Undesirable residual effects in the post-anesthetic patient are not an uncommon occurrence. However, these symptoms can be effectively antagonized using either pharmacological or physiological antagonists. For example, naloxone is the antagonist of choice for narcotic-induced respiratory depression; physostigmine is effective in antagonizing the central anticholinergic syndrome produced by many commonly used agents; and doxapram is useful in selected situations to antagonize persistent depression and to hasten arousal. The use and limitations of these agents will be thoroughly discussed in this article.

A large variety of drugs and agents are used in modern anesthesia practice today. There is a wide individual variation in patient response to these agents and it is often times difficult, if not impossible, to accurately predict in advance how a particular patient will respond to some of the more potent agents that we use. Therefore, it is a very unusual anesthetist who does not find himself confronted at some time with a patient exhibiting undesirable residual effects in the post-anesthetic period. The purpose of this article is to review several agents which are useful in antagonizing these undesirable residual effects.

It is important to distinguish between pharmacological antagonism and physiological antagonism. For pharmacological antagonism to exist, one drug must exert an effect by competitively inhibiting the action of another drug. Generally, pharmacological antagonistic drugs, which act as competitive inhibitors, are quite specific in their actions, exerting their (often dose-related) effects on specific receptor sites. For example, phentolamine (an alpha adrenergic blocker) would counteract the pressor effect of norepinephrine (an alpha adrenergic agonist) by competitive antagonism at the vascular sympathetic effector site. Curare blocks the effect of acetylcholine at the motor end plate.

Physiological antagonism exists when a drug counteracts one effect by producing an opposite effect. The resultant antagonistic action does not have to be a specific action, and it is not always dose related. For example, sodium nitroprusside counteracts the pressor effect of norepinephrine by acting directly on vascular smooth muscle to cause dilatation. This is known as physiological antagonism.

We will discuss three drugs which possess either pharmacological or physiological antagonistic properties making them uniquely useful to us in anesthesia.

Narcotic antagonists
Clinically significant narcotic antagonists first became available in 1951 with the introduction of nalorphine (Nalline®), and later in 1956, levalorphan (Lorfan®) was introduced. Basically, it was determined that substitution of an allyl group for the methyl
group of a narcotic agent (Figure 1), produced compounds which were antagonistic to, or "reversed", the effects of their parent compound. Thereby, the concept of "reversing" narcotic-induced respiratory depression was introduced.

However, it became apparent that these earlier agents shared agonistic and antagonistic properties, which limited their usefulness. In the presence of a strong narcotic effect, they behaved as narcotic antagonists. In the presence of mild respiratory depression due to previous administration of small doses of narcotics or in respiratory depression due to non-narcotic drugs or other causes, these agents could increase respiratory depression.

These earlier narcotic antagonists often produced subjective reactions in patients which ranged from anxiety to hallucinations. In addition, these agents were observed to produce tolerance and physical dependence with withdrawal symptoms in man.

In the mid-1960's, naloxone, the N-allyl derivative of oxymorphone, (Narcan®), was made available clinically. In general, there is a close relationship between the analgesic and respiratory depressant potency of the parent compound and the potency of the antagonist derived from it. Oxymorphone was more potent than morphine, and accordingly, in terms of antagonistic potency, naloxone is 10-15 times as potent as nalorphine.

The main advantage of naloxone is that it possesses only an "antagonistic" action with no "agonistic" effects. Naloxone is the narcotic antagonist of choice, since it causes no respiratory depression on its own, no analgesia, no evidence of physical dependence or abstinence syndrome, and no psychotomimetic effects. Naloxone is also effective
in antagonizing respiratory depressant effects of non-narcotics, including penta-
zoine (Talwin®) and propoxyphene (Darvon®). In addition, naloxone has been found useful in management of overdosages of these non-narcotic anal-
gesics.

The pharmacological effects of narcotic antagonists are complex, and their mechanism of action is not completely understood. It is believed that competitive antagonism occurs between the narcotic and the antagonist for the same enzyme and receptor sites, that is, pharmacological antagonism. This may be an overly simplified concept by which it is difficult to explain the dual effects of narcotic agonist and narcotic antagonist properties in the same compound.

Receptor "dualism" has been suggested as an explanation of that interaction. Theoretically, morphine-like compounds, with strong agonistic and weak antagonistic properties act on one receptor site, whereas compounds with weak agonistic and strong antagonistic properties (like levallorphan or nalorphine) act at different receptor sites.

Naloxone is available in two strengths—0.4 mg/ml intended for adult use and 0.02 mg/ml intended for neo-
atal use in a recommended dosage of 0.01 mg/kg. Naloxone is rapidly effective when given IV, IM, or subcutaneously. The duration of action is directly proportional to the dose given and varies with the manner in which it is given. The duration of action IM is significantly longer than IV.

What is most significant is the concept of the duration of naloxone’s antagonistic action relative to the duration of action of the narcotic being reversed. The duration of action of many narcotics often exceeds that of naloxone and repeat doses of the antagonist may be necessary. There has been no convincing evidence that naloxone can reverse the respiratory depression of a narcotic without simultaneously erasing the analgesic effect of the narcotic. It is important to use naloxone in incremental doses of 0.1-0.2 mg at a time, aiming at providing that dose which will achieve adequate respiration but still allow some degree of analgesia to persist.

Naloxone is a safe drug and fairly large doses have been given in pharmacological studies without producing significant problems. The main side effects are nausea and vomiting. The largest single dose given to a patient was 10 mg IV, and the largest cumulative dose given to a patient was 1,260 ml subcutaneously, given as 15 mg subcutaneously every 4 hours for two weeks.

**Physostigmine as a reversal agent**

The second category of reversal agents involves an old drug in a new use which is becoming more widespread and popular every year. Physostigmine has been used by man for quite some time. As an extract of the calabar bean, it was utilized as a poison by the primitive peoples of Africa. In 1863, Frazer isolated the active principle and for years, physostigmine was used in oph-
thalmology as a miotic agent.

In 1958, two psychiatrists (Forrer and Miller) were using atropine in large doses (200-212 mg dose range) to produce coma as a somatic treatment for psychosis. They found that physostig-
mine in a dose of 1-4 mg IV was ca-

pable of alleviating the delirium, con-
fusion, and coma produced by atropine.

In 1968, Duvoisin and Katz reported physostigmine was useful in reversing undesirable postoperative effects associated with scopolamine as well as other hypnotics and antihistamines. The syndrome of confusion, prolonged somnolence, occasional coma, delirium and hallucinations, agitation, restlessness or hyperactivity, ataxia and speech dis-
turbances, which occurred in varying combinations and severity after the use of scopolamine, was called the Central Anticholinergic Syndrome (CAS).

The CAS may be mild and self-
limiting, but on occasion, it can be dis-
ruptive to a recovery room and haz-
ardous to a patient who is unable to
cooperate with a “stir-up” regimen or is injured through hyperactivity. There are often compelling indications to alleviate this undesirable postanesthetic effect, and physostigmine is very effective in this regard.

Physostigmine produces its cholinergic effect by inhibiting cholinesterase activity in the same manner as the other anti-cholinesterases used in anesthesia, including neostigmine, pyridostigmine, and edrophonium. The essential difference is that of all of these, physostigmine alone has a cholinergic effect both centrally and peripherally, whereas the others have no central effect.

By explanation, consider the chemical structure of these agents (Figure 2). Note that all except physostigmine have a quaternary ammonium radical present in the formula which makes these agents more highly ionized and, hence, less able to pass through the blood brain barrier to produce a central effect.

The significance of this drug in anesthesia was first apparent when physostigmine was demonstrated to be very effective in abolishing the CAS in the postanesthetic patient who was given scopolamine preoperatively, with no apparent change in level of analgesia. In recent years, a whole host of drugs\(^8\)\(^\text{14}\), (Table 1), have been demonstrated to produce the CAS, and physostigmine has been effective in alleviating the symptoms. A review of the list reveals many agents that are widely used preoperatively and intraoperatively are capable of producing undesirable residual effects in the postanesthetic state which can be “reversed” with physostigmine.

The exact mechanism of action of physostigmine in this situation is not totally clear. This action of physostigmine is apparent with the belladonna compounds and with the antihistamines that have a belladonna-like effect, thus constituting a pharmacological antagonism. The exact mode of action of tranquilizers is not known, but it is postulated that one possible method is that they may influence the levels of biological amines centrally, producing either a relative or absolute imbalance between the adrenergic and the cholinergic systems. In any event, there is no doubt that physostigmine is effective.

The dose is 1-2 mg IV, with a rapid onset of action in a few minutes. The duration of action is brief, usually less than 3-4 hours, and repeat doses may be necessary. The major side effects are cholinergic in nature and consist primarily of hypersalivation, nausea or vomiting, bradycardia, increased intestinal motility, and bronchial constriction.

All side effects should be carefully considered before use of this drug in a postanaesthetic patient. The use of an anticholinergic agent can control side effects. Some authors recommend use of atropine, while others recommend use

![Figure 2](image-url)

- Neostigmine
- Pyridostigmine
- Physostigmine
- Edrophonium
Drugs capable of producing the central anticholinergic syndrome

**Belladonna-type preparations**
1. Atropine, scopolamine
2. Synthetic belladonna preparations, primarily "gut" products
   - Mepenzolate (Cantil®)
   - Methanthilene (Banthine®)
   - Isopropamide (Darbid®)
   - Propantheline (Probanthine®)
   - Pipenzolate (Piptal®)
   - Dicyclomine (Bentyl®)
3. Belladonna eye preparations—cyclopentolate (Cyclogel®)
4. Over-the-counter preparations (combination of scopolamine and antihistamine)
   - Sominex®, Sleep-tite®, Travel-eze®, Sleep-eze®, Compoz®
5. Anti-parkinsonism drugs
   - Trihexyphenidyl (Artane®)
   - Benzotropine (Cogentin®)
   - Antihistamines
     - Diphenhydramine (Benadryl®)
     - Chlorpheniramine (ChlorTrimeton®)
     - Promethazine (Phenergan®)
6. Tranquilizers
   1. Phenothiazines
      - Chlorpromazine (Thorazine®)
      - Benactyzene (Deprol®)
      - Thioridazine (Mellaril®)
   2. Benzodiazepenes
      - Diazepam (Valium®)
      - Flurazepam (Dalmane®)
      - Doxepin (Sinequan®)
   3. Butyrophenones
      - Droperidol (Inapsine®, Innovar®)
      - Haloperidol (Haldol®)
   4. Tricyclic antidepressants
      - Amitriptyline (Elavil®, Triavil®)
      - Nortriptyline (Aventyl®)
      - Protriptyline (Vivactil®)
      - Desipramine (Pertofane®)
      - Imipramine (Tofranil®)

of an agent which acts only peripherally—for example, glycopyrolate or propantheline. Little is known of the toxicity of phystostigmine, but investigators, have given 0.05 mg/kg to healthy volunteers with no apparent problem.

These two categories of drugs just discussed represent pharmacological antagonism of undesirable residual effects in the postanesthetic patient. The final category, the analeptics, and specifically doxapram, are examples of physiological antagonism.

The analeptics—doxapram

Doxapram (Dopram®), is a synthetic compound in the same family of compounds that includes nikethamide (Coramine®), pentylene tetrazol (Metrazol®) and methyl phenidate (Ritalin®). Doxapram has several advantages over the older analeptics. It is a somewhat more specific respiratory stimulant, is
more potent\textsuperscript{16}, (twice as potent as nikel-thamide and five times as potent as methyl phenidate), and it is safer than the older drugs in that its effective dose is much lower than its convulsive dose, producing a wide margin of safety. Doxapram has been used in rather large doses postoperatively by intravenous drip with no convulsive action resulting.

Doxapram is a CNS stimulant but exerts no specific antagonism toward narcotics or other depressant drugs and has no specific antagonistic effect on muscular relaxants. Without reversing the analgesic effect of narcotics, doxapram will reverse the respiratory depressant effect of the narcotics and counteract\textsuperscript{16} the displacement of the CO\textsubscript{2} response curve by the narcotic.

In studies of postoperative anesthetic patients\textsuperscript{17}, doxapram stimulated respiration, causing increased tidal volume, minute volume, and respiratory rate, with decreased PaCO\textsubscript{2} and increased pH of arterial blood. However, the respiratory stimulation was not necessarily accompanied by an increased PaO\textsubscript{2}. This represents the area in which there is a lack of universal acceptance of the concept of using analeptic agents.

Analeptic agents have not been widely accepted in medicine because: (1) they produce a non-specific diffuse CNS stimulation which is short and self-limited, and (2) often times, the principle indication for their usage is a situation where CNS depression is also associated with hypoxia. CNS stimulation increases the brain’s requirement for oxygen; and under these circumstances, such stimulation could aggravate an already present hypoxic situation.

A more recent study\textsuperscript{18} on critically ill patients questions this concept of adverse effects from analeptic agents. The use of doxapram in these patients produced hemodynamic changes (increased mean arterial pressure and increased cardiac output) which, coupled with the ventilatory response, produced a small but significant decrease in shunting which, in turn, increased the amount of oxygen available. Both oxygen consumption and oxygen availability increased about equally in these patients, indicating that the use of doxapram may be useful, provided that myocardial reserves are not impaired.

Given this background, doxapram does appear to be useful in some situations for antagonizing undesirable residual effects in the postanesthetic state. First, doxapram may be of value in determining the cause of apnea that persists or recurs in the immediate postoperative period. If postoperative apnea is due to hypocapnia from hyperventilation, or a decreased respiratory response to an elevated PaCO\textsubscript{2} (due to narcotics, non-narcotics, or inhalational agents), or a depressed respiration from residual deep anesthesia, Doxapram will overcome this apnea and give a transient period of increased respiration, without altering the analgesic state.

In addition, if apnea is a result of residual or persistent skeletal muscle relaxation from incomplete reversal of relaxants, doxapram will produce a diaphragmatic type of respiration in varying degrees of effectiveness. Such a result can be construed as an absolute indication for ventilatory assistance with oxygen so as to avoid any CNS hypoxic disturbances.

A second use of doxapram is to hasten arousal after general anesthesia. It would appear to be most useful\textsuperscript{19} in those cases of delayed awakening after long administration of volatile agents (alone or in combination with other depressant agents), since improved ventilation would speed up elimination of the inhalational drug. However, it has also been used to hasten arousal following intravenous anesthesia with thiopental and methyl hexital\textsuperscript{20}. Doxapram does not affect the speed of metabolism of barbiturates, and there is no assurance that the stimulant effect of doxapram will always outlast the residual effects of the barbiturates.

Doxapram is available in a solution
of 20 mg/ml with the usual dose of 1-2 mg/kg as an IV bolus or 0.2-0.4% solution as an IV drip. When given as a bolus, the peak effect occurs in 2 minutes, with a duration of action of 5-10 minutes. The duration of action by IM use is significantly longer, and a prolonged effect can be obtained by using an IV drip. The clinically available solution of doxapram (Dopram®) has a pH of 3.5-5.0, and the larger volumes required (5-10 ml) for IM use cause significant muscle pain which may last for a considerable time⁶.

All CNS stimulants can cause convulsions, but doxapram has been given to epileptic patients postoperatively in doses of 10 mg/kg per half hour without seizures¹⁷. The possibility of seizures should be considered and treatment with diazepam or barbiturates should be readily available.

The other major side effect is the release of catecholamines and doxapram can produce hypertension, tachycardia, or arrhythmias. These effects would be more marked in patients receiving sympathomimetic drugs. Thus, doxapram should be used cautiously in patients who are receiving inhalational agents such as halothane, methoxyflurane, and possibly enflurane, which sensitize the myocardium to catecholamines.

REFERENCES

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