish the pupillary signs and increase chances of gastric reflux by decreasing tone of lower esophageal sphincter (LES). They should not be used in febrile patients. Dryness of mouth

in the pre- and postoperative period may be distressing. As such, they are now mostly used i.v. intraoperatively when need arises.

4. Neuroleptics Chlorpromazine (25 mg), trifluopromazine (10 mg) or haloperidol (2–4 mg) i.m. are infrequently used in premedication. They allay anxiety, smoothen induction and have antiemetic action. However, they potentiate respiratory depression and hypotension caused by the anaesthetics and delay recovery.

Involuntary movements and muscle dystonias can occur, especially in children.

5. H_2 blockers/proton pump inhibitors Patients undergoing prolonged operations, caesarian section and obese patients are at increased risk of gastric regurgitation and aspiration pneumonia. Ranitidine (150 mg)/famotidine (20 mg) or omeprazole (20 mg)/pantoprazole (40 mg) given night before and in the morning benefit by raising pH of gastric juice and may also reduce its volume and thus chances of regurgitation. The chances of reflux and damage to lungs on aspiration is minimal if volume of gastric juice is <25 ml and pH is >3.5. Prevention of stress ulcers is another advantage. They are now routinely used before prolonged surgery.

6. Antiemetics *Metoclopramide* 10–20 mg i.m. preoperatively is effective in reducing postoperative vomiting. By enhancing gastric emptying and tone of LES, it reduces the chances of reflux and its aspiration. Extrapyramidal effects and motor restlessness can occur. Combined use of metoclopramide and H_2 blockers is more effective.

Domperidone is nearly as effective and does not produce extrapyramidal side effects.

Ondansetron (4–8 mg i.v.) the selective 5-HT_3 blocker has been found highly effective in reducing the incidence of post-anaesthetic nausea and vomiting (*see* Ch. 47). It is practically devoid of side effects and has become the antiemetic of choice in anaesthetic practice.