

Controversies in Anaesthesia-Designer Drugs

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Abstract

In the past, the discovery of new drugs often occurred by chance. Over recent years, an increasing knowledge of the mode of drug action and receptor sites has improved our ability to design new drugs. While the mode of action of volatile and intravenous anaesthetic agents remains unclear, neuromuscular blocking agents and opioids have undergone considerable development and design. Drugs are being tailored to produce fewer side effects and to improve desirable properties. As a result, the introduction of new drugs has helped to improve techniques in anaesthesia.

The development of remifentanyl is an example of this which is discussed. The application of modern technology with target controlled infusions (TCI) for the administration of remifentanyl represents further advancement in techniques which may become available to anaesthetists in the future.

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Key words: Context-sensitive half-time, Receptor site, Remifentanyl, Structure relationship, Target-controlled infusion

Introduction

The discovery of new drugs in anaesthesia previously relied completely on chance. Chemical compounds produced by pharmaceutical companies were screened by a variety of different teams looking for effects of interest to their own area. If they were fortunate, then a compound which had valuable therapeutic properties could be discovered. All drugs used in anaesthesia were discovered in this way until a few decades ago. In the 1970s, several 100 compounds would be tested each year by a large pharmaceutical company but this increased to about 10,000 each year by the mid 1980s and to that number each week by the mid 1990s.

Halothane was tested for use as an insecticide but the insects were found to recover after their apparent demise from this agent which was then developed to be one of the most successful inhalational anaesthetics. Around the 1950s and 1960s, receptors for naturally occurring compounds were discovered and led to the development of newer compounds which could be designed specifically to target a particular receptor.

Neuromuscular Blockers

As an example of this approach, acetylcholine (Ach) has a quaternary ammonium component which was found to be essential for its neuromuscular activity

(Fig. 1). Any neuromuscular blocker (NMB) has to be structurally similar to Ach to achieve its effect. For example, suxamethonium is made of two molecules of Ach linked together (Fig. 2). It was introduced in 1952 and was the first synthetic neuromuscular blocker. It revolutionised anaesthetic practice by providing an intense block of short duration. When new NMBs such as pancuronium were designed, Ach-like groups were deliberately incorporated into molecule to enable the molecule to bind to the receptor site and produce neuromuscular blockade. The structure was also designed to allow metabolism by the liver via deacetylation of the acetoxy group. This was an improvement on *d*-tubocurarine which is not metabolised. When it was first used in clinical practice, pancuronium was also found to have less cardiovascular and autonomic side effects than *d*-tubocurarine.¹

Further research led to consideration of the optimum interonium distance between the two quaternary nitrogen atoms. A distance of 12-14 Angstroms was thought to be necessary for NM blocking activity. A distance of 8 Angstroms appeared to promote the development of ganglion-blocking activity in steroid molecules² and this adverse effect was minimised by developing NMBs with interonium distances of 10 (pancuronium), 12 (vecuronium), and 21 Angstroms (atracurium and

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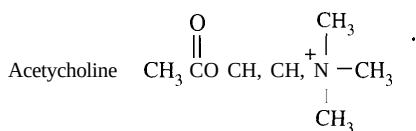


Fig. 1. The structure of acetylcholine demonstrating its quaternary ammonium component.

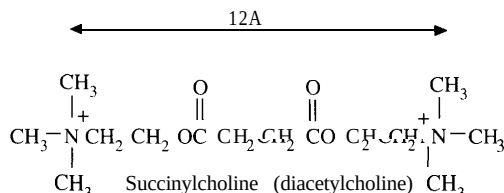


Fig. 2. The structure of suxamethonium (diacetylcholine) showing the interonium distance between the two quaternary nitrogen atoms.

mivacurium). The development of atracurium and vecuronium further improved clinical practice by producing blockade of intermediate duration of action with more rapid onset, recovery and minimal dependence on renal elimination. As a steroidal NM blocker, vecuronium had been modified from pancuronium by removing the quaternizing methyl group in the 2-position, thus markedly reducing the antimuscarinic (vagolytic) effects which are associated with pancuronium.³ Atracurium is degraded by the chemical process of Hofmann elimination, with as much as 90% being destroyed in the plasma, and therefore can be used in the presence of renal and hepatic failure.⁴ Mivacurium, a benzylisoquinolinium diester, was introduced to clinical practice in the early 1990s. It produces blockade which lasts approximately between twice as long as suxamethonium and half as long as the intermediate-acting nondepolarisers.⁵ It is rapidly hydrolysed by plasma cholinesterase, which is facilitated by the orientation of the ether oxygen of the carboxyl group toward the quaternary nitrogen atom.⁶ Mivacurium and atracurium, both benzylisoquinoline substances, cause histamine release. This effect is reduced in atracurium by the electron withdrawing effect of the carboxyl groups in the chain and by altered stereochemistry (cis orientation) at the 1-to 2 positions in the benzylisoquinoline structure.⁷ Cis-atracurium which contains only the R-cis, R'-cis isomer of atracurium has recently been developed and introduced. It is about three to four times more potent than atracurium and does not cause histamine release.⁸

The progressive development of NMBs is demonstrated in Table I. An increased understanding of the structure-relationship for NMBs led to improved and more specific drugs which had fewer adverse effects. This class of drugs therefore represents a successful application of drug design in anaesthesia.

Anaesthetic Agents

Attempts have been made over many decades to un-

TABLE I: DURATION OF ACTION AND METABOLISM OF DIFFERENT NEUROMUSCULAR BLOCKERS

Drug	Duration	Metabolism
d-tubocurarine	Long	none
Pancuronium	Long	Hepatic (10% to 20%)
Vecuronium	Intermediate	Hepatic (30% to 40%)
Cis-atracurium	Intermediate	Hofmann elimination and non-specific esterases (60% to 90%)

derstand the mode of action of general anaesthetics. Lipid solubility appeared to provide the best physical correlate with the anaesthetic potency of volatile agents, which implies a hydrophobic site of action. Enflurane and isoflurane are structural isomers with about the same oil/gas partition coefficient (Fig. 3). However, the minimum alveolar concentration or MAC of enflurane is 45% to 90% greater than that of isoflurane which suggests that factors other than lipid solubility must be important in determining the activity of volatile anaesthetics.

The MAC of volatile agents is known to be lowered by the administration of α_1 -adrenergic agonists such as clonidine. Medetomidine, another α_1 -adrenergic agonist which is more selective for the α_1 -adrenoceptor would be assumed to behave in the same way. The two isomers, d-medetomidine and l-medetomidine, have identical oil/gas solubilities. The MAC of halothane in dogs is reduced by almost 90% using the d-medetomidine isomer, however the l-isomer has no effect on decreasing MAC.⁹ It is clear that there must be another site of action. There are various possibilities including the lipid bilayer of the cell membrane, or a protein site bounded by lipid. The most likely site involves the GABA-activated channel. Propofol, for example, probably acts by enhancing the function of this channel as do etomidate and etanolone. The anaesthetic action on this site can be reversed by pressure. Keita and colleagues studied the effect of propofol and etomidate on the GABA receptor in rats of different ages. They found that ageing selectively decreased the sensitivity of the GABA receptor to both propofol and etomidate.¹⁰ The ability to design better drugs requires a knowledge of the receptor site occupied by the drug. While the receptor sites for general anaesthetic agents are still under investigation, there is a better understanding for opioids.

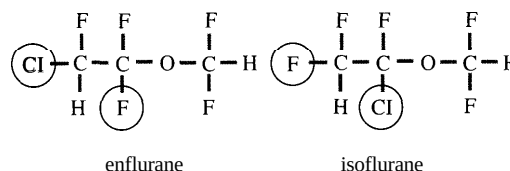


Fig. 3. The structural isomers enflurane and isoflurane

Opioids

The understanding of the sites of action for opioids has improved considerably. This has enabled development of a range of different opioid molecules from the first such as pethidine which had a duration of action similar to morphine, to the latest short acting opioid, remifentanyl. An agonist such as morphine can be considered to fit into a receptor site to exert its action. An antagonist, such as naloxone, may fit into the receptor but not correctly (Fig. 4). This has the effect of blocking entry to a molecule of morphine without exerting the same action as morphine.

One profile of the 'perfect' agent for anaesthesia is rapid onset of action with short duration. Suxamethonium achieves ultra short duration of activity by undergoing metabolism in the blood by pseudocholinesterase. A similar approach was used to develop remifentanyl which is metabolised by different tissue cholinesterases which exist throughout the body, unlike pseudocholinesterase which exists only in the blood (Fig. 5). Anaesthetic drugs are delivered into the blood stream and then must pass to the sites within the brain where they have their action. There is an inevitable delay before the drug can move from the blood into the brain to exert its effect and the half-time of this is termed the $t_{1/2, \text{keo}}$ (Fig. 6). The $t_{1/2, \text{keo}}$ for several opioids is shown in Table II. The onset time of remifentanyl is about the same as that of alfentanil which is itself much faster than fentanyl.

Context-Sensitive Half-time

The offset time for drugs varies with the duration over which they have been infused. The context-sensitive

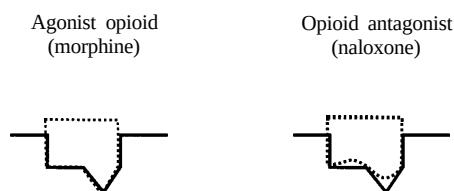


Fig. 4. Opioid agonist/antagonist and receptor site.

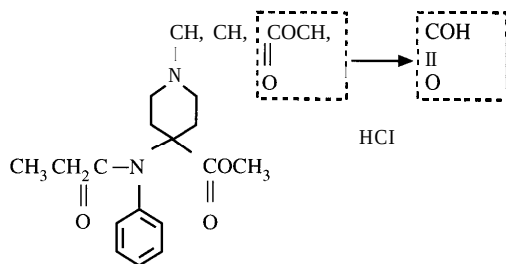


Fig. 5. The structure of remifentanyl demonstrating site of metabolism by tissue cholinesterase.

half-time is the time to halving of the blood concentration after termination of drug administration by an infusion designed to maintain a constant concentration.¹¹ This is illustrated in Figure 7 which shows the time course for alfentanil which has been infused to achieve a target concentration of 200 ng/ml for only 10 minutes. The time taken for the concentration of alfentanil to decrease by half is also about 10 minutes. Figure 8 illustrates the time course when the alfentanil is infused to achieve and maintain the same target concentration of 200 ng/ml but this time it is infused for 100 minutes. The time required for the concentration to half has now increased to about 40 minutes. When remifentanyl is infused to an equivalent target of 10 ng/ml for 100 minutes and then switched off, the concentration decreases to half in about 3 to 4 minutes. A comparison between remifentanyl infused for 100 minutes and alfentanil infused for 10 and 100 minutes is shown in

TABLE II: ONSET TIME OF ACTION FOR DIFFERENT OPIOIDS

Drug	$t_{1/2, \text{keo}}$
Morphine	15 to 20 minutes
Pethidine	Long
Fentanyl	5.4 minutes
Alfentanil	1.2 minutes
Remifentanyl	1.6 minutes

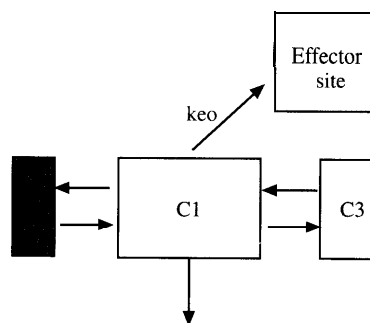


Fig. 6. Illustration of the distribution of anaesthetic drugs from the bloodstream (compartment I, C1) to the effector site (brain) and other compartments (C2, C3). keo is the rate constant for distribution from blood to brain.

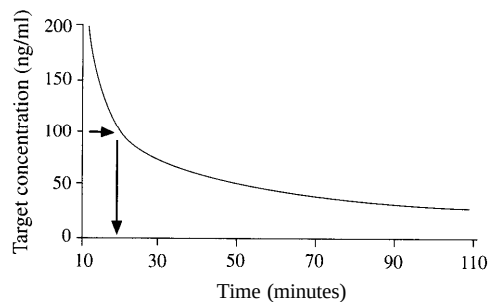


Fig. 7. Illustration of the context-sensitive half-time of alfentanil after infusion for 10 minutes.

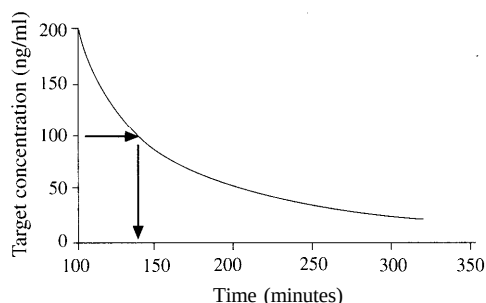


Fig. 8. Illustration of the context-sensitive half-time of alfentanil after infusion for 100 minutes.

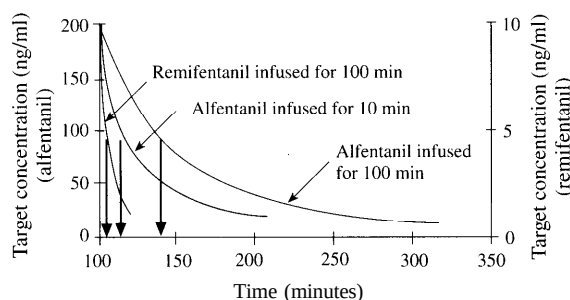


Fig. 9. A comparison of the context-sensitive half-time of remifentanyl infused for 100 minutes and alfentanil infused for 10 and 100 minutes.

Figure 9. The context-sensitive half-time is dependent on the duration of infusion and with the sole exception of remifentanyl, the half-time of opioids increases considerably with the duration of infusion (Fig. 10).

Remifentanyl

Remifentanyl, synthesised by Feldman and colleagues, has a 4-anilidopiperidine structure with an ester side chain. The introduction of the methyl ester group on to the N-acyl side chain of the piperidine ring resulted in increased susceptibility to hydrolytic metabolism by non-specific esterases and rapid termination of effect. It is the first μ -opioid receptor agonist in this class of drugs.¹² When compared with alfentanil, remifentanyl has been found to be 20 to 30 times more potent (milligram to milligram) after a single bolus dose when assessed by either analgesic efficacy or respiratory measures. Pharmacodynamically, both drugs are otherwise quite similar in terms of the time required for equilibration between blood and effect site concentrations. Evaluating pharmacokinetics, remifentanyl has been found to have a relatively small volume of distribution, a rapid clearance and therefore a very short terminal half-life of only 10 minutes.¹³

In recent years, there has been an increasing trend towards the use of short-acting agents of all types in anaesthesia including volatile agents, muscle relaxants and hypnotics. The development of a short-acting opioid such as remifentanyl with predictable pharmacokinetics is proving to be useful in a variety of clinical settings.

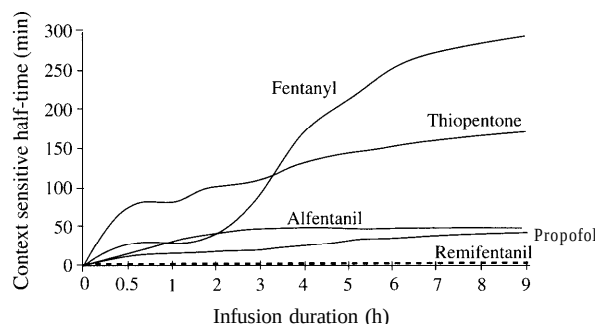


Fig. 10. Illustration of the increase in context-sensitive half-time with infusion duration (with the exception of remifentanyl).

There are advantages for day-case surgery where recovery times are important, as well as for long, unpredictable operations with varying levels of surgical stimulation. Remifentanyl has been found to be suitable for use in neurosurgery where the benefits of rapid recovery and neurological assessment postoperative are obvious.^{14,15}

The drawback of any opioid which possesses such a short recovery period is that any interruption in its delivery either intentionally or inadvertently could result in sudden severe pain or an inappropriate depth of anaesthesia. In addition, postoperative analgesia must be reliably provided with another drug or local technique.

Remifentanyl would be considered inappropriate for use as a sole anaesthetic agent but ideally used as part of a balanced technique of hypnosis and analgesia.

Schüttler and colleagues compared the efficacy and safety of remifentanyl and alfentanil for patients undergoing major abdominal surgery. Remifentanyl was continued into the immediate postoperative period at a reduced dose for postoperative analgesia. This technique would theoretically allow adequate analgesia in the postoperative patient while alternative longer acting analgesics such as morphine were titrated to effect. They found that the incidence of intraoperative hypotension and bradycardia was higher in the remifentanyl group but overall there was better intraoperative haemodynamic stability during stressful surgical events than alfentanil. However, in the postoperative setting, rapid bolus doses ($0.5 \mu\text{g.kg}^{-1}$) and infusion rate increases (doubling the infusion rate from an initial $0.05 \mu\text{g.kg.min}^{-1}$) resulted in a relatively high incidence of muscle rigidity, respiratory depression and apnoea. The study was modified so that the initial infusion rate was $0.1 \mu\text{g.kg.min}^{-1}$ and the bolus reduced to $0.25 \mu\text{g.kg}^{-1}$ given in a dilute form over 30 to 60 seconds. These changes resulted in a marked reduction in the incidence of adverse events. However, administration of bolus doses was not recommended in this setting.¹⁶

In an attempt to produce a safer method of administer-

ing remifentanyl for postoperative analgesia, Schraag and his colleagues carried out a study using the new technology of patient-demand, target-controlled infusion (TCI). The system was used following a propofol-remifentanyl anaesthetic technique. Since TCI systems increase the blood concentration by a controlled stepwise titration of only small boluses, the problem of overshoot associated with manual boluses would be avoided. In addition, since remifentanyl equilibrates rapidly with the effect site ($t_{1/2, \text{keo}} = 1.6 \text{ min}$)¹⁷ each new target is achieved and maintained rapidly. The study found that the mean remifentanyl target concentration for recovery of spontaneous ventilation at the end of surgery was approximately 50% of that for adequate pain control thereafter. This was attributed to the residual anaesthetic effect of propofol, possibly reflecting a pharmacodynamic interaction between the two drugs. There was no episode of hypoxaemia or apnoea and the majority of patients had adequate analgesia within 30 minutes. However, the frequency of nausea and vomiting was 26% and seemed to occur particularly in patients with relatively high and rapid increases in target concentrations of remifentanyl. They concluded that the system was an effective tool for transition to sufficient analgesia in the early postoperative period but would require adequate supervision and monitoring.¹⁸ Further controlled studies are needed to ensure its safety and effectiveness compared with the standard PCA morphine bolus method.

These developments in the techniques used for postoperative analgesia are further examples of continuing drug design with the application of modern technology to apply them more effectively in anaesthesia. TCI systems for remifentanyl are not yet commercially available but they are proving useful as part of the technique of total intravenous anaesthesia (TIVA).

Dosing recommendations from the datasheet produced by GlaxoWellcome for systemic administration of remifentanyl (Ultiva™) by conventional bolus infusion and continuous infusion are shown in Table III. It should be noted however that these doses are not recommended by these authors on the basis of work carried out at our institution using infusions of remifentanyl. The doses recommended in the datasheet are significantly higher than we found were required and more likely to result in side effects. Using TCI of remifentanyl, which adjust for age, gender and body surface area, we have found that target blood concentrations of no more than 10 ng.ml⁻¹ to 15 ng.ml⁻¹ are required for intraoperative use when combined with TCI propofol. Another local centre uses a maximum target of 15 ng.ml⁻¹ for cardiac anaesthesia. Using the recommended maximum infusion rate of 2 µg.kg.min⁻¹ in a young healthy person, the estimated blood concentration (from TIVA simulator programme) after 30 minutes would be approximately 50 ng.ml⁻¹. In

TABLE III: DOSING GUIDELINES FOR ULTIVA™-BASED ANAESTHESIA

Indication	Bolus infusion (µg/kg)	Continuous infusion (µg/kg/min)	
		Starting rate	Range
Induction of anaesthesia	1 (give over not less than 30 seconds)	0.5 to 1	
Maintenance of anaesthesia in ventilated patients			
. Nitrous oxide (66%)	0.5 to 1	0.4	0.1 to 2
. Isoflurane (starting dose 0.5 MAC)	0.5 to 1	0.25	0.05 to 2
. Propofol (starting dose 100 µg/kg/min)	0.5 to 1	0.25	0.05 to 2

an older and more overweight person, the estimated blood concentration achieved could be more than double this value, which is excessive.

Milne and colleagues have recently completed a study at our institution demonstrating the propofol sparing effects of remifentanyl¹⁹ using a closed-loop (CLAN) system monitoring the AEP index.²⁰ The results have financial implications in helping to reduce the cost of TIVA in addition to possibly improving recovery time from anaesthesia.

In summary, the design of new drugs in anaesthesia depends on an understanding of the receptor sites involved and the drug action, which of course is not always possible. We must know what we require the drugs to do and be able to demonstrate pharmacoeconomic benefits. Finally, the pharmaceutical industry must be prepared to invest in the development of new drugs for anaesthesia.

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