ANESTHETICS

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Summary

The pharmacology knowledge of an anesthetist is extensive. Achieving the desired anesthetic state while preserving or improving vital organ function during surgery requires an understanding of the physiologic actions of anesthetics, individually and in combination, in patients with a wide range of medical conditions.

Anesthetists must appreciate the physiological consequences and potential anesthetic interactions of all drugs patients may be administered perioperatively. Anesthetists must also understand the pharmacology of all drugs a patient may be taking in order to appropriately maintain physiological health and treat complications during the stress of anesthesia and surgery and in the postoperative period.

Historically, anesthesia was achieved with high concentrations of a single agent (ether or chloroform). This practice often resulted in significant side effects and complications. Modern anesthesia is achieved with a combination of specific drugs: “balanced anesthesia”.

The fundamental drugs for inducing anesthesia are specific to anesthesia, having no or minimal application within other medical disciplines. They are potent and potentially lethal, however because of the development of predictable and favorable pharmacodynamics and pharmacokinetics, modern anesthetic drugs have greatly improved safety margins.

Anesthesia is being challenged with progressively more complex surgery and increasingly complicated patients. Advancement of surgery and patient safety cannot occur without the advancement in anesthetic pharmacology.

Though essential in anesthesia, analgesics are used by many medical specialties and are discussed more fully elsewhere. Those drugs specific to anesthesia include inhalation agents, neuromuscular blocking drugs, local anesthetics and induction agents.

1. Inhalation Agents

1.1. Introduction

Inhalational anesthesia forms the basis of most general anesthetics. In developed countries where ultra-short acting intravenous anesthetic drugs and computer delivery systems are available, some anesthetists favor total intravenous anesthesia (TIVA).

Inhalational anesthetic agents include nitrous oxide and the volatile agents such as ether, chloroform, halothane, isoflurane, enflurane, methoxyflurane, sevoflurane, desflurane, cyclopropane and trichloroethylene. Many of the older agents are no longer available in developed countries and some newer agents are not available in developing countries. The newer agents offer improved patient safety and pharmacokinetics.

Prepared originally in 1540 by Valerius Cordus, Frobenius named “sweet oil of vitriol” ether in 1730. Priestly discovered nitrous oxide in 1772 and Davy described its analgesic properties, naming it “laughing gas” in 1800. It was another two decades in 1824 before Henry Hickman used the inhalation of a gas or vapor to perform painless operations on animals. His results were published in “A letter on Suspended Animation” but gained little attention and it was not until the 16 October 1846 that anesthesia was successfully produced by the inhalation of gases and vapors when W.T.G Morton gave ether at the Massachusetts General Hospital.

Horace Wells had unsuccessfully demonstrated the use of nitrous oxide for dental extraction at the Harvard Medical School one year previously. Though successful for some time after this failed demonstration, Horace Wells eventually became a chloroform addict and committed suicide aged 33. G Colton successfully reintroduced nitrous oxide in 1863.

Von Lieberg in Germany, Soubeiran in France and Guthrie in New York independently discovered chloroform in 1831. In 1847, Marie Flourens described its anesthetic properties. The same year, James Simpson experimented on himself and his assistants with chloroform. Four days later he used it clinically and within a week presented a “Notice of a New Anesthetic Agent as a Substitute for Sulfuric Ether in Surgery and Midwifery”. James Simpson attracted much criticism for providing pain relief in labor on theological grounds (Genesis, Chapter 3, Verse 16) but gained respectability after John Snow administered chloroform to Queen Victoria for the delivery of Prince Leopold in 1857. John Snow was initially interested in ether, inventing the ether inhaler but later abandoned ether for chloroform. He was the first to attempt scientific investigation into the inhalation agents and their methods of administration. His last book, “On Chloroform and Other Anesthetics”, was published posthumously in 1858. John Snow recognized that anesthetists must rely on a series of physical signs to monitor the onset and depth of anesthesia. In 1920, Guedel developed his classic table of the signs of the depth of anesthesia, dividing the disappearance of reflexes into 4

stages. Stage one (analgesia) is from the beginning of anesthesia to the loss of consciousness. The patient initially experiences analgesia then later both analgesia and amnesia. In stage two (excitement), the patient may appear delirious and excited, but is amnesic. Respiration is irregular and vomiting and struggling may occur. Stage three (surgical anesthesia) begins with the onset of regular breathing and the loss of the lid reflex and ends with the cessation of respiration. This stage is divided into four planes. During plane one, respiration increases, eye movements decrease and laryngeal and pharyngeal reflexes are lost. With increasing depth of anesthesia there is progressive decrease in respiration, dilatation of pupils, loss of muscle tone and loss of corneal and glottic reflexes. Plane four extends from the time of paralysis of the intercostal muscles to cessation of breathing. Stage four (medullary depression) extends from the cessation of respiration to the failure of the circulation. This stage is pre-mortem.

For many years, chloroform (a respiratory and cardiovascular depressant) was used almost exclusively in Britain, administered only by physicians, whilst ether (a respiratory and cardiovascular stimulant) was used in the United States of America, administered by less skilled “etherizers”.

The first anesthetic death from chloroform was reported in 1848. The two World Wars and increasing complexity of operations sparked the development of the anesthesia specialty and the search for a better agent.

In present day anesthesia, combining drugs that selectively provide hypnosis, amnesia, analgesia, and muscle relaxation permits control of the anesthetic state and minimizes side effects of a single anesthetic drug (chloroform or ether) used in high concentrations. John Lundy of the Mayo Clinic introduced the term “balanced anesthesia: in 1926 for the combination of agents.

Cyclopropane was first synthesized by August von Freund of Poland in 1882, and its anesthetic properties shown in 1929 by G Lucas and V Henderson. Trichloroethylene was introduced to clinical anesthesia in 1935.

The introduction of halothane, a halogenated alkane first used clinically in 1956, heralded a new era of inhalational anesthesia. Prior to the introduction of halothane, most anesthetic vapors and gases were flammable or had limitations such as nausea, arrhythmias or slow recovery. Halothane was a major advance in anesthesia and was the first of the modern volatile inhalational agents. Induction was uncomplicated and relatively fast, recovery was rapid, there was no salivation or excessive nausea and vomiting, and it was non-flammable, allowing the safe use of diathermy. Halothane has some disadvantages, including respiratory depression, arrhythmias, no analgesia, poor muscle relaxation, uterine relaxation and halothane hepatitis. Subsequently a series of halogenated ethers (enflurane, isoflurane, sevoflurane and desflurane) were introduced with improved pharmacokinetic and side effect profiles. The “ideal” inhaled anesthetic is yet to be discovered.

1.2. Pharmacokinetics and Pharmacodynamics

An inhaled anesthetic agent is delivered into a breathing circuit, from which the patient

inhales the agent into the lungs, then the blood. The circulation will carry the agent to all the organs of the body including the brain. The depth of anesthesia is related to the partial pressure of the agent in the brain. There are many factors that determine the rate of onset of an inhaled anesthetic agent, including the inspired concentration, alveolar ventilation, solubility of the agent and cardiac output.

The higher the inspired concentration of the agent, the more rapid is the rise in the partial pressure in the brain. Agents with a low boiling point will evaporate easily (are more volatile) and therefore can be delivered in higher concentrations. Ether has a boiling point of 35 degrees Celsius and could produce a maximum concentration of 56%. In contrast, trichloroethylene has a boiling point of 87 degrees Celsius and can only be given at a maximum concentration of 8%. Another way of expressing volatility is the saturated vapor pressure (SVP). The SVP is the pressure exerted by the vapor phase of an agent when in equilibrium with the liquid phase at a given temperature. The SVP of ether is 425 mmHg (59 kPa). The SVP of halothane is 243 mmHg (32 kPa). The SVP of trichloroethylene is 60 mmHg (8 kPa).

The greater the solubility of the gas in the blood, the slower the rise in the partial pressure of the agent in the brain, and therefore the slower the onset of anesthesia. A very soluble agent such as ether will dissolve in large quantities in blood before the partial pressure in the brain is sufficient to cause anesthesia. More soluble agents will also produce longer recovery times. The solubility of an agent is called its blood-gas partition coefficient. The blood-gas coefficient is the ratio of the amount dissolved in blood to the amount in the same volume of gas in contact with that blood. Ether is very soluble, with a blood gas coefficient of 12. Halothane is less soluble with a blood gas coefficient of 2.3, and therefore has a much more rapid onset of anesthesia. Trichloroethylene has high solubility with a blood gas coefficient of 9.

Inhalation agents also vary in their potency. The minimum alveolar concentration (MAC) is used to express the potency of inhalation agents. The MAC is the minimum alveolar concentration of an inhaled anesthetic (in the absence of all other drugs) at a pressure of one atmosphere, in oxygen, that produces immobility in 50% of healthy patients to a standard surgical incision. The lower the MAC, the more potent is the agent. The MAC of an agent may be reduced (potency increased) by many factors including combining other central nervous system (CNS) depressants, hypothermia, severe hypotension and extremes of age. The MAC of an agent can be increased (potency reduced) by factors such as hyperthermia, hyperthyroidism and alcoholism. MAC is maximal at about 6 months of age and decreases by about 6% per decade. All inhaled anesthetics have a steep concentration-response curve so that at concentrations 20% lower than MAC, almost all patients will move in response to a surgical stimulation, and at concentrations 20% greater than MAC, few will move. Trichloroethylene has high potency (MAC 0.17%), halothane has a lower potency (MAC 0.75%) and ether has an even lower potency (MAC 1.92%).

The concept of MAC has been expanded by the use of other clinical end points or stimuli. MAC-awake is the concentration that would allow opening of the eyes on verbal command during emergence from anesthesia. MAC-intubation and MAC BAR is the minimum alveolar concentration that eliminates movement and adrenergic response

respectively with endotracheal intubation.

The anesthetist can predict the behavior of a volatile anesthetic agent by the SVP, blood gas coefficient and MAC. Ether is highly soluble (blood-gas coefficient 12) and will have a slow onset. With a MAC of 1.92% it has low potency but fortunately has an SVP of 425 mmHg, which means that it can be given in high concentrations. Trichloroethylene is potent (MAC 0.17%) but is a weak anesthetic because vaporizers cannot produce high enough concentrations because the volatility is very low (SVP 60 mmHg). It has a high blood solubility (blood-gas coefficient 9) so has a slow onset. Halothane is volatile (SVP 243 mmHg) so adequate concentrations can be delivered by a vaporizer. The solubility is low (blood gas coefficient 2.3), allowing rapid induction and recovery.

The Meyer-Overton rule states that the potency of an anesthetic gas correlates with its solubility in relatively non-polar solvents and it has been widely believed that inhaled anesthetic gases acted by dissolving in lipid bilayers and altering the biophysical properties of biological membranes. This was the basis for the Unitary Theory of Anesthesia, which states that all anesthetics act by a common mechanism based on physical rather than structural properties of the anesthetic molecule, however current evidence challenges the Unitary Theory. There is a growing body of evidence that inhaled anesthetic agents, belong to a heterogeneous group, which mediate their effects in various specific anatomical locations in the nervous system by direct binding to specific molecular targets.

1.3. Specific Agents

The modern era of inhalation anesthesia started with the introduction of halothane. With development of the newer volatile agents (enflurane, isoflurane), the use of halothane has declined. Halothane is now rarely used in western countries, however it is still of importance in some developing countries.

1.3.1. Diethyl Ether (Ether)

(MAC 1.92, blood gas coefficient 12.0, SVP 425 mmHg).
Diethyl ether (C_2H_5-0-C_2H_5) is an inexpensive, colorless agent with a strong irritant smell, made from sugar cane. Ether has some significant advantages. It is both an anesthetic and analgesic. As with other inhalation anesthetics, ether is a myocardial depressant. However, unlike other volatile agents, this effect is opposed by increased activity of the sympathetic nervous system. Cardiac output and arterial pressure usually remain at normal levels. Heart rate tends to remain slightly elevated. Very high concentrations of ether may cause direct myocardial depression. Splanchnic and renal blood flows are reduced.

Importantly, spontaneous respiration remains adequate, though the central response to carbon dioxide is reduced. (Ether is safe to use for spontaneous respiration without additional oxygen for most patients, and is an excellent inhalation agent where oxygen is unavailable). Ether results in bronchodilatation. It does not relax the uterus like other volatile agents but gives good abdominal muscle relaxation. 10 to 15% is metabolized to

carbon dioxide and non-volatile urinary products by the hepatic enzymes. It should be stored in a cool dark place to prevent decomposition to acetaldehyde and ether peroxide impurities.

Although ether can be used as a sole anesthetic agent, as it is both anesthetic and analgesic, it has several properties that make it less than ideal. Inhalational induction by ether is very difficult because it has an unpleasant smell, is very slow (blood-gas coefficient 12), causes marked airway secretions (requiring atropine premedication), bronchial irritation, breath holding, laryngospasm and coughing. Ether may cause postoperative nausea and vomiting (PONV) and recovery is slow.

Ether is flammable in air and explosive in oxygen and nitrous oxide. The safest practice is to not use ether with diathermy. Ether vapor is flammable within the patient (airway, lung or stomach) and within 30 cm of the anesthetic circuit. No sources of ignition should be permitted within 30 cm of this zone of risk. Scavenging must always be carried out if possible. If diathermy must be used with ether, supplementary oxygen must be turned off well beforehand.

1.3.2. Chloroform

(MAC unknown, blood gas coefficient 8.4, SVP 120 mmHg)
Chloroform's advantages over ether were that it was relatively non-irritant during induction and non-flammable and non-explosive. Like ether, it was a good muscle relaxant, cheap and an analgesic, but unfortunately had prolonged onset and recovery. Unlike ether, chloroform caused cardiovascular and respiratory depression, occasional sudden death and toxicity.

Chloroform produces a dose dependent reduction in blood pressure. Dysrhythmias are common, especially during light anesthesia. Sudden cardiac death can occur due to ventricular fibrillation (catecholamines acting on a chloroform sensitized heart), intense vagal inhibition or myocardial depression. Chloroform may cause toxic hepatitis with symptoms of increasing nausea and vomiting, jaundice, coma and death.

In 1912, the Committee of Anesthesia of the American Medical Association recommended that chloroform no longer be used as an anesthetic because of the unacceptable incidence of hepatic and cardiovascular collapse (John Snow (1813-1858) gave over 4000 chloroform anesthetics without a death).

1.3.3. Cyclopropane

(MAC 9.2, blood gas coefficient 0.46, boiling point -34C)
Cyclopropane was a simple cyclic hydrocarbon, introduced into anesthesia by Waters in 1934. It was a remarkably potent anesthetic with rapid smooth induction of anesthesia and recovery (blood gas co-efficient 0.46). A few breaths of 50% cyclopropane in oxygen are sufficient to induce anesthesia. Unfortunately, cyclopropane was a marked explosive hazard. It also caused marked respiratory depression, although blood pressure was well maintained due to sympathetic nervous system stimulation. Ventricular arrhythmias were common with hypercapnia, hypoxaemia, and atropine or epinephrine

administration. Nausea and vomiting were common. It was very explosive in oxygen (between 2.5 and 50 percent oxygen) and air. Cyclopropane was not metabolized.

1.3.4. Trichloroethylene

(MAC 0.17, blood gas coefficient 9.0, SVP 60 mmHg)
Trichloroethylene CHClCCl2 is a colorless, non-irritant, safe agent that is decomposed by light. It has been superseded by modern agents. It was first used as an industrial solvent and was introduced to anesthesia by Jackson in 1934. The commercial preparation (Trilene) was colored blue for identification purposes. Trichloroethylene maintains cardiac output and provides good analgesia but it cannot be used as a sole anesthetic agent. Trichloroethylene has a SVP of 60 mmHg so it is impossible to deliver a high enough concentration to cause anesthesia. A blood/gas coefficient of 9.0 means that induction and recovery are slow. Higher concentrations of trichloroethylene can cause arrhythmias and epinephrine should not be administered with trichloroethylene. Trichloroethylene causes an increase in respiratory rate but a decrease in tidal volume so that $PaCO_2$ rises and PaO_2 falls in spontaneously breathing patients. It is a poor muscle relaxant and causes more post operative nausea and vomiting than halothane.

Trichloroethylene must never be used in a circle system with soda lime. In the presence of alkali and heat, trichloroethylene degrades into the cranial neurotoxin, dichloroacetylene (especially targeting cranial nerves 5, 7 and 8) and the pulmonary irritant, phosgene. Trichloroethylene was an excellent agent to use as background analgesia. The initial dose is 0.5 to 1%, reducing to 0.2 to 0.5%.

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Bibliography

Goodman and Gilman's The pharmacological basis of therapeutics 11th Edition. [A multi-author pharmacology text with standardized organization of chapters].

McCaughey W Clarke R S J Fee J P Wallace W F M Anaestheia Physiology and Parmacology 1st Edition 1997. [Covers the basic knowledge required by an anesthetic trainee].

Stoelting R K and Hillier S C. Pharmacology and Physiology in Anesthetic Practice. 4th Edition Williams and Wilkins. 2006. [Provides students as well as practicing anesthetists with an in-depth but concise presentation of those aspects of pharmacology and physiology that are relevant either directly or indirectly to perioperative anesthetic management of patients].

Trevor AJ and White PF. General anesthetics in Basic and Clinical Pharmacology – 10th Edition. Lange Medical Books/McGraw-Hill. New York 2007 2007. [This book is designed to provide a complete, authoritative , current and readable pharmacology textbook for students in the health sciences].

Wood M and Wood AJJ. *Drugs and Anesthesia. Pharmacology for Anesthesiologists*. Second Edition.

Williams and Wilkins. Baltimore, Maryland 1990. [Applies knowledge of the basic principles of pharmacology and pharmacokinetics to anesthesia].

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