CLINICAL REVIEW

ANAESTHESIA AND ANALGESIA: CONTRIBUTION TO SURGERY, PRESENT AND FUTURE

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Anaesthetists provide comprehensive perioperative medical care to patients undergoing surgical and diagnostic procedures, including postoperative intensive care when needed. They are involved in the management of perioperative acute pain as well as chronic pain. This manuscript considers some of the recent advances in modern anaesthesia and their contribution to surgery, from the basic mechanisms of action, to the delivery systems for general and regional anaesthesia, to the use of new drugs and new methods of monitoring. It assesses the resulting progress in acute and chronic pain services and looks at patient safety and risk management. It speculates on directions that may shape its future contributions to the management of the patient undergoing surgery.

Key words: anaesthesia, analgesia, contribution to surgery.

Abbreviations: AEP, auditory-evoked potentials; COX-2, cyclo-oxygenase 2; CSA, continuous spinal anaesthesia; CSE, combined spinal and epidural; EEG, electroencephalograph; GABA_A, gamma-aminobutyric acid-A; PONV, postoperative nausea and vomiting; TCI, target-controlled infusion; TOE, transoesophageal echocardiography.

INTRODUCTION

William Morton first publicly showed inhalational anaesthesia in 1846 with the use of diethyl ether. At the end of the nineteenth century, August Bier discovered that a class of drugs (local anaesthetics) could stop neural transmission. Since those humble beginnings, the application of anaesthesia and analgesia has advanced rapidly particularly in the past 50 years, making surgery much safer and allowing more sophisticated surgery to take place. The explosion hazard with anaesthetic gases was largely conquered with the development of the halogenated agents in the 1950s. Introduction of sevoflurane and desflurane during the last decades offered new perspectives to clinical anaesthesia, characterized by rapid onset of and recovery from anaesthesia.

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MECHANISMS OF ACTION

How do anaesthetics work? Despite the widespread presence of clinical anaesthesiology in surgical practice, the mechanisms by which diverse inhalational agents give general anaesthesia remain unknown. There are complex multisite, multilevel (molecular, subcellular, cellular, local microcircuit) interactions.1 Binding sites for general anaesthetics have been identified on several ion channels, including the nicotinic acetylcholine and gamma-aminobutyric acid-A (GABA_A) receptors.2 At clinically effective concentrations, a broad variety of general anaesthetics increase apparent GABA sensitivity and prolong inhibitory post-synaptic current mediated by GABA_A receptors. Advancement in molecular techniques has allowed greater understanding of the action of anaesthetic agents through the use of the ‘knock-in’ mice model.3 Conception of the mechanisms of action of many drugs routinely given in the operating room can be improved by the use of protein biomarker technology (such as protein microarray chips).4 A greater understanding of the mechanisms of anaesthesia will allow the development of more selective anaesthetics to achieve maximal clinical efficacy with minimal adverse effects.

REGIONAL ANAESTHESIA

Regional anaesthesia provides a substitute for general anaesthesia. Alternatively, it can be used to supplement general anaesthesia and provide postoperative analgesia. There is continuous development and refinement of regional anaesthetic techniques for various types of surgery, as well as for continuous regional analgesia.5 The quality of blockade and analgesia depends on accurate administration of local anaesthetic around the intended nerve structures. The use of nerve stimulation and insulated needles plus the development of ultrasound guidance (with an accurate depiction of the underlying anatomy) allows for precise needle placement.6 Ultrasound helps monitor the real-time
administration of local anaesthetics or analgesics.\textsuperscript{6} Ultrasound or even computed tomography-guided nerve block techniques are particularly useful when the underlying anatomy is complex.\textsuperscript{7–10}

Regional anaesthesia precludes the disadvantages seen with general anaesthesia (intubation, long recovery, postoperative nausea and vomiting (PONV), impaired oxygenation and depressed ventilation). It has been successfully used in the fields of obstetrics and in lower-extremity, cardiothoracic,\textsuperscript{11–13} breast \textsuperscript{14} and laparoscopic surgeries.\textsuperscript{15} The risks of anaesthetic and surgical complications are not any higher with regional anaesthesia than with general anaesthesia.\textsuperscript{14} However, it is not without its risks, including drug adverse effects, such as cardiovascular toxicity and neurotoxicity.

NEURAXIAL ANAESTHESIA/ANALGESIA

Combining the use of spinal and epidural techniques (CSE) has been gaining popularity over recent years.\textsuperscript{16} It provides rapid onset of anaesthesia without increasing the complications.\textsuperscript{17} Recent evidence shows that lower doses provide adequate analgesia while reducing the incidence of motor block.\textsuperscript{18,19} The spinal needle can be used as a guide for the advancement of epidural needle and prevent the epidural catheter from puncturing the dura.\textsuperscript{20} A lower incidence of unintentional 'wet tap' has been shown with this technique. Fetal/neonatal bradycardia is occasionally seen with CSE technique, but is not associated with increased rates of emergency caesarean sections.\textsuperscript{21}

In elderly and frail patients, in whom general or epidural anaesthesia may be too risky,\textsuperscript{22} continuous spinal anaesthesia (CSA) has recently regained popularity.\textsuperscript{23} CSA offers haemodynamic stability, as hypotension is less likely with CSA when compared with CSE.\textsuperscript{24,25} However, with any neuraxial administration, hypotension and haematoma formation remain concerns that deserve further attention and research.\textsuperscript{26} In neuraxial opioid anaesthesia, opioid physicochemical properties determine efficacy and safety. Intrathecal morphine, fentanyl and sufentanil are most commonly used.\textsuperscript{26} Other analgesic adjuvants include clonidine, dexmedetomidine and adrenaline, all working through \(\alpha\)-adrenergic receptors.\textsuperscript{26} Other agents in the early stages of investigation for neuraxial analgesia include neostigmine, ketamine, midazolam, adenosine and ziconotide.\textsuperscript{26}

NEW DRUGS

The quest for safety has long been a central part of the search for new anaesthetic/analgesic agents. Recent fields examined include the inert gases, the racemic mixtures (ketamine, ropivacaine, levbupivacaine), the coxibs and the cyclo-dextrins (Table 1).

Xenon

Of all the inert gases, only xenon has considerable anaesthetic properties under normobaric conditions.\textsuperscript{27} Xenon’s anaesthetic effect is possibly achieved through the non-competitive antagonism of \(N\)-methyl-D-aspartate receptor.\textsuperscript{28} It is highly lipid soluble with a very low blood/gas partition coefficient (0.14)\textsuperscript{28} that makes induction of and emergence from anaesthesia more rapid compared with other inhalational anaesthetic agents.\textsuperscript{27} Xenon has also been shown to possess cardioprotective and neuroprotective effects.\textsuperscript{29,30} It may prove beneficial in patients at high risk for neurological or cardiac damage during surgery. With the advancement in anaesthetic delivery systems, the cost–benefit of using xenon gas may in future justify its use in high-risk surgical patients.

Table 1. New drugs in clinical and research development in anaesthesia and in analgesia

<table>
<thead>
<tr>
<th>Clinical anaesthesia</th>
<th>New drugs</th>
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<tr>
<td>Racemic mixtures</td>
<td>Ketamine</td>
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<td>Adenosine-1 receptor agonists</td>
<td>Ropivacaine, Levbupivacaine</td>
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<td>Adenosine</td>
<td>Adenosine</td>
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<td>Inert gases</td>
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<td>Clinical analgesia</td>
<td>Xenon</td>
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<td>Cyclo-dextrins</td>
<td>Sugammadex</td>
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<td>Cyclo-oxygenase 2 inhibitors</td>
<td>Paracoxib</td>
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<td>Paracetamol</td>
<td>Etoricoxib</td>
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<td>Encapsulation matrices</td>
<td>Lumaricoxib</td>
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<td>Encapsulation matrices</td>
<td>L.v. paracetamol</td>
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<td>Endocannabinoids</td>
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<td>Nitric oxide-releasing paracetamol</td>
<td>Nitroxy-paracetamol</td>
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<td>Sodium channel blockers</td>
<td>Microspheres</td>
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<td>Selective potassium channel openers</td>
<td>CB2 cannabinoid receptor agonists</td>
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Ketamine

The availability of the stereoisomer of ketamine with its increased potency and lower incidence of psychomimetic adverse effects in equianalgesic doses (compared with the racemate) has increased its non-anaesthetic use as an adjunct analgesic.\textsuperscript{31}

Cyclo-oxygenase 2 inhibitors

Provided there are no contraindications, the use of the cyclo-oxygenase 2 (COX-2) inhibitors (the coxibs) preoperatively show clear benefits in terms of reduced postoperative pain, analgesic consumption and patient satisfaction.\textsuperscript{32} With their chronic use, peptic ulceration remains a reduced but significant adverse effect.\textsuperscript{33} Their lack of antiplatelet effects is important in patients on anticoagulants and in neuraxial blockade.\textsuperscript{33} COX-2 inhibitors may not produce bronchospasm (at analgesic doses), but may have similar adverse effects as general non-steroidal anti-inflammatory drugs on renal function.\textsuperscript{33} More trials are needed to determine their possible prothrombotic effect.

Local anaesthetics

With regard to local anaesthetics, the main focus has been on the development of the enantiomer-specific compounds, ropivacaine
and levobupivacaine. These provide similar efficacy to bupivacaine in peripheral and central nerve blockade, but with reduced risk of severe cardiotoxicity.\textsuperscript{34} Human studies have borne this out with levobupivacaine having fewer effects than bupivacaine on QRS prolongation, central nervous system symptoms and electrocardiograph excitation.\textsuperscript{34}

There has been no effective antidote for toxic doses of local anaesthetics. Recently, intralipid was shown to effectively reverse local anaesthetic toxicity in the animal model by hastening the loss of bupivacaine from cardiac tissue.\textsuperscript{35,36} Several human case reports using a bolus of 20\% intralipid followed by an intralipid infusion show promising efficacy.\textsuperscript{37,38} As other effective alternatives have not been found, the use of intralipid is worth considering in the management of local anaesthetic toxicity.\textsuperscript{39}

**Adenosine**

Adenosine-1 receptors play a role in antinociception in the spinal cord.\textsuperscript{40} The direct administration of adenosine reduces the amount of intraoperative volatile anaesthetic required and contributes to postoperative pain relief.\textsuperscript{51} An additional advantage of adenosine is its cardioprotective effect, making it an attractive future option as part of a balanced anaesthetic technique.\textsuperscript{42}

**Sugammadex**

Over the past decades, the search for short termination of action of non-depolarizing muscle relaxants has continued. Sugammadex (Org 25969) is a cyclodextrin.\textsuperscript{43} It forms a tight complex with aminosteroid-based non-depolarizing muscle relaxants (rocuronium, pancuronium, vecuronium). Animal and human studies show a rapid dose-dependent decrease in the concentration of free and bound non-depolarizing muscle relaxants.\textsuperscript{44,45} It is devoid of the cardiovascular side-effects associated with acetylcholinesterase inhibitors such as neostigmine. Continued research is required to clarify the role of sugammadex before this termination technique can replace the standard use of succinylcholine for short-term muscle relaxation.\textsuperscript{46}

**PRECONDITIONING**

Anaesthetic agents interact with the underlying pathological mechanisms of ischaemia reperfusion injury and protect the myocardium by a preconditioning mechanism.\textsuperscript{47} Volatile anaesthetics activate ATP-sensitive potassium channels (similar to ischaemia-induced preconditioning) thereby providing a cardioprotective effect.\textsuperscript{48-50} Preconditioning by volatile anaesthetics involves the activation of protein kinase C and mitogen-activated protein kinases. Transcription factors are activated, resulting in the induction of specific genes in the heart.\textsuperscript{51} The effects are most evident when the volatile agent is given throughout the entire procedure.\textsuperscript{52} The anaesthetist may therefore substantially influence the critical situation of ischaemia-reperfusion during surgery by choosing the appropriate anaesthetic agent.

**IMMUNE RESPONSE**

Knowledge of the host immune response to anaesthesia/analgesia and surgery needs to be integrated with the role of immunity in general in the progression of many of the chronic diseases.\textsuperscript{53} Volatile anaesthetics appear to suppress effector functions of both the innate and adaptive immunity and may facilitate the proliferation of tumour and certain neurodegenerative disease proteins.\textsuperscript{54} Local anaesthetics in turn have been shown to have potent anti-inflammatory properties.\textsuperscript{55} Some of the new synthetic opioids are devoid of immunosuppressive functions seen with morphine.\textsuperscript{56} There remains a need to examine how genetic diversity or acquired defects alter the immune response to tissue injury and infection.\textsuperscript{57} This will improve risk stratification and create possible pre-emptive therapies.

**TARGET-CONTROLLED INFUSIONS**

Progress in computing technology has allowed the development of target-controlled infusion (TCI) devices, with drugs delivered to achieve specific predicted target blood drug concentrations.\textsuperscript{58} A set of pharmacokinetic parameters is selected using computer simulation of a known infusion scheme. The selected model is incorporated into a computer-compatible infusion pump. Clinical trials with such systems provide appropriate target concentrations.\textsuperscript{58} TCI allows for the administration of small doses of short-acting anaesthetic drugs, such as opioids (remifentanil and fentanyl) and propofol.\textsuperscript{57} The use of TCI has been extended to include paediatric anaesthesia and sedation.

**MONITORING**

Continuous electronic physiological monitoring is core to the safe delivery of anaesthesia during surgery. Devices are being developed that can assess depth of sedation and anaesthesia, stroke volume, cardiac output, systemic vascular resistance, cerebral haemodynamic and metabolic variables.\textsuperscript{58} Some new ventilators are capable of monitoring lung mechanics and of automatically adjusting the ventilator settings to prevent ventilator associated lung injury or to aid weaning.\textsuperscript{58} New monitors include cerebral microdialysis to provide online analysis of tissue biochemistry.\textsuperscript{58} Novel imaging methods include positron emission tomography and functional magnetic resonance imaging.\textsuperscript{58}

**Non-invasive**

Non-invasive monitoring is increasingly being developed for use in anaesthesia. For example, the use of continuous cerebral oximetry protects against the risk of intraoperative cerebral ischaemia.\textsuperscript{59} Aortic blood flow can be determined with the use of non-invasive oesophageal echo-Doppler monitoring.\textsuperscript{60} Thoracic bioimpedance has been used as well to investigate haemodynamic changes.\textsuperscript{61}

**Depth of anaesthesia**

Over the past 10 years, depth of anaesthesia monitoring has emerged to aid anaesthetists by the development of processed electroencephalographic methods, such as bispectral index, mid-latency auditory-evoked potentials (AEP), and spectral entropy.\textsuperscript{62-64} These correlate well to clinical observed level of consciousness.\textsuperscript{62-64} These monitoring techniques improve the titration of both inhaled and i.v. anaesthetic agents by avoiding excessive anaesthesia and awareness, promoting faster emergence from anaesthesia, and managing conscious and deep sedation.\textsuperscript{65}

Auditory evoked potentials form an electrical manifestation of the brain response to an auditory stimulus. Mid-latency auditory evoked potentials as well as the coherent frequency of the auditory evoked potential are useful for monitoring depth of anaesthesia.\textsuperscript{66} It is possible to acquire and process raw electroencephalograph
(EEG) and frontal electromyogram signals and produce two spectral entropy-based indices (namely response entropy and state entropy). The M-Entropy module provides useful information on the cortical state of the patient during general anaesthesia. It acts as an indirect measure of the adequacy of analgesia. With the use of these new monitoring technologies, closed loop anaesthesia in the true sense has finally emerged.

CLOSED LOOP SYSTEMS

In closed or rebreathing circuits, fresh gas supply matches uptake. A lower fresh gas flow rate is therefore used. Humidity and temperature are conserved. In recent years, new computer-assisted control of gas delivery has dramatically improved the gas composition in closed circuits. Fast gas analysers and appropriate algorithms regulate the exact amount of volatile and fresh gas injected into the system. This minimizes the difference between the actual volatile gas concentration and vaporizer setting seen in the traditional closed loop low-flow system. Closed loop systems are able to reach and maintain a preset target. The computer program takes over the role of dose administration while the anaesthetist only enters the desirable level to be maintained. Closed-loop feedback allows the realization of ‘quantitative closed-system anaesthesia’ in the operating room.

To monitor muscle relaxation, a closed-loop muscle relaxation system can be formed by the connection of a muscle relaxation monitor (TOF Watch SX; Organon Schering-Plough, Kenilworth, NJ, USA) to a laptop computer. A controller algorithm programme then communicates with a syringe pump.

The linking of EEG monitoring to TCI for closed loop anaesthesia remains a research tool. Nunes et al. recently developed a fuzzy relational classifier that uses AEP features to classify the depth of anaesthesia. It is a machine-learning model based on fuzzy clustering and fuzzy relationship that somehow mimics human thinking.

AIRWAY MANAGEMENT

In addition to fibre-optic airway devices, supraglottic airway devices have revolutionized airway management in anaesthesia over the last 15 years. Examples include the classic, intubating and ProSeal (LMA North America, Inc., San Diego, CA, USA) laryngeal mask airway, the Combitube (Tyco-Kendall, Mansfield, MA, USA), the laryngeal tube, and laryngeal tube sonda mark I and II. The Glidescope (Verathon Inc., Bothell, WA, USA) is a new videolaryngoscope. It has a digital camera incorporated in its blade that displays a view of the vocal cords on a monitor. This allows visual placement of a tracheal tube. Improved designs include the paediatric ProSeal—Laryngeal mask airway and the Micrscuff (Kimberly-Clark Health Care, Roswell, GA, USA) paediatric endotracheal tube.

TRANSOESOPHAGEAL ECHOCARDIOGRAPHY

Transoesophageal echocardiography (TOE) has proved useful to anaesthetists in guiding therapy in haemodynamically unstable patients in the operating room and intensive care unit. TOE provides real-time dynamic information about the anatomy and physiology of the whole heart. It is of value in the management of patients undergoing procedures (including cardiac valvular repair), in surgery for endocarditis and in surgery of the thoracic aorta. It contributes useful information in a wide range of cardiac pathologies.

POSTOPERATIVE NAUSEA AND VOMITING

Postoperative nausea and vomiting remains problematic to every anaesthetist and surgeon. There is strong evidence that volatile anaesthetics (like opioids) are emetogenic with no meaningful differences between halothane, enflurane, isoflurane, sevoflurane and desflurane. Various anti-emetic strategies are associated with a reduction rate of approximately 25–30%. However, when a propofol technique is substituted for a volatile anaesthetic technique, the risk for PONV is reduced by approximately one-fifth. Interestingly, all anti-emetics (dexamethasone, droperidol and ondansetron) work independently, so a combination benefit can be derived. If PONV is a serious problem, general anaesthesia can be avoided by using a regional, opioid-free anaesthetic instead.

PATIENT SAFETY AND RISK PREVENTION

Anaesthesia was one of the first medical professions to treat patient safety as an independent problem. Preoperative evaluation carried out by anaesthetists aims primarily to estimate the risk of perioperative complications and to create opportunities to optimize the patient’s condition before surgery. Patient safety is primarily determined by quality of systems of care. There has been steady progress in anaesthesia safety because of the development of performance standards, an increase in error reporting, integration of information technology and improved safety systems. This has led to a 10-fold reduction in anaesthesia-related deaths over the past few decades, despite the increase in more challenging operations and the number of older and sicker patients. According to the Institute of Medicine’s 1999 report entitled To err is human, ‘... anaesthesia has successfully reduced anaesthesia mortality rates from two deaths per 10 000 anaesthetics administered, to one death per 200 000 to 300 000 anaesthetics administered’.

ADVANCES IN ANAESTHETIC-LED ACUTE PAIN SERVICES

The occurrence of postoperative pain remains problematic. In 2003, Apfelbaum found that 80% of patients still experience postoperative pain. Acute pain management services first entered clinical practice in the late 1980s. Anaesthetists have played an important role in this interdisciplinary approach to managing postoperative pain. Evidence of earlier discharge with the use of an acute pain service has been shown. Inadequately relieved postoperative pain leads to complications, such as deep vein thrombosis, lung infections and myocardial ischaemia, which may extend hospital stay. New analgesics and analgesic drug delivery systems are being developed. For example, the use of i.v. paracetamol avoids absorption and bioavailability variability and produces more predictable plasma paracetamol concentrations than the oral route. Nitroxyparacetamol (or nitroacetaminophen) is a new, potent nitric oxide-releasing version of paracetamol that has analgesic and anti-inflammatory properties. It should prove a useful analgesic for patients with paracetamol-induced liver damage. The anticonvulsant gabapentin has shown analgesic efficacy in several surgical procedures, particularly to reduce post-surgical neuropathic pain.

Advances in neurobiology and clinical medicine have established that the fetus and newborn may experience acute and even

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CHRONIC PAIN SERVICES

Anaesthetists often lead the medical specialist team involved in chronic pain management. In some patients, the hyperphenomena (primary and secondary hyperalgesia, mechanical allodynia) that are normal in the first days or weeks after surgery, do not regress, but persist beyond the usual course of an acute surgical injury. Acute persistent pain soon becomes chronic pain. Chronic pain demands a greater use of the health resources and has proved to be a major public health burden. Unrelieved postoperative pain and severe perioperative pain have been shown to be risk factors for the development of chronic pain. This emphasizes the need for effective perioperative pain management.

There has been tremendous progress in pain medicine (particularly interventional pain medicine) enhancing the contribution of the anaesthetist in managing post-surgical pain syndromes. Advances in neuroimaging techniques (positron emission tomography, functional magnetic resonance imaging) help identify brain mechanisms for more effective treatments for chronic pain. Rapid progress is being made towards the development of gene therapy. For example, viral vector-mediated gene transfer achieves focal production of short-lived analgesic peptides (or growth factors). This prevents disc degeneration and promotes chondrocyte and disc regeneration. This should soon have clinical application for both the anaesthetist and the surgeon involved in pain medicine.

New techniques in neuromodulation have promoted existing teamwork between the anaesthetist and the surgeon. The reduced demand for health-care resources by patients receiving neuromodulation (peripheral nerve stimulation, spinal cord stimulation) suggests substantial long-term economic benefits in patients with neuropathic pain and chronic refractory angina receiving these. Anaesthetists may aid the orthopaedic surgeons by the radiofrequency heating of annular tears, leading to an improvement in the pain of internal disc disruption. In addition they can help out by carrying out kyphoplasty, a minimally invasive technique that appears to improve both pain and function in patients with vertebral fractures because of osteoporosis.

New analgesic delivery systems are being developed for anaesthetists to assist surgeons in perioperative pain relief. Progress is being made in the ability to combine local anaesthetics with liposomes (bupivacaine, morphine) and polymer microspheres. Systems designed to transiently circumvent the barrier function of the stratum corneum, using iontophoresis and sonophoresis, will expand the range of drugs that can be delivered transdermally. New analgesic drugs are being studied as well to treat post-surgical neuropathic pain. These include pregabalin, a novel alpha (2)-delta ligand, ziconotide, a drug derived from a snail toxin that works on the calcium channels and endocannabinoids, that naturally suppress nociceptive neurotransmission.

FUTURE FOCUS

How could anaesthetists aid the patient undergoing surgery in future? Software could be developed to integrate patient monitoring and response to anaesthesia and surgery, resulting in an early warning system that alerts the anaesthetist to impending disaster. New techniques like nanotechnology could enable precise timing and site of drug delivery. Delivery systems under development could deposit drugs at the desired site of action, control their rate of release, and to neutralize overdose, bind and eliminate previously given drugs. Emerging applications could be developed by pharmacogenomic research as well. In post-surgical pain medicine, Anaesthetists could make use of new molecular targets, such as sodium channel blockers (Nav 1.3, Nav 1.7 and Nav 1.8); potassium channel openers in sensory neurons; N-type calcium channels (Cav 2.2) blockers; P2X4 and P2X7 receptor antagonists in microglia; vanilloid receptor-1 antagonists; and the cannabinoid-2 receptor agonists.

CONCLUSION

Anaesthesia historically grew out of surgery and the two disciplines continue to work in close partnership. Anaesthetists and surgeons form an integrated team linking together to do their utmost for the good of the patient. This relationship plays an important role in enabling patient safety and avoiding errors. Of importance to the surgeon are the recent developments in anaesthetic technology and the advances in drugs and monitoring methods. As illustrated in this manuscript, these developments have accelerated and altered the work carried out in the operating room. In addition, evidence is just beginning to emerge on the relation between specific anaesthetics and anaesthetic techniques and long-term clinical outcomes after surgery.

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