Kirk-Othmer Encyclopedia of Chemical Technology.

ANESTHETICS

The term anesthesia comes from the Greek "anaisthai" or insensibility and constitutes a state in which perception of noxious events such as surgical procedures are imperceptible. This state may or may not be accompanied by loss of consciousness. A complete or general anesthetic given by the inhalation or intravenous route produces hypnosis (profound sleep), analgesia, muscle relaxation, and protection against the increase in blood pressure and heart rate resulting from surgical stress (maintains homeostasis). An anesthetic which blocks the neural transmission of painful stimuli through afferent nerves and does not affect the level of consciousness can be classified as a local anesthetic.

The induction of general anesthesia produces a progressive deepening of the anesthetic state and represents, in the anatomical sense, a descending desensitization of the central nervous system (CNS). A progression of clinical signs are useful for estimating the depth of anesthesia. These signs vary somewhat for each anesthetic, but in general four stages can be defined (1): (*1*) State of altered consciousness and analgesia indicative of action on cerebral canticle areas begins. (*2*) Loss of consciousness, often accompanied by delirium and excitement, occurs. Irregular respiration and motor movement result from depression of higher motor inhibitory centers with the release of lower motor mechanisms. (*3*) Stage of surgical anesthesia is reached in which spinal cord and spinal reflexes are abolished providing relaxation of skeletal musculature. Within the four planes in this state are loss of corneal, conjunctival, pharyngeal, and laryngeal reflexes as the depth of anesthesia progresses. (*4*) Onset of respiratory paralysis occurs resulting from significant depression of the medullary respiratory center. Subsequent cardiovascular collapse ensues.

Most signs which require a skeletal muscle reflex would not be apparent after treatment with a neuromuscular blocking drug or would be altered significantly by preoperative drugs. In these cases central nervous system monitoring via an electroencephalogram (EEG), and hemodynamic and blood gas monitoring, help assess the depth of anesthesia. The potency of inhaled agents is expressed as the minimum alveolar concentration (MAC) that is required to prevent spontaneous movement in response to a surgical or equivalent stimulus in 50% of patients (2).

The onset of action is fast (within 60 seconds) for the intravenous anesthetic agents and somewhat slower for inhalation and local anesthetics. The induction time for inhalation agents is a function of the equilibrium established between the alveolar concentration relative to the inspired concentration of the gas. Onset of anesthesia can be enhanced by increasing the inspired concentration to approximately twice the desired alveolar concentration, then reducing the concentration once induction is achieved (3). The onset of local anesthetic action is influenced by the site, route, dosage (volume and concentration), and pH at the injection site.

1. Theories of General Anesthesia

Although the modern practice of anesthesia is exceedingly sophisticated, the basic molecular mechanism underlying it is still lacking. Even whether the target sites of the inhalational anesthetics are lipid or protein

remains unknown, although it is likely that proteins are intimately involved. The inhalational anesthetics are very diverse chemically and extrapolation from the effect of a particular agent to the physiological state of anesthesia is problematic. However, anesthesia theories may be roughly divided into two categories: lipid theories and protein theories (4–6).

1.1. Lipid Theories

Although there are many varieties of the lipid theory, all postulate that inhalational anesthetics exert their primary effects by dissolving in the lipid portions of nerves thereby altering the conductivity. This theory is based on observations made at the turn of the twentieth century on the relationship between anesthetic potency and the partition coefficient of the agent between olive oil and gas (7–9). The anesthetic potency of a wide variety of anesthetics, covering four orders of magnitude, correlates exceedingly well with the agent's oil-gas partition coefficient.

The primary site of action is postulated to be the lipid matrix of cell membranes. The lipid properties which are said to be altered vary from theory to theory and include: enhancing membrane fluidity; volume expansion; melting of gel phases; increasing membrane thickness, surface tension, and lateral surface pressure; and encouraging the formation of polar dislocations (10, 11). Most theories postulate that changes in the lipids influence the activities of crucial membrane proteins such as ion channels. The lipid theories suffer from an important drawback: at clinically used concentrations, the effects of inhalational anesthetics on lipid bilayers are very small and essentially undetectable (6, 12, 13).

1.2. Protein Theories

The direct interaction of inhalation anesthetics and proteins (qv) has been proposed as the cause of anesthesia (12, 14). An inhalation agent, whether a noble gas or a fluorinated ether, could dissolve asymmetrically in a protein (6, 15). Resultant conformational changes in the protein, if these changes occur, could then cause changes in activity, for example, the chloride ion channel which is modulated by many of the intravenous agents. Quantitative data on the binding of anesthetics to proteins are limited but are related to anesthetic partition coefficients (16, 17). Although binding to a soluble protein and modulation of its function are not necessarily coupled (18, 19), the proteins of interest are those involved in nerve impulse transmission and are embedded in lipid membranes. Thus dissociation of lipid and protein effects is not possible.

The membrane enzyme luciferase , responsible for light emission in fireflies, is sensitive to anesthetics (20, 21), and the concentrations of inhalational agents which inhibit luciferase are the same as those which cause general anesthesia. Studies of various classes of inhalational agents and luciferase demonstrated that above a certain chain length in a homologous series, a point is reached where higher members are not anesthetic. The same cut-off effect in efficacy is observed in anesthesia (22). This effect is not explainable by lipid theory.

2. Anesthetic Agents

2.1. Inhalation Agents

An ideal inhalation anesthetic would exhibit physical, chemical, and pharmacological properties allowing safe usage in a variety of surgical interventions. The agent should be odorless, nonflammable at concentrations which are likely to be used in the operating room, and stable both on storage and to soda lime , which is used as the CO_2 absorber in the anesthetic circuit. Induction of, and recovery from, anesthesia should be rapid, and minimal side effects should be observed on the cardiovascular (depression and epinephrine compatibility) or central nervous systems (EEG activation) (see Epinephrine and norepinephrine; Neuroregulators). The drug should not be metabolized.

Table 1. Properties and Partition Coefficients of Inhalation Anesthetics

Agent	CAS Registry Number	Molecular formula	Partition coefficients[a]		Boiling point, °C	Year introduced
			Oil/gas	Blood/gas		
ethyl ether	[60-29-7]	$C_4H_{10}O$	65	12.1	35	1842
chloroform	[67-66-3]	$CHCl_3$	394	8.4	61	1847
trichloroethylene	[79-01-6]	C_2HCl_3	200–250	9.0	87	1934
fluoroxene	[406-90-6]	$C_4H_5F_3O$	47	1.37	43.1	1960
halothane	[151-67-7]	$C_2HBrClF_3$	224	2.3	50.2	1956
isoflurane	[26675-46-7]	$C_3H_2ClF_5O$	90.8	1.4	48.5	1980
enflurane	[13838-16-9]	$_3H_2ClF_5O$	96.5	1.9	56.5	1972
methoxyflurane	[76-38-0]	$C_3H_4Cl_2F_2O$	970	12.0	105	1962
sevoflurane	[28523-86-6]	$C_4H_3F_7O$	42	0.6	58	1989
desflurane	[57041-67-5]	$C_3H_2F_6O$	18.7	0.42	23.5	
nitrous oxide	[10024-97-2]	N_2O	1.4	0.46	−89.5	1850s
cyclopropane	[75-19-4]	C_3H_6			−33	1934

[a] Ref. 23.

A number of inhalation anesthetics have been introduced to clinical practice, some of which are listed in Table 1. All agents introduced after 1950, except ethyl vinyl ether, contain fluorine. Agents such as ether, chloroform, trichloroethylene (Trilene), cyclopropane, and fluoroxene (Fluoromar), which were once used, have been displaced by the newer fluorinated anesthetics.

2.1.1. Historical Inhalation Agents

Diethyl ether produces excellent surgical anesthesia, but it is flammable (see Ethers). Chloroform is a nonflammable, sweet smelling, colorless liquid which provides analgesia at nonanesthetic doses and can provide potent anesthesia at 1% (see Chlorocarbons and chlorohydrocarbons). However, a metabolite causes hepatic cell necrosis. Trilene, a nonflammable colorless liquid, has a slower onset and recovery and a higher toxicity and chemical reactivity than desirable. Cyclopropane is a colorless gas which has rapid induction (2–3 min) and recovery characteristics and analgesia is obtained in the range of 3–5% with adequate skeletal muscle relaxation (see Hydrocarbons). The use of cyclopropane has ceased, however, because of its flammability and marked predisposition to cause arrhythmias.

Because of the flammable nature of diethyl ether and cyclopropane, a number of hybrid molecules were prepared in an attempt to improve on the useful characteristics of each, but none were marketed (24, 25). Structure activity relationships for halogenated hydrocarbons and ethers (26) indicated that fluorine (qv) was the most suitable halogen to use in order to decrease the potential for cardiac arrhythmias. In addition, the introduction of fluorine decreases flammability and boiling point and increases stability (see Fluorine compounds, organic). It also decreases anesthetic potency. Fluoroxene, 2,2,2-trifluoroethyl vinyl ether [406-90-6] , the first fluorinated ether prepared and commercialized (27), has oil/gas and blood/gas partition coefficients (Table 1) lower than ether, chloroform, or Trilene, contributing to a rapid onset and recovery. This agent is less potent (MAC = 3.4%) than other fluorinated hydrocarbons introduced later and its flammability is close to MAC. Whereas the agent is stable to soda lime, it is readily oxidized and hydrolyzed to trifluoroethanol and acetaldehyde and is unstable to light (28). Fluoroxene is also metabolized to a significant extent (29, 30). Thus it is no longer used.

2.1.2. Clinical Inhalation Agents

2.1.2.1. Nitrous Oxide. Nitrous oxide, described by Priestly in 1772, was first used to relieve severe dental pain in the latter part of the 18th century. Sometime in the mid-1800s N_2O was successfully used as an

anesthetic, and its widespread usage coincided with the development of anesthesia machines. Nitrous oxide is a nonflammable, colorless, odorless, and tasteless gas that can exist as a liquid under pressure at room temperature. It is normally stored in cylinders. However, it supports combustion.

A mixture of 20% nitrous oxide and 80% oxygen produces analgesia equivalent to 15 mg of morphine in humans (see Analgesics, antipyretics, and antiinflammatory agents) (31, 32). Effects of nitrous oxide can be partially reversed using opiate antagonists and it has been suggested that the agent interacts with endogenous opioids (23, 33, 34) (see Opioids, endogenous). Because of analgesic properties, N_2O is added to other inhaled anesthetics and to opioids at concentrations usually between 30 and 70% in oxygen. Nitrous oxide is a very weak anesthetic, $\mathrm{MAC} = 104\%$. However, the blood/gas partition coefficient has been established to be about 0.46 (35, 36) allowing the agent to come into rapid equilibrium with the inspired and alveolar concentrations (37). Because of poor solubility in blood and other tissues, induction and recovery from nitrous oxide administration is rapid.

Nitrous oxide produces respiratory depression (38, 39). It has been shown to produce a direct myocardial depressant effect in dogs (40) and in humans breathing a 40% N_2O/60% oxygen mixture (41); however, this may be offset by the activation of the sympathetic nervous system (42). The combination of nitrous oxide and opioids can produce decreases in myocardial contractility, heart rate, and blood pressure (43).

There appear also to be toxic effects. In animals, nitrous oxide has been shown to inactivate methionine synthetase which prevents the conversion of deoxyuridine to thymidine and thus has the potential for inducing megaloblastic anemia, leukopenia, and teratogenicity (44–46). A variety of epidemiologic surveys suggest positive correlations between exposure to nitrous oxide and spontaneous abortion in dental assistants (47).

2.1.2.2. Methoxyflurane. Methoxyflurane (2,2-dichloro-1,1-difluoroethyl methyl ether) [76-38-0] , a clear colorless liquid having a vapor pressure of 2.70 kPa (20.3 mm Hg) at 20°C, is not irritating to the respiratory tract. Its odor has been described as sweet or fruity. Whereas the odor may make this agent suitable for inhalation induction, the blood/gas and oil/gas partition coefficients (Table 1) are very high and thus onset and recovery are the slowest of all anesthetics (48). Methoxyflurane is stable to light and soda lime, but not to oxygen; it is nonflammable and nonexplosive at anesthetic concentrations (28). Methoxyflurane is the most potent of the inhaled anesthetics having $\mathrm{MAC} = 0.6\%$. The agent is both a respiratory and cardiovascular depressant (49). It also produces muscle relaxation as the depth of anesthesia increases.

Approximately 50% of an absorbed dose is transformed to fluoride ion, dichloroacetic acid , methoxydifluoroacetic acid , and oxalic acid (50). Because of fluoride ion associated renal impairment, the duration of anesthesia using methoxyflurane must be limited (51, 52).

2.1.2.3. Halothane. Halothane or Fluothane , 2-bromo-2-chloro-1,1,1-trifluoroethane [151-67-7] , is a colorless liquid with a pleasant odor. Its lower flammability limit, 4.8% in 70% N_2O/30% O_2, renders it essentially nonflammable. It has a vapor pressure of 32.5 kPa (244 mm Hg) at 20°C and is stable to soda lime. However, it is photochemically reactive.

Halothane is a potent anesthetic having a MAC value of 0.77%. MAC requirements, as in other inhaled anesthetics, increase in younger patients and decrease in the elderly (53). Halothane is a cardio-respiratory depressant which produces changes in cardiac output and arterial pressure comparable to the other inhalation agents, isoflurane or enflurane. Halothane does not decrease peripheral vascular resistance as do these others. It is also the least likely of the inhalants to cause an increase in heart rate. The ability of halothane to sensitize the heart to arrhythmogenic effects of epinephrine is the greatest of the inhalants (54), although halothane produces less muscle relaxation than isoflurane (55). Approximately 20% of an absorbed dose of halothane is oxidatively metabolized to trifluoroacetic acid (56, 57) and halothane has been implicated in producing liver dysfunction in a very small number of patients (58). Fluoride produced from the biodegradation of halothane or the other agents has little effect on normal kidney function (59). Halothane usage has been declining because of the potential liver effects, although the agent is used where inhalation induction is desired, especially in pediatrics.

2.1.2.4. Enflurane. Enflurane or Ethrane, 2-chloro-1,1,2-trifluoroethyl difluoromethyl ether[13838-16-9] , was synthesized in 1963. This agent is a mildly pungent colorless liquid having a vapor pressure of 22.85 kPa (171.8 mm Hg) at 20°C. Enflurane is stable to soda lime and light (28). The minimum flammable concentration is 5.8% in 70% N_2O/30%O_2, placing its flammability between that of halothane and isoflurane. Enflurane is the least potent of the inhaled anesthetics marketed in 1990. It has a MAC value of 1.7% (60), although the solubility characteristics of enflurane are similar to those of isoflurane and halothane (Table 1) and recovery is both rapid and less complicated by nausea than in the case of halothane (61–63).

When compared with isoflurane and halothane at equi-anesthetic concentrations, enflurane produces a greater degree of respiratory depression (64). Hemodynamic parameters such as cardiac output, stroke volume, and blood pressure decrease where heart rate is only slightly changed. Surgical stimulation tends to reverse depressed cardiac output and arterial blood pressure (65). In the presence of epinephrine, enflurane does not potentiate arrhythmias to the same extent as halothane (66). Enflurane provides muscle relaxation and when combined with neuromuscular blocking drugs, the block is enhanced, allowing lower doses of the relaxant to be used (67, 68). Unlike other inhalational anesthetics, enflurane at high concentrations causes EEG changes which are seizurelike. Enflurane is oxidatively metabolized in the liver. In humans, about 2.4% of the enflurane is metabolized (69), but clinically significant hepatic dysfunction is rare.

2.1.2.5. Isoflurane. Isoflurane or Forane , 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether [26675-46-7] , was prepared in 1965 (28). It is a clear, colorless liquid having a vapor pressure of 31.85 kPa (239.5 mm Hg) at 20°C. It has an ethereal odor which may limit the rate at which the inspired concentration may be increased for a rapid induction. The agent is stable to soda lime and light, and does not react with metals. The minimum flammable concentration is 7% in 70% N_2O/30% O_2. Isoflurane is a potent anesthetic having a MAC value of 1.15% in O_2 (70). MAC requirements are decreased by increasing age, decreasing body temperature, pregnancy, and a variety of depressant drugs. This agent is the least soluble of the modern volatile agents (Table 1) allowing for a rapid onset and recovery.

Isoflurane is a respiratory depressant (71). At concentrations which are associated with surgical levels of anesthesia, there is little or no depression of myocardial function. In experimental animals, isoflurane is the safest of the oral clinical agents (72). Cardiac output is maintained despite a decrease in stroke volume. This is usually because of an increase in heart rate. The decrease in blood pressure can be used to produce "deliberate hypotension" necessary for some intracranial procedures (73). This agent produces less sensitization of the human heart to epinephrine relative to the other inhaled anesthetics. Isoflurane potentiates the action of neuromuscular blockers and when used alone can produce sufficient muscle relaxation (74). Of all the inhaled agents currently in use, isoflurane is metabolized to the least extent (75). Unlike halothane, isoflurane does not appear to produce liver injury and unlike methoxyflurane, isoflurane is not associated with renal toxicity.

Isoflurane is the most widely used inhalational anesthetic and more closely approaches the ideal than other marketed drugs. It has found application in the anesthetic management of all types of surgical procedures.

2.1.3. Developmental Inhalational Agents

2.1.3.1. Sevoflurane. Sevoflurane, 1,1,1,3,3,3-hexafluoro-2-propyl fluromethyl ether [28523-86-6] , is nonpungent, suggesting use in induction of anesthesia. The blood/gas partition coefficient is less than other marketed products (Table 1) yet similar to nitrous oxide, suggesting fast onset and recovery. In animal studies, recovery was faster for sevoflurane than for isoflurane, enflurane, or halothane (76). Sevoflurane is stable to light, oxygen, and metals (28). However, the agent does degrade in soda lime (77).

Sevoflurane is less potent than clinically used inhalation agents having MAC of 1.71% and 2.05% in humans (78, 79). Sevoflurane is also a respiratory depressant similar to other agents (78, 80) decreasing both blood pressure and heart rate (80). Sevoflurane decreases myocardial oxygen blood flow (81) and the potential to sensitize the mycocardium to epinephrine induced arrhythmias is similar to isoflurane (82). Other positive characteristics include sufficient muscle relaxation and an EEG pattern which is devoid of convulsant activity

(78, 79). Sevoflurane appears to have advantages over current products, especially in regard to onset, recovery, and no increase in heart rate. The primary disadvantage appears to be its instability to soda lime. The drug was launched in Japan in late 1989.

2.1.3.2. Desflurane. Suprane or desflurane, 1,2,2,2-tetrafluoroethyl difluoromethyl ether [57041-67-5] , has a structure similar to isoflurane except for the substitution of a fluorine for the chlorine on the alpha methyl carbon. The agent has a vapor pressure of 88.3 kPa (664 mm Hg) at 20°C. The partition coefficients for blood/gas and tissue/gas (Table 1) suggest that this agent should have a faster onset and recovery than current agents including sevoflurane (76, 83). Its odor is milder than isoflurane when used for induction. In unpremedicated patients upper airway tolerance was good: only transient coughing and easily managed secretions were observed. Desflurane is stable to O_2, light, and metals, and also to soda lime in systems where sevoflurane, halothane, and isoflurane are forced to degrade (84).

Desflurane is less potent than the other fluorinated anesthetics having MAC values of 5.7 to 8.9% in animals (76, 85), and 6% to 7.25% in surgical patients. The respiratory effects are similar to isoflurane. Heart rate is somewhat increased and blood pressure decreased with increasing concentrations. Cardiac output remains fairly stable. Desflurane does not sensitize the myocardium to epinephrine relative to isoflurane (86). EEG effects are similar to isoflurane and muscle relaxation is satisfactory (87). Desflurane is not metabolized to any significant extent (88, 89) as levels of fluoride ion in the serum and urine are not increased even after prolonged exposure. Desflurane appears to offer advantages over sevoflurane and other inhaled anesthetics because of its limited solubility in blood and other tissues. It is the least metabolized of current agents.

2.2. Intravenous Anesthetic Agents

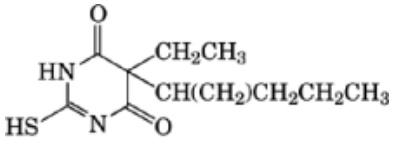
The intravenous (iv) anesthetic agents are of two types: those which are used to induce, but not maintain, anesthesia, and those which are useful not only for induction, but also for maintenance. The period of induction is perhaps the most crucial part of the anesthesia. The need is for an anesthetic agent having an extremely fast rate of onset and limited side effects. Fast onset minimizes the stress and agitation which could arise during a more lengthy induction. An ideal maintenance iv anesthetic has been a goal for over a century. Various classes of compounds have been used. Among these are: barbiturates , opioids , and hindered phenols . But the ideal agent for both induction and maintenance has not yet been found. For this reason, balanced anesthesia is often used: a potent opioid is combined with an inhalational agent.

A major difference between the inhalational agents and the iv anesthetics is that the former probably exert their biological activity through physical effects while the latter, in most cases, function through a biological receptor mediated pathway. There are two primary biochemical receptors used for iv anesthesia in the CNS, the gabaergic (90) and the opiate (91). The γ-aminobutyric acid [56-12-2] (GABA) receptor controls a chloride ion channel and the GABA receptor itself is modulated by various drug receptors for the barbiturates, anesthetic steroids, and benzodiazepines. An increase in GABA binding results in a variety of effects: anesthesia, sleep, amnesia, muscle relaxation, and an antianxiety effect. The opiate receptor, of which there are various types, controls analgesia (92). Its primary endogenous ligands are the enkephalins and endorphins . However, the more familiar plant alkaloid morphine [57-27-2] also binds strongly to this receptor (93). Because anesthesia using iv agents is receptor based, antagonists have been developed which can reverse the activity of these anesthetics.

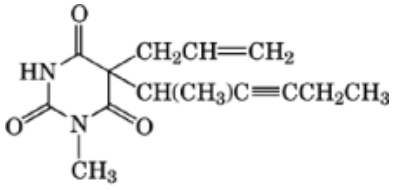
2.2.1. Barbiturates

The first class of readily accepted iv anesthetics were barbiturates . This group's biological activity results from interaction with a drug receptor that modulates GABA binding (94, 95). The first of these agents was thiopental [76-75-5] (Pentothal a) $C_{11}H_{18}N_2O_2S$, (**1**) which is still the most widely used drug for induction. Thiopentone is an ultra short-acting depressant for the CNS which induces hypnosis and amnesia, but not analgesia, within one armbrain circulation time (30–40 s) (96). Its action is predictable, induction is smooth, and recovery after

a small dose is rapid, accompanied by some somnolence and retrograde amnesia. The agent does, however, cause respiratory and cardiovascular depression and it accumulates as a result of redistribution into the fatty tissues, so repeated doses are not advisable (97). A general problem with thiobarbiturates is a poor therapeutic index. There is continued research into safer, more effective iv anesthetics (98).



(**1**)

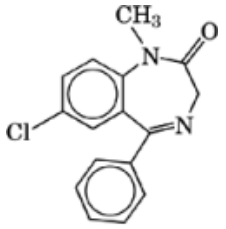


(**2**)

Methohexital [18652-93-2] (Brevital), $C_{14}H_{18}N_2O_3$, (**2**) is a barbiturate iv anesthetic induction agent that has a slightly faster onset than thiopentone and less accumulation. The recovery from anesthesia is also slightly faster and better. However, induction is associated with an increased incidence of excitatory phenomena. Methohexital also causes respiratory and cardiovascular depression and is unstable in solution, necessitating reconstitution before use (99).

2.2.2. Benzodiazepines

Librium and Valium were first introduced for their muscle relaxant activity, but became widely used for their antianxiety (minor tranquilizer) activity. The benzodiazepines bind to a drug receptor which modulates the binding of GABA to its receptor (100). Diazepam [439-14-5] (Valium), $C_{16}H_{13}ClN_2O$, (**3**) is used as a premedicant to anesthesia to lessen preoperative anxiety and to prevent recall of the operative procedure. Midazolam [59467-70-8] (Versed) $C_{18}H_{13}ClFN_3$, (**4**) a water soluble benzodiazepine having a shorter duration of action than diazepam (101), has specific applications in anesthesia. Its primary intramuscular use is as a premedicant similar to diazepam. As an iv anesthetic it is comparable to thiopentone for induction but has a slower onset, approximately 1.5 min after opioid premedication and 2–2.5 min without. Recovery is slower using midazolam than it is using thiopentone.



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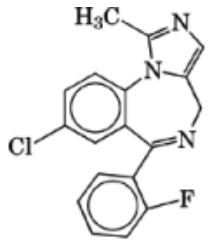

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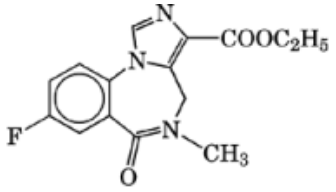
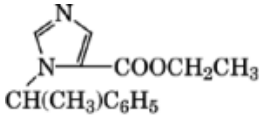


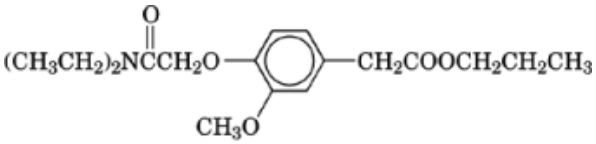
(**5**)

Midazolam and diazepam decrease arterial pressure without a change in heart rate. Like thiopentone, midazolam is a respiratory depressant. Advantages of midazolam are its amnestic effect, coupled with less postoperative depression (102). A reversal agent for the benzodiazepines has also become available. Flumazenil [78755-81-4] , $C_{15}H_{14}FN_3O_3$, (**5**) displaces the benzodiazepines from their receptor but has little demonstrable activity of its own (103, 104).

2.2.2.1. Etomidate. Etomidate [33125-97-2] (Hypnomidate , Amidate), $C_{14}H_{16}N_2O_2$, (**6**) is a relatively simple imidazole carboxylic ester developed in the 1970s as an iv anesthetic that became available in the United States in the mid-1980s (105). Etomidate has almost as rapid an onset and short duration of action as thiopentone, but it is approximately twelve times as potent. In contrast to other agents, it is rapidly and extensively metabolized by liver and plasma esterases. It causes less respiratory and cardiovascular depression than thiopentone and does not release histamine. In addition to pain on injection, there is frequent occurrence of extraneous muscle movement (myoclonus), controllable by benzodiazepine or opiate premedication (106). There is also a relatively high frequency of nausea and vomiting, particularly when opiate premedication is used. Despite these disadvantages, etomidate is extensively used in neuro and cardiovascular surgery (107).



(**6**)



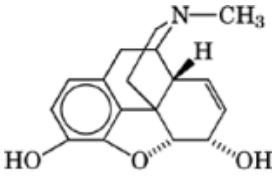
(**7**)

2.2.2.2. Propanidid. Propanidid [1421-14-3] (Epontol), $C_{18}H_{27}NO_5$, (**7**) a derivative of the propyl ester of homovanillic acid, has been in clinical use in Europe for a number of years. Its main advantage is rapid onset of action and a fast recovery which, like etomidate, is because of rapid metabolism by esterases rather than redistribution (108). Excretion is rapid: 75 to 90% of the drug is eliminated as metabolites within two hours. Propanidid side effects include hypotension, tachycardia, and hyperventilation followed by apnea, as well as excitatory side effects such as tremor and involuntary muscle movement (109).

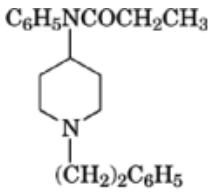
2.2.2.3. Propofol. 2,6-Diisopropylphenol [2078-54-8] , propofol , $C_{12}H_{18}O$, is a newer intravenous anesthetic used for both induction and maintenance (110). This drug, also known as Diprivan , is chemically unlike any of the previously described iv agents and was developed following the discovery of the anesthetic activity of the 2,6-diethyl analogue (111). Propofol itself is insoluble in water and is usually formulated in a soya bean oil emulsion. Propofol induction, with or without an opioid, is smooth and similar to that of other agents, although pain at the injection site and apnea have been reported (112, 113). Recovery after induction and maintenance is faster, with fewer side effects, than with thiopentone (114), although sexual disinhibition has been anecdotally reported (115). Propofol is rapidly distributed, metabolized, and eliminated (116).

2.2.2.4. Opioids. Morphine [57-27-2] , $C_{17}H_{19}NO_3$, (**8**) the most prevalent and analgesically potent of the naturally occurring opium alkaloids (qv), has been used as an anesthetic premedication for over one hundred years (93). It has also been used as an iv analgesic for the last four decades, and, since 1969, in high doses as an anesthetic agent (117).

Morphine has certain undesirable side effects. Among these are respiratory depression, nausea, and vomiting, depression of the cough reflex, cardiovascular depression and hypotension, smooth muscle contraction (constipation), and histamine release (93). Morphine's onset of action, duration, and low therapeutic indices have prompted a search for a more effective opiate iv anesthetic. Extreme simplification of the complex morphine molecule has resulted in anilido–piperidines, the fentanyl class of extremely potent opiate iv anesthetics (118, 119).



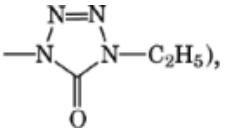
(**8**)



(**9**)

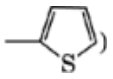
Fentanyl [437-38-7] (Sublimaze , Leptanal), $C_{22}H_{28}N_2O$, (**9**) has been extensively used since its introduction into clinical practice in the 1960s (119). Because of its potency, which is 50–100 times that of morphine, a rapid onset of action and a short duration, its use as an iv anesthetic is widespread. The short duration results from redistribution from the brain to other tissues, rather than elimination. It does, however, have the usual opiate disadvantages; respiratory depression, chest wall rigidity, nausea, and bradycardia. Fentanyl has an extremely wide therapeutic ratio. The size of the dose influences its duration of action which, after iv administration, may last from approximately 30 min to 2 to 3 h (120, 121). In cardiac surgery fentanyl is administered in very large doses to produce profound analgesia and suppress cardiovascular reflex responses. This technique is particularly useful for patients with compromised circulation where any increase in cardiac demand could precipitate myocardial ischemia (122).

Approved for clinical use in 1986, alfentani [71195-58-9](Alfenta, Rapifen),

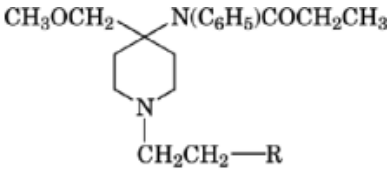
$C_{21}H_{32}N_6O_3$, (**10**, R = ),

is about one fourth as potent as fentanyl and has a rapid onset. Alfentanil has an extremely short duration of action, from 0.2–0.3 times that of fentanyl (123, 124), paralleling its rapid elimination. Thus alfentanil has been given by infusion pumps. Although alfentanil has the usual opiate side effects, its rapid elimination leads to a more rapid recovery and less frequent side effects and complications (125, 126).

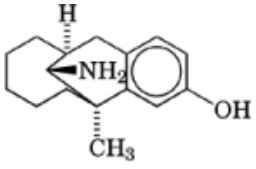
Sufentanil [56030-54-7] (Sufenta),

$C_{22}H_{30}N_2O_2S$, (**10**, R = )

is five to ten times as potent as fentanyl. Sufentanil also has a short duration of action, but has an extremely high therapeutic ratio (127). Sufentanil, with less respiratory depression than either alfentanil or fentanyl, is used in high dose opioid anesthesia for cardiac surgery, and as a low dose supplement in balanced anesthesia for general and outpatient surgery (128, 129).



(**10**)



(**11**)

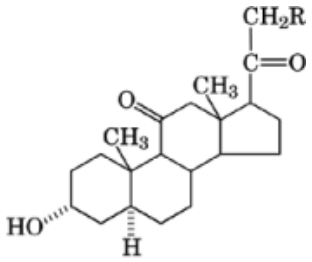
Dezocine [53648-55-8] (Dalgan), $C_{16}H_{23}NO$, (**11**) is an opiate having both agonist and antagonist properties which lowers MAC requirements for cyclopropane with a ceiling effect on respiratory depression in rats (130) and reduces the MAC requirement for enflurane in dogs (131). Dezocine was effective against post operative pain, producing sedation as a primary side effect (132). The compound has also produced respiratory depression in volunteers but was reported to have a ceiling effect (133, 134), and there has been a suggestion of psychotomimetic effects (134).

2.2.3. Opioid Reversal Agents

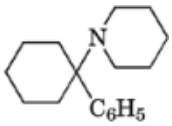
At the end of a surgery, when the decision is made to reverse opioid induced activity, the primary concern is to eliminate the respiratory depressant effects inherent in the potent opiates used as anesthetics. This reversal, brought about by opioid reversal agents (Table 2), can also diminish the analgesic effects of the opiates. There are two types of reversal agents: pure antagonists and mixed agonist–antagonists. Antagonism of the opiate agonist effect may be viewed as lowering agonist activity below a series of thresholds. The dose can be titrated so that a significant degree of analgesia can remain even though clinically significant respiratory depression is reversed. The antagonists naloxone (**12**, R = C_3H_5) and naltrexone (**12**, R = C_4H_7) are the most commonly used, although the use of the agonist–antagonist nalbuphine (**15**, R = C_4H_7) is increasing because it maintains a moderate level of analgesia while reversing the side effects (143). Nalmefene (**13**), a long acting reversal agent, is in clinical trials (144). The agonist–antagonist nalorphine (Lethidrone) (**15**, R = C_2H_3) is not available in the United States. Levallorphan (**14**) is little used because of nalorphinelike psychotomimetic effects.

2.2.4. Steroid Anesthetics

The anesthetic properties of a number of steroids were discovered in 1941 (145) and Althesin , a mixture of alfaxalone [23930-19-0] , $C_{21}H_{32}O_3$, (**16**, R = H), and alfadone acetate [23930-37-2] , $C_{23}H_{34}O_5$, (**16**, R = $OOCH_3$), was introduced in 1971 (146). *Althesin* appeared to have many of the ideal iv anesthetic properties. However, it was associated with a high incidence of allergic reactions and implicated in the development of renal failure (147); it was withdrawn in 1984. Like the barbiturates and benzodiazepines, the anesthetic steroids bind to a drug receptor which modulates GABA control of a chloride ion channel (148, 149).

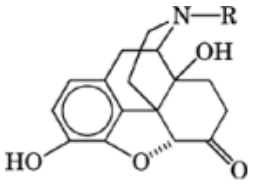
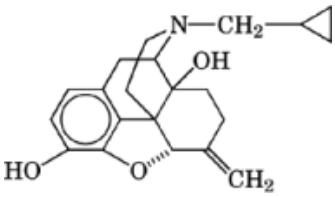
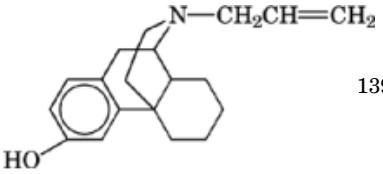
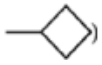
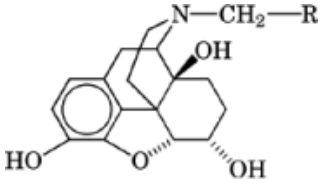


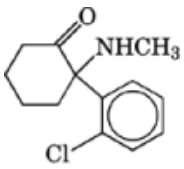
(16)



(17)

Table 2. Opioid Reversal Agents

Compound name	CAS Registry Number	Trade name	Molecular formula	Structure number	Structure	Reference
				Antagonists		
naloxone	[465-65-6]	Narcan	$C_{19}H_{21}NO_4$	(**12**, R = $CH_2CH{=}CH_2$)		135
naltrexone	[16590-41-3]	Trexan	$C_{20}H_{23}NO_4$	(**12**, R = )		(136–138)
nalmefene	[55096-26-9]		$C_{21}H_{25}NO_3$	(**13**)		144
				Agonist–antagonists		
levallorphan	[152-02-3]	Lorfan	$C_{19}H_{25}NO$	(**14**)		139
nalorphine	[62-67-9]	Lethidrone	$C_{19}H_{21}NO_3$	(**15**, R = $CH{=}CH_2$)		(140, 141)
nalbuphine	[20594-83-6]	Nubain	$C_{21}H_{27}NO_4$	(**15**, R = )		(142, 143)

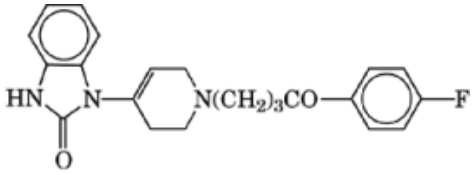


(**18**)

2.2.5. Other Anesthetic Agents

Dissociative anesthesia is so called because of the feeling of dissociation engendered by administration of drugs related to phencyclidine [77-10-1] (PCP), $C_{17}H_{25}N$, (**17**). The anesthesia, different from that produced by the inhalational and other iv agents, is characterized by a trancelike cataleptic state. However, the eyes can remain open and light reflexes are retained. Ketamine [6740-88-1] (Ketalar), $C_{13}H_{16}ClNO$, (**18**) is chemically related to phencyclidine (150). Ketamine anesthesia is characterized by rapid onset but slow recovery, a profound analgesia, and a lack of clinical cardiovascular depression. Unlike other iv agents, it can also be administered intramuscularly. Its greatest disadvantage is that, like PCP, it is a potent psychotomimetic. For this reason, it is only used for trauma patients, asthmatics, children, and patients at high risk (151).

Neuroleptic analgesia is so called because the combination of a major tranquilizer, a neuroleptic drug, and a potent opiate produces an anesthetic state characterized by sedation, apathy, and mental detachment (see Psychopharmacological agents) (152). Innovar [8067-59-2] , a combination of droperidol [548-72-2] , $C_{22}H_{22}FN_3O_2$, (**19**) and fentanyl (**9**) citrate, is used for procedures that do not require muscle relaxation. However, the onset of action is slow.



(**19**)

2.3. Local Anesthetics

Local anesthetics produce anesthesia by blocking nerve impulse conduction in sensory, as well as motor nerve, fibers. Nerve impulses are initiated by membrane depolarization, effected by the opening of a sodium ion channel and an influx of sodium ions. Local anesthetics act by inhibiting the channel's opening; they bind to a receptor located in the channel's interior. The degree of blockage on an isolated nerve depends not only on the amount of drug, but also on the rate of nerve stimulation (153–156).

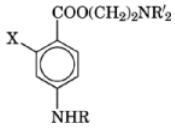
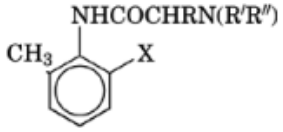
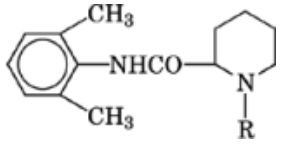
Local anesthetic activity is usually demonstrated by compounds which possess both an aromatic and an amine moiety separated by a lipophilic hydrocarbon chain and a polar group (153, 157). A selection of local anesthetic agents is given in Table 3. In the clinically useful agents, the polar group is an ester (**20**) or an amide (**21**). Activity may be maintained, however, when the polar function is an ether, thioether, ketone, or thioester. The amino esters, more susceptible to hydrolysis than the amino amides, are metabolized in the plasma by cholinesterases . The metabolites of the amino esters are derivatives of 4-aminobenzoic acid (PABA) and these substances are capable of inducing allergic reactions in a small percentage of patients. The amino amides undergo enzymatic degradation in the liver and allergic reactions are rare.

2.3.1. Pharmacological Profile

The profile of the ideal local anesthetic agent depends largely on the type and length of the surgical procedure for which it is applied (157). Procedures could include neuraxial (spinal and epidural) anesthesia, nerve and plexus blocks, or field blocks (local infiltration). In general, the ideal agent should have a short onset of anesthesia and be useful for multiple indications such as infiltration, nerve blocks, intravenous, extradural, spinal, and topical administration. The therapeutic indexes for systemic CNS and cardiovascular toxicity should be high and the agent should be compatible with the vasoconstrictor epinephrine.

The pharmacological profile of local anesthetic agents depends largely on the physicochemical properties given in Table 4 (153). Lipophilicity appears to be the primary determinant of *in vitro* (isolated nerve)

Table 3. Local Anesthetic Agents

Name	CAS Registry Number	Molecular formula	Structure number	Structure
procaine	[59-46-1]	$C_{13}H_{20}N_2O_2$	(**20**, $_{X=R}$, H, $_{R'=}$ C_2H_5)	
chloroprocaine	[133-16-4]	$C_{13}H_{19}ClN_2O_2$	(**20**, X = Cl, R = H, R′ = C_2H_5)	
tetracaine	[94-24-6]	$C_{15}H_{24}N_2O_2$	(**20**, X = H, R = n-C_4H_9, R′ = CH_3)	
lidocaine	[137-58-6]	$C_{14}H_{22}N_2O$	(**21**, X = CH_3, R = H, R′ = R = C_2H_5)	
prilocaine	[721-50-6]	$C_{13}H_{20}N_2O$	(**21**, X = H, R = CH_3, R′ = H, R = n-C_3N_7)	
etidocaine	[36637-18-0]	$C_{17}H_{28}N_2O$	(**21**, X = CH_3, R = R′ = C_2H_5, R = n-C_3H_7)	
mepivacaine	[96-88-8]	$C_{15}H_{22}N_2O$	(**22**, R = CH_3)	
bupivacaine	[2180-92-9]	$C_{18}H_{28}N_2O$	(**22**, R = n-C_4H_9)	
ropivacaine	[84057-95-4]	$C_{17}H_{26}N_2O$	(**22**, R = n-C_3H_7)	

potency. Agents which are lipophilic penetrate nerve membranes more easily than more hydrophilic compounds resulting in a greater concentration of agent at the interior sodium ion channel receptor. The *in vivo* potency, however, is also dependent on such other factors as vasodilator and tissue redistribution properties. The duration of anesthesia is primarily dependent on the agent's protein binding capability. Long duration agents, eg, bupivacaine (**22**, R = n-C_4H_9) and tetracaine (**20**, X = H, R = n-C_4H_9, R′ = CH_3), appear to be more tightly bound to proteins than those possessing short durations such as procaine (**20**, X = R = H, R′ = C_2H_5) and lidocaine (**21**, X = CH_3, R = H, R′ = R = C_2H_5) hydrochloride.

The rate of onset of local anesthetic activity *in vitro* is primarily determined by the pK_a of the local anesthetic agent. The protonated species of the agent is the active form whereas the free base possesses little or no activity. However, it is the basic form of the drug which diffuses through the nerve sheath. Consequently the higher the concentration of the free base, ie, the lower the pK_a, the more rapid is the onset of anesthesia. The *in vivo* onset is also determined by the nonnervous tissue diffusability of the compound. Many long duration local anesthetics exhibit long anesthetic onsets. Mixtures of these long duration agents and a short duration drug possessing a rapid onset have been used.

Table 4. *In Vitro* Conduction Blocking and Physiochemical Properties of Local Anesthetic Agents[a]

	Conduction blocking properties[b]			Physiochemical properties		
Agent	Potency	Onset	Duration	pK_a	Lipid solubility	Protein binding, %
			Low potency			
procaine	1	1	1	8.9	0.6	5.8[c]
			Intermediate potency			
mepivacaine	2	1	1.5	7.6	1.0	77[c]
prilocaine	3	1	1.5	7.7	0.8	55[d]
chloroprocaine	4	0.8	0.75	8.7		
lidocaine	4	0.8	1.5	7.7	2.9	64[d]
			High potency			
tetracaine	16	2	8	8.5	80	76[d]
bupivacaine	16	0.6	8	8.1	28	95[d]
etidocaine	16	0.4	8	7.7	141	94[d]

[a] Ref. 153.
[b] Relative to procaine. Data are derived from isolated frog sciatic nerve.
[c] Nerve homogenate binding.
[d] Plasma protein binding.

The rate of removal of the local anesthetic from the site of injection also affects its profile. All local anesthetic agents possess some vasodilatory activity at clinically useful concentrations. Agents which are more potent in this regard tend to be absorbed more rapidly by the vasculature. They are less potent anesthetics and have shorter durations than those having lower vasodilatory activity. A comparison of potency, onset, and duration as a function of physiochemical properties is presented in Table 4.

Another clinical consideration is the ability of local anesthetic agents to effect differential blockade of sensory and motor fibers. In surgical procedures such as obstetrics or postoperative pain relief, an agent which produces profound sensory block accompanied by minimal motor block is desirable. On the other hand some procedures such as limb surgery require both deep sensory and motor blockade. In clinical practice, bupivacaine (**22**, R = n-C_4H_9), in low doses, exhibits the former behavior and is used primarily as an extradural agent in obstetrics. The lowest effective extradural concentration of etidocaine (**21**, X = CH_3, R = R′ = C_2H_5, R = n-C_3H_7), however, shows both adequate sensory and profound motor blockade so that it is useful in surgical situations where maximum neuromuscular blockade is necessary. In an isolated nerve preparation, bupivacaine blocks unmyelinated C fibers which are mainly responsible for pain perception at a much greater extent than the myelinated A fibers which carry motor impulses. It is postulated that absorption of bupivacaine by the vasculature at the site of injection, combined with the slow diffusion of this agent, results in an insufficient amount of the drug penetrating the large A fibers to cause motor conduction blockade. Clinically, motor block can be observed in some procedures.

2.3.2. Specific Local Anesthetic Agents

Clinically used local anesthetics and the methods of application are summarized in Table 5. Procaine hydrochloride [51-05-8] (Novocain), introduced in 1905, is a relatively weak anesthetic having a long onset and short duration of action. Its primary use is in infiltration anesthesia and differential spinal blocks. The low potency and low systemic toxicity result from rapid hydrolysis. The 4-aminobenzoic acid formed is, however, thought to be responsible for allergic reactions caused by the drug.

Chloroprocaine hydrochloride [3858-89-7] is characterized by low potency, rapid onset, short duration of action, and low systemic toxicity. It is indicated for infiltration anesthesia at 1–2% and for extradural

Table 5. Clinically Used Local Anesthetic Agents

Agent	Method of application	Comment
	Amino esters	
procaine	infiltration, spinal	slow onset, short duration
chloroprocaine	peripheral nerve and obstetric extradural	fast onset, short duration, low systemic toxicity
tetracaine	spinal	slow onset, long duration, high systemic toxicity
	Amino amides	
lidocaine	infiltration, iv regional, peripheral nerve block, extradural block, spinal and topical	fast onset, moderate duration, low systemic toxicity, most versatile agent
mepivacaine	infiltration, peripheral nerve block, extradural	similar to lidocaine
prilocaine	similar to lidocaine	safest amino amide, methemoglobinemia at high doses
bupivacaine	infiltration, peripheral nerve block, extradural	moderate onset, long duration, potential for cardiovascular side effects, sensory/motor separation
etidocaine	infiltration, peripheral nerve block, extradural	fast onset, long duration, profound motor block

anesthesia at 2–3% when short surgical procedures are performed under regional anesthesia. Chloroprocaine may be mixed with long duration agents such as bupivacaine (**22**, R = n-C_4H_9) to afford a more rapid onset and shorter duration of action than bupivacaine alone.

Tetracaine (**20**, X = H, R = n-C_4H_9, R′ = CH_3) is primarily used in spinal anesthesia providing a slow onset, high potency, and a long duration of action. Its potential for systemic toxicity limits its use in other forms of regional anesthesia. Tetracaine possesses excellent topical anesthetic activity and has been used in endotracheal surface and opthalmic anesthesia.

Lidocaine hydrochloride [73-78-9] (Xylocaine), is the most versatile local anesthetic agent because of its moderate potency and duration of action, rapid onset, topical activity, and low toxicity. Its main indications are for infiltration, peripheral nerve blocks, extradural anesthesia, and in spinal anesthesia where a duration of 30 to 60 min is desirable. Because of its vasodilator activity, addition of the vasoconstrictor, epinephrine , increases the duration of action of lidocaine markedly. It is also available in ointment or aerosol preparations for a variety of topical applications.

Mepivacaine hydrochloride [1722-62-9] , similar in profile to lidocaine, is used for infiltration, peripheral nerve blocks, and extradural anesthesia. It appears to be less toxic than lidocaine in adults but more toxic in newborns. The duration of action is longer than that of lidocaine because of its lower vasodilator activity. Mepivacaine has little topical activity.

Prilocaine hydrochloride [1786-81-8] is also similar in profile to lidocaine, although prilocaine has significantly less vasodilator activity. Prilocaine is the least toxic of the amino amide local anesthetics. However, its tendency to cause methemoglobinemia, especially in newborns, has eliminated its use in obstetric surgery.

Bupivacaine hydrochloride [14252-80-3] (Marcaine), one of the most potent and longest duration agents in clinical use, is also one of the most toxic. The onset of anesthesia is moderate to long, but it is generally acceptable. Applications include infiltration, peripheral nerve blocks, extradural, and spinal anesthesia at 0.25 to 0.75%, although use at the high concentration is limited by the tendency to produce profound cardiovascular toxicity upon overdose. Advantages are in extradural obstetric procedures and postoperative pain relief because

Table 6. 1990 U.S. Sales for Anesthetic Drugs[a]

Drug	Market value, $\$ \times 10^6$
Inhalational agents	
fluothane (halothane)	2.5
ethrane (enflurane)	18.1
forane (isoflurane)	133.9
Injectable (iv) agents	
pentothal (thiopental)	26.0
diprivan (propofol)[b]	29.0
sublimaze (fentanyl)	19.9
alfenta (alfentanyl)	8.6
sufenta (sufentanyl)	28.0
Local injectable	
novocain (procaine)	0.7
xylocaine (lidocaine)	22.5
marcaine (bupivacaine)	10.7

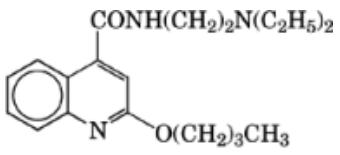
[a] Ref. 162. Actual 1990 sales figures, generic and name brand products combined.
[b] Launched November 1989.

bupivacaine produces profound sensory but little motor block. Additionally, its high efficacy and long duration of action decreases the need for repeated injections.

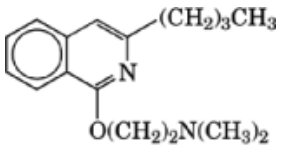
Etidocaine (**21**, X = CH_3, R = R′ = C_2H_5, R = *n*-C_3H_7), characterized by high efficacy, short onset, and long duration of action, may be used for infiltration, peripheral nerve block, and extradural anesthesia at 1.5 percent. Both sensory and profound motor block result. Thus this agent is useful only in procedures such as lower limb orthopedic and abdominal surgeries where neuromuscular blockade is necessary.

2.3.3. Anesthetic Agents Under Development

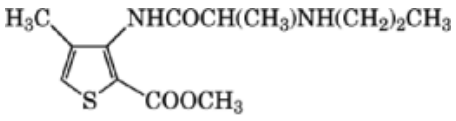
Ropivacaine (AL-381) (**22**, R = *n*-C_3H_7), similar in structure to mepivacaine and bupivacaine, has potency, duration, and CNS and cardiovascular toxicity somewhat lower than those of bupivacaine. Thus the advantage of ropivacaine is the significantly higher cardiovascular and CNS therapeutic indexes (158). Carbizocaine [76629-87-3] (BK-95), $C_{21}H_{36}N_2O_3$, (**23**) is an amino carbamate possessing high potency as a topical, infiltration, and peripheral nerve blocking agent. Its potency in the rat sciatic nerve block test is ten times higher than that of bupivacaine (159). Heptacaine [55792-21-7] , $C_{21}H_{36}N_2O_3$, (**24**), also an amino carbamate, is somewhat more potent and has a slightly longer duration of action than lidocaine. The acute toxicity of heptacaine is comparable to that of lidocaine (160). Carticaine [23964-58-1] $C_{13}H_{20}N_2O_3S$, (**25**) may be useful as an infiltration anesthetic with a somewhat longer duration of action than lidocaine and similar toxicity (161).



(**23**)



(24)



(25)

3. Economic Aspects

The total U.S. market value for the anesthetic agents listed was $299.9 million in 1990 (162). General inhalation agents, valued at $154.5 million, comprised over half (51.5%) of the 1990 market. General iv anesthetics were valued at $111.5 million (37.2%). Local injectable agents, at $33.9 million, represented the smallest portion of the market (11.3%). U.S. sales for selected anesthesia pharmaceuticals are given in Table 6.

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