Anaesthesia

Anaesthesia allows surgery to be performed while the patient is asleep and with no memory of the operation.
The pharmaceutical industry is researching newer and better anaesthetic agents.

What is anaesthesia?

Anaesthesia is the process of relieving or blocking the perception of pain and bodily sensations through medicines (anaesthetics) or in combination with complementary measures. This allows individuals to undergo surgery and other medical procedures without the distress and pain they would otherwise experience. Anaesthesia is one of the most significant developments of modern medicine, because it allows treatment involving unbearable pain to be performed while the person is relaxed, asleep and with no memory of the operation.

The word "anaesthesia" comes from the Greek and means absence or loss of sensation. In the first century, the Greek physician Dioscorides described the use of wine made from the plant mandragora (mandrake) to produce a deep sleep in patients undergoing surgery. In his writings, he used the word "anaesthesia" to describe the state of unconsciousness. The noun was re-devised in 1846 by American anatomy professor Dr. Oliver Wendell Holmes, after, in a public demonstration, surgeons in Boston had successfully used ether for the first time to render a patient unconscious before an operation.

Anaesthesia can be (i) **local**, leading to loss of sensation of the body part into which the medication was applied, e.g. an injection prior to having a tooth pulled, a wound stitched or a mole removed while being fully conscious; (ii) **regional**, e.g. spinal, when anaesthetic medication is injected into the spinal canal of the vertebral column, numbing the body from the waist down, allowing operations in the pelvic region; or (iii) **epidural**, which uses a similar technique to spinal anaesthesia, with a narrow plastic tube (cannula) left in position near to the nerves in the back. Epidural anaesthesia allows application of repeated doses of local anaesthetics and analgesics without further use of needles, because the cannula can be left in place for up to several days. Similar techniques of regional anaesthesia are used for other parts of the body; e.g. the arm can be numbed with an injection into the upper arm or armpit to allow a bro-

Types of anaesthesia

- **Local anaesthesia**

  This form is used to numb a small part of the body, blocking pain signals from being sent through the body, but allowing the patient to remain fully alert.

- **Regional anaesthesia**

  This form of anaesthesia is used to block sensation in a particular region of the body. The anæsthetic is injected around a single nerve or a larger network of nerves that branches out and serves that area, keeping pain signals from reaching the brain.

  Spinal, epidural and caudal anaesthesia involve injecting an anaesthetic into or near the spinal fluid, effectively numbing nerves that serve the lower half of the body. They are often used for pelvic operations and lower extremity surgery.

- **General anaesthesia**

  This form is appropriate for more extensive surgery. The medicines used in general anaesthesia are given intravenuously or are inhaled. They act as hypnotics, painkillers and muscle relaxants, and they block one's memory of the surgery. Because one is unconscious, the brain does not perceive any pain signals.

ken wrist to be treated; (iv) **general**, when medicines and anaesthetic gases or vapours are administered for major surgical interventions, where complete stillness is required for a prolonged period of time. The patient loses consciousness and wakes up when the procedure is over.

Tumescent anaesthesia is a special form of local anaesthesia. It is carried out by injecting larger amounts of fluids containing a combination of a diluted local anaesthetic and adrenaline. It is used for plastic, cosmetic and dermatological procedures involving large areas of skin surgery, such as liposuction.

General anaesthesia usually begins when an anaesthetic is injected through a cannula inserted into a vein in the arm or the back of the hand. This quick and smooth way of sending someone to sleep is known as the "induction" of anaesthesia. It is also possible to induce anaesthesia with anaesthetic vapours, breathed through a mask. These volatile anaesthetics all share the property of being liquid at room temperature but vaporising easily.

To maintain unconsciousness, a mixture of oxygen and anaesthetic vapours are given to breathe; or, instead of anaesthetic vapours, a medicine can be administered by slow intravenous infusion to maintain unconsciousness. This element of anaesthesia is known as "maintenance". During this time, all vital parameters of the patient, such as heart rate, blood pressure, body temperature, the amount of oxygen in the blood and breathing, are monitored.

It is sometimes necessary to have muscle-relaxing medicines, to allow the surgeon to perform an operation by relaxing the body's natural muscle tone, which is present even when an individual is asleep. Muscle relaxants or so-called neuromuscular blocking agents (NMBAs) work by temporarily preventing the passage of impulses between a nerve and a muscle. They were introduced into clinical practice in 1942. The first known muscle relaxant was curare, already used in the 14th century by South American Indians on arrow tips to paralyse their prey.

When an NMBA is used, the breathing muscles are also effectively paralysed and the patient's breathing has to be controlled. To do this, a plastic tube is inserted into the windpipe and a machine known as ventilator inflates and deflates the lungs of the patient in an accurate and controlled rhythm.

A general anaesthetic can interfere with the body's natural cough reflex, which normally helps prevent foreign bodies entering the airways. When this protection is

affected, the contents of the stomach could seep back into the throat during an operation and be inhaled, causing damage to delicate lung tissues. This is one reason why people are not allowed to eat or drink before an operation.

Who needs anaesthesia?

It takes little imagination to realise that an unanaesthetised individual suffering from a surgical wound or another trauma experiences severe pain and undergoes emotional distress as well as maximum tension in skeletal muscles. The massive increase in tone of the autonomous sympathetic nerve leads to evasive action, to sweating, tachycardia, and hypertension. Such an experience creates a vivid and unpleasant memory of the event forever.

According to the latest available figures, the number of registered anaesthesiologists in Europe is estimated to be around 60,000; among others, 1,100 in the Czech Republic, 800 in Finland, 8,900 in France, 11,600 in Germany, 1,500 in Greece, 500 in Hungary, 9,500 in Italy, 350 in Latvia, 225 in Slovenia, 4,800 in Spain, 950 in Sweden and 3,000 in the UK. On the assumption that every anaesthesiologist performs on average between five to ten procedures of anaesthesia per working day, the estimated number of procedures involving anaesthesias carried out in Europe per year is some 90 million.

Present treatments

Anaesthesia often starts with pre-medication. The goal is to have the patient arrive in the operation theatre in a calm, relaxed frame of mind, while causing minimal interference with breathing and cardiovascular status. The most commonly used pre-medications are short-acting tranquillisers. In anticipation of surgical pain, non-steroidal anti-inflammatory drugs (NSAIDs) or other pain relieving substances can be administered pre-emptively. When a history of gastro-oesophageal reflux exists, H_2-blockers and antacids are given.

For 50 years, the most commonly used induction agents were rapidly acting water-soluble barbiturates. These medicines are still in use today and have a long record of safety and reliability.

More recently, a non-barbiturate intravenous medicine has displaced barbiturates, as it is associated with less post-operative nausea and vomiting (PONV) and a more rapid, clear-headed recovery. The compound can also be administered by slow intravenous infusion instead of anaesthetic vapours to maintain the anaesthesia. It is also in use for the sedation of intensive care unit patients and general sedation during diagnostic or surgical procedures.

Anaesthesia can also be induced by inhalation of a vapour. This is how all anaesthetics were once given and is still a common and useful technique in uncooperative patients today. Chlorofluorocarbons and ether compounds are the most commonly used preparations for this purpose.

One of the most significant changes in surgical practice during the past two decades has been the growth in day surgery. To outpatients undergoing surgery, regional anaesthesia, whether by epidural, spinal or peripheral routes, offers a number of advantages, as these techniques provide freedom from pain without sedation, earlier discharge and prolonged post-operative analgesia.

For local or regional anaesthesia, injectable solutions of anaesthetics, of the amino amide or the amino ester classes have been used since the mid 1950s. The reason for developing further compounds was the need for long-acting local anaesthetics with

advantageous safety profiles. The more recently introduced medicines have a particular molecular structure providing them with different characteristics, e.g. reduced lipid solubility, which leads to a slightly shorter duration of analgesia and a shorter block of motor nerves.

Solutions of newer compounds at different concentrations are indicated for epidural anaesthesia, for application into joints, for major and minor nerve blocks and for infiltration anaesthesia in adults and children. They are also recommended for spinal anaesthesia and for postoperative and labour pain management, via intermittent or continuous administration through an indwelling catheter. Research groups have also shown that epidural infusion of such medicines can provide adequate pain relief up to 72 hours after major abdominal surgery. The admixture of an opioid compound improves pain control in a dose-dependent manner.

In regional anaesthesia, several adjuvant medicines are used in combination with local anaesthetic agents leading to lower doses of each medication and maintaining analgesic efficacy while reducing the incidence and severity of unwanted effects.

Compounds with partial alpha2-agonist activity produce analgesia by activating the noradrenergic inhibitory system of the descending nerves and by inhibiting transmission from one nerve to another. Such molecules act synergistically with local anaesthetics because they open potassium channels, resulting in a state in which the cell is unresponsive to stimuli.

The N-methyl-d-aspartate (NMDA) receptor plays an important part in the development of neuropathic pain. When administered together with local anaesthetics, compounds which act as NMDA receptor antagonists have been shown to decrease the onset time of sensory block and to improve post-operative pain relief.

Compounds which inhibit the action of the neurotransmitter acetylcholine also known as anticholinergic medicines have been shown to retard the duration of sensory and motor blockade. They are also administered routinely in anticipation of a fibre-optic intubation.

Alpha-agonistic vasoconstrictor medicines are given to delay the systemic absorption of local anaesthetics. This causes increased neuronal uptake with improved depth and prolonged duration of local anaesthesia. Combining appropriate opioids with local anaesthetics reduces the dose requirements for both groups of medicines. The choice of opioid is made according to the onset and duration of action, and its propensity to produce unwanted effects.

Adequate post-operative analgesia is a prerequisite for successful day surgery. About 30-40 per cent of discharged patients may suffer moderate to severe pain during the first two days following surgery and post-operative pain is a common reason for delayed discharge. Oral analgesics such as pain-relieving medicines, weak opioids or NSAIDs are the mainstay of continuing pain control at home. It is important to encourage patients to take their medication pre-emptively and regularly, before the local anaesthetic effect has worn off.

For patients with intractable PONV after previous anaesthetics, 5HT3-receptor antagonists are given. In general they provide a good protection against nausea.

Under certain circumstances, a topical anaesthetic representing an emulsion of two local anaesthetics may be applied. The medicine is able to numb intact skin prior to needle insertion and superficial surgical procedures and is applied on intact skin, genital mucous membranes and leg ulcers. When applied on intact skin or leg ulcers, the cream is covered with an occlusive dressing, which facilitates absorption.

What's in the development pipeline?

Research on muscle-relaxing medicines focuses on onset times for NMBAs and reversal of the neuromuscular block (NMB). For more than two decades, attempts have been made to develop a fast-acting reversal agent which would enable patients under general anaesthesia to recover rapidly from total NMB. Current reversal agents can only be administered when muscle relaxation is starting to wear off naturally, delaying the reversing of the blockage up to 30 minutes.

Newer methods under development include "wrapping", or chemical encapsulation of the NMBA by exogenous host molecules, which reduce the amount of active NMBA molecules at the neuromuscular junction. Tests with certain encapsulating cyclodextrins have shown rapid and effective complex formation with steroidal NMBAs.

Meanwhile, a group of investigators has pursued this line of research and developed the first selective relaxant binding agent (SRBA) which achieves reversal from steroidal NMBA-induced block within three minutes after administration, enabling spontaneous breathing to recommence quicker. This novel SRBA has entered phase 3 clinical trials.

A new group of muscle relaxants with rapid onset and ultra-short duration, consisting of quaternary tropinyl diester compounds, are currently undergoing animal tests. Another neuromuscular blocking agent is being tested in phase 1/2 clinical studies. It has been shown to have an onset and duration of action similar to existing compounds, and without accumulation.

Intravenous anaesthesia still continues to evolve. There is better understanding of the distribution, the metabolism and the action of anaesthetics in the human body, which leads to the development of better and more accurate models. Scientists are developing a new intravenous hypnotic agent, which has some characteristics of existing compounds, but has a more rapid elimination time and does not accumulate after prolonged infusion. Due to its different pharmacokinetic profile, it may be a new option. Studies in man have still not been performed. Such progress will not only influence clinical practice of intravenous anaesthesia, but of all general anaesthesia.

Researchers also work on new delivery systems. Several groups are busy developing a patient-controlled transdermal system (PCTS) for needle-free delivery of an opioid anaesthetic using a special so-called iontophoretic technique. PCTS could be used for pain management after abdominal, orthopaedic and thoracic surgery.

The PCTS device is a self-contained credit card-sized patch that is applied to the arm or upper chest. It is pre-programmed to deliver several defined doses per hour on demand and can last for a whole day. The main benefits of the PCTS are considered to be ease of use and increased patient mobility. Other advantages may be reduced burden on nurses and healthcare resources, and lower risk of dosing errors.

Other interesting needle-free modes of delivery for opioids are intranasal administration and inhalation. Intranasal administration of opioids may be very useful in paedi-

atric patients. Other studies are ongoing with liposome-encapsulated opioids for long-term epidural analgesia. This administration would still need a needle and/or catheter.

The longer-term future

Refinements and advances in pharmacology, coupled with high-tech monitoring devices, will further contribute to safe and efficacious processes of anaesthesia. Another aspect represents data management. Information previously obtainable only from a cannula in a major blood vessel can now be derived using a skin-probe which sits comfortably around a finger.

Such methods reduce once complex procedures to something that is less costly and less time-consuming. Large anaesthetic machines have been developed that come with memory which permits trend analysis and paperless recording.

To find improved agents for hypnosis and sedation, three main strategies appear promising: (i) possible re-formulation and optimisation of existing molecules; (ii) development of precursor compounds of medicines already in use to reduce problems related to their administration and dosage, e.g. water solubility; and (iii) synthesis of new "soft molecules" that are rapidly broken down into inactive metabolites, leading to rapid recovery and less respiratory depression.

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