Drug interactions in anaesthesia were reviewed more than 10 years ago (Grogono, 1974) and more recently have been the subject of short chapters in textbooks (Dundee and McCaughey, 1980; Thornton, 1981). One of the best general reviews on drug interactions from the point of view of clinical pharmacology was written by Prescott in 1973, but this contained very few examples of drugs used in anaesthesia. The traditional approach to the topic either classifies the interactions on the basis of where they occur in the body or, alternatively, lists the anaesthetic and additional drugs with an outline of the adverse reactions that may be encountered. It did not seem very profitable for the present review solely to update such tables of interactions; instead an alternative approach has been attempted which is particularly relevant to anaesthesia—namely to consider drug interactions in terms of two broad classes of underlying mechanisms: pharmacodynamics and pharmacokinetics. Pharmacodynamics describes the relationships between drug concentration and drug response; pharmacokinetics describes the relationships between the rates of change of drug concentrations in the different parts of the body.

The pharmacodynamic interactions occur between drugs with similar or opposite pharmacological effects or "side effects". The underlying mechanisms include competition at molecular or cellular sites of action. The effects are generally common to related drugs. The pharmacokinetic interactions occur when one drug alters the absorption, distribution, metabolism or excretion of the other drug. As will be seen, this type of response varies between patients without any particular drug pattern and is difficult to predict. Mechanisms include altered protein binding, enzyme induction and inhibition and impaired renal clearance. Examples of both of these classes of drug interactions occur with the volatile anaesthetics.

Potential clinical importance

There has sometimes been a tendency to overemphasize the clinical importance of drug interactions. Any response that is potentially lethal (such as those associated with oral anti-coagulants, hypoglycaemic agents and cytotoxic drugs (Prescott, 1973)) is of undisputed importance. However, other interactions (such as the interaction of local anaesthetics and sulphonamides (Martindale, 1977)) may be equally well established, but are primarily of academic interest only.

Nevertheless, the overall potential for drug interactions is greater in anaesthesia than among other areas of medicine, for three reasons. First, the patient who is being considered for anaesthesia may be already receiving several drugs. It has been reported that patients in one London hospital are receiving concurrently five to six drugs, while one patient in every 10 receives 10 drugs at the same time. The supreme example was from another hospital when one patient was given 41 drugs during a single admission (Prescott, 1973). A wider perspective on the problem as related to anaesthesia was provided by the multicentre study on isoflurane (Levy, 1984). This included specific questions about concurrent medical therapy related to digitalis, beta-blockers, diuretics, nitrates and bronchodilators as well as recording any history of smoking (fig. 1). However, it should be noted that these data provide an estimate only of the minimum drug usage in this particular group of patients, because other types of drugs were not listed on the questionnaire.

The second reason for anaesthetists being more aware of the potential problem is that, even if the patient has no concurrent drug therapy, he may receive as many as 9 or 10 drugs as part of his anaesthetic regimen. These might include, for example: an opioid or tranquilizer, and atropine.

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FIG. 1. The incidence of preoperative medications in the multi-centre clinical trial of isoflurane. Only the five groups of drugs and smoking were recorded. (Reproduced, with permission, from Levy (1984).)

as preanaesthetic medication; a barbiturate for induction; suxamethonium for intubation (with lignocaine spray or gel on the tube); nitrous oxide, oxygen and a volatile agent (or synthetic opioid) for maintenance of anaesthesia; another neuromuscular blocking drug during the operation and finally a “reversal” agent such as neostigmine (with atropine). Although such polypharmacy would not necessarily be recommended, it should be noted that, not only do several drug interactions occur between the different types of drugs, but also the anaesthetist utilizes the predictable synergism or antagonism as part of his anaesthetic technique.

The third reason for being concerned about drug interactions in anaesthesia in particular is that the majority of the responses are associated with acute depression of the nervous system and the inhibition of protective reflexes. Without any intervention the results are potentially catastrophic, and long term consequences may occur when the patient is not being intensively monitored.

Additivity of drug responses

Many actions of closely related drugs in anaesthesia are additive rather than synergistic or antagonistic. The distinction is important, in that the former effect is not a drug interaction as formally defined. Thus the apparent effects of one drug can be increased or decreased by the previous or concurrent administration of another agent.

However, the essential evidence for a drug interaction is that the results of such a combination are different from the sum of the effects of the two drugs given separately; the difference can be either quantitative or qualitative, and allowance must be made for the shapes of the dose–response curves.

It has generally been thought that, when two gaseous anaesthetics are administered together, their anaesthetic effects are additive. However, most of the clinical studies quoted in support of this statement only demonstrate that the use of the second agent (such as nitrous oxide) reduced the requirement of the first (such as halothane). This reduction in requirement may have been either exactly that predicted from the individual potencies (i.e. additivity) or a greater or lesser reduction (i.e. synergism or antagonism respectively). It was not until the anaesthetic potency (MAC) of nitrous oxide on its own was determined in a clinical study under hyperbaric conditions (Hornbein et al., 1982) that it was possible to test directly the additivity of its combination as determined in much earlier studies with halothane (Saidman and Eger, 1964), fluroxene (Munson, Saidman and Eger, 1965), methoxyflurane (Stoelinga, 1971), enflurane (Torri, Damia and Fabiani, 1974) or isoflurane (Stevens et al., 1975) (fig. 2). It was found, for example, that 50 % of the nitrous oxide minimum alveolar concentration (MAC)
The additivity of the anaesthetic potencies of nitrous oxide and volatile agents (fig. 2) might suggest that there were no drug interactions of any kind between these agents. However, in contrast to the anaesthetic potency studies, the cardiovascular and respiratory effects of mixtures of these agents are very complex. One of the questions in the early clinical studies with isoflurane was whether its marriage with nitrous oxide would be for better or for worse? It was known that isoflurane on its own could produce depression of both ventilation and arterial pressure (Cromwell et al., 1971; Stevens et al., 1971). Since the addition of nitrous oxide to another cardiorespiratory depressant, halothane, attenuates such effects (Hornbein, Martin and Bonica, 1969), it was possible that nitrous oxide would produce similar changes towards awake values during isoflurane anaesthesia. In volunteer studies, under controlled ventilation conditions and at equivalent values of MAC, nitrous oxide did produce a 10–25% increase in mean arterial pressure. Nitrous oxide does have effects on its own, but the result of the combination with the volatile agent is not simple additivity. In contrast, in an additional study when the patients were allowed to breathe spontaneously, nitrous oxide failed to reverse the respiratory depression seen with isoflurane alone (Dolan et al., 1974). These two sets of data are part of the mass of clinical information about the combination of the two agents which indicate a spectrum of underlying drug interactions. The picture is complicated by apparent conflicts between the data of different studies. For example, another investigation (Eger et al., 1972) is sometimes quoted as evidence for nitrous oxide attenuating the respiratory depression of isoflurane. However such a conclusion is questionable, since the groups of patients in that particular study were different in other ways (especially age). The complexities of such clinical data mean that it is not very profitable to attempt to dissect out underlying drug interactions and better examples of the topic are to be found in more precisely defined physiological responses such as those discussed in the rest of this review.

**PHARMACODYNAMIC INTERACTIONS**

*catecholamines*

It is well established that halothane causes arrhythmias and sensitizes the myocardium to the effects of both endogenous and exogenous cate-
cholamines. Various reports indicate an incidence of ventricular arrhythmias of 3–7% without or with exogenous adrenaline (Katz, Matteo and Papper, 1962; Reisner and Lippmann, 1975). This incidence increases with increase in $P_{\text{CO}_2}$. A direct comparison is often made between halothane, enflurane and isoflurane in this type of drug interaction (fig. 4). At first sight it would appear that isoflurane does not interact with adrenaline. However, a closer examination of the numerical data (table I) indicates that enflurane, rather than isoflurane may produce the least potentiation. The $\text{ED}_{50}$ was defined by the investigators as the concentration of adrenaline injected submucosally which produced three or more ventricular extrasystoles in 50% of the patients. On the other hand, the threshold concentration is the lowest concentration at which any patient developed arrhythmias. This threshold concentration can be increased two- to three-fold by the addition of 0.5–1% lignocaine to the adrenaline in the case of halothane and enflurane. The effect of lignocaine on adrenaline threshold concentration in the presence of isoflurane has not been determined.

The only method of demonstrating unequivocally that there is or is not a drug interaction is to determine the effects of the two drugs separately and then combined together. The arrhythmic threshold following infusion of adrenaline to unanaesthetized man has not been determined adequately. However, the analogous experiment in animals indicates that isoflurane at 1.25 MAC reduces control adrenaline arrhythmic doses by as much as 40% (Joas and Stevens, 1971), although scatter of the data in the awake control group prevented this decrease from being statistically significant.

Catecholamine–anaesthetic drug interactions are clearly clinically relevant, but it should be noted that the site of administration is as important as the dose of adrenaline injected (Cotton et al., 1986). In our hospital, surgeons administer up to 500 μg of adrenaline during certain operations (Nunn, 1985) and in a 70-kg man the resulting dose (7.1 μg kg$^{-1}$) is certainly within the range of potential problems in some patients (table I). An example of endogenous release of adrenaline occurs during surgery for the removal of phaeochromocytoma. Isoflurane anaesthesia, without any anti-arrhythmic drugs, has been successfully used and has not produced any ventricular arrhythmias despite a demonstrable increase in adrenaline concentrations (Suzukawa et al., 1983).

**Neuromuscular blocking drugs**

The inhalation anaesthetics cause a dose-related potentiation of the actions of neuromuscular blockers. The anaesthetics themselves have blocking effects, as revealed by the impairment of the ability to sustain a response to high frequencies of tetanic stimulation (160–200 Hz) (Miller et al., 1971a,b). Studies with a wider range of anaesthetics at higher concentrations using the rat phrenic nerve–diaphragm preparation revealed that there were no noticeable effects on twitch height until concentrations were at least twice those required for the maintenance of anaesthesia (Pollard and Millar, 1973). However, at the higher concentrations there was a striking difference.

**Table I. Adrenaline doses associated with arrhythmias.** (Data from Johnston, Eger and Wilson (1976) and Horrigan, Eger and Wilson (1978))

<table>
<thead>
<tr>
<th>Agent</th>
<th>Arrhythmic threshold dose (μg kg$^{-1}$)</th>
<th>$\text{ED}_{50}$ dose (μg kg$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halothane</td>
<td>1.8</td>
<td>2.1</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>5.4</td>
<td>6.7</td>
</tr>
<tr>
<td>Enflurane</td>
<td>3.6</td>
<td>10.9</td>
</tr>
</tbody>
</table>
between the anaesthetics. Diethyl ether, methoxyflurane and trichloroethylene caused a depression of twitch height at all concentrations; cyclopropane caused potentiation at all concentrations, while halothane and chloroform caused potentiation at lower concentrations and depression at higher concentrations. It is clear that the effects of the anaesthetics on the neuromuscular junction are complex, although under clinical conditions very little apparent effect is observed when the agents are used alone. However, the drug interactions between the neuromuscular blocking agents and inhalation anaesthetics are now widely recognized. Smaller doses of blocking agents are required for equivalent blockade during enflurane and isoflurane anaesthesia than during halothane anaesthesia (all at equi-MAC conditions). Furthermore, increasing alveolar concentrations of all the agents decrease the amount of neuromuscular blocking drug needed (Miller et al., 1972). The dose-dependent degree of enhancement of blocking effects differs between the different agents and sometimes between the different anaesthetics with the same blocker. For example, the effect of increasing the halothane concentration on tubocurarine requirement is much more dramatic than the equivalent effect with isoflurane. Thus the ranking order of dose dependencies is different from that of agent dependencies. On the other hand, the effects of increasing halothane or isoflurane concentrations on pancuronium requirement appear to parallel each other (Miller et al., 1972). It is potentially misleading to compare relevant doses at only one anaesthetic concentration but, in order to provide a general comparison, table II indicates the relative effects at 1.25 MAC.

Table II does not imply that halothane itself has no potentiating action. For example, the dose of tubocurarine required during halothane anaesthesia is 70% of that required during nitrous oxide–barbiturate–narcotic anaesthesia (Ali and Savarese, 1976). There is no effect of the duration of anaesthesia on the potentiation of tubocurarine by halothane (Miller, Crique and Eger, 1976) but, unexpectedly, potentiation by enflurane of this drug is time-dependent. Paralysis with tubocurarine under enflurane anaesthesia increased at a rate of 9 ± 4% per hour, despite a constant blood concentration of the neuromuscular blocking agent (Stanski, Ham and Miller, 1979). This may relate to the different mechanisms by which the different anaesthetics augment the blocking action and it is probable that more than one site (e.g. neuromuscular junction and skeletal muscle) is involved.

A series of mechanisms have been proposed to explain the differences in anaesthetic potentiation of neuromuscular blocking actions. In vitro studies (Vitez et al., 1974; Chaudry, Ohta and Nagashima, 1980) demonstrated that the relative potentiation was enflurane > halothane = isoflurane. Thus in vivo differences between halothane and isoflurane may be related to differences in regional blood flow allowing a greater fraction of injected agent to reach a particular site of action rather than to inherent differences in sensitivity at the sites. This would, of course, be an example of a pharmacokinetic interaction, but the neuromuscular blocking drug interactions are included in the pharmacodynamic class because it has been demonstrated unequivocally that halothane decreases the steady state plasma concentration of tubocurarine required to produce a 50% blockade of neuromuscular function (fig. 5). These data (Stanski et al., 1979) incidentally demonstrate the decreased variability in the response in the presence of the drug interaction with halothane which appears to be one of the characteristics of this type of pharmacodynamic mechanism.

The clinical implications are that smaller doses of myoneural blockers are needed to give satisfactory operating conditions during enflurane and isoflurane anaesthesia than with other anaesthetic techniques. This has the advantage that, when the appropriate amount of blocker is used, neuromuscular activity returns to normal more quickly at the end of an operation using enflurane or isoflurane anaesthesia when the administration of the volatile agent is discontinued.

The demonstration (Rupp, Miller and Gencarelli, 1984) that the order of potency potentiation for vecuronium (enflurane > isoflurane > halo-
1.1. Morphine Halothane Halothane

(0.5-0.7% end-tidal) (1.0-1.2% end-tidal)

**Fig. 5.** The steady state plasma concentrations of tubocurarine required to produce a 50% blockade of neuromuscular function during morphine—nitrous oxide anaesthesia compared with halothane—nitrous oxide anaesthesia (at two different concentrations of end-tidal halothane). (Reproduced, with permission, from Stanski and colleagues (1979).)

Drugs (such as pancuronium or tubocurarine) raise the possibility of a spectrum of interactions. The other new neuromuscular blocking drug is atracurium, which has been studied in patients anaesthetized with halothane (Payne and Hughes, 1981), enflurane (Ramsey et al., 1982) and isoflurane (Sokoll et al., 1983). Because of the experimental differences between the studies, it is not appropriate to compare quantitatively the interactions with these agents. However, in a comparison with "balanced" anaesthesia (nitrous oxide and fentanyl), it was found that both enflurane and isoflurane potentiated the effect of atracurium: with the volatile agents, patients required approximately 50-75% of the dose of atracurium to attain a given degree and duration of block (Sokoll et al., 1983).

Finally, the volatile agents modify the characteristics of suxamethonium neuromuscular blockade. With prolonged administration of suxamethonium the transition from phase I (depolarizing) blockade to phase II (non-depolarizing) blockade occurs at a lower cumulative dose of the blocker during nitrous oxide—halothane, nitrous oxide—enflurane and nitrous oxide—isoflurane compared with nitrous oxide—narcotic (Hilgenberg and Stoelting, 1981; Donati and Bevan, 1983a). This phenomenon has been demonstrated with both intermittent bolus injections of suxamethonium and continuous infusion of the agent (Donati and Bevan, 1982).

It has been argued that the rapidity of onset of phase II blockade seen with inhalation anaesthetic agents is a disadvantage, because suxamethonium can only be administered for a short time (Hilgenberg and Stoelting, 1981). The alternative view is that inhalation agents appear to have many advantages when used with suxamethonium (Donati and Bevan, 1983a); because of its reversibility with anticholinesterase agents (Donati and Bevan, 1982) phase II blockade does not need to be avoided. Furthermore, although the characteristics of the blockade generally change later with nitrous oxide—narcotic anaesthesia, this change is less predictable than with isoflurane. As a result, if one tried to determine a "safe" period during which phase II blockade does not occur in most patients, it would not be much different with either form of anaesthesia. Finally, a rapid transition from phase I to phase II blockade, as seen with inhalation agents, can minimize the occurrence of "mixed" blockade, for which anticholinesterases are poorly effective. A recent study has demonstrated that isoflurane not only accelerates the onset of the phase II blockade, but also potentiates its intensity (Donati and Bevan, 1983b). This, of course, is similar to the effects with other neuromuscular blocking agents, although the relationships between a phase II blockade and a non-depolarizing blockade are not yet clear mechanistically.

**Calcium antagonists**

Although calcium antagonists were discovered more than 20 years ago, it is only in the past few years that their potential interactions with anaesthetics have started to be systematically investigated. It has been argued that the anaesthetics themselves may be considered to be non-specific calcium antagonists (Jones, 1984), while it is now clear that particular calcium entry blockers have unique haemodynamic effects. For example, in the presence of halothane, nifedipine decreases sys-
tomic vascular resistance, while verapamil decreases cardiac output (Kates et al., 1984). It is not yet clear whether such effects are simply additive or involve specific drug interactions. The differences in both magnitude and concentration dependence of the depressant effect of verapamil in the presence of enflurane or isoflurane (fig. 6) suggest that drug interactions may prove to be more important than has previously been thought (Reves, 1984).

More unequivocal evidence for drug interactions between calcium antagonists and anaesthetics has now been demonstrated for their central nervous system effects as distinct from their cardiovascular actions. In rodent studies, nitrendipine, flunarizine and verapamil significantly increased anaesthetic potencies of pentobarbitone and ethanol as measured by the loss of righting reflex (Dolin and Little, 1986). These calcium antagonists, even at doses up to 10 times greater than those used to determine the anaesthetic potency changes, did not themselves produce a state of anaesthesia. Possible pharmacokinetic mechanisms appear to have been excluded and, if such interactions do prove to occur also in man, the clinical implications could be as interesting as the mechanistic implications.

PHARMACOKINETIC INTERACTIONS

Anaesthetic metabolism

This type of drug interaction is associated with the rate of change of either the anaesthetic or some toxic product produced by biotransformation of the agent. The resulting concentration of the toxic substance is dependent on both its rate of formation, rate of deactivation and rate of excretion. Little is known about the pharmacokinetics of the latter processes, but the rate of formation is clearly linked to enzyme induction or inhibition. Enzyme induction is produced by prior treatment with drugs or by chronic exposure to environmental chemicals. Enzyme inhibition can be produced in the experimental situation by a variety of drug treatments and has been covered in another review (Davie, 1977).

It has been argued that the majority of drug interactions associated with enzyme induction do not have major effects on the conduct of anaesthesia (Mazze, 1984), but there are definite patients for whom ignoring the potential for anaesthetic metabolism could prove fatal.

The first example is halothane hepatitis. The link between halothane anaesthesia and liver damage has been reviewed again recently (Neu-berger and Williams, 1984; Brown and Gandolfi, 1987). Studies of the mechanisms of halothane hepatitis have shown how differences in drug metabolism may interact with individual variations in immune responses to determine the type of liver injury. Animal models have shown one form of direct hepatotoxic effect of halothane which is dependent on enzyme induction either with polychlorinated biphenyls (at one stage an industrial pollutant) or with phenobarbitone pre-treatment followed by administration of halothane with limited cellular oxygen supply. Clinical studies have shown that patients with severe hepatic necrosis following halothane administration have circulating antibodies reacting with altered liver cell membrane determinants, which are generated by the oxidative route of metabolism (Neuberger et al., 1981). The evidence for the immunological hypothesis of the mechanism of halothane hepatitis is now quite strong, but there seems the possibility that the observed alterations in immunological sensitivity may be the result of this particular type of liver injury, rather than the cause of it. The final elucidation of the mechanisms is still awaited, but at the moment all the postulates include a role for enzyme induction (to a greater or lesser extent). In this example the drug interaction is changing qualitatively the type of response, rather than having only a quantita-tive effect.
A second example of anaesthetic metabolism is provided by the defluorination of the volatile anaesthetics (fig. 7). The animal data demonstrate first that there is a considerable difference between the agents in their responses to enzyme induction following pretreatment with specific drugs. More interestingly, the optimum enzyme inducing agent for one anaesthetic is not the same for another. In general, it appears that the overall order of susceptibility to enzyme induction is related to the ease of biotransformation in the untreated animals. It is not possible to extrapolate quantitatively from
such in vitro animal derived data to in vivo biotransformation.

One of the most interesting clinical studies of enzyme induction has been with isoniazid. There appears to be a bimodal distribution in the response, with isoniazid pretreatment enhancing defluorination in only nine of 20 subjects studied (fig. 8). It has been postulated that this difference may be related to the distribution of slow and rapid acetylators of isoniazid which is known to exist in the normal population. The acetylation of isoniazid results in the formation of hydrazine,
DRUG INTERACTIONS IN ANAESTHESIA

which in turn induces formation of cytochrome P451, which leads to enhanced enflurane defluorination. Thus this example of a drug interaction is the result of biotransformation of the drug, which in turn alters the biotransformation of the other drug. The result is more than academically interesting, because the result in some cases is a serum fluoride concentration increased to more than 100 μmol litre⁻¹, which has definite nephrotoxic potential.

CONCLUSION

This review has concentrated on specific examples of drug interactions in anaesthesia, which have been divided into those which are based on pharmacodynamic mechanisms and those which are related to pharmaco kinetic mechanisms. This distinction may be useful because pharmacodynamic interactions predominate between those drugs which have related pharmacological effects and it appears that one of the characteristics is a decreased variability in patient response. If this hypothesis proves correct in general, and the majority of pharmacodynamic interactions result in a decreased biological variability, the clinical implications could be at least as important as those of the interactions themselves. In contrast, pharmaco kinetically based interactions definitely produce responses which vary widely between patients and occur between drugs which appear to be pharmacologically unrelated. As such they are difficult to predict and the clinical consequences in a few instances can be catastrophic (for example halothane hepatitis).

This review has not attempted to be comprehensive, but a table of cross references to the interactions with the volatile anaesthetics (table III) includes other drugs which may be relevant to the topic. In addition, the reviews by Sear (1987) and Hunter (1987) in this postgraduate educational issue include further examples of interactions with i.v. anaesthetics and with neuromuscular blocking drugs, respectively.

The introduction of both new volatile anaesthetics and new drugs administered concomitantly during anaesthesia has highlighted the potential importance of drug interactions. However, it should be emphasized that drug interactions in themselves are not necessarily good or bad factors. Some obviously lead to contraindications for certain circumstances; others—like the potentiation of neuromuscular activity—can actually be an advantage if the drugs are used appropriately. It is hoped that this review has emphasized the considerable importance of drug interactions in clinical anaesthesia. Knowledge of the basic interactions must form an increasing part of the essential information on modern anaesthetics.

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REFERENCES


