



Anaesthetics

Considering modern anaesthetics are, along with antibiotics, the cornerstone of modern medicine, why do so few investors understand how they work?



What is the current state of the anaesthetic market?

The market for anaesthetics is growing as the population ages and innovative surgeries become more popular.

Safer surgical techniques, like keyhole operations, are partly responsible, with their lower risk profiles increasing doctors' willingness to operate.

At the same time non essential surgery, from cochlear implants to laser eye correction and cosmetic operations are becoming widely available.

How do anaesthetics work?

The consensus is most anaesthetics interfere with ion channels. Complex systems that regulate the proportion of negatively charged electrons in living cells.

When neurotransmitters released by the brain bind to ligand-gated ion channels they open, allowing positively or negatively charged ions to flow through them and thus transmit an electrical signal.

Anaesthetics interfere with the normal function of neurotransmitters and ion channels and thus interfere with signal transduction by nerve cells and CNS neurons.

Channels which transport sodium (Na⁺), potassium (K⁺) or calcium (Ca²⁺) ions are among those most likely to be affected by local anaesthetics. General anaesthetics tend to act upon GABA receptors.

What are GABA receptors?

GABA receptors react to the neurotransmitter gamma-aminobutyric acid (GABA), a chemical messenger which regulates the central nervous system (CNS).

Many general anaesthetics enhance the activity of GABA at inhibitory neurons, stopping the CNS from receiving signals. The result is unconsciousness as the brain becomes unable to communicate with the body. GABA receptors are

separated into two distinct groups. Fast acting GABA_A receptors are ligand-gated ion channels, similar to those found in local anaesthetics. GABA_B receptors release G proteins that in turn affect the potassium ion channels in the CNS.

How do we define the effectiveness of an anaesthetic?

A common scale used in the measurement of general anaesthetics effectiveness is the BIS index. The index supplies a single number ranging from 0 to 100. A value of 100 being full consciousness and a range of between 40 and 60 being appropriate for general anaesthesia.

The BIS index is calculated from an electroencephalogram that detects electrical activity in the brain. It correlates with a patient's brain glucose metabolic rate.

The respiration rate of the patient and the level of hypotension, low blood pressure, are also monitored during anaesthesia.

Blood pressure tends to be defined by arterial pressure monitoring (APM). Respiration by the proportion of oxygen saturated haemoglobin in the patient's blood compared to its unsaturated variant.

Which are the most commonly used anaesthetics today?

The most popular local anaesthetics tend to be derivatives of cocaine and are often given the caine designation. Among these are the popular lidocaine, benzocaine and novacaine, all of which act primarily on sodium ion channels.

General anaesthetics, the realm of anaesthesiologists who decide on a complex mix of drugs on a case by case basis, are a lot more complex.

In the cocktail of drugs given to a patient during surgery, not all are anaesthetics. Neuromuscular blocking drugs (NMBDs) act as paralytics and are often prescribed for

Edison's Insight:

"Paion is preparing to file for approval of I.V. remimazolam for procedural sedation (US) and general anaesthesia (Japan). Remimazolam combines the best features of the leading I.V. anaesthetics propofol and midazolam, both of which were approved in the 1980s." Dr Dennis Hulme, Edison healthcare analyst.

surgery. So are painkillers, like fentanyl and sufentanil.

On top of these come the intravenous anaesthetics, commonly propofol, etomidate or barbiturates. Inhalation anaesthetics like Isoflurane, sevoflurane, or desfluran are also used in combination with nitrous oxide.

Then there is the entire class of pre surgery intravenous sedatives like benzodiazepines, diazepam, or lorazepam. These agents are often used to sedate the patient before surgery or to induce a light level of anaesthesia referred to as conscious sedation.

Which anaesthetic trials are moving towards approval?

Most clinical trials are iterating on current generation anaesthetics, especially the popular anaesthetic propofol.

It was the side effects of propofol that led Chemic Laboratories to develop Phaxan. The company carried out successful phase I trials in 2015 and is currently recruiting for a Phase III pilot study. AstraZeneca has also begun pre clinical testing of a propofol derivative in its Azd-3043.

[Paion will shortly file for approval of remimazolam, an ultra-short acting benzodiazepine sedative/anaesthetic which combines the rapid onset and recovery of propofol with improved safety due to the availability of the benzodiazepine reversal agent flumazenil.](#) Hypotension occurs less often with remimazolam than with propofol.

Primex Pharmaceuticals recently received EU approval for a midazolam derivative for use as an oral sedative in paediatric patients.

There have also been developments in post-operative recuperation, with Merck & Co's neuromuscular blockade antidote, Bridion, being approved in the US. The drug helps in the reversal of rocuronium- or vecuronium-induced paralysis.