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Contents

Chapter - 3
Drug Interactions in Anaesthetic Practice

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Chapter - 3

Drug Interactions in Anaesthetic Practice

Dr. Parthasarathy S and Dr. Monisha Sundararajan

Abstract

Drug interaction in simple terms is defined as an influence of the first drug on the second drug administered. Anesthesiologists administer multiple drugs, especially life threatening, that too in a short span of time. Hence, the knowledge of interactions among each drug is absolutely necessary for them. The common classification of interactions is pharmaceutical, pharmacokinetic and pharmacodynamic. The pharmaceutical interaction means the occurrence of interaction before the administration of drug. The precipitation of local anesthetic drug with sodium bicarbonate is a classic example for the same. The pharmacokinetic interaction is about the influence in absorption, metabolism or elimination of the other drug. The absorption of local anaesthetic is delayed by the addition of adrenaline. The third one is pharmacodynamic which is at the receptor level modulation. To cite an example, the addition of benzodiazepines will affect the action of inhalational agents. The concept of agonists, partial agonists antagonists among opioid drugs is described. The modulation of local anaesthetic drug in regional anaesthesia by the addition of multiple adjuvants like, opioids, alpha agonists, dexamethasone are touched in brief. Overall, we have attempted to cover the clinically important drug interactions in anaesthetic practice.

Keywords: anesthesia, drugs, interactions, agonists, antagonists.

Definition and introduction

A drug interaction is defined as a change in the action of the first drug by the addition of the second drug. The change may be either beneficial or dangerous to the patient to whom they have been administered. The second drug may either completely annul the effect of the first or enhance its effect. The first drug is called an object and the second one is called a precipitant. The basic requirement of drug interaction to take place is polypharmacy i.e., the prescription and intake of multiple drugs through similar or different routes. In a study by Das *et al*., the incidence of polypharmacy is 50% or more

[1]. The incidence of actual occurrence of drug interactions has been reported up to be 1.3%. Whether many such incidents are reported or not is a big question. Another significant factor is that the interaction has to be clinically symptomatic to attract attention and reporting. If it's going to be mild and unnoticeable, they will not come to the attention of the physician. Hence in a setting of difficult case reporting in a normal conscious patient, the tasks become more difficult in unconscious patients. To deduce, many drug interactions may go unnoticed in anaesthetized patients. But any disturbance in the internal milieu under anaesthesia may cause either serious hemodynamic disturbances or an unknown increase in drug action. Unlike a normal scenario, anesthetic drugs are administered in absolutely precise doses, especially in children. Any abnormal action is likely to increase morbidity and rarely mortality. The triangle of anaesthesia is formed by hypnosis, analgesia and muscle relaxation. Now a fourth component of reflex suppression is added. Hence polypharmacy is intertwined with anaesthesia. The incidence of drug interaction depends upon the number of drugs administered. It is under 5% with three drugs but increases to 10% with eight drugs. The pertinent question is that why we should add many drugs? The most common reason cited is that we can come down on the dosage of each drug which means we are safe and clearly well below the toxic range. There are certain conditions like seizures and malignancies which are usually dealt with multiple drugs. With this in mind, it is essential to understand the different drug interactions in anesthesia and the relevance of the same in clinical day to day anaesthetic practice.

Classification

There are basically three/ four types of drug interactions

1. Pharmaceutical
2. Pharmacokinetic
3. Pharmacodynamic
4. Thermodynamic interaction

Pharmaceutical interaction

A pharmaceutical interaction is defined as a chemical or physical interaction which occurs either before a drug is administered or absorbed systemically. This usually represents incompatibilities of drugs given by intravenous infusion. There will be colour changes, haziness or precipitation if we combine such drugs. These happen usually before administration. The proposed mechanisms of such interactions prior to administration are

Let us describe this with a few examples

If a non-aqueous drug is mixed with saline or water or the purpose of dilution, it is likely to precipitate. This is very obvious with a commonly used sedative diazepam. This forms white precipitate and it is less likely to revert with shaking if the dilution is more than fourfold. There is practice saying that the precipitation is unlikely to adversely affect the potency of the drug.

Precipitation of a drug can occur with change in pH. If a drug is a base the ionisation is achieved by making it as a salt with hydrochloride in a low pH. E.g. lignocaine is made as lignocaine hydrochloride. The pH of the solution is acidic. If we add sodium bicarbonate, its likely to precipitate as white coloured separate solution. This phenomenon occurs more readily with one tenth of the doses of sodium bicarbonate with the drug bupivacaine [2].

The salts of monovalent cations are generally more soluble than those of divalent cations. The salts of sodium and potassium are more soluble than those by calcium and magnesium. Mixing solutions containing calcium or magnesium ions with certain drugs used before surgery can be potentially catastrophic. The anaesthesiologists commonly use Hartmann solution which is rich in calcium along with the antibiotics like ceftriaxone used as prophylaxis just before other drugs. These two can combine to form an insoluble precipitate before surgery [3].

There are a few drugs like insulin which undergo biologic degradation in different circumstances. Bahendeka S *et al.* [4] have studied the different aspects of various insulins and given guidelines about temperature maintenance, adherence to plastic syringes and vials.

After injection of intravenous thiopentone, Succinyl choline produced a mild precipitate, which is followed by atracurium. vecuronium and rocuronium in the order of severity [5]. Hence at induction, where these drugs are combined, extreme precautions need to be taken to decrease adverse events.

The mechanism which causes pain on injection of propofol is thought to be mediated by the kallikrein-kinin pathway resulting in the production of bradykinin. This pathway may be inhibited by lidocaine. In clinical practice, a propofol lignocaine combination is administered for induction of anaesthesia without completely understanding whether they are compatible. Masaki *et al*., concluded that if lidocaine to propofol is added, the combination increased the diameter of the lipid vesicles. This made the mix physically and chemically unstable in time. which in turn proposes the theory of the combination's propensity to cause pulmonary embolism [6].

In palliative care centres and in control of chronic, multiple combinations of as many as four drugs may be mixed in the same syringe for use in a syringe pump over 24 hours. To summarize, it is better to avoid mixing and to read compatibility studies in research works and pamphlets before combining in a same syringe. If a running solution before administration of each drug is not available, better to employ saline flush prior to injection of the next drug. There is no substitute for continued and strict vigilance. Among the inhalational agents, trilene was incompatible with soda lime in the canister of the circuit. Hence the agent went out of use. The newer agent sevoflurane was originally feared of an interaction with soda lime to produce compound A which was nephrotoxic. After consistent studies, the amount of compound A produced was found to be less with sevoflurane even with administration of six hours with low flows of gases.

Pharmacokinetic interaction

A pharmacokinetic interaction is defined as an interaction when the first administered drug alters the absorption, distribution, metabolism, or elimination of another drug. We will try to understand each of the pharmacokinetic variables and its importance in anesthetic drug interactions. Considering absorption, the most important phenomenon is second gas effect.

Absorption: If we add up nitrous oxide (N_2O) with volatile anaesthetic agents, then N_2O quickly replaces the nitrogen, which was previously present in the alveoli. So, the volume of N_2O taken up by the blood is greater than the volume of nitrogen entering the alveoli from the blood. Hence, the alveoli become smaller and thereby the fractional concentration of the second volatile anaesthetic agent in the alveoli increases. This phenomenon is called the 'second gas effect'. Adding N_2O with an inhalational agent like halothane or isoflurane enhances the absorption of the agent [7]. Another important pharmacokinetic interaction involving absorption is the addition of local anaesthetics with adrenaline. The drug adrenaline is a vasoconstrictor and varies the absorption of the local anaesthetic. The addition of adrenaline has some alpha agonist action to have minimal pharmacodynamic interaction. Oral administration of paracetamol after a halothane diazepam combination is absorbed with delay and less predictability. Hence intravenous preparations are preferable.

Distribution: Anaesthetic agents may affect drug distribution, and they may alter the peak concentrations of propranolol. The induction agent propofol decreases the cardiac output and the preferable increase in the vascular supply to the brain. This is in turn increases the agent inflow to the

brain. The drug warfarin is notorious for the fact that it interacts with innumerable drugs like amiodarone in the context of affecting the distribution of the other drug.

Metabolism: Liver usually does oxidation, reduction or hydrolysis to make the drugs water soluble to get excreted easily through the kidneys. Any drug which decreases the hepatic blood flow like inhalational agents can alter the pharmacokinetics of liver dependent other anaesthetic drugs. Propofol can decrease the cardiac output in select cases and thereby the blood flow to liver may be altered. Such variations in blood flow to liver can alter metabolism of select drugs. Propranolol, noradrenaline and anaesthetic agents decrease hepatic blood flow, thereby increasing the half-life of lignocaine. The induction agent, etomidate blocks the synthesis of cortisol and aldosterone by inhibiting the P450-dependent mitochondrial enzymes, 17α-hydroxylase and 11β-hydroxylase. Protease inhibitors such as saquinavir and ritonavir can inhibit the metabolism of midazolam and fentanyl [8]. The commonly used sedative in the initial phase of anaesthetic drug paraphernalia is midazolam. This drug interferes with the metabolism of other medications due to the inhibition of cytochrome P4503A4. The drugs with such interactions are dexamethasone, fentanyl, prednisolone, ketamine, antidepressants and alfentanil.

Elimination: There are basically two ways of elimination of drugs. The first one is through the lungs, which happens to anaesthetic inhalational agents like halothane and sevoflurane. The second one is through the kidneys. To put in simple words, cardiac output and pulmonary ventilation are the two distinct clinical parameters which affect elimination. For example, opioids and benzodiazepines decrease pulmonary ventilation and they may change the uptake of inhalational agents. The administration of sodium bicarbonate makes the urine more alkaline and thereby increased the excretion of drugs like barbiturates.

Pharmacodynamic interaction

A pharmacodynamic interaction is said to occur when one drug alters the sensitivity of a target receptor or the tissue to the effects of a second administered drug. Drug combinations by way of such interactions may produce additive, supra-additive (synergistic) or antagonistic effects. To explain in simple terms

Additive ---------- 1 + 1 = 2

Supra additive ---- 1 +1 = 3

Antagonistic ----- 1 + 1 = 0

Additive interactions are likely to occur when drugs of the same class with identical mechanisms of actions are combined. Examples of this may include combinations of two benzodiazepines. Supra additive interaction or a synergistic reaction are peculiar in that a combination of two different classes of drugs enhance the action of a different class of drugs. Antagonistic reactions or interactions are the effect of the second drug annulling the effect of the first. The most common mechanism is the antagonist also binds to the receptor but does not produce the intrinsic effect. E.g. Sodium channel opening. The intrinsic activity principle and affinity are essential in understanding is opioid-related depression. The answer is using naloxone, a very high affinity opioid (it binds to the opioid receptor with ease) but with poor intrinsic activity. Another example of good affinity with minimal intrinsic activity is a non-depolarizing neuromuscular relaxant used to displace acetyl-choline. Flumazenil is a benzodiazepine antagonist. It competitively (means the inhibition depends upon the relative concentration of the agonist and the antagonist) inhibits the activity of benzodiazepine and also a few non-benzodiazepine substances that gets bound with benzodiazepine receptors site on the GABA receptor complex. It can reverse the binding of benzodiazepines to those benzodiazepine receptors and make patients awake in a few minutes. A non-competitive antagonist traditionally described as binding to an allosteric site on the receptor to prevent activation of the receptor. It cannot be washed out as in the case of competitive antagonists like naloxone. The classic example is ketamine on (N Methyl D Aspartate) NMDA receptors [9]. (Fig 1)

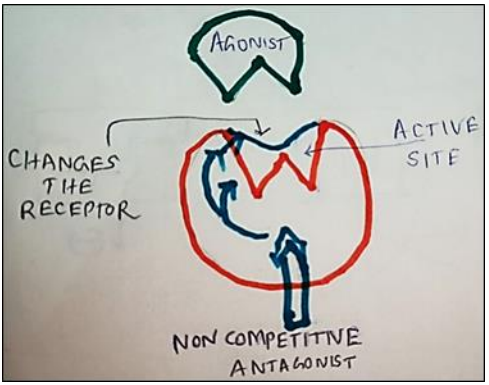

Fig 1: Showing Noncompetitive antagonism

The other drugs which act on a non-competitive basis on NMDA are flupirtine a centrally acting non opioid analgesic and dextromethorphan an antitussive. In patients with organophosphorous poisoning, the need for sedation should not be taken care by phenothiazines as these may worsen the

basic problem with unclear pharmacodynamic interaction [10]. The other drug commonly used in respiratory distress theophylline is also not indicated in case of distressed poisoning with organophosphorous compounds. There are significant pharmacodynamic interactions which need attention in relation to potent anaesthetic drugs.

The common interactions usually talked about are

- Opioid-opioid
- Opioid-benzodiazepine
- Inhalational Agents-opioids-benzodiazepines
- Intravenous hypnotics-opioids
- Others

Opioid-opioid interactions

Opioids belong to a different class of drugs with unique property of acting differently in their own receptors. Opioids like morphine gets attached to mu receptors and produce its full intrinsic effect. These are called agonists. A same drug may be agonist in a receptor and antagonistic in a different receptor. E.g. Pentazocine, butorphanol and nalbuphine are weak mu-antagonists and kappa-partial-agonists. They are called agonist antagonists. A few drugs like buprenorphine sits on the mu receptors but a full intrinsic activity is not produced, they are called partial agonists. See table 1 and fig. 2. Hence a combination of two drugs with different receptor activation may lead on to unexpected actions. Example supplementing analgesia with pentazocine where a patient is already on fentanyl.

Table 1: Showing the different drugs and actions on receptors

	Mu receptor	**Kappa receptor**
Pure Agonist	Agonist	Agonist
Agonist antagonist	antagonist	Agonist
Pure Antagonist	antagonist	antagonist

Fig 2: Showing Competitive antagonism

Opioid and inhalational anaesthetics

Inhalational anaesthetic agents and opioids exhibit strong supra-additive or synergistic interactions. Even small doses of opioids increase the action and reduce the (Minimum Alveolar Concentration (MAC) of volatile anaesthetics [11]. The above said synergic potential between inhalational agents and opioids is found for skin incision (on starting the surgery) for verbal response at emergence from anaesthesia and for an autonomic response to skin incision. Clinically adequate concentrations of narcotics like fentanyl or remifentanil decreased the MAC of desflurane, sevoflurane to approximate 50% [12]. After a thorough understanding of MAC equipotency and opioid equivalencies, the extrapolation of interaction have been proved to be supra-additive.

Opioids and intravenous anaesthetics

The interaction between opioids and the intravenous anaesthetic agents is synergistic. The fentanyl propofol combinations have been well studied. This combination is one of the common drug interactions used in clinical anaesthetic practice. A routine premedicant dose of 100 mcg of fentanyl decreases the induction time and also reduced the total propofol requirement to cause unconsciousness. This fact caused decreased need for propofol and whether this can be transformed to better hemodynamics depends upon the user. There are similar studies with remifentanil. The addition of fentanyl (0.6 mg/kg) to propofol alone (1mg/kg) or a midazolam (0.7mg/kg) or a combination of midazolam and fentanyl to propofol (0.4mg/kg). The propofol doses to get 100% of patients unresponsive are given in brackets.

Usually, a barbiturate and a benzodiazepine are combined to produce hypnosis. Both the drugs act on the gamma aminobutyric acid-A chloride ionophore complex, increase chloride conductance to produce neuronal depression. Still the mechanisms are not very similar. The barbiturates sit on the GABA receptor to stimulate the same with increasing chloride conductance. But the benzodiazepines increase the GABA level at the site of the receptor. Hence, we need some GABA for the benzodiazepines to act. The patients getting premedicated with benzodiazepine will need less thiopental or propofol for induction but whether this decreased need results in better awakening is not established [11].

The role of alpha 2 agonists

The dugs clonidine and dexmedetomidine are the drugs of this class in anaesthesia practice. The hypnotic effect of such drugs is due to depression of function in the Locus Coeruleus, the key adrenergic nucleus in the brain [13]. The drug produced sedation and a decreased central sympathetic drive. They

decreased the requirements of both the inhalational agents and the intravenous anaesthetics.

Combined interactions: The addition of local anaesthetics to sodium bicarbonate cause precipitation which is a pharmaceutical reaction while the alkalinisation increased the absorption of local anaesthetic drug which a pharmacokinetic interaction. Similarly, addition of adrenaline to local anaesthetics caused vasoconstriction to decrease vascular uptake (Pharmacokinetic) while the alpha agonism of adrenaline may play a pharmacodynamic enhancement of local anaesthetic drug. The interactions of combined use of opioids and benzodiazepines will definitely decrease the need of either the volatile agents and induction agents.

Non-specific and miscellaneous interactions

Administration of subanaesthetic doses of ketamine potentiate opioid analgesia acting through the NMDA receptors [14]. All volatile anaesthetics enhanced the action of non-depolarizing muscle relaxants. Ye *et al*. studied and asserted that sevoflurane has no proved direct effects on the power and contractility of adductor pollicis, but increased the sensitivity of such skeletal muscle to atracurium [15]. The intraoperative use of magnesium, reduced the need for anaesthetics and/or muscle relaxants for similar clinical effects [16]. Even in terms of postoperative pain relief, intraoperative magnesium decreased opioid consumption in the first postoperative 24 hours. A study by Weinberg *et al*. in their study used intravenous lignocaine and deduced that volatile anaesthetic agent needs are decreased in patients undergoing open radical prostatectomy [17]. Gupta *et al*. have studied premedication with pregabalin and they stated that the consumption of all anaesthetic agents during induction and maintenance of anaesthesia are reduced when compared to diazepam [18]. Alcohol and smoking are two independent factors which can affect the anaesthesia process but they are out of the preview of this chapter.

Adjuvants with local anaesthetics in neuraxial and peripheral nerve blocks

Almost all opioids like morphine, pethidine, fentanyl, tramadol [19], diamorphine and buprenorphine have been used to prolong the action of local anaesthetics. Additional use of preservative free morphine with local anaesthetics has been used extensively in neuraxial blocks. Intrathecal fentanyl in the dose range of 10-25μg has been shown to prolong the duration and extent of sensory block of the local anaesthetic used with a favourable adverse effect profile which is comparable to morphine [20]. The mechanism of such action is described to have spinal and supraspinal mediated actions.

Evidence favours better analgesic outcomes with buprenorphine in peripheral nerve blocks than other opioids when combined with local anaesthetic drugs. The addition of sodium bicarbonate is associated with pharmaceutical interaction (as described earlier) but the alkalinization can increase the lipid soluble portion of the local anaesthetic drug favouring entry into the nerve cell. Midazolam as an adjuvant to local anaesthetic drugs in intrathecal and nerve plexus have been described to be beneficial in terms of both quality and duration of blockade [21]. Intrathecal neostigmine was used as an adjunct to local anaesthetics but became out of use due to vomiting and fasciculations. The addition of dexamethasone to bupivacaine or ropivacaine in brachial plexus block provided early post-operative analgesia and with earlier onset and prolonged duration of sensory and motor block [22, 23]. Intrathecal clonidine as an adjuvant prolongs analgesia of local anaesthetic drugs. Clonidine in a dose of 1.5 mic/kg when added to local anaesthetic drugs in brachial plexus blocks have hastened the onset with prolonged analgesia [24]. Establishment of specific alpha 2 receptors both in the central nervous system and peripheral nervous system, have delineated the mechanism of extending the action of local anaesthetics. The thermo dynamic interactions have been described for opioids and their receptors and clearly delineated the type of mu receptors and their differences in affinity to different drugs.

Conclusion

Drug interactions and their understanding are essential in clinical practice. This fact becomes more important among anaesthesiologists as they use life threatening drugs. Routinely used adjuncts like opioids and benzodiazepines increase the potency of both the inhalational and intravenous anaesthetic agents. Innumerable drugs including opioids, benzodiazepines, alpha 2 agonists, dexamethasone have been added to local anaesthetics in nerve blocks. Simulation of drug administration is to be used to train anaesthetists to improve the quality of anaesthetic care helping them to select the appropriate drug doses and mixtures.

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