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General Anaesthesia

Practical Recommendations and Recent Advances

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Abstract

General anaesthesia has become, thanks to recently developed drugs, monitoring devices and delivery systems, a very well tolerated method of making the great surgical opportunities of the last few years available to all ages of patient. With a balanced and rational use of drug profiles, general anaesthesia allows even

frail and very ill patients a margin of tolerability inconceivable just a few years ago. For the vast majority of patients, the risk from the general anaesthetic technique is so small it can be considered negligible.

However, the majority of general anaesthetic drugs are both highly potent and very toxic, with many of the volatile agents still having a therapeutic ratio of about 4 : 1. The anaesthetic staff have to continually upgrade their skills and knowledge to ensure that harm does not result. It is, however, reasonable to offer some practical guidelines from the current literature on when to choose a general anaesthetic technique, either alone or with a regional local anaesthetic method, and when to avoid loss of consciousness.

The complications expected from the use of general anaesthesia are reviewed, and the basis for these complications investigated. The currently available drugs and their place in anaesthetic practice are also assessed.

Recent developments in the area of total intravenous anaesthesia and monitoring for potential awareness using bispectral analysis suggest that this technique should now be included in the choice of anaesthetic. Recommendations are made on both the selection of the technique, and the appropriate agents for a given group of patients.

General anaesthesia and its usage vary across national boundaries in response to such wide influences as social acceptability, availability of skilled anaesthetic staff and financial constraints. General anaesthesia can be defined as the use of one or more potent drugs to achieve a state where there is loss of consciousness, immobility and analgesia in a patient undergoing surgery. It may be combined with 'local anaesthesia' where nerve conduction blockade limits the transmission of painful stimuli from the site of surgery to the central nervous system. However, the key features of general anaesthesia are loss of consciousness and a reduction in autonomic control systems. This state is reversible and largely predictable across patients. Recent developments in the drugs available for use in general anaesthesia, and more detailed trials on the role of anaesthetic technique on outcome, have made it timely to review the status of 'general anaesthesia' again[1] and to try to offer some practical recommendations on its current role in anaesthesia as a whole.

General anaesthesia often has unfounded but frightening associations in the minds of patients and many doctors; of awareness during surgery, of failure to recover completely and of loss of autonomy. Indeed, for many years, there has been widespread publicity surrounding cases of painful awareness during surgery, of postoperative mental failure and of death. There have been many studies within the anaesthetic literature trying to explain the causes for some of these complications, yet there is very little consensus from the results.[2] There are firmly held beliefs on the merits or otherwise of general anaesthesia, especially in the elderly, and these must be reviewed briefly to place general anaesthesia in its appropriate context. Data from France demonstrate that there is an excess of cognitive decline in surgical patients compared with an age-matched group,[3] and a European multicentre trial has confirmed that general anaesthesia is associated with more cognitive changes with increasing age of the patient.[4]

There are several other factors that influence the choice of agent or technique, and these include the detailed assessment of the functional status of the patient, the expected surgical procedure and finally, the location of the procedure. The implementation of these recommendations depends on the availability of sufficient resources to allow the anaesthetist a real choice between techniques and drugs. Worldwide, this may limit the utility of this review depending on the country concerned.

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1. Specific Complications of General Anaesthesia

1.1 Immediate Problems

The solution to more than 200 years of research into how general anaesthetics work finally appears to be closer to resolution. It seems that anaesthesia is probably achieved by drug effects at both voltage-gated and ligand-gated ion channels; intracellular sites such as protein kinase C and phospholipase A2.[5]

Regardless of the route of administration chosen, general anaesthetic drugs have to cross the blood-brain barrier to achieve their effect. The most common routes are intravenous and inhalational, and only rarely are the enteral or transcutaneous routes chosen. The intravenous and inhalational routes depend on the maintenance of an adequate cardiac output to deliver the drugs to the brain. Any reduction in either peripheral circulation or pulmonary function, respectively will limit the efficiency of drug delivery.

Following administration of these drugs they may pass through several organ systems before reaching the systemic circulation and hence the brain. All the organs involved may be affected by, or alter, the drugs. For intravenously administered drugs, the first active organ encountered will be the lung where significant first pass metabolism may occur. For volatile anaesthetics, and the intravenous drugs after the pulmonary circulation, the myocardium is the next critical organ. Depression of either conduction or contractility will reduce cardiac output, and transfer of drug to the brain. The resulting fall in cardiac output will also affect perfusion-dependent organ systems such as the kidneys, brain and liver. These effects occur on the initial administration of the drugs before they reach the brainstem where they may also cause autonomic depression. Once in the systemic circulation they may also have direct effects on the peripheral vasculature leading to alterations in muscular tone and further changes in organ perfusion.

The changes that occur once the drugs pass the blood-brain barrier depend on several factors. One of the first is a change from the awake behavioural control from cortical and other higher centres of the autonomic nervous system to a purely brain stem reflex control. There is inevitably a period of instability as the transition occurs, and there may be profound alterations in the essential control of cardiac output leading to hypotension, or of the airway muscles leading to airway collapse and obstruction. Uncoupling of brain stem reflexes may occur, for instance, a reduction in the baroreceptor/hypotension responses may lead to profound hypotension and bradycardia. Changes in the ventilation/perfusion (V/Q) matching will lead to alterations in pulmonary shunt with the risk of hypoxia.

Other immediate problems may relate to true hypersensitivity to the anaesthetic agents used (table I). This is much more common with the intravenous anaesthetic agents than the volatile anaesthetics, but is still rare. It is, however, a potentially lethal reaction and must influence the choice of technique.

There are also patients who have genetic abnormalities which make them much more sensitive to the otherwise normal action of these ‘anaesthetic drugs’. Two of the most common disorders are the reduction in plasma cholinesterase activity seen in patients sensitive to suxamethonium, the depolarising neuromuscular blocking agent, and the sensitivity of some patients’ intracellular calcium

Table I. Specific complications of general anaesthesia

Immediate problems
Administration of drugs
Loss of autonomic control:
cardiovascular
respiratory
immunological
Hypersensitivity to general anaesthesia
Awareness
Genetic hazards
Delayed problems
Metabolic derangements
Pharmacokinetic factors
Cognitive deficits
Unexpected death

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metabolism to general anaesthetics leading to an uncoupling of sarcolemmal function. This causes excessive release of calcium and a reduced uptake leading to hypermetabolic activity. This, in turn, leads to the syndrome of malignant hyperpyrexia and may be caused[6] by the substitution of cysteine for arginine 614 (Arg614Cys) in the human ryanodine receptor gene.

1.2 Delayed Problems

These occur following general anaesthesia, and are usually the result of an interaction between the drugs and the patient (table I). They may occur within hours of the patient leaving the recovery area, or after several days (or nights). Some of these problems appear to have a cause beyond simple drug interaction. Metabolic consequences of anaesthesia, such as the effect of certain volatile anaesthetic agents (halothane and chloroform) on the liver, have been known for years.[7-9] The extent and severity of damage is related to both the route of metabolism of the volatile agent and the reductive state of the hepatic enzymes during anaesthesia. The effects are cumulative, and repetitive exposure greatly increases the risk of a life-threatening hepatitis.

Changes in cardiac output may affect the redistribution of potent drugs such as the nondepolarising neuromuscular blocking agents, and occasionally result in prolonged paralysis despite apparently adequate reversal with antagonist drugs.[10] A reduction in cardiac output will slow down the delivery of volatile anaesthetic agents back into the pulmonary circulation and prolong the process of their subsequent elimination.

There has been concern that general anaesthesia is specifically associated with prolonged, if not permanent, cognitive changes, especially in the elderly. These effects have been debated since the early 1950s[11] and have been the subject of several studies, both small and large.[4] The fact that cognitive deficit following surgery exists, and is quite common, is now proven beyond doubt, but the causes remain as inscrutable as ever. The largest studies to date have failed to show any greater adverse effect of general anaesthesia, compared with local anaesthesia for instance, on outcome.[2] Smaller studies have been reported where the advantages between general and local anaesthesia were more clear cut, but there have been unjustified recommendations[12,13] made on the basis of these small samples of the population. Duration of exposure to anaesthesia has also been identified in some studies[14] as a predictor of a poorer outcome in the elderly. However, whether this is caused by the complexity of the surgery or the duration of anaesthesia is unclear.

These data, while interesting, are now largely historical for many reasons. Cohorts of the elderly have changed over time with increasingly better social conditions and improved healthcare, reducing the burden of damage caused by infections and malnutrition. Furthermore, advances have been made over the last 5 years in both the monitoring of and better tolerability of novel anaesthetic agents. Integrated anaesthetic machines where both the patient's physiological variables, and the anaesthetic machine functions, can be monitored in real time now allow a degree of control which was impossible just a few years ago. This, combined with advances in the theoretical basis of drug delivery, its modelling and computer software development, has provided anaesthetists with the opportunity to rationalise their choices not only between local or general anaesthesia, but also between different techniques of general anaesthesia. International drives to participate in continuing medical education has allowed these developments to spread more rapidly, and yet safely, into routine practice rather than remaining as specialised techniques only available in teaching hospitals.

There are clinical areas of anaesthetic practice where there are clear indications of benefit of one system of anaesthesia over another, such as the current use of regional local anaesthesia[15] in operative obstetric care instead of the more traditional general anaesthesia-based care. Equally, there are specific areas of surgery where the reverse is true, and where general anaesthesia offers the only real technique to allow successful surgery, such as lap-

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aroscopic upper abdominal surgery. The increasing use of day care surgery, where a rapid return to normal function is essential, has also focused attention on the role of anaesthetic techniques in the recovery of these patients. Increasingly complex surgery is being undertaken, on increasingly less fit patients and the burden of their care is resting with primary care physicians. The use of short-acting anaesthetic drugs, with rapid elimination kinetics, has greatly improved the likelihood of surgical success.

2. Specific Anaesthetic Drugs

2.1 Volatile Anaesthetic Agents

Two volatile anaesthetic agents have been made available since the last review 5 years ago:[1] desflurane and sevoflurane. These agents are much more lipid insoluble than the previously available agents in common usage (isoflurane, enflurane and halothane) and, therefore, produce a predictably more rapid induction and recovery. They have individual properties that have marked influences on their clinical usage.

2.1.1 Desflurane

Desflurane (difluoromethyl 1-fluoro-2,2,2-trifluoroethyl ether) is both nonflammable, and noncorrosive to metals. It is stable in carbon dioxide (CO_2) absorbers and is only of limited solubility in rubber and plastics. Desflurane has a vapour pressure of 664mm Hg at 20°C, and a special heated vaporiser is used to generate pure desflurane at twice atmospheric pressure. This vapour is then diluted with the anaesthetic carrier gases for clinical use.

General Characteristics

The substitution of the chlorine for fluorine in isoflurane to produce desflurane dramatically reduces the blood/gas partition coefficient to 0.45, which is nearly as low as nitrous oxide, but it also greatly reduces the potency of desflurane. Its minimum alveolar concentration (MAC), a guide to relative potency, is 6.0%. Unfortunately, inhaled concentrations greater than the MAC can cause irritation, with coughing, breath holding or laryngospasm, and this makes induction of anaesthesia with desflurane very difficult in practice. If induction is achieved intravenously, introduction of desflurane is then rapidly effective because of the fast equilibration between inspired alveolar concentrations and those in the brain; 80% equilibration occurring within 5 minutes. Recovery, even after prolonged administration, is equally rapid.[16]

The physiological effects of desflurane are similar to isoflurane, and blood pressure decreases in a dose-dependent manner, while cardiac output is preserved. These changes are largely caused by a fall in systemic resistance unless excessive concentrations are administered. There are transient increases in catecholamine levels[17] with rapid alterations in desflurane concentrations but these do not appear to cause clinically significant problems, and there is conflicting evidence regarding the existence of clinically significant coronary ischaemia.[17,18]

Desflurane is a potent ventilatory depressant. The CO_2 concentration increases and at a concentration above 10 to 12%, apnoea is likely. It has similar effects to other halogenated anaesthetics on the cerebral circulation, and autoregulation is maintained, but there is an increase in intracranial pressure. Splanchnic blood flow is maintained which preserves hepatic and renal function. There is very little metabolism of desflurane, with only 0.002% of the inhaled dose being recovered as metabolic breakdown products. Importantly, there is evidence that desflurane should not be used in circle systems where the CO_2 absorbent has dried out.[19] There have been cases where carboxyhaemoglobin formation has occurred in this situation. Drying, however, is only likely if the system is left with fresh gas flowing for several hours.

The anaesthetic disadvantages of the airway irritability caused by desflurane are offset by the rapid recovery profile even after very prolonged anaesthesia. The very low solubility in fatty tissue and the minimal metabolism make this an ideal agent for prolonged surgery. It has also been extensively used in day care surgery because of its rapid equilibration on induction, and the benefit of a

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rapid recovery profile, although this may be an expensive method of anaesthesia because of the high gas flows commonly used in such short procedures. The high cost of this agent can be limited if it is used in either a closed or very low flow circle system.

2.1.2 Sevoflurane

Sevoflurane (fluoromethyl 2,2,2-trifluoro-1-trifluoromethyl ethyl ether) is similar to desflurane in that it is also nonflammable. It also has a low blood/gas partition coefficient (0.65) but is much more potent than desflurane with a MAC of 2%. It has a saturated vapour pressure of 160mm Hg, and can be administered from a standard plenum type vaporiser.

Its physiological effects are similar to those of desflurane with the exception of a greater degree of cardiovascular stability with increasing concentration. It is not associated with the catecholamine release seen with sudden changes in desflurane concentrations, and theoretically may be considered to be preferable in the high-risk noncardiac surgical patient with severe ischaemic heart disease. It has the same profile of action on the cerebrovascular system, and again causes increases in intracranial pressure above 0.5 MAC.

It is metabolised more extensively than desflurane (3% of the inspired vapour is metabolised largely to hexafluoroisopropanol) and there has been concern about the level of fluoride produced. However, several studies[20,21] have shown little clinical significance concerning fluoride production. Degradation of sevoflurane by CO_2 absorbents, especially baralyme, with the production of 'compound A' [CF2 = C(CF3)-O-CH2F] has also caused concern.[22] Compound A is an olefin, and these compounds have caused nephrotoxicity in rats. Production of compound A may be increased during low flow (<1 L/min fresh gas flow) because of an increase in the temperature of the CO_2 absorbent, and during very prolonged administration (6 to 10 hours). It is likely that it is the cumulative dose that is important, and the use of the 'area under the curve' method of calculating this may be help ful. Currently, these concerns appear to be largely theoretical, and clinical data confirming adverse effects are lacking.

The clinical use of sevoflurane has become based on its excellent induction properties, largely as a result of its combination of high potency, low blood/gas solubility and lack of airway irritability. It is widely used for gaseous induction in both children and adults (where it has been used for single breath induction). The much more limited metabolism and current lack of evidence of a hepatotoxic reaction have led many anaesthetists to prefer its use for paediatric gaseous induction rather than halothane. It is, however, much more expensive, and with the wasteful high fresh gas flows necessary for a gas induction, it cannot be considered as the ideal gaseous induction agent. It has the same benefits for day care surgery as desflurane, and may prove to be as acceptable an anaesthetic agent in this population.

The progressive difference between the recovery profiles of sevoflurane and desflurane with increasing duration of anaesthesia would suggest that for short procedures (between 30 and 60 minutes), the clinical advantages lie with sevoflurane. However, once the procedure extends for more than 1 hour, desflurane maintains its recovery profile far better than sevoflurane, and should be the agent of choice.

2.1.3 Other Gaseous Anaesthetic Agents

Nitrous Oxide

This 'grandfather' of anaesthetic agents has been used since 1844, but its place as a routine adjuvant to general anaesthesia is becoming challenged. Its presence on anaesthetic machines demands the expensive provision of alarms and control systems to prevent the delivery of hypoxic gas mixtures, and yet it is the least potent of anaesthetics. It has limited effects on organ systems, partly because of its low rate of metabolism (0.004%), and partly because it is always given with other, more potent agents since its use as a sole anaesthetic agent is highly likely to result in awareness. Prolonged administration causes inactivation of methionine synthase, a cyanocobalamin (vitamin B12)-dependent enzyme. Inactivation of this en-

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zyme causes interference with DNA synthesis and prevents the bone marrow production of both leucocytes and red blood cells. Megaloblastic changes in the bone marrow can follow oxidation of the cobalt atom in cyanocobalamin by nitrous oxide, and it has caused neuropathy in some experimental animals, although the clinical significance of these findings is unclear.[23]

Nitrous oxide will continue to be used as an analgesic agent for dental surgery and in obstetric practice but the routine administration of nitrous oxide for general anaesthesia is unlikely to extend far into the next millennium. It is used currently to limit the use of more potent volatile anaesthetic agents and to try to avoid the risk of awareness. Better availability of devices that can reliably indicate the lack of awareness will overcome many of these concerns, and bispectral analysis may prove to be one such device.

Xenon

Xenon has been investigated as an alternative gaseous inhalation anaesthetic over the years, but while it has been proved to be effective, and only moderately expensive, it has too few exceptional characteristics to commend as an alternative for routine anaesthetic use.

2.2 Intravenous Induction and Maintenance Anaesthetic Agents

Until recently, the agents available for the intravenous induction of anaesthesia were either unsuitable, or difficult to use for the maintenance of anaesthesia. The introduction of propofol and the concurrent developments in the understanding of the action, kinetics and dynamics of intravenous anaesthetic drugs have allowed the generation of delivery systems for propofol, both for induction of anaesthesia and its maintenance. The place of total intravenous anaesthesia is becoming established, as are the specific indications for its preference over inhalational methods. Clinical trials with other new induction agents have also reduced the indications for barbiturate-based anaesthetic agents, such as thiopental (thiopentone), because the profile of adverse effects are much better with these newer agents, which often have a shorter duration of action.

2.2.1 Propofol

Propofol became clinically available in the UK in 1989 and has been released worldwide since then. It has been extensively studied clinically and its advantages are well documented. It provides a pleasant gradual induction for the patient, with a lack of airway irritability. It has a very short duration of action and results in a very rapid recovery.[24] Propofol is potent and has anti-emetic effects as well as anticonvulsant properties. It does, however, have a series of adverse effects that offset these advantages. These include both cardiovascular and respiratory depression, as well as pain on intravenous injection. The cardiovascular effects include marked bradycardia, and even asystole has been recorded. However, the initial data on the cardiovascular effects of induction of anaesthesia with bolus injections of propofol were biased against the elderly patient, partly because of a poor study design (rapid repetition of bolus dosages against a clinical indicator of loss of consciousness with no regard to arm-brain circulation times).[25]

More recent work supports a fall in systemic vascular resistance and cardiac output, with a resetting of the baroreceptor reflex, leading to significant hypotension, especially in patients with hypovolaemia. Slow rates of propofol infusion do not cause such obvious changes, although there are still significant falls in arterial blood pressure and systemic vascular resistance.[26]

The ventilatory effects of propofol include a significant fall in tidal and minute volumes, leading to apnoea when an excessive dosage (>2.5 mg/kg) is administered. There are also reductions in both the hypercarbic and hypoxic ventilatory response curves.[27,28] Propofol, at clinically used plasma concentrations, has an inhibitory action on drug metabolism. Although the increasing use of propofol as a sedative agent in intensive care settings has many positive characteristics (such as rapid recovery), this needs to be balanced against its excitatory activity seen in very ill children, where it may contribute to an increased mortality.

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2.2.2 Other Novel Intravenous Induction Agents

Other newer induction agents have also been investigated in clinical trials, including corticosteroids such as eltanolone, (5β-pregnanolone), and the α_2-adrenergic agonists such as dexmedetomidine, clonidine and azepexole.[29,30] Specific enantiomers of existing anaesthetic drugs, such as ketamine, have also been assessed.[31]

Corticosteroid-Based Anaesthetic Drugs

Progesterone and some of its derivatives have potent hypnotic activity because they are converted to 3α-OH,5α-pregnan-20-one in the brain. However, there are currently no well tolerated and effective agents that are likely to become clinically available from this family of drugs.[32]

α_2-Adrenergic Agonists

The antihypertensive drug clonidine reduces the dose requirement for anaesthetic and analgesic drugs[33] because of stimulation of central α_2-adrenergic receptors. Oral clonidine administered 90 minutes before surgery, results in sedation and a reduction in anxiety. It lowers the anaesthetic dosage requirements of both inhalational anaesthetics and opiates.

Further research has demonstrated that α_2-adrenergic agonists not only markedly reduce the dose requirements of anaesthetic agents but also are capable of inducing anaesthesia themselves. Rapid intravenous infusion of these agents is associated with bradycardia and hypertension but these effects can be avoided by either a slow intravenous infusion or by intramuscular injection. These findings have led to a series of highly selective, centrally acting α_2-adrenergic agonists being developed; 2 such drugs are dexmedetomidine and azepexole. Dexmedetomidine has been used in veterinary practice for some time but has marked motor activity on induction. It has been used clinically for pre-medication (as an injection of dexmedetomidine 2.5 μg/kg) where it reduces the induction dose of anaesthetic drugs, but it also increases the incidence of hypotension.[34] The drug has also been investigated as an intravenous anaesthetic agent but, as yet, has not demonstrated any clear advantages over current intravenous induction agents.

2.2.3 Ketamine

The enantiomers of ketamine have been investigated for individual advantages over the racemic mixture. Whilst differences in potency and recovery can be identified, there are few clinical advantages over the original racemic ketamine. They are all associated with an equal incidence of dreaming on emergence from anaesthesia, although the dysphoric effects were less with the S-isomer.

2.3 Neuromuscular Junction Blocking Agents (Muscle Relaxants)

There have been great changes in the availability of muscle relaxants over the last 5 years. Some of these drugs have broad clinical applications whereas others are of limited use. There is still the need for a very rapidly acting nondepolarising muscle relaxant, capable of rapid reversal and with no context sensitive half-life. While several drugs have moved some way towards that goal, there is still an uncontested place for the depolarising neuromuscular blocking drug suxamethonium chloride (suxamethonium). There is the possibility that rapacuronium bromide (rapacurium; Org-9487), currently under clinical investigation, may come close to meeting these requirements.

2.3.1 Specific Drugs

Mivacurium Chloride

Mivacurium chloride (mivacurium) is a modified benzylisoquinoline similar to atracurium besilate (atracurium), with an onset time of 2 to 3 minutes and a brief duration of action. This short duration of action is useful for many operative procedures. Mivacurium provides 10 to 18 minutes of profound relaxation and, because it is broken down by plasma cholinesterase activity, there is also rapid spontaneous recovery. However, there have been reports of a prolongation of action in patients who have abnormalities of these enzymes. Mivacurium can cause histamine release, especially if injected rapidly, and it requires a high dose to produce sat-

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isfactory intubating conditions within a short time scale (less than 2 minutes).

Cisatracurium Besilate

Refinement of the enantiomers of the benzylisoquinoline atracurium has led to the commercial availability of cisatracurium besilate (cisatracurium). Clinically, this has provided a cardio-stable, nonhistamine releasing, nondepolarising muscle relaxant that also undergoes both plasma esterase metabolism and Hofmann degradation. When incubated in human plasma[35] cisatracurium degrades to form laudanosine, and significant amounts of the monoquaternary alcohol that also slowly degrades to laudanosine. The characteristics of cisatracurium include a slow onset of relaxation and an intermediate duration of action. It is highly potent and, because of its routes of metabolism, can be administered for prolonged periods with little change in its context sensitive (the context sensitive half-life describes the effect of accumulation of a drug within other tissues, such as fat, over time which then increases the time that the effect site concentration returns to sub-therapeutic levels). The more tissue deposition over time, the longer the recovery period will be) half-life. The drug is of great value in patients with poor cardiac output states, or if organic damage of the liver or kidneys is likely to be present. It does not cause histamine release from mast cells and this leads to marked cardiovascular stability compared with other relaxants.

Rocuronium Bromide

The development of a relatively potent but rapidly acting nondepolarising relaxant that can replace suxamethonium has been awaited for some time and rocuronium bromide (rocuronium), a steroid-based relaxant, was hoped to be that agent. It has a rapid onset of action, with times to safe intubation of under 1 minute [especially in high dose ranges (1.2 mg/kg)], but with a prolonged duration of action of up to 90 minutes. It is partly metabolised by the liver and has a longer, but unpredictable, half-life in patients with cirrhosis. This is because of a larger volume of distribution and lower clearance. Rocuronium is cardio-stable, with little ganglionic activity but its place as an alternative to suxamethonium is restricted by its duration of activity.

Other New Relaxants

Pipecuronium bromide, a steroid-based relaxant, and doxacurium chloride, a benzylisoquinoline-based relaxant, are 2 other nondepolarising neuromuscular blocking agents that have minimal effects on the cardiovascular system. However, their long duration of action (up to 120 minutes) and variable onset time of 2 to 6 minutes limit their usefulness. The development of both cisatracurium and rocuronium make the clinical need for either pipecuronium or doxacurium questionable.

2.4 Opioid Analgesic Drugs

Bolus injections or infusions of opiates to provide analgesia and an anaesthetic-sparing effect have been used for many years, but the introduction of a novel opioid with esterase breakdown (remifentanil), has revolutionised the tolerability of this technique. Remifentanil has an ester structure and is very rapidly metabolised by blood and tissue esterases. It is highly potent, and clinical studies have shown only a very limited accumulation of the drug.[36] This very flat context-sensitive half-life allows remifentanil to be used for procedures of varying length while maintaining a predictable recovery profile.

Remifentanil is cardio-stable and has limited toxicity in high dosage. The lack of accumulation of remifentanil, even after prolonged administration at high concentrations,[36] allows the clinician to rapidly titrate the concentration of analgesic to the surgical stimulus rather than trying to increase the concentration of the anaesthetic agent itself. This flexibility in being able to swiftly reduce the concentration as well as to raise it, is the major advantage of remifentanil. The use of this agent with the intravenous anaesthetic propofol has been demonstrated to reduce the propofol concentration necessary for anaesthesia by up to 75%.[37]

Remifentanil is not without its drawbacks however, and if given prior to the induction of anaesthesia is associated with marked muscle ri-

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gidity and apnoea. These effects are both rapid and severe, and can occur in the recovery or post-anaesthetic care unit if the cannula used for its administration has not been flushed through per-operatively. Extreme caution is necessary to avoid these complications. There are currently no data on whether the rigidity caused by remifentanil leads to rhabdomyolysis, but delaying the drug administration until after induction of anaesthesia should avoid most of the potential problems.

2.4.1 Trefentanil

Trefentanil is a new opioid with a very short duration of action. Compared with alfentanil it has a larger volume of distribution but a large clearance leading to very similar half-lives. It is likely to be of little clinical benefit given the current usage of alfentanil and the major advantages of remifentanil.

3. Patient Influences

3.1 Population Features

3.1.1 Age-Related Factors: The Extremes of Age

Old age

The change in the distribution of age groups within populations has an immediate effect on surgical patients presenting to hospital. The progressive increase in elderly patients to over 75 years of age, and the very elderly to over 85 years of age, must dictate, to a degree, the basis for the proposed recommendations. Younger adults are both more robust from a physiological and functional reserve point of view, and are more tolerant of adverse events during surgery and anaesthesia. The changes in the distribution of ages across the surgical population will continue for the foreseeable future, and need to be incorporated in the planning for rational use of general anaesthesia. Increasing the use of drugs that have limited lipid solubility and, therefore, little accumulation and a rapid reversal of effect, is one way to provide the elderly patient with as well tolerated an anaesthetic as their younger counterparts.

Paediatric Patients

Many of the novel drugs are, as yet, unlicensed for use in children, and particular care has to be taken, especially with vagotonic drugs (e.g. propofol), which may cause marked bradycardia even in conventional doses.

3.2 Specific Disease States

3.2.1 Cardiovascular disease

Cardiovascular disease may be congenital or acquired. There are now increasing numbers of patients with corrected congenital disease presenting for surgery in their second decade with severely disordered cardiovascular function. However, this area of anaesthetic practice is beyond the scope of the current review.

Acquired cardiovascular disease is the most common coexisting condition in the western population presenting for surgery. In this situation, the anaesthetic technique needs to maintain the precarious balance between oxygen delivery to the myocardium and to the rest of the patient's organs. Haemodynamic stability on induction of anaesthesia can be achieved with balanced techniques utilising high concentrations of potent opioids and induction agents with minimal cardio-depressant activity. The stress of laryngoscopy is also usually prevented by this technique.

Maintenance requires a balance between the changing surgical stresses and painful stimuli, and the autonomic depression caused by both volatile and intravenous anaesthetic agents. Recovery from anaesthesia has been haphazard until recently, with simple cessation of drug delivery and a reliance on the elimination of these potent drugs being the usual technique. Patients with very compromised cardiac function were admitted to intensive care units to maintain stability whilst stresses such as re-warming had occurred and good analgesia was established. Recently, managed recovery has become possible with the gradual titration of depth of anaesthesia and analgesia to allow a controlled and smooth emergence from anaesthesia.

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3.2.2 Pulmonary Disease

Severe pulmonary disease reduces the ability of the patient to maintain adequate ventilation and gas exchange, which can be compromised during general anaesthesia. Poor matching between ventilation and perfusion, especially with the very lipid insoluble volatile agents, desflurane and sevoflurane, will lead to slow and possibly inadequate induction of anaesthesia. There will be a greater 'fixed' gradient between the partial pressure of the volatile anaesthetic in the alveoli and that in the blood. The monitoring of inspired gas concentrations may lead to a false sense of security and an aware patient. This gradient will also affect the reverse process and lead to a slow and incomplete recovery from anaesthesia.

3.2.3 Hepatic Dysfunction

The majority of the older anaesthetic agents relied on hepatic elimination and renal clearance. Increasingly, anaesthetic drugs are being developed that avoid direct hepatic degradation (e.g. mivacurium and cisatracurium), or are so minimally metabolised that they pose little challenge to hepatic function (e.g. desflurane).

4. Specific General Anaesthetic Techniques

4.1 Total Intravenous Anaesthesia

Until the introduction of propofol, attempts to provide anaesthesia entirely by intravenous agents had failed for a variety of reasons, such as dysfunction of steroid production following etomidate infusions. There also remained the need to support ventilation, and this generally included nitrous oxide/oxygen gas mixtures. The incorporation of a volatile anaesthetic agent then seemed overwhelmingly logical. Importantly, there is an increased incidence of awareness using total intravenous anaesthesia (TIVA), especially when combined with muscle relaxation, and this limited its development for many years. Infusion schemes to allow practising anaesthetists to maintain anaesthetic levels of drugs without overdose have been published, but the great variability across age groups has limited their utility. Computerised control of the infusions was, until recently, little better.

The concurrent investigation of the pharmacology of propofol with developments in computer-controlled infusions to target concentrations at the effect site, led to the practical realisation of 'target controlled infusions' (TCI).[38,39] The only available system at present is based on propofol and uses pre-filled, computer tagged 50ml syringes containing 1 or 2% propofol. The apparent simplicity of use is comparable to the familiar control of vapour concentration with the volatile anaesthetic agents: the anaesthetist dials up the required effect site concentration and the pump either delivers more propofol to achieve this level or stops until the effect site concentration falls. Unfortunately, the longer the infusion is in progress the more prolonged recovery becomes because of accumulation in the tissues.

The latest version of the TCI software includes a 'time to wake' indication that calculates the impact this accumulation has on the free plasma drug concentration at the effect site. Analysis of the performance of this system is still preliminary, but suggests that it is failsafe by providing greater than predicted concentrations at the effect site.[40,41] This feature may encourage greater use of TIVA. The final link in the TIVA chain, that of closed loop control, is limited by the lack of a reliable indicator of anaesthetic depth.

Following the clinical release of remifentanil, it has become possible to provide TIVA for very prolonged procedures with almost the same recovery profile as that of short (<30 minute) procedures. This is because of a marked propofol sparing effect of remifentanil. Anaesthesia can be maintained with a 50 to 75% reduction of the propofol concentration. This dramatically reduces the time to wake, and allows profound anaesthesia to be maintained until the completion of surgery. Caution is necessary when the 2 agents are administered to patients with a high resting vagal tone, or where the surgery can be predicted to cause vagal stimulation, because these drugs are both vagotonic making significant bradycardia a likely risk. The addition of

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cisatracurium infusions provides muscle relaxation, where appropriate, again without the risks of accumulation.

4.2 Volatile Anaesthesia Utilising Circle Systems

The development of integrated anaesthetic machines, with comprehensive monitoring and the ability to limit flows of fresh gases, has allowed the clinical use of expensive new volatile agents without vastly increasing the direct costs of each procedure.[42] The cardiovascular stability of the recent volatile anaesthetics and the reliability of safely monitored ventilation, allow the provision of stable conditions in patients of all ages. While the choices between controlled and spontaneous ventilation, and between differing methods of airway protection are still subject to debate, they can be made more easily with the sophisticated anaesthetic equipment now available.

5. Recommendations

It is worth restating that surgery and anaesthesia have long term complications in a certain proportion of patients, and that this proportion increases with advancing age.[4] The severity of these complications and the long term consequences are not related specifically to general anaesthesia. The avoidance or otherwise of one anaesthetic technique for another has to be based on the judgement of the anaesthetist on clinical grounds.

5.1 Choice of Technique

The debate concerning the choice between specific anaesthetic techniques is highly polarised and controversial, and is largely beyond the scope of this review. However, there are a few areas where there is some consensus. When the patient is healthy, and there are no surgical reasons for making a particular decision, the choice should depend on the patient's preferences. There is no current outcome data on whether this choice influences recovery of the patient or surgical success. Again, if the patient is healthy, there is little to choose between the general anaesthetic techniques. Convenience, practical skills and departmental policy may dictate which induction and maintenance regimens are followed.

There are some indications regarding when a specific technique holds more benefit, although the outcome data are hardly robust. These areas relate to patients with significant coexisting disease which may be exacerbated by a particular general anaesthetic technique, or where the disease process may interfere with the safe and predictable administration of the anaesthetic. The choice between a general and a local anaesthetic technique will also be influenced by the surgical procedure and the expertise and experience of the surgeon and anaesthetist.

5.2 Indications for Specific Techniques

5.2.1 Patient Influences

Ischaemic Heart Disease

Patients with severe ischaemic heart disease are often unable to meet the criteria for an entirely regional local anaesthesia because they are too vulnerable to the rapid changes in pre- and after-load that occur unpredictably following intrathecal local anaesthesia. To offer any advantage, a general anaesthetic technique has to be capable of maintaining myocardial contractility and vascular tone, and avoiding significant changes in blood pressure and heart rate, whatever the anaesthetic or surgical stimulation. The use of a balanced technique utilising a potent opioid and an intravenous induction agent, with a cardio-stable muscle relaxant to permit endotracheal intubation, followed by maintenance with a volatile anaesthetic in an air/oxygen mixture will meet these criteria. This is especially so if some of the surgical stimulation can be modified by local anaesthetic techniques. The choice of agent is dependent on the likely duration of the surgery and the need, or otherwise, for a rapid, complete return to full wakefulness.

The most physiologically stable induction agents, ketamine and etomidate, have undesirable cognitive or movement problems and are becoming less frequently used. Propofol, in appropriate dose

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ranges (1 to 1.5 mg/kg), is replacing these drugs because of physiological stability especially when combined with a potent opioid. Until recently, the choice lay between alfentanil and fentanyl as the per-operative analgesic. Where rapid protection against the stress of laryngoscopy was most important, or in short procedures, alfentanil has the better therapeutic profile because the time to peak action following intravenous injection is approximately 1 minute, with a fall to below respiratory depressant levels in a further 5 minutes. With fentanyl, there is a slower (5 minutes) time to peak action, and it takes 20 minutes for levels to fall below those causing respiratory depression. The drug is therefore suited to more prolonged surgery. Remifentanil has the potential to replace both drugs because its very rapid action equals that of alfentanil, and its potency is greater than that of fentanyl. Infusions can be titrated against surgical stresses even over prolonged periods, equalling the effectiveness of fentanyl, but with an unequalled rapidity of recovery.

Neuromuscular blocking drugs were used according to whether there was a need for rapidly securing the airway in the risk of gastric regurgitation and acid aspiration. The place of suxamethonium in this context has remained unchallenged, although rocuronium in high doses can provide a poorer alternative, for instance, if there is hypersensitivity to suxamethonium. Where the risk of aspiration is minimal, there is a choice between bolus doses of rocuronium or cisatracurium for intermediate duration procedures, or infusions of cisatracurium for prolonged cases. Mivacurium is suitable for short procedures where there is also the need for muscle relaxation.

Maintenance of anaesthesia can be either with volatile or intravenous anaesthetic agents. Of the current volatile anaesthetic agents, the 2 recent drugs (sevoflurane and desflurane) would appear to be equally balanced regarding risks and benefits. Sevoflurane is the more cardio-stable agent, especially with rapidly changing concentrations, but it is limited to low gas flow rates of more than 1 L/min (<2 L/min in North America) to avoid the risks of compound A formation. Desflurane has the problem of catecholamine release with rapid alterations of concentration, but can be used at low fresh gas flow (200 ml/min) and has a faster recovery time following prolonged surgery. In real terms, there is still little clinical need to alter the use of older volatile agents such as isoflurane; apart from the possible cost savings[42] that can be made if the highly lipid insoluble agents are used with rapid reductions down to basal gas flows in a circle system.

Recovery from anaesthesia in the patient with ischaemic heart disease has to be managed, and maintenance of anaesthesia or sedation until the return of normal physiology is essential. This can be easily achieved with the latest drugs (such as infusions of remifentanil and propofol) and may prove to be their greatest indication. The only problem at present is the need to titrate pain relief before terminating the remifentanil infusion.

Pulmonary Disease

Patients with pulmonary disease provide a different series of problems, and the fundamental issue is whether to use a disordered organ system for drug delivery and elimination if there is an alternative. For many years the use of volatile anaesthetic agents has been the only practical alternative to regional local anaesthetic techniques. However, the improvements in the mechanics of TIVA have altered this situation.

Controlled ventilation with in-line monitoring of inspired and expired gases only gives an approximation of the delivery of anaesthetic into the systemic circulation, and the risks of patient awareness increase. Using supra-maximal breaths or sighs during ventilation may relieve earlier concerns regarding the reduction in pulmonary function, especially where the predicted falls in functional residual capacity may precipitate respiratory failure postoperatively. These supra-maximal breaths reexpand the collapsed alveoli seen immediately on induction of anaesthesia. Such findings support the use of controlled ventilation as a well tolerated and positive method of preserving pulmonary function. TIVA with propofol, remifentanil and cisatracurium (and an anticholinergic agent) may provide

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well tolerated, controlled and reliable anaesthesia when volatile agents would be unpredictable. Their use also allows gradual awakening and assessment of respiratory function on recovery.

The concern of an increased risk of unidentified awareness during total intravenous anaesthesia may be addressed as methods of measuring brain activity (such as the bispectral analysis technique) are validated and become affordable routine monitors.

6. Conclusion

There have been several new anaesthetic drugs released over the last 5 years, and these, combined with advances in delivery and monitoring systems, have brought about changes in the practice of anaesthesia. Certain techniques, such as TIVA, are becoming more commonly used as the appropriate training and skills develop, and the indications for its usage become clearer. It is now possible to provide stable, profound anaesthesia for very long procedures with rapid return to wakefulness. Monitoring and integrated anaesthetic machines allow the anaesthetist to clearly measure the delivery of anaesthetic to the patient, and observe their recovery following surgery. Direct monitoring of unconsciousness remains out of reach; until it is achieved, closed loop control of anaesthesia continues to elude us.

General anaesthesia remains incredibly well tolerated for the majority of patients, and because of the newer agents this tolerability margin is extending into patient groups who would have been classed as very high risk only a few years ago.

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