Prof.dr. J.G. Bovill

Anaesthesia - A medical and pharmacological revolution

Universiteit Leiden

Anaesthesia - A medical and pharmacological revolution

Rede uitgesproken door

Prof.dr. J.G. Bovill

ter gelegenheid van zijn afscheid als hoogleraar in de Anesthesiologie aan de Universiteit Leiden op 19 januari 2007.

Universiteit Leiden

Ladies and Gentlemen,

During the past 150-200 years there have been many remarkable advances in medicine; the discovery of insulin, of penicillin, the virtual abolition of diseases such as smallpox, unlocking the secrets of DNA, to name but a few. But the greatest discovery of all, the one that has by far brought the most benefit to mankind, has to be the discovery of anaesthesia. Without anaesthesia few, if any, of the advances in surgery we take so much for granted today would have been possible. On average about 200 000 surgical operations are performed annually in the Netherlands, and worldwide that number is more that 10 million. Few of these would be possible without anaesthesia. Just consider what patients undergoing surgery in the days before anaesthesia suffered, and compare that with how it is today.

Until the advent of anaesthesia, a surgeon's prowess was measured not by morbidity or mortality (both were exceptionally high by today's standards) but typically by the time he took to operate. The most common operation, amputation of a limb, often could be performed in minutes. The French army surgeon, Larrey, recorded that during the Battle of Borodino, one of the bloodiest single-day battles of the Napoleonic Wars, he carried out 200 amputations on injured soldiers, all of course without anaesthesia.

During the first half of the 19th century the Lancet published weekly lists of operations at London teaching hospitals, and many interesting operations were reported in detail. In the year from October 1826 to September 1827 a total of 213 operations were reported, including lithotomies, strangulated hernias, amputations, mastectomies and excision of the mandible. All were performed without anaesthesia. A typical case was that of a young girl described as being of small stature and feeble habit who had a stone in her bladder. The operation commenced at 2 o'clock in the afternoon and finished at half past five. The pain was reported to be "as severe as can be conceived and altogether without remission". Can you even begin to imagine the suffering and agony endured by that poor girl and by many other wretched patients like her?

In the days before anaesthesia many patients were taken to the limits of their endurance, and beyond, without much hope of subsequent cure. Indeed surgery was often considered as the last resort, often not carried out until the patient was in extremis. The discovery of anaesthesia was to change this in a dramatic way.

The discovery of general anaesthesia is a remarkable story rich with tales of impropriety, noble ambition and inflated egos, a story that would not be out of place in a modern television soap drama. The first practitioner of modern general anaesthesia was Crawford Long in the early 1840s. Unfortunately he did not report his work until 1849, by which time William Morton's fame was already well established. In 1844, the Connecticut dentist Horace Wells started using nitrous oxide in his practice. However, when he went to demonstrate nitrous oxide anaesthesia to a larger audience at the Harvard Medical School in Boston, the affair was a fiasco. The patient complained of pain and Wells was hissed out of the room as a fraud. He gave up dentistry, became a chloroform addict, and travelled round the country with a troop of performing canaries. He committed suicide in 1848, aged 33 years.
A colleague of Horace Wells, William Morton, is generally credited with the introduction of ether anaesthesia. On the

morning of Friday 16th October 1846, in front of an invited audience in the Bullfinch operating theatre of the Massachusetts General Hospital in Boston, Morton administered ether to Edward Abbott for the excision of a tumour from his neck. This was the first successful public demonstration of anaesthesia with ether in man. A newspaper reporter was present in the audience, and thus the discovery of surgical anaesthesia soon spread. Ether anaesthesia was being used in Europe within 2 months of Morton's demonstration.
There followed several years of unedifying wrangling between Morton, Jackson, who had suggested using ether to Morton, and Wells as to who deserved credit for the discovery of anaesthesia, with Wells eventually committing suicide, Jackson dying in an insane asylum and Morton dying penniless at the age of 48. This was a sad backdrop to one of the most momentous discoveries of modern pharmacology. Morton was never officially recognized in his lifetime as the pioneer of ether anaesthesia and died a disappointed man. Time, however, was to vindicate his claim. The inscription on his tombstone, composed by Henry Bigelow, Professor of Pharmacology in Boston, reads: "Inventor and Revealer of Inhalation Anaesthesia: Before Whom, in All Time, Surgery was Agony; By Whom, Pain in Surgery was Averted and Annulled; Since Whom, Science has Control of Pain".

Within a few years of Morton's historical demonstration ether anaesthesia had become commonplace. Chloroform was introduced soon after ether, by the Scottish obstetrician James Young Simpson in 1847, and for about one hundred years ether and chloroform had no rivals. Indeed it was not until the introduction of halothane in 1956 that the popularity of ether waned. The first half of the twentieth century saw the introduction of a variety of volatile liquids and gases as anaesthetics. Most of these were explosive, toxic or both, and are now only of historical interest. Of the three pillars of early anaesthetic practice - nitrous oxide, chloroform and ether - only nitrous oxide remains in regular use, and even its popularity has waned considerably in recent years.

Today in anaesthesia we have some of the most potent and potentially dangerous drugs in medicine, drugs we use to take our patients on that journey from life towards death called anaesthesia, what the Edinburgh anaesthetist, John Gillies, very aptly described as "physiological trespass". As anaesthetists we take away our patients ability to breathe for themselves, remove their protective reflexes and, perhaps the greatest trespass of all, we render them unconscious; we take from them, albeit temporarily, that what is 'the person'. As an example of just how potent some of our drugs are, consider the opioid, sufentanil, widely used in anaesthesia as an analgesic. The little sachet of sugar we use with our coffee contains 5 g sugar. If instead of sugar the sachet contained sufentanil, I would need to dissolve its contents into 25 million litres water, the equivalent of 10 Olympic-size swimming pools, to achieve a concentration equivalent to that used clinically. Again if this sachet contained sufentanil there would be enough to render more than 20 000 people deeply unconscious and unable to breath. Without expert help from an anaesthesiologist they would all die within 3-4 minutes.

How do anaesthetics work?

The exceptionally wide range of compounds that possess anaesthetic activity has long intrigued anaesthesiologists and pharmacologists alike. Today, more than 160 years after the discovery of anaesthesia, research into the mechanisms of anaesthesia continues unabated. As an editor of the journal

Anesthesia and Analgesia, I deal with about 200 manuscripts submitted annually to my section, Anaesthetic Pharmacology. One quarter of these report research into some aspect of the mechanism of anaesthesia.

Theories about how anaesthetics work have been as diverse as the compounds themselves. An early suggestion, made in 1847 by von Bibra and Harless, was that anaesthetics dissolve and remove lipids in the brain.[1] Happily, this idea proved to be false or the anaesthetic revolution might have been short-lived. Around the turn of the 20th century two investigators, Hans Meyer and Charles Overton, independently observed that the anaesthetic potency of a wide range of compounds was highly correlated with their solubility in olive oil, i.e. their lipid solubility.[2,3] The Meyer-Overton relationship as it came to be known was taken to imply that anaesthesia was produced by perturbing the lipid structure of neuronal membranes.

Lipid theories of anaesthesia fell broadly into four different camps. Anaesthetics were said either to increase lipid fluidity, trigger lipid phase transitions, to change lipid bilayer dimensions or to alter membrane permeability. All of these had serious problems. For example, an increase in membrane disorder (increase fluidity) was proposed as a basis for anaesthesia. However, the changes produced by anaesthetics are extremely small and can be mimicked by a very small rise in temperature. Further, these theories cannot account for the fact that anaesthetic enantiomers usually have markedly different anaesthetic potencies, yet are equally effective in disrupting lipid bilayers. Finally the discovery of inhaled compounds with potencies that do not correlate with lipophilicity added a further nail in the coffin of lipid theories.[4] The seminal paper by Nick Franks and Bill Lieb from the Imperial College, London, in 1984, showing that a wide variety of anaesthetics could inhibit lipid-free preparations of the firefly luciferase enzyme by direct binding shifted the focus from lipids as targets of anaesthetic activity.[5] There is now a consensus that anaesthetics act by binding to protein, specifically ligand-gated ion channels such as the -aminobutyric acid type A (GABAA), the glycine receptor and the N-methyl-D-aspartate (NMDA) receptor.[6] Intravenous anaesthetics, with the exception of ketamine, and the volatile anaesthetics cause unconsciousness primarily via GABAA receptors in the brain containing beta3 subunits, whereas receptors containing beta2 subunit, which make up more than 50% of all GABAA receptors in the central nervous system, mediate sedation. Some of the most convincing evidence for the role of the GABAA receptor has come from molecular genetics. Mutation of a single critical amino acid within the receptor renders an animal resistant to the hypnotic and immobilizing effects of anaesthetics.[7] The anaesthetic gases nitrous oxide, xenon, and cyclopropane and the intravenous anaesthetic ketamine show little, if any, activity at GABAA or glycine receptors, but strongly inhibit the NMDA receptors and open TREK-1 potassium channels.

In addition to their central actions in producing unconsciousness, volatile anaesthetics produce immobility primarily by actions on the spinal cord,[8] but there does not seem to be a dominant molecular mechanism that accounts for their spinal actions. A recent study showed that GABAA and glycine receptors only contribute 30-40% to their depressant actions on spinal neurones.[9] Two-pore-domain potassium channels, which act as regulators of membrane excitability, have emerged recently as a target for the immobilizing actions of the volatile anaesthetics.[10] The two-pore channel TREK-1 is particularly sensitive to inhalational anaesthetics, and TREK-1-deficient mice are resistance to anaesthesia.

The theories of anaesthesia that concentrate on actions on ion channels and receptors do not provide a fully satisfactory explanation as to how the state of anaesthesia is actually generated. The potentiation of GABA receptors, for example, may be more accurately regarded as an action rather than a mechanism. The one defining feature anaesthetics have in common is that they induce a reversible loss of consciousness. Anaesthesia can therefore be considered as a state in which, as a result of reversible, drug-induced unconsciousness, the patient neither perceives nor recalls noxious stimuli.[11]

However, the question 'How does anaesthesia occur?' is unanswerable in the absence of a definition of consciousness.[12] The "dynamic core" of consciousness is thought to be coordinated synchronous activity mediated by electrical synapses known as gap junctions under the control of the thalamus.[13,14] A useful analogy is of a symphony orchestra. Individual musicians or groups of musicians each process musical information in a particular way. The final product is coherent music rather than meaningless noise because of the organization that is achieved by the conductor. Distinct neuronal subpopulations of the cortex (the individual musicians) are synchronized by resonance with a common rhythmical oscillator (the conductor), such as 40-Hz pacemaker neurons in the thalamus. Anaesthetics, by their actions on ion channels, hyperpolarize neurons in these thalamocortical loops, uncoupling and disrupting this coherent cortical oscillation. Thus anaesthesia may dependent less on depressive actions of anaesthetics but instead result from the disorganization or disintegration of cognitive processes that bind information together.[15]

Long-term effects of anaesthesia

As anaesthesiologists we are used to thinking on a short time scale. The drugs we use are among the fastest acting in clinical medicine, with onset and offset times measured in seconds or minutes. We often assume, therefore, that their effects dissipate quickly without long-term sequelae. However, in addition to their profound immediate effects, anaesthetics can have subtle but measurable long-term consequences, some beneficial, others potentially damaging. The discovery that volatile anaesthetics and some opioids protect the myocardium from ischaemia, a process known as anaesthetic preconditioning, is an obvious beneficial effect that can manifest for several days after the anaesthetic has been withdrawn. On the other hand volatile anaesthetics can cause profound and long-lasting changes in gene and protein expression in the brain that could adversely influence cerebral function far beyond the time of anaesthesia.[16,17] These changes may contribute to long-term effects such as memory alteration and cognitive dysfunction reported mainly by elderly patients after anaesthesia and surgery. Inhalational anaesthetics may enhance microaggregation of the amyloid peptide, resulting in long-lasting increases of the neurotoxic form of amyloid in the brain of susceptible subjects.[18] However, it must be emphasised that the most extensive clinical trials published to date have neither proven nor excluded a direct causal link between anaesthetics and cognitive impairment.

What may the future hold for anaesthetic pharmacology?

Can we expect many new and revolutionary drugs reaching clinical application in the future? I think the answer must be, unlikely. One reason is that, while the drugs available today may not be ideal, they are close enough to make it difficult to

improve upon them without very considerable effort and expense. Drug development is largely determined by commercial considerations. The likely return on pharmaceutical company investment in new anaesthetics is low compared with other areas of medicine, and the costs of failure extremely high. In recent years attempts to develop new water-soluble intravenous agents as alternatives to propofol have not been successful because of unwanted effects or slow recovery.

The success of remifentanil and its esterase metabolism has encouraged attempts at developing compounds with recovery profiles faster than propofol.[19,20] The question is, however, do we need or want such ultra-rapid recovery from anaesthesia – is it possible for an anaesthetic to wear off too quickly? At the other end of the spectrum is propofol phosphate, a water-soluble propofol prodrug which is enzymatically converted to propofol. Because it is a prodrug the onset is much slower than for propofol. Again, it is difficult to see the advantage of modifying a drug in such a way as to slow its onset of action when almost the entire focus of anaesthetic drug development has been to achieve the opposite effect.[21]

There is one drug currently undergoing phase III clinical trials, sugammadex, that does have the potential to revolutionise one aspect of anaesthesia, the management of neuromuscular block. Sugammadex is a modified -cyclodextrin that was engineered to specifically reverse the effects of aminosteroid muscle relaxants, specifically rocuronium. It rapidly removes rocuronium molecules from the plasma by encapsulating them within its inner structure, forming a water-soluble complex that is renally excreted.[22] Sugammadex is ineffective against succinylcholine and benzylisoquinolinium neuromuscular blockers because it cannot form inclusion complexes with these drugs. Sugammadex will facilitate the use of rocuronium for rapid sequence induction of anaesthesia by providing a faster onset-offset profile than that seen with succinylcholine. Why ever give succinylcholine if you can give high doses of rocuronium and then reverse it more quickly than the succinylcholine would wear off?

Genetics

Molecular biology and transgenic/knockout mouse biology has led in the last decades to very significant advances in anaesthetic pharmacology. Studies in mice, for example, suggest that there are likely to be genetic factors that influence anaesthetic requirements.[23] Understanding these genetic factors could help provide still safer anaesthesia. In the coming decade genomics, the study of genetic variants has the potential to answer some fundamental questions in anaesthetic pharmacology and in clinical anaesthesia. Increasingly genomic technology is providing valuable information about DNA variants responsible for the variability in patients' responses to drugs, in particular variability due to single-nucleotide polymorphism (SNP). The exploitation of genomics, by offering the opportunity to customize individual patients' drug therapy to their genotype, may prove tobe the next revolution in anaesthesia. The increasing speed of PCR analysis of genetic material - what 5 years ago took weeks now takes only hours - will make rapid preoperative screening of patients for genetic variation a reality. Whether this will be economically viable or clinically acceptable remains to be seen.

Ladies and Gentlemen,
The pharmacological basis of anaesthesia has changed dramatically during the 40 years I have worked in the speciality. When I started my training in 1967, pancuronium

had not yet been discovered, and tubocurarine and gallamine were the standard muscle relaxants. I was taught not only how to administer the relatively new anaesthetic, halothane, but also how to use ether and cyclopropane. Today we have much more sophisticated pharmacological tools at our disposable, many of which I have already mentioned in this lecture, and we have a much better understanding about their pharmacology than was ever dreamed about by our predecessors.

Anaesthesiologists have made very significant contributions not only to the pharmacology of drugs related specifically to anaesthesia, but also to the wider field of general pharmacology. One field where they have been especially productive is in PK/PD modelling. Indeed one of the early pioneers in this field was Chris Hull, professor of anaesthetics in Newcastle upon Tyne, and his initial ideas were subsequently expanded upon by Don Stanski and Lewis Sheiner from the departments of anaesthesiology and pharmacology at the University of Stanford in California. And our own department in Leiden has been among the world leaders in research and development in this and related fields of anaesthetic pharmacology during the past three decades. Despite all the remarkable advances of the past decades, there remain many unanswered questions, sufficient to keep those interested in this branch of pharmacology busy for many years to come. I am confident that, as in the past, the department of anaesthesiology of the LUMC will continue in the future to maintain its reputation as world leaders in research into anaesthetic pharmacology.

Ik heb gezegd.

Bibliography

1 Mashour GA. Integrating the science of consciousness and Anesthesia. Anesth Analg 2006; 103: 975-82.

2 Meyer HH. Theorie der Alkoholnarkose. Arch Exp Pathol Pharmakol 1899; 42: 109-18.

3 Overton E. Studien über die Narkose, Zugleich ein Beitrag zur allgemeinen Pharmakologie. Jena, Germany: Gustav Fischer, 1901: 1-195.

4 Koblin DD, Chortkoff BS, Laster MJ, et al. Polyhalogenated and perfluorinated compounds that disobey the Meyer-Overton hypothesis. Anesth Analg 1994; 79: 1043-8.

5 Franks NP, Lieb WR. Do general anaesthetics act by competitive binding to specific receptors? Nature 1984; 310, 599–601.

6 Rudolph U, Antkowiak B. Molecular and neuronal substrates for general anaesthetics. Nat Rev Neurosci 2004; 5: 709-20.

7 Franks NP. Molecular targets underlying general anaesthesia. Br J Pharmacol. 2006; 147 Suppl 1: S72-81.

8 Sonner JM, Antognini JF, Dutton RC. Inhaled anesthetics and immobility: mechanisms, mysteries, and minimum alveolar anesthetic concentration. Anesth Analg 2003; 97: 718-40.

9 Grasshoff C, Antkowiak B. Effects of isoflurane and enflurane on GABAA and glycine receptors contribute equally to the depressant actions on spinal ventral horn neurones in rats. Br J Anaesth 2006; 97: 687-94.

10 Franks NP, Honore E. The TREK K2P channels and their role in general anaesthesia and neuroprotection. Trends Pharmacol Sci. 2004; 25: 601-8.

11 Prys-Roberts C. Anaesthesia: a practical or impractical construct? Br J Anaesth 1987, 11, 1341-5.

12 Millar RA. Anaesthetic actions. Br J Anaesth 1975; 47: 335-49.

13 Di Garbo A, Panarese A, Chillemi S. Gap junctions promote synchronous activities in a network of inhibitory interneurons. Biosystems 2005; 79: 91-9.

14 Edelman GM. The remembered present: A biological theory of consciousness. New York: Basic Books, 1989

15 Mashour GA. Consciousness unbound: toward a paradigm of general anesthesia. Anesthesiology 2004; 100: 428-33.

16 Rampil IJ, Moller DH, Bell AH. Isoflurane modulates genomic expression in rat amygdala. Anesth Analg 2006; 102: 1431-8.

17 Pan JZ, Wei H, Hecker JG, et al. Rat brain DNA transcript profile of halothane and isoflurane exposure. Pharmacogen Genomics 2006; 16: 171-82.

18 Eckenhoff RG, Johansson JS, Wei HF, et al. Inhaled anesthetic enhancement of amyloid-beta oligomerization and cytotoxicity. Anesthesiology 2004; 101: 703-9.

19 Bennett DJ, Anderson A, Buchanan K, et al. Novel water soluble 2,6-dimethoxyphenyl ester derivatives with intravenous anaesthetic activity. Bioorg Med Chem Lett 2003; 13: 1971-5.

20 Egan TD, Shafer SL, Jenkins TE, Beattie DT, Jaw-Tsai SS. The pharmacokinetics and pharmacodynamics of THRX-918661, a novel sedative/hypnotic agent. Anesthesiology 2003; 99: A516

21 Sneyd JR. Recent advances in intravenous anaesthesia. Br J Anaesth 2004; 93: 725-36.

22 Sorgenfrei IF, Norrild K, Larsen PB, et al. Reversal of rocuronium-induced neuromuscular block by the selective relaxant binding agent sugammadex: a dose-finding and safety study. Anesthesiology 2006; 104: 667-74.

23 Mogil JS, Smith SB, O'Reilly MK, Plourde G: Influence of nociception and stress-induced antinociception on genetic variation in isoflurane anesthetic potency among mouse strains. Anesthesiology 2005; 103: 751-8.

In deze reeks verschijnen teksten van oraties en afscheidscolleges.

Meer informatie over Leidse hoogleraren:
Leidsewetenschappers.Leidenuniv.nl

Professor Dr. James G. Bovill, MD, PhD, FFARCSI, FRCA.

1960 - 1966	Medical School: The Queens University of Belfast, Northern Ireland
1972	PhD (Honours), Belfast. Title of thesis: "Pharmacological and clinical studies during ketamine anaesthesia"
1972 - 1977	Consultant Anaesthetist, Altnagelvin Hospital, Londonderry, Northern Ireland
1977 - 1985	Senior Lecturer, Department of Anaesthesia, University of Amsterdam
1985 - 2007	Professor of Anaesthesia, University of Leiden

The discovery of anaesthesia ranks as one of most far-reaching medical discoveries of the past 150-200 years. Without anaesthesia few, if any, of the advances in surgery we take so much for granted today would have been possible. The pharmacological basis of anaesthesia has changed dramatically during the 40 years I have worked in the speciality. Today we have some of the most potent and potentially dangerous drugs in medicine, drugs we use to take our patients on that journey from life towards death called anaesthesia. Anaesthesiologists have made very significant contributions not only to the pharmacology of drugs related specifically to anaesthesia, but also to the wider field of general pharmacology. Our department in Leiden has been among the world leaders in research and development in anaesthetic pharmacology during the past three decades. I am confident that it will continue to maintain this reputation well into the future.

Universiteit Leiden