Anesthesia Related Drugs

Researchers, technicians and care-persons must have knowledge of the actions, methods of administration, and nursing considerations associated with each drug used in our laboratory. Drugs are commonly placed into categories according to their similarities in action and/or their physiologic effect when introduced into the system. The following two sections describe the basic categories of drugs commonly used in our laboratory. While these two chapters have some detailed descriptions of drugs that are important for our laboratory, they are still useful for the non-specialist, as they explain the specific uses of these drugs in the laboratory, and their dosages for different procedures.

Anticholinergics

Anticholinergic agents may be indicated prior to the administration of a variety of anesthetic and related agents, including sedatives, narcotics, barbiturates, and inhalant anesthetic agents. Atropine sulfate, scopolamine, and glycopyrrolate are the three principle anticholinergics used in the laboratory. All three substances are antimuscarinic agents. Muscarinic receptor antagonists prevent the effects of ACh by blocking its binding to muscarinic cholinergic receptors at neuroeffector sites on smooth muscle, cardiac muscle, and gland cells; in peripheral ganglia; and in the central nervous system.

In general, muscarinic receptor antagonists cause little blockade of the effects of ACh at nicotinic receptor sites. Thus, at autonomic ganglia, where transmission primarily involves an action of ACh on nicotinic receptors, atropine produces partial block only at relatively high doses. At the neuromuscular junction, where the receptors are principally or exclusively nicotinic, extremely high doses of atropine or related drugs are required to cause any degree of blockade. However, quaternary ammonium analogs of atropine and related drugs generally exhibit a greater degree of nicotinic blocking activity and, consequently, are likely to interfere with ganglionic or neuromuscular transmission in doses that more closely approximate those that produce muscarinic block. In the CNS, cholinergic transmission appears to be predominantly nicotinic in the spinal cord and both muscarinic and nicotinic at subcortical and cortical levels in the brain. Autoradiographic studies have revealed a widespread distribution of muscarinic receptors throughout the human brain. More recent studies using muscarinic receptor subtype-specific antibodies demonstrate discrete localization of these subtypes within brain regions. Many or most of the CNS effects of therapeutic doses of atropine-like drugs are probably attributable to their central muscarinic blockade. At high or toxic doses, the central effects of atropine and related drugs generally consist of stimulation followed by depression. Since quaternary compounds penetrate the blood-brain barrier poorly, antagonists of this type have little or no effect on the CNS.

Parasympathetic neuroeffector junctions in different organs are not equally sensitive to the muscarinic receptor antagonists. Small doses of muscarinic receptor antagonists depress salivary and bronchial secretion and sweating. With larger doses, the pupil dilates, accommodation of the lens to near vision is inhibited, and vagal effects on the heart are blocked so that the heart rate is increased. Larger doses inhibit the parasympathetic control of the urinary bladder and gastrointestinal tract, therein inhibiting micturition and decreasing the tone and motility of the gut. Still larger doses are required to inhibit gastric secretion and motility. Thus, doses of atropine and most related muscarinic receptor antagonists that reduce gastrointestinal tone and depress gastric secretion also almost invariably affect salivary secretion, ocular accommodation, and micturition. This hierarchy of relative sensitivities probably is not a consequence of differences in the affinity of atropine for the muscarinic receptors at these sites, because atropine does not show selectivity toward different muscarinic receptor subtypes. More likely determinants include the degree to which the functions of various end organs are regulated by parasympathetic tone and the involvement of intramural neurons and reflexes.

The muscarinic receptor antagonists block the responses of the sphincter muscle of the iris and the ciliary muscle of the lens to cholinergic stimulation. Thus, they dilate the pupil (mydriasis) and paralyze accommodation (cycloplegia).

The wide pupillary dilatation results in photophobia; the lens is fixed for far vision, near objects are blurred, and objects may appear smaller than they are. The normal pupillary reflex constriction to light or upon convergence of the eyes is abolished. These effects can occur after either local or systemic administration of the alkaloids. However, conventional systemic doses of atropine (0.6 mg) have little ocular effect, in contrast to equal doses of scopolamine, which cause definite mydriasis and loss of accommodation. Locally applied atropine or scopolamine produces ocular effects of considerable duration; accommodation and pupillary reflexes may not fully recover for 7 to 12 days. The muscarinic receptor antagonists used as mydriatics differ from the sympathomimetic agents in that the latter cause pupillary dilatation without loss of accommodation. Pilocarpine, choline esters, physostigmine, and isoflurophate (DFP) in sufficient concentrations can partially or fully reverse the ocular effects of atropine.

Muscarinic receptor antagonists administered systemically have little effect on intraocular pressure except in patients with narrow-angle glaucoma, where the pressure may occasionally rise dangerously. The rise in pressure occurs when the anterior chamber is narrow and the iris obstructs entry of aqueous humor into the trabeculae. This interferes with drainage of aqueous humor. The drugs may precipitate a first attack in unrecognized cases of this rare condition. In patients with open-angle glaucoma, an acute rise in pressure is unusual. Atropine-like drugs generally can be used safely in this latter condition, particularly if the patient is also adequately treated with an appropriate miotic agent.

Atropine Sulfate

Description: **:** It acts directly on the smooth muscles and secretory glands innervated by postganglionic cholinergic nerves, blocking the para-sympathomimetic effects of acetylcholine. Penetrates the Blood-Brain barrier.

Usage: As a preanesthetic it is used both because of the mild respiratory stimulation because it inhibits salivary secretion. In reversing paralysis it is used in conjunction with the administration of prostigmin to block the muscarinic receptors. Administration of prostigmin without atropine can cause parasympathetic hyperactivity. Atropine is distributed as such by Elkins-Sinn, Eli Lilly and Astra.

Dosage and Administration: As preanesthetic -- 0.05 mg/kg To reverse paralysis -- 0.15 mg/kg We usually use the 0.54 mg/ml concentration. For this concentration the dosage for atropine as preanesthetic is 0.1 ml/kg.

Robinul

Description: Glycopyrrolate, like other anticholinergic (antimuscarinic) agents, inhibits the action of acetylcholine on structures innervated by postganglionic cholinergic nerves and on smooth muscles that respond to acetylcholine but lack cholinergic innervation. These peripheral cholinergic receptors are present in the autonomic effector cells of smooth muscle, cardiac muscle, the sinoatrial node, the atrioventricular node, exocrine glands, and, to a limited degree, in the autonomic ganglia. Thus, it diminishes the volume and free acidity of gastric secretions and controls excessive pharyngeal, tracheal, and bronchial secretions.

Glycopyrrolate antagonizes muscarinic symptoms (e.g., bronchorrhea, bronchospasm, bradycardia, and intestinal hypermotility) induced by cholinergic drugs such as the anticholinesterases. The highly polar quaternary ammonium group of glycopyrrolate limits its passage across lipid membranes, such as the blood-brain barrier, in contrast to atropine sulfate and scopolamine hydrobromide, which are non-polar tertiary amines which penetrate lipid barriers easily.

Peak effects occur approximately 30 to 45 minutes after intramuscular administration. The vagal blocking effects persist for 2 to 3 hours and the antisialagogue effects persist up to 7 hours, periods longer than for atropine. With intravenous injection, the onset of action is generally evident within one minute.

Usage: In anesthesia: Robinul (glycopyrrolate) Injectable is indicated for use as a preoperative antimuscarinic to reduce salivary, tracheobronchial, and pharyngeal secretions; to reduce the volume and free acidity of gastric secretions; and, to block cardiac vagal inhibitory reflexes during induction of anesthesia and intubation. When indicated, Robinul Injectable may be used intraoperatively to counteract drug-induced or vagal traction reflexes with the associated arrhythmias. Glycopyrrolate protects against the peripheral muscarinic effects (e.g., bradycardia and excessive secretions) of cholinergic agents such as neostigmine and pyridostigmine given to reverse the neuromuscular blockade due to nondepolarizing muscle relaxants. Investigate any tachycardia before giving glycopyrrolate since an increase in the heart rate may occur. Use with caution in monkeys with cardiac arrhythmias or hypertension.

In case of overdosage, to combat peripheral anticholinergic effects, a quaternary ammonium anticholinesterase such as neostigmine methylsulfate (which does not cross the blood-brain barrier) may be given intravenously in increments of 0.25 mg in adults. This dosage may be repeated every five to ten minutes until anticholinergic overactivity is reversed or up to a maximum of 2.5 mg. Proportionately smaller doses should be used in children. Indication for repetitive doses of neostigmine should be based on close monitoring of the decrease in heart rate and the return of bowel sounds. In the unlikely event that CNS symptoms (excitement, restlessness, convulsions, psychotic behavior) occur, physostigmine (which does cross the blood-brain barrier) should be used. Physostigmine 0.5 to 2 mg should be slowly administered intravenously and repeated as necessary up to a total of 5 mg in adults. Proportionately smaller doses should be used in children. Fever should be treated symptomatically. In the event of a curare-like effect on respiratory muscles, artificial respiration should be instituted and maintained until effective respiratory action returns.

Dosage and Administration: Robinul (glycopyrrolate) Injectable may be administered intramuscularly, or intravenously, without dilution, in the following indications:

Preanesthetic medication. The recommended dose of Robinul (glycopyrrolate) Injectable in children 1 month to 12 years of age is 0.002 mg (0.01 mL) per pound of body weight intramuscularly, given 30 to 60 minutes prior to the anticipated time of induction of anesthesia or at the time the preanesthetic narcotic and/or sedative are administered. Children 1 month to 2 years of age may require up to 0.004 mg (0.02 mL) per pound of body weight.

Intraoperative medication. Because of the long duration of action of Robinul (glycopyrrolate) if used as preanesthetic medication, additional Robinul (glycopyrrolate) Injectable for anticholinergic effect intraoperatively is rarely needed; in the event it is required the recommended pediatric dose is 0.002 mg (0.01 mL) per pound of body weight intravenously, not to exceed 0.1 mg (0.5 mL) in a single dose which may be repeated, as needed, at intervals of 2-3 minutes. The usual attempts should be made to determine the etiology of the arrhythmia, and the surgical or anesthetic manipulations necessary to correct parasympathetic imbalance should be performed.

Reversal of neuromuscular blockade. The recommended pediatric dose of Robinul (glycopyrrolate) Injectable is 0.2 mg (1.0 mL) for each 1.0 mg of neostigmine or 5.0 mg of pyridostigmine. In order to minimize the appearance of cardiac side effects, the drugs may be administered simultaneously by intravenous injection and may be mixed in the same syringe.

Anticholinesterases

These agents inhibit acetylcholinesterase (anti-ChE), which is concentrated in synaptic regions and is responsible for the rapid hydrolysis of acetylcholine. Transmitter thus accumulates, and the response to ACh that is liberated by cholinergic impulses or that is spontaneously released from the nerve ending is enhanced. The anticholinesterases reverse the antagonism caused by competitive neuromuscular blocking agents.

The cardiovascular actions of anti-ChE agents are complex, since they reflect both ganglionic and postganglionic effects of accumulated ACh on the heart and blood vessels. The predominant effect on the heart from the peripheral action of accumulated ACh is bradycardia, resulting in a fall in cardiac output. Higher doses usually cause a fall in blood pressure, often as a consequence of effects of anti-ChE agents on the medullary vasomotor centers of the CNS.

Anti-ChE agents augment vagal influences on the heart. This shortens the effective refractory period of atrial muscle fibers, and increases the refractory period and conduction time at the SA and AV nodes. The blood vessels are in general dilated, although the coronary and pulmonary circulation may show the opposite response. At the ganglionic level, accumulating ACh initially is excitatory on nicotinic receptors, but at higher concentrations, ganglionic blockade ensues as a result of persistent depolarization of the cell membrane. The excitatory action on the parasympathetic ganglion cells would tend to reinforce the diminished cardiac output, whereas the opposite sequence would result from the action of ACh on sympathetic ganglion cells. Excitation followed by inhibition also is produced by ACh at the medullary vasomotor and cardiac centers. All of these effects are complicated further by the hypoxemia resulting from the bronchoconstrictor and secretory actions of increased ACh on the respiratory system; hypoxemia, in turn, would reinforce both sympathetic tone and ACh-induced discharge of epinephrine from the adrenal medulla. Hence, it is not surprising that an increase in heart rate is seen with severe cholinesterase inhibitor poisoning.

The effects of anti-ChE drugs on the CNS likewise are characterized by stimulation or facilitation at various sites, succeeded by inhibition or paralysis at higher concentrations. Hypoxemia is probably a major factor in CNS depression that appears after large doses of anti-ChE agents. The stimulant effects are antagonized by atropine, although not as completely as are the muscarinic effects at peripheral autonomic effector sites.

Prostigmin (neostigmine methylsulfate)

Description: Prostigmin (neostigmine methylsulfate) Injectable, an anticholinesterase agent, is a sterile aqueous solution intended for intramuscular, intravenous or subcutaneous administration. Prostigmin Injectable is available in the following concentrations: Prostigmin 1:2000 Ampoules--each ml contains 0.5 mg neostigmine methylsulfate compounded with 0.2% parabens (methyl and propyl) as preservatives and sodium hydroxide to adjust pH to approximately 5.9.

Prostigmin 1:1000 Multiple Dose Vials--each ml contains 1 mg neostigmine methylsulfate compounded with 0.45% phenol as preservative, 0.2mg sodium acetate, and acetic acid and sodium hydroxide to adjust pH to approximately 5.9. Prostigmin 1:2000 Multiple Dose Vials--each ml contains 0.5 mg neostigmine methylsulfate compounded with 0.45% phenol as preservative, 0.2mg sodium acetate, and acetic acid and sodium hydroxide to adjust pH to approximately 5.9. Chemically, neostigmine methylsulfate is (m- hydroxyphenyl) trimethylammonium methylsulfate dimethylcarbamate. It has a molecular weight of 334.39

Neostigmine inhibits the hydrolysis of acetylcholine by competing with acetylcholine for attachment to acetylcholinesterase at sites of cholinergic transmission. It enhances cholinergic action by facilitating the transmission of impulses across neuromuscular junctions. It also has a direct cholinomimetic effect on skeletal muscle and possibly on autonomic ganglion cells and neurons of the central nervous system. Neostigmine undergoes hydrolysis by cholinesterase and is also metabolized by microsomal enzymes in the liver. Protein binding to human serum albumin ranges from 15 to 25 percent. Following intramuscular administration, neostigmine is rapidly absorbed and eliminated. In a study of five patients with myasthenia gravis, peak plasma levels were observed at 30 minutes, and the half-life ranged from 51 to 90 minutes. Approximately 80 percent of the drug was eliminated in urine within 24 hours; approximately 50% as the unchanged drug, and 30 percent as metabolites. Following intravenous administration, plasma half-life ranges from 47 to 60 minutes have been reported with a mean half-life

of 53 minutes. The clinical effects of neostigmine usually begin within 20 to 30 minutes after intramuscular injection and last from 2.5 to 4 hours.

Prostigmin does not antagonize, and may in fact prolong, the Phase I block of Depolarizing muscle relaxants such as succinylcholine or decamethonium. Certain antibiotics, especially neomycin, streptomycin and kanamycin, have a mild but definite nondepolarizing blocking action which may accentuate neuromuscular block. These antibiotics should be used in the myasthenic patient only where definitely indicated, and then careful adjustment should be made of the anticholinesterase dosage. Local and some general anesthetics, antiarrhythmic agents and other drugs that interfere with neuromuscular transmission should be used cautiously, if at all, in patients with myasthenia gravis; the dose of Prostigmin may have to be increased accordingly.

Overdosage of Prostigmin can cause cholinergic crisis, which is characterized by increasing muscle weakness, and through involvement of the muscles of respiration, may result in death. Myasthenic crisis, due to an increase in the severity of the disease, is also accompanied by extreme muscle weakness and may be difficult to distinguish from cholinergic crisis on a symptomatic basis. However, such differentiation is extremely important because increases in the dose of Prostigmin or other drugs in this class, in the presence of cholinergic crisis or of a refractory or "insensitive" state, could have grave consequences.

Usage: For the reversal of effects of nondepolarizing neuromuscular blocking agents:

Dosage and Administration: When Prostigmin is administered intravenously, it is recommended that atropine sulfate (0.6 to 1.2 mg) also be given intravenously using separate syringes. Some authorities have recommended that the atropine be injected several minutes before the Prostigmin rather than concomitantly. The usual dose is 0.5 to 2 mg Prostigmin given by Slow intravenous injection, repeated as required. Only in exceptional cases should the total dose of Prostigmin exceed 5 mg. It is recommended that the patient be well ventilated and a patent airway maintained until complete recovery of normal respiration is assured. The optimum time for administration of the drug is during hyperventilation when the carbon dioxide level of the blood is low. It should never be administered in the presence of high concentrations of halothane or cyclopropane. In cardiac cases and severely ill patients, it is advisable to titrate the exact dose of Prostigmin required, using a peripheral nerve stimulator device. In the presence of bradycardia, the pulse rate should be increased to about 80/minute with atropine before administering Prostigmin.

Tranquilizers/Anticonvulsants

A number of different drug categories can be used as tranquilizers, including barbiturates and benzodiazepines. Benzodiazepine derivatives are the *chlordiazepoxide, diazepam, oxazepam, clorazepate, lorazepam, prazepam, alprazolam,* and *halazepam.* Although commonly used for treating anxiety, these drugs share other therapeutic indications—notably sedation and induction of sleep.

The effects of the benzodiazepines in the relief of anxiety has been demonstrated readily in experimental animals. In conflict punishment procedures, benzodiazepines greatly reduce the suppressive effects of punishment. Positive effects in this experimental model are not seen with antidepressants and antipsychotics.

In common with barbiturates, benzodiazepines block EEG arousal from stimulation of the brainstem reticular formation. Benzodiazepines exert central-depressant actions on spinal reflexes, in part mediated by the brainstem reticular system. Like meprobamate and the barbiturates, chlordiazepoxide depresses the duration of electrical afterdischarge in the limbic system, including the septal region, the amygdala, the hippocampus, and the hypothalamus. Virtually all benzodiazepines elevate seizure threshold and are anticonvulsant. Clonazepam, diazepam, and clorazepate are used clinically for this purpose.

There is also much interest in the effects of benzodiazepines on neurotransmission in the forebrain that is mediated by gamma-aminobutyric acid (GABA). One of the most important inhibitory neurotransmission systems in the brain is mediated by $GABA_A$ receptors and Cl^- ion channels. Research on this system has been stimulated by electrophysiological observations of the potentiation of the inhibitory effects of GABA by benzodiazepines (as well as by alcohol and barbiturates) and by the discovery of specific binding sites for benzodiazepines in various brain regions, particularly cerebellum, cerebral cortex, and the limbic system. These sites are believed to occur in a protein macromolecular complex that includes the large family of $GABA_A$ receptors and a Cl^- channel. Binding of benzodiazepines can be modulated by both GABA and Cl^- even after extensive purification of the binding sites. Several imidazole-benzodiazepines, which act as benzodiazepine antagonists (*e.g.,* flumazenil or Ro-15-1788), and carboline compounds with opposite physiological actions to those of benzodiazepines [inverse agonists, including ethyl-β-carboline-3-carboxylate (β-CCE) and its 6,7-dimethoxy congener (DMCM)] competitively inhibit the binding of the benzodiazepines. At concentrations in the therapeutic range, benzodiazepines also can reduce the excitability of some neurons by actions that involve neither GABA nor alterations in membrane permeability to Cl^-. Thus, cellular mechanisms in addition to the important facilitation of GABA-mediated Cl^- conductance may contribute to the behavioral effects of benzodiazepines.

The benzodiazepines as a class tend to have minimal pharmacokinetic interactions with other drugs, although their oxidative metabolism may be inhibited by cimetidine, disulfiram, isoniazid, and oral contraceptives and appears to be increased by rifampin.

Diazepam (Valium)

Description: Diazepam is a benzodiazepine derivative acting on parts of the limbic system, thalamus and hypothalamus inducing calming effects.

Usage: It can be given as an anticonvulsant, but beware of blood pressure changes. It is distributed as Valium by Roche Products.

Dosage and Administration: 2-5 mg IM or IV.

Phenytoin

Description: Phenytoin is an antiepilectic drug. Dilantin is indicated for the control of tonic-clonic and psychomotor (grand mal and temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery.

Usage: Diazepam is to be used before phenytoin. It is distributed as Dilantin by Parke-Davis.

Dosage and Administration: 50-100 mg IM 5-10 mg/kg slowly IV.

Phenobarbital

Description: Nonselective CNS depressant of the barbiturate class, that produces drowsiness, sedation, hypnosis, and anticonvulsant effects by depressing sensorimotor activity and cerebellar function. It has a rapid onset of action (about 5 minutes), with peak effects within 30 minutes, and lasts for about 10 hours.

Usage: For depressing seizure activity in animals that may develop an implant infection, or a minor stroke as a result of recording-guide-tube placement. If the monkey is in epileptic status multiply the total amount drug by 3 (i.e. 15 mg/kg) and ***inject it over 10-15 minutes*.** For anticonvulsant therapy administer the total daily amount in 2 doses. Makes antibiotics such as chloramphenicol less effecitve. If respiratory depression occurs respirate the monkey using our bag-mask resuscitator (Ambu). If depression persist administer doxapram.

Dosage and Administration: 0.025 ml/kg/day

Dissociation Anesthetics

Some arylcycloalkylamines may induce a state of sedation, immobility, amnesia, and marked analgesia. The name *dissociative anesthesia* is derived from the strong feeling of dissociation from the environment that is experienced by the subject to whom such an agent is administered. This condition is similar to neurolept analgesia but results from the administration of a single drug. Phencyclidine was the first drug used for this purpose, but the frequent occurrence of unpleasant hallucinations and psychological problems soon led to its abandonment. These effects are much less frequent with *ketamine hydrochloride* (2-[*o*-chlorophenyl]-2-[methylamino] cyclohexanone hydrochloride; Ketalar), which is available for intravenous or intramuscular injection.

Ketamine Hydrochloride (Ketalar)

Description: Ketamine is a non-narcotic, non-barbiturate anesthetic which produces a dissociative mental state characterized by sedation, amnesia and analgesia. Its pharmacological action is characterized by profound analgesia, normal pharyngeal- laryngeal reflexes.

Effects on CNS: The primary site of CNS action of ketamine appears to be the thalamo-neocortical projection system. It selectively depresses neuronal function in parts of the cortex (especially association areas) and thalamus, while simultaneously stimulating parts of the limbic system, including the hippocampus. This creates what is termed a functional disorganization of nonspecific pathways in midbrain and thalamic areas. There is also evidence that ketamine depresses transmission of impulses in the medial medullary reticular formation, which is important to transmission of the affective-emotional components of nociception from the spinal cord to higher brain centers. Blockade of CNS sodium channels has been shown not to be the mechanism of action by which ketamine produces anesthesia. There is some evidence that ketamine occupies opiate receptors in the brain and spinal cord, which could account for some of the analgesic effects. N-Methyl-d-aspartate (NMDA) receptor interaction may mediate the general anesthetic as well as some analgesic actions of ketamine. The spinal cord analgesic effect of ketamine is postulated to be due to inhibition of dorsal horn wide dynamic range (WDR) neuronal activity. Although a number of drugs have been used to antagonize ketamine, no specific receptor antagonist is yet known that reverses all the CNS effects of ketamine. Ketamine increases cerebral metabolism, CBF, and intracranial pressure (ICP).

Effects on the Respiratory System: Ketamine has minimal effects on the central respiratory drive as reflected by an unaltered response to carbon dioxide. There can be a transient (1- to 3-minute) decrease in minute ventilation after the bolus administration of an anesthetizing dose of ketamine (2 mg/kg IV). Unusually high doses can produce apnea, but this is seldom seen. Arterial blood gases are generally preserved when ketamine is used alone for anesthesia or analgesia. However, with the use of adjuvant sedatives or anesthetic drugs, respiratory depression can occur. Ketamine has been shown to affect ventilatory control in children and should be considered a possible respiratory depressant when given to them in bolus doses.

Ketamine is a bronchial smooth muscle relaxant. When it is given to patients with reactive airway disease and bronchospasm, pulmonary compliance is improved. Ketamine is as effective as halothane or enflurane in preventing experimentally induced bronchospasm. The mechanism for this effect is probably a result of the sympathomimetic response to ketamine, but there are isolated bronchial smooth muscle studies showing that ketamine can directly antagonize the spasmogenic effects of carbachol and histamine. Owing to its bronchodilating effect, ketamine has been used to treat status asthmaticus unresponsive to conventional therapy.

A potential respiratory problem is the increased salivation that follows ketamine. This can produce upper airway obstruction, which can be further complicated by laryngospasm. The increased secretions may also contribute to or further complicate laryngospasm. Also, although swallow, cough, sneeze, and gag reflexes are relatively intact after ketamine, there is evidence that silent aspiration can occur during ketamine anesthesia.

Effects on the Cardiovascular System: Ketamine also has unique cardiovascular effects; it stimulates the cardiovascular system and is usually associated with increases in blood pressure, heart rate, and cardiac output. Other anesthetic induction drugs either cause no change in hemodynamic variables or produce vasodilation with cardiac depression. The increase in hemodynamic variables is associated with increased work and myocardial oxygen consumption. The normal heart is able to increase oxygen supply by increased cardiac output and decreased coronary vascular resistance, so that coronary blood flow is appropriate for the increased oxygen consumption. The hemodynamic changes are not related to the dose of ketamine (e.g., there is no hemodynamic difference between administration of 0.5 and 1.5 mg/kg IV). It is also interesting that a second dose of ketamine produces hemodynamic effects less than or even opposite to those of the first dose. The hemodynamic changes after anesthesia induction with ketamine tend to be the same in healthy patients and those with a variety of acquired or congenital heart diseases. In patients with congenital heart disease, there are no significant changes in shunt directions or fraction or systemic oxygenation after ketamine induction of anesthesia. In patients who have elevated pulmonary artery pressure (as with mitral valvular and some congenital lesions), ketamine seems to cause a more pronounced increase in pulmonary than in systemic vascular resistance.

The mechanism by which ketamine stimulates the circulatory system remains enigmatic. It appears not to be a peripheral mechanism such as baroreflex inhibition, but rather to be central. There is some evidence that ketamine will attenuate baroreceptor function via an effect on NMDA receptors in the nucleus tractus solitarius. Ketamine injected directly into the CNS produces an immediate sympathetic nervous system hemodynamic response. Ketamine also causes the sympathoneuronal release of norepinephrine, which can be detected in venous blood. Blockade of this effect is possible with barbiturates, benzodiazepines, and droperidol. Ketamine in vitro probably has negative inotropic effects. Myocardial depression has been demonstrated in isolated rabbit hearts, intact dogs, chronically instrumented dogs, and isolated canine heart preparations. However, in isolated guinea pig hearts, ketamine was the least depressant of all the major induction drugs. The fact that ketamine may exert its myocardial effects by acting upon myocardial ionic currents (which may exert different effects from species to species or among tissue types) may explain the tissue and animal model variances in direct myocardial action.

The centrally mediated sympathetic responses to ketamine usually override the direct depressant effects of ketamine. There are some peripheral nervous system actions of ketamine that play an undetermined role in the hemodynamic effects of the drug. Ketamine inhibits intraneuronal uptake of catecholamines in a cocaine-like effect and inhibits extraneuronal norepinephrine uptake.

Usage: Ketamine can be used as a supplement or adjunct to regional anesthesia, extending the usefulness of the primary (local anesthetic) form of anesthesia. In this setting ketamine can be used prior to the application of painful blocks, but more commonly it is used for sedation or supplemental anesthesia during long or uncomfortable procedures. When used for supplementation of regional anesthesia, ketamine (0.5 mg/kg IV) combined with diazepam (0.15 mg/kg IV) is better accepted by human patients and not associated with greater side effects as compared with unsedated patients.

We use it mainly as a mild means for restraining the animal (changing collars etc.), and for preparing the animal for anesthesia (placement of the catheter, oxygenation, induction, etc.).

Dosage and Administration: It can be given IM or IV. It is distributed as Ketalar by Parke-Davis and as Ketaset or Ketaject by Bristol Laboratories. Atropine should be administered beforehand. It causes mild respiratory depression and mild cardiac stimulation. Dosages for different primate species can be found in the following table.

Species	*Restraint (mg/kg)*	*Preanesthetic (mg/kg)*
Aotus trivirgatus (owl)	10-12	20-25 mg/kg
Cebus capuchin	13-15	25-30
Cercopithicus aethiops	10-12	25-30
Macaca Fascicullaris .	12-15	20-25
M. fuscata (japanese)	5	10
M. mulata (rhesus)	5-10	20-25
M. nemestrina (pig-tail)	5-7.5	15-20
M. radiata (bonnet)	12-15	25-30
M. arctoides (stump-tail)	5-7.5	20-25
Saimiri sciureus (squirrel)	12-15	25-30

Inhalation Anesthetics

Nitrous Oxide

Description: Nitrous oxide is probably the most common supplement used with opioid-based anesthesia. Nitrous oxide has minimal effects on cardiovascular dynamics, but still can depress myocardial contractility. In addition, nitrous oxide in combination with opioids is usually associated with significant cardiovascular depression. After administration of morphine (2 mg/kg), nitrous oxide produces concentration-dependent decreases in stroke volume, cardiac output, and arterial blood pressure and increases in SVR. While fentanyl alone produces no ventricular dysfunction (even in the presence of significant coronary artery stenosis), the addition of nitrous oxide can result in significant cardiovascular depression. Perhaps a lower FIO2 in addition to nitrous oxide reduces cardiovascular performance. Myocardial ischemia and dysfunction may occur during inhalation of nitrous oxide as coronary blood flow decreases as a result of hypotension and an increase in coronary vascular resistance. Alternatively, increases in SVR associated with nitrous oxide supplementation of opioids may in part cause the deterioration in cardiac output and function. Other studies demonstrate that nitrous oxide does not exacerbate myocardial ischemia. Myocardial dysfunction with nitrous oxide may not be evident with routine monitoring (i.e., arterial blood pressure), because of the elevated SVR. In spite of these potential problems, nitrous oxide remains a popular supplement. Nitrous oxide may be valuable and safe as a supplement to opioid anesthesia in children undergoing repair of congenital cardiac defects.

Usage: For all procedures in which cortical suppression must be avoided. It must always be used together with analgesics.

Dosage and Administration: We typically use this in 1lt/min with 1lt/min Oxygen flow (50%).

Isoflurane

Description: Isoflurane is the newest inhalant anesthetic available. The vapor pressure of isoflurane resembles that of halothane so that it can be administered in a halothane-type vaporizer. Isoflurane has the largest circulatory margin of safety of all potent halogenated agents. It produces the least myocardial depression at a given multiple of the minimum alveolar concentration. In young animals it may increase heart rate, and thus it is occasionally

associated with tachycardia. Similar to halothane, isoflurane does cause respiratory depression, and hence it should be used carefully, with continuous monitoring of the animal. In our procedures, we usually restrain the animal with Ketamine, and we perform the intubation under propofol or barbiturate anesthesia. Induction of surgical anesthesia is therefore accomplished with lower isoflurane concentrations.

Isoflurane was the most slowly metabolized of the fluorinated inhaled anesthetics until the recent introduction of desflurane. What little metabolism there is results from oxidation of the a-carbon. As with enflurane, the difluoromethyl carbon of isoflurane is resistant to oxidation. However, traces of trifluoroacetic acid may be excreted in the urine of rats and humans. Trifluoroacetaldehyde and trifluoroacetyl chloride, expected intermediates between isoflurane and trifluoroacetic acid, may also be produced. Although phenobarbital, phenytoin, ethanol, and isoniazid pretreatments increase the defluorination of isoflurane, enzyme induction has not produced serum F-concentrations of clinical significance. Prolonged exposure to subanesthetic concentrations of isoflurane enhanced the hexobarbital sleeping time of rats. Mice exposed to as much as 0.5 percent isoflurane for 4 hours per day, 5 days per week for 9 weeks had no significant changes in hepatic microsomal cytochrome P450 or b5 contents or in defluorination rates of methoxyflurane, enflurane, or isoflurane.

Usage: We use it for all surgical procedures requiring general surgical anesthesia.

Dosage and Administration: We typically use 3.5% for a 6 to 8kg animal for about 3 minutes, and subsequently reduce the concentration to 1.2 - 1.5%. Isoflurane is metabolized to such a small extent that any increase in metabolism would be inconsequential (see details in Charles Short, 1987). There is greater protection of the liver during isoflurane anesthesia than halothane. Finally, in sharp contrast to halothane, isoflurane is nonflammable.

Desflurane

Description: Desflurane (SUPRANE) is the newest volatile anesthetic and has low solubility in lipids and blood. Chemically it is the difluoromethyl 1-fluoro-2,2,2-trifluoroethyl ether. Desflurane is nonflammable, stable in carbon dioxide, absorbent, and noncorrosive to metals. Solubility in rubber and plastics is unimportant clinically. The boiling point of desflurane is close to room temperature, and delivery of precise concentrations is achieved by using a special heated vaporizer to generate pure vapor, which is diluted appropriately with gases (*i.e.,* oxygen with or without nitrous oxide).

Although the substitution of the chlorine of isoflurane with the fluorine in desflurane reduces the blood solubility to near that of nitrous oxide, the potency of desflurane, which is less than that of isoflurane, is much greater than that of nitrous oxide. The result is a precisely controlled anesthetic with rapid onset and rapid recovery. These characteristics are particularly desirable for the expanding practice of out- patient surgery.

At inhaled concentrations greater than 6%, the pungency of desflurane may cause irritation, with coughing, breath holding, or laryngospasm. Consequently, anesthesia usually is induced with an intravenous agent, and desflurane is introduced after intubation of the trachea to secure the airway. The properties of desflurane permit anesthesia to be established rapidly. Unlike situations with halothane, isoflurane, or enflurane, the alveolar (or blood) concentration of desflurane will be 80% of that delivered from the vaporizer after only 5 minutes. Conversely, when desflurane is discontinued, the small blood and tissue solubility coefficients ensure that the agent is eliminated rapidly in the exhaled gas. Recovery is approximately twice as rapid as with isoflurane, and patients are able to respond to commands within 5 to 10 minutes of discontinuing desflurane.

Circulatory Effects: The circulatory effects of desflurane resemble those of isoflurane. Blood pressure decreases in a dose-dependent manner, mainly by decreasing systemic vascular resistance, while cardiac output is preserved until excessive doses of desflurane are administered. Cardiac rate tends to increase, particularly during induction or abrupt increases in delivered concentration. This may be accompanied by an increase in systemic blood pressure associated with increased plasma catecholamines. However, these changes are transient, and, like the other halogenated ethers, desflurane does not predispose to ventricular arrhythmias.

The distribution of systemic blood flow is altered in a subtle fashion during desflurane anesthesia. Splanchnic, renal, cerebral, and coronary blood flows are preserved in the absence of hypotension, whereas hepatic blood flow may be reduced. Coronary vascular dilatation leading to ischemia as a result of "coronary steal" has not been observed with desflurane in animal models, and desflurane is not associated with increased adverse outcomes in patients with coronary artery disease.

Respiration:. Ventilatory depression is profound with desflurane; in patients breathing spontaneously, the arterial carbon dioxide tension increases, and ventilation may cease at a concentration of 2 MAC. These and other effects of desflurane on respiratory function are similar to those of other volatile anesthetics

Nervous System: Desflurane decreases cerebral vascular resistance and cerebral metabolic rate and is associated with an increase of intracranial pressure. Autoregulation of cerebral blood flow is maintained, and blood flow remains responsive to changes in carbon dioxide concentration. These effects of desflurane are similar to those of the other agents discussed previously. Changes in EEG with desflurane are similar to those with isoflurane, and seizure-like activity is not observed.

Usage: We use it for procedures that require immediate waking up of the animal.

Dosage and Administration: 4-6% with air or 3% with N_2O.

Intravenous Barbiturate Anesthetics

The barbiturates reversibly depress the activity of all excitable tissues. The CNS is exquisitely sensitive, and, even when barbiturates are given in anesthetic concentrations, direct effects on peripheral excitable tissues are weak. However, serious deficits in cardiovascular and other peripheral functions occur in acute barbiturate intoxication.

The barbiturates can produce all degrees of depression of the CNS, ranging from mild sedation to general anesthesia. Certain barbiturates, particularly those containing a 5-phenyl substituent (phenobarbital, mephobarbital), have selective anticonvulsant activity. The antianxiety properties of the barbiturates are not equivalent to those exerted by the benzodiazepines, especially with respect to the degree of sedation that is produced. The barbiturates may have euphoriant effects.

Except for the anticonvulsant activities of phenobarbital and its congeners, the barbiturates possess a low degree of selectivity and therapeutic index. Thus, it is not possible to achieve a desired effect without evidence of general depression of the CNS. Pain perception and reaction are relatively unimpaired until the moment of unconsciousness, and in small doses the barbiturates increase the reaction to painful stimuli. Hence, they cannot be relied upon to produce sedation or sleep in the presence of even moderate pain. In some individuals and in some circumstances, such as in the presence of pain, barbiturates cause overt excitement instead of sedation. The fact that such paradoxical excitement occurs with other CNS depressants suggests that it may result from depression of inhibitory centers.

Pentobarbital

Description: Pentobarbital is a barbiturate anesthetic, supplied as Nembutal by Abbott Laboratories. It is used to provide anesthesia for long surgical procedures. Its duration of action ranges from 30-60 minutes. There is a tendency to underdose small animals and overdose large animals in the same species and age group because drug doses within a group ultimately depend on metabolic size. This is the anesthetic most commonly used in this laboratory.

Usage: Rarely for general anesthesia.

Dosage and Administration: Nembutal 24-30mg/kg, but when ketamine or other preanesthetic on board, use about 1/3 to 1/6 of it, so either 8mg/kg or 4mg/kg. Induction dose depends on the drugs used to restrain the animal. We

typically use 8 mg/kg as an induction dose, with 4mg/kg given as maintenance doses. We use the 50 mg/ml concentration. For this concentration the dosage is 0.16 ml/kg (for Induction) 0.08 ml/kg (for Maintenance).

Thiopental

Description: Thiopental is an ultra-short-acting thio- barbiturate used for induction of anesthesia. It is distributed as Pentothal by Abbott Laboratories.

Respiration:. Unlike some of the inhalational anesthetics, thiopental is not irritating to the respiratory tract, and yet coughing, laryngospasm, and even bronchospasm occur with some frequency. The basis of these reactions is unknown; they disappear as a deeper plane of anesthesia is established. The presence of saliva, the insertion of an airway, or partial obstruction by soft tissues may trigger one or all of these responses. Moderate doses of thiopental do not depress these airway reflexes.

Thiopental produces a dose-related depression of respiration that can be profound. Both the response to carbon dioxide and the response to hypoxia are reduced or even abolished. Following a dose of thiopental sufficient to cause sleep, tidal volume is decreased, and, despite a small increase of respiratory rate, the minute volume is reduced; the functional residual capacity may be reduced, especially if coughing occurs; and the arterial tension of carbon dioxide rises slightly. Larger doses of thiopental cause more profound changes, and respiration is maintained only by movements of the diaphragm. Surgical manipulations provide a stimulus to respiration and, within limits, can offset the respiratory depression.

Circulation:. Following the administration of an anesthetic dose of thiopental to a normal adult, the arterial blood pressure decreases only transiently and then returns essentially to normal. Cardiac output usually is decreased somewhat, but total peripheral vascular resistance is unchanged or increased. Blood flow to the skin and brain is decreased, but that to other organs remains essentially normal.

In the presence of hemorrhage or other form of hypovolemia, circulatory instability, sepsis, toxemia, or shock, the administration of a "normal" dose of thiopental may result in hypotension, circulatory collapse, and cardiac arrest. Thiopental or any other general anesthetic agent should be used very cautiously in patients with these conditions. The baroreceptor system appears unaffected by thiopental, but sympathetic nerve activity is reduced. Concentrations of catecholamines in plasma are not increased, and the heart is not sensitized to epinephrine. Arrhythmias are uncommon except in the presence of hypercapnia or arterial hypoxemia.

Cerebral blood flow and cerebral metabolic rate are reduced with thiopental and other barbiturates. Intracranial pressure is reduced markedly, and this effect is utilized clinically in anesthesia for neurosurgery or in other circumstances when elevated intracranial pressures are expected. Doses of thiopental sufficient to cause an isoelectric EEG protect the brain during ischemia, but not if cardiac arrest or head injury has already rendered the EEG isoelectric.

Usage: For single-unit recordings is the only appropriate barbiturate since pentobarbital suppresses cell activity.

Dosage and Administration: A total 15-20 mg/kg IV Should be given to effect (at 30 sec. intervals) Start with a third to a half of the calculated dosage.

Intravenous Non-barbiturate Anesthetics

Diprivan Injection (Propofol)

Description: Diprivan Injection is an intravenous sedative hypnotic agent for use in the induction and maintenance of anesthesia or sedation. Intravenous injection of a therapeutic dose of propofol produces hypnosis rapidly with minimal excitation, usually within 40 seconds from the start of an injection (the time for one arm- brain circulation). As with other rapidly acting intravenous anesthetic agents, the half-time of the blood-brain equilibration is approximately 1 to 3 minutes, and this accounts for the rapid induction of anesthesia.

The pharmacodynamic properties of propofol are dependent upon the therapeutic blood propofol concentrations. Steady state propofol blood concentrations are generally proportional to infusion rates, especially within an individual patient. Undesirable side effects such as cardiorespiratory depression are likely to occur at higher blood concentrations which result from bolus dosing or rapid increase in infusion rate. An adequate interval (3 to 5 minutes) must be allowed between clinical dosage adjustments in order to assess drug effects. The hemodynamic effects of Diprivan Injection during induction of anesthesia vary. If spontaneous ventilation is maintained, the major cardiovascular effects are arterial hypotension (sometimes greater than a 30% decrease) with little or no change in heart rate and no appreciable decrease in cardiac output. If ventilation is assisted or controlled (positive pressure ventilation), the degree and incidence of decrease in cardiac output are accentuated. Addition of a potent opioid (e.g., fentanyl, sufentanil) when used as a premedicant further decreases cardiac output and respiratory drive.

If anesthesia is continued by infusion of Diprivan Injection, the stimulation of endotracheal intubation and surgery may return arterial pressure towards normal. However, cardiac output may remain depressed. Comparative clinical studies have shown that the hemodynamic effects of Diprivan Injection during induction of anesthesia are generally more pronounced than with other IV induction agents traditionally used for this purpose. During maintenance, Diprivan Injection causes a decrease in ventilation usually associated with an increase in carbon dioxide tension which may be marked depending upon the rate of administration and other concurrent medications (e.g., opioids, sedatives, etc.).

Usage: Diprivan Injection is an IV anesthetic agent that can be used for both induction and/or maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery in adults and in children 3 years of age or older.

Induction Of General Anesthesia: Monkeys require 2.5 to 3.5 mg/kg of Diprivan Injection for induction when unpremedicated or when lightly premedicated with oral benzodiazepines or intramuscular opioids. As with other sedative hypnotic agents, the amount of intravenous opioid and/or benzodiazepine premedication will influence the response of the patient to an induction dose of Diprivan Injection. Attention should be paid to minimize pain on injection when administering Diprivan Injection to animals. Rapid boluses of Diprivan Injection may be administered if small veins are pretreated with lidocaine or when antecubital or larger veins are utilized. Diprivan Injection administered in a variable rate infusion with nitrous oxide 60-70% provides satisfactory anesthesia for most pediatric patients 3 years of age or older, ASA I or II, undergoing general anesthesia.

Maintenance Of General Anesthesia: Maintenance by infusion of Diprivan Injection at a rate of 200-300 mcgm/kg/min should immediately follow the induction dose. Following the first half hour of maintenance, if clinical signs of light anesthesia are not present, the infusion rate should be decreased; during this period, infusion rates of 125-150 mcgm/kg/min are typically needed. However, younger children (5 years or less) may require larger maintenance infusion rates than older children.

Precautions: Monkeys should be continuously monitored for early signs of significant hypotension and/or bradycardia. Treatment may include increasing the rate of intravenous fluid, elevation of lower extremities, use of pressor agents, or administration of atropine. Apnea often occurs during induction and may persist for more than 60 seconds. Ventilatory support may be required.

Attention should be paid to minimize pain on administration of Diprivan Injection. Transient local pain can be minimized if the larger veins of the forearm or leg (e.g. safenous). Pain during intravenous injection may also be reduced by prior injection of IV lidocaine (1 mL of a 1% solution). With lidocaine pretreatment, pain is minimal (incidence less than 10%) and well tolerated. Venous sequelae (phlebitis or thrombosis) have been reported rarely (<1%). In two well- controlled clinical studies using dedicated intravenous catheters, no instances of venous sequelae were observed up to 14 days following induction. Intra-arterial injection in animals did not induce local tissue effects. Accidental intra- arterial injection has been reported in human patients, and, other than pain, there were no major sequelae.

Intentional injection into subcutaneous or perivascular tissues of animals caused minimal tissue reaction. During the post-marketing period, there have been rare reports of local pain, swelling, blisters, and/or tissue necrosis following accidental extravasation of Diprivan Injection. Perioperative myoclonia, rarely including convulsions and opisthotonos, has occurred in temporal relationship in cases in which Diprivan Injection has been administered. Clinical features of anaphylaxis, which may include angioedema, bronchospasm, erythema and hypotension, occur rarely following Diprivan Injection administration, although use of other drugs in most instances makes the relationship to Diprivan Injection unclear.

There have been rare reports of pulmonary edema in temporal relationship to the administration of Diprivan Injection, although a causal relationship is unknown. Diprivan Injection has no vagolytic activity. Reports of bradycardia, asystole, and rarely, cardiac arrest have been associated with Diprivan Injection. The intravenous administration of anticholinergic agents (e.g. atropine or glycopyrrolate) should be considered to modify potential increases in vagal tone due to concomitant agents (e.g., succinylcholine) or surgical stimuli.

Drug Interactions: The induction dose requirements of Diprivan Injection may be reduced in patients with intramuscular or intravenous premedication, particularly with narcotics (e.g., morphine, meperidine, and fentanyl, etc.) and combinations of opioids and sedatives (e.g., benzodiazepines, barbiturates, chloral hydrate, droperidol, etc.). These agents may increase the anesthetic or sedative effects of Diprivan Injection and may also result in more pronounced decreases in systolic, diastolic, and mean arterial pressures and cardiac output.

Diprivan Injection does not cause a clinically significant change in onset, intensity or duration of action of the commonly used neuromuscular blocking agents (e.g., succinylcholine and nondepolarizing muscle relaxants). No significant adverse interactions with commonly used premedications or drugs used during anesthesia or sedation (including a range of muscle relaxants, inhalational agents, analgesic agents, and local anesthetic agents) have been observed.

If overdosage occurs, Diprivan Injection administration should be discontinued immediately. Overdosage is likely to cause cardiorespiratory depression. Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression may require repositioning of the patient by raising the patient's legs, increasing the flow rate of intravenous fluids and administering pressor agents and/or anticholinergic agents.

Dosage And Administration: Induction dose for monkeys: 2.5 to 3.5 mg/kg administered over 20-30 seconds. Infusion for monkeys: 125 to 300 mcgm/kg/min (7.5 to 18 mg/kg/h). When indicated, initiation of sedation should begin at 5 mcgm/kg/min (0.3 mg/kg/h). The infusion rate should be increased by increments of 5 to 10 mcgm/kg/min (0.3 to 0.6 mg/kg/h) until the desired level of sedation is achieved. A minimum period of 5 minutes between adjustments should be allowed for onset of peak drug effect. Bolus administration of 10 or 20 mg should only be used to rapidly increase depth of sedation in patients where hypotension is not likely to occur

Dilution Prior To Administration: When Diprivan Injection is diluted prior to administration, it should only be diluted with 5% Dextrose Injection, USP, and it should not be diluted to a concentration less than 2 mg/mL because it is an emulsion. In diluted form it has been shown to be more stable when in contact with glass than with plastic (95% potency after 2 hours of running infusion in plastic).

Administration With Other Fluids: Compatibility of Diprivan Injection with the coadministration of blood/serum/plasma has not been established. Diprivan Injection has been shown to be compatible when administered with the following intravenous fluids.

- 5% Dextrose Injection, USP
- Lactated Ringers Injection, USP
- Lactated Ringers and 5% Dextrose Injection

- 5% Dextrose and 0.45% Sodium Chloride Injection, USP
- 5% Dextrose and 0.2% Sodium Chloride Injection, USP

Handling Procedures: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Propofol undergoes oxidative degradation, in the presence of oxygen, and is therefore packaged under nitrogen to eliminate this degradation path. Store below 22 deg C (72 deg F). Do not store below 4 deg C (40 deg F). Refrigeration is not recommended. Shake well before use. Diprivan Injection is a sterile emulsion containing 10 mg/mL of propofol suitable for intravenous administration. In addition to the active component, propofol, the formulation also contains soybean oil (100 mg/mL), glycerol (22.5 mg/mL) and egg lecithin (12 mg/mL); with sodium hydroxide to adjust pH. The emulsion is isotonic and has a pH of 7-8.5. Strict aseptic technique must always be maintained during handling.

Xylazine

Description: Xylazine is a non-narcotic compound acting as sedative and analgesic as well as a muscle relaxant. Xylazine is distributed as Rompun by Bayvet Division of Miles Laboratories. The principal pharmacological activities develop 3 to 5 min after IV and 10 to 15 min after IM injection. Its major usefulness, however, is when combined with ketamine. Always premedicate with atropine. Xylazine can cause vomiting.

Usage: We mainly use it in combination with Ketamine for minor procedures, which however require the avoidance of unwanted animal-movements.

Dosage and Administration: Dosage 0.5-1.0 mg/kg IM. The combination of ketamine and xylazine provides effect anesthesia for moderate duration procedures. The two substances can be delivered from the same syringe. Dosage 0.6 mg/kg xylazine and 7 mg/kg ketamine

Local Anesthetics

Local anesthetics prevent the generation and the conduction of the nerve impulse. Their primary site of action is the cell membrane. Conduction block can be demonstrated in squid giant axons from which the axoplasm has been removed. Local anesthetics block conduction by decreasing or preventing the large transient increase in the permeability of excitable membranes to Na^+ that normally is produced by a slight depolarization of the membrane. This action of local anesthetics is due to their direct interaction with voltage-gated Na^+ channels. As the anesthetic action progressively develops in a nerve, the threshold for electrical excitability gradually increases, the rate of rise of the action potential declines, impulse conduction slows, and the safety factor for conduction decreases; these factors decrease the probability of propagation of the action potential, and nerve conduction fails.

In addition to Na^+ channels, local anesthetics also can bind to other membrane proteins. In particular, they can block K^+ channels. However, since the interaction of local anesthetics with K^+ channels requires higher concentrations of drug, blockade of conduction is not accompanied by any large or consistent change in resting membrane potential due to block of K^+ channels.

Quaternary analogs of local anesthetics block conduction when applied internally to perfused giant axons of squid, but they are relatively ineffective when applied externally. These observations suggest that the site at which local anesthetics act, at least in their charged form, is accessible only from the inner surface of the membrane. Therefore, local anesthetics applied externally first must cross the membrane before they can exert a blocking action. Although a variety of physicochemical models have been proposed to explain how local anesthetics achieve conduction block, it is now generally accepted that the major mechanism of action of these drugs involves their interaction with one or more specific binding sites within the Na^+ channel.

Lidocaine

Lidocaine is used to produce local anesthesia following subcutaneous injection. It is distributed as Xylocaine by Astra and as Lidocaine by Elkins-Sinn. Dosage 0.5% solution for infiltration anesthesia.

Procaine

Procaine is a synthetic local anesthetic. It is readily absorbed following parenteral administration and thus does not long remain at the site of injection. It is supplied as Novocaine by Winthrop-Breon. Dosage 0.25-0.5% for infiltration anesthesia, 0.5-2.0% for peripheral nerve block, and 10% for spinal anesthesia.

Muscle Relaxants

Vecuronium bromide

Description: Norcuron (vecuronium bromide) for injection is a nondepolarizing neuromuscular blocking agent of intermediate duration. Norcuron is supplied as a sterile nonpyrogenic freeze-dried buffered cake of very fine microscopic crystalline particles for intravenous injection only. Each 10 mL vial contains 10 mg vecuronium bromide, 20.75 mg citric acid anhydrous, 16.25 mg sodium phosphate dibasic anhydrous, 97 mg mannitol (to adjust tonicity), sodium hydroxide and/or phosphoric acid to buffer and adjust to a pH of 4. Each 20 mL vial contains 20 mg of vecuronium bromide, 41.5 mg citric acid anhydrous, 32.5 mg sodium phosphate dibasic anhydrous, 194 mg mannitol (to adjust tonicity), sodium hydroxide and/or phosphoric acid to buffer and adjust to a pH of 4.

Norcuron acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by acetylcholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Norcuron is about 1/3 more potent than pancuronium; the duration of neuromuscular blockade produced by Norcuron is shorter than that of pancuronium at initially equipotent doses.

The time to onset of paralysis decreases and the duration of maximum effect increases with increasing Norcuron doses. The use of a peripheral nerve stimulator is recommended in assessing the degree of muscular relaxation with all neuromuscular blocking drugs. The ED90 (dose required to produce 90% suppression of the muscle twitch response with balanced anesthesia) has averaged 0.057 mg/kg (0.049 to 0.062 mg/kg in various studies). An initial Norcuron dose of 0.08 to 0.10 mg/kg generally produces first depression of twitch in approximately 1 minute, good or excellent intubation conditions within 2.5 to 3 minutes, and maximum neuromuscular blockade within 3 to 5 minutes of injection in most patients. Under balanced anesthesia, the time to recovery to 25% of control (clinical duration) is approximately 25 to 40 minutes after injection and recovery is usually 95% complete approximately 45-65 minutes after injection of intubating dose. The neuromuscular blocking action of Norcuron is slightly enhanced in the presence of potent inhalation anesthetics. If Norcuron is first administered more than 5 minutes after the start of the inhalation of enflurane, isoflurane, or halothane, or when steady state has been achieved, the intubating dose of Norcuron may be decreased by approximately 15%.

Repeated administration of maintenance doses of Norcuron has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeat doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.08 to 0.10 mg/kg under balanced anesthesia, the first maintenance dose (suggested maintenance dose is 0.010 to 0.015 mg/kg) is generally required within 25 to 40 minutes; subsequent maintenance doses, if required, may be administered at approximately 12 to 15 minute intervals. Halothane anesthesia increases the clinical duration of the maintenance dose only slightly. Under enflurane a maintenance dose of 0.010 mg/kg is approximately equal to 0.015 mg/kg dose under balanced anesthesia. The recovery index (time from 25% to 75% recovery) is approximately 15-25 minutes under balanced or halothane anesthesia. When recovery from Norcuron neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started, the neuromuscular block produced by Norcuron is readily reversed with various anticholinesterase agents, e.g. pyridostigmine, neostigmine, or edrophonium in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. Rapid recovery is a finding consistent with Norcuron's short elimination

half-life, although there have been occasional reports of prolonged neuromuscular blockade in patients in the intensive care.

Unlike other nondepolarizing skeletal muscle relaxants, Norcuron has no clinically significant effects on hemodynamic parameters. Norcuron will not counteract those hemodynamic changes or known side effects produced by or associated with anesthetic agents, other drugs or various other factors known to alter hemodynamics. Studies involving routine hemodynamic monitoring in good risk surgical patients reveal that the administration of Norcuron in doses up to three times that needed to produce clinical relaxation (0.15 mg/kg) did not produce clinically significant changes in systolic, diastolic or mean arterial pressure. The heart rate, under similar monitoring, remained unchanged in some studies and was lowered by a mean of up to 8% in other studies. A large dose of 0.28 mg/kg administered during a period of no stimulation, while patients were being prepared for coronary artery bypass grafting, was not associated with alterations in rate-pressure- product or pulmonary capillary wedge pressure. Systemic vascular resistance was lowered slightly and cardiac output was increased insignificantly.

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron is capable of triggering malignant hyperthermia.

Adverse Reactions: The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiration insufficiency or apnea. Inadequate reversal of the neuromuscular blockade is possible with Norcuron as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action with Norcuron is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol.

Overdosage: Prolonged to profound extensions of paralysis and/or muscle weakness as well as muscle atrophy have been reported after long-term use to support mechanical ventilation in the intensive care unit. The administration of Norcuron has been associated with rare instances of hypersensitivity reactions (bronchospasm, hypotension and/or tachycardia, sometimes associated with acute urticaria or erythema).

The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation. Excessive doses of Norcuron produced enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed may occur with Norcuron as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol (pyridostigmine bromide) injection, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

Usage: Used for muscle relations in neurophysiology experiments and some of the MRI experiments.

Dosage and Administration: Norcuron (vecuronium bromide) for injection is for intravenous use only. To obtain maximum clinical benefits of Norcuron and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised. The recommended initial dose of Norcuron is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED90) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron is enhanced. If Norcuron is first administered more than 5 minutes after the start of inhalation agent or when steady-state has been achieved, the initial Norcuron dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron are recommended; after the initial Norcuron injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses.

Since Norcuron lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.) Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained.

Use By Continuous Infusion: After an intubating dose of 80-100 mcgm/kg, a continuous infusion of 1 mcgm/kg/min can be initiated approximately 20-40 min later. Infusion of Norcuron should be initiated only after early evidence of spontaneous recovery from the bolus dose. Long- term intravenous infusion to support mechanical ventilation in the intensive care unit has not been studied sufficiently to support dosage recommendations. The infusion of Norcuron should be individualized for each patient. The rate of administration should be adjusted according to the patient's twitch response as determined by peripheral nerve stimulation. An initial rate of 1 mcgm/kg/min is recommended, with the rate of the infusion adjusted thereafter to maintain a 90% suppression of twitch response. Average infusion rates may range from 0.8 to 1.2 mcgm/kg/min.

Inhalation anesthetics, particularly enflurane and isoflurane may enhance the neuromuscular blocking action of nondepolarizing muscle relaxants. In the presence of steady-state concentrations of enflurane or isoflurane, it may be necessary to reduce the rate of infusion 25-60 percent, 45-60 min after the intubating dose. Under halothane anesthesia it may not be necessary to reduce the rate of infusion. Infusion solutions of Norcuron can be prepared by mixing Norcuron with an appropriate infusion solution such as 5% glucose in water, 0.9% NaCl, 5% glucose in saline, or Lactated Ringers. Unused portions of infusion solutions should be discarded.

Compatibility: Norcuron is compatible in solution with: 0.9% NaCl solution, 5% glucose in water Sterile water for injection 5% glucose in saline, Lactated Ringers, Use within 24 hours of mixing with the above solutions. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Opioid Analgesics and Anti-Opioids

Opioid drugs are used primarily for the treatment of pain. Some of the CNS mechanisms that reduce the perception of pain also produce a state of well-being or euphoria. Thus, opioid drugs also are taken outside of medical channels for the purpose of obtaining the effects on mood. This potential for abuse has generated

much research on separating the mechanism of analgesia from that of euphoria in the hope of eventually developing a potent analgesic that does not produce euphoria. Although this research has led to advances in understanding the physiology of pain, the standard medications for severe pain remain the derivatives of the opium poppy (opiates) and synthetic drugs that activate the same receptors (opioids). Drugs modeled after the endogenous opioid peptides may one day provide more specific treatment, but none of these currently is available for clinical use. Medications that do not act at opiate receptors, such as the nonsteroidal anti-inflammatory drugs, have an important role in certain types of pain, especially chronic pain; but for acute pain and for severe chronic pain, the μ-agonist opioid drugs are the most effective. Potential future treatments may include preventing the development of μ opioid tolerance using NMDA receptor antagonists.

The most common use of opioid drugs is for the treatment of acute pain. Some patients in pain like the relaxing, anxiolytic, euphorigenic properties of opioids as much as the relief of pain. This is particularly true in high-anxiety situations, such as the crushing chest pain of a myocardial infarction. Normal volunteers with no pain given opioids in the laboratory may report the effects as unpleasant because of the side effects such as nausea, vomiting, and sedation. Patients with pain rarely develop abuse or addiction problems. Of course, patients receiving opioids develop tolerance routinely, and if the medication is stopped abruptly, they will show the signs of an opioid withdrawal syndrome, the evidence for physical dependence.

The major risk for abuse or addiction occurs in patients complaining of pain with no clear physical explanation or with evidence of a chronic disorder that is not life threatening. Examples are chronic headaches, backaches, abdominal pain, or peripheral neuropathy. Even in these cases, an opioid might be considered as a brief emergency treatment, but long-term treatment with opioids is not advisable. In those relatively rare patients who develop abuse, the transition from legitimate use to abuse often begins with patients returning to their physician earlier than scheduled to get a new prescription or visiting emergency rooms of different hospitals complaining of acute pain and asking for an opioid injection.

Mechanisms and Sites of Opioid-Induced Analgesia: Opioid-induced analgesia is due to actions at several sites within the CNS; both spinal and multiple supraspinal sites have been identified. Morphine and other m-opioid agonists selectively inhibit various nociceptive reflexes and induce profound analgesia when administered intrathecally or instilled locally into the dorsal horn of the spinal cord; other sensory modalities (*e.g.,* touch) usually are unaffected. At least three mechanisms appear to be involved. Opioid receptors on the terminals of primary afferent nerves mediate inhibition of the release of neurotransmitters, including substance P. Morphine also antagonizes the effects of exogenously administered substance P by exerting postsynaptic inhibitory actions on interneurons and on the output neurons of the spinothalamic tract that conveys nociceptive information to higher centers in the brain. Both d and k agonists appear to act similarly; however, k agonists suppress noxious thermal stimuli only slightly, and their maximal effects on visceral pain are distinctly lower.

Profound analgesia also can be produced by the instillation of morphine into the third ventricle or in various sites in the midbrain and medulla, most notably the periaqueductal gray matter, the nucleus raphe magnus, and the locus ceruleus. Either electrical or chemical stimulation at these sites also induces analgesia that is antagonized by naloxone, suggesting mediation by endogenous opioid peptides. Although the circuitry has not been clearly defined, all of these maneuvers result in enhanced activity in descending aminergic bulbospinal pathways that exert inhibitory effects on the processing of nociceptive information in the spinal cord. Analgesia due to d-opioid receptors is mediated spinally through the dorsal horn. Although d drugs also are analgesic supraspinally in animal models, the sites of action have not been identified. Animal models suggest that agonists at k_1 receptors mediate analgesia spinally, while agonists at k_3 receptors act supraspinally.

Simultaneous administration of morphine at both spinal and supraspinal sites results in synergy in analgesic response, with a tenfold reduction in the total dose of morphine necessary to produce equivalent analgesia at either

site alone. The mechanisms responsible for spinal/supraspinal synergy are readily distinguished from those involved with supraspinal analgesia. In addition to the well described spinal/supraspinal synergy, synergistic m/m- and m/d-receptor interactions also have been observed within the brainstem between the periaqueductal gray, locus ceruleus, and nucleus raphe magnus.

Mechanism of Other CNS Effects: High doses of opioids can produce muscular rigidity in human beings. Chest wall rigidity severe enough to compromise respiration is not uncommon during anesthesia with fentanyl, alfentanil, and sufentanil. Opioids and endogenous peptides cause catalepsy, circling, and stereotypical behavior in rats and other animals.

The mechanism by which opioids produce euphoria, tranquility, and other alterations of mood is not entirely clear. Microinjection of m opioids into the ventral tegmentum activates dopaminergic neurons that project to the nucleus accumbens; this pathway is postulated to be a critical element in the reinforcing effects of opioids and, by inference, opioid-induced euphoria. Animals will work to receive such injections or injections into the nucleus accumbens itself or its projection areas. The administration of dopaminergic antagonists does not consistently prevent the reinforcing effects of opioids, suggesting that some nondopaminergic mechanisms may also play a role. The neural systems that mediate opioid reinforcement in the ventral tegmentum appear to be distinct from those involved in the classical manifestations of physical dependence and analgesia. The activation of d receptors also may produce reinforcing effects. In contrast to m agonists, k agonists inhibit the firing of dopamine-containing cells in the substantia nigra and inhibit dopamine release from cortical and striatal neurons. As mentioned above, they produce dysphoric effects rather than euphoria. The locus ceruleus contains both noradrenergic neurons and high concentrations of opioid receptors and is postulated to play a critical role in feelings of alarm, panic, fear, and anxiety. Activity in the locus ceruleus is inhibited by both exogenous opioids and endogenous opioid-like peptides.

Effects on the Hypothalamus: Opioids alter the equilibrium point of the hypothalamic heat-regulatory mechanisms, such that body temperature usually falls slightly. However, chronic high dosage may increase body temperature.

Miosis: Morphine and most m and k agonists cause constriction of the pupil by an excitatory action on the parasympathetic nerve innervating the pupil. Following toxic doses of m agonists, *the miosis is marked and pinpoint pupils are pathognomonic;* however, marked mydriasis occurs when asphyxia intervenes. Some tolerance to the miotic effect develops, but addicts with high circulating concentrations of opioids continue to have constricted pupils. Therapeutic doses of morphine increase accommodative power and lower intraocular tension in both normal and glaucomatous eyes.

Convulsions: In animals, high doses of morphine and related opioids produce convulsions. Several mechanisms appear to be involved, and different types of opioids produce seizures with different characteristics. Morphine-like drugs excite certain groups of neurons, especially hippocampal pyramidal cells; these excitatory effects probably result from inhibition of the release of gamma-aminobutyric acid (GABA) by interneurons. Selective d agonists produce similar effects. These actions may contribute to the seizures that are produced by some agents at doses only moderately higher than those required for analgesia, especially in children. However, with most opioids, convulsions occur only at doses far in excess of those required to produce profound analgesia, and seizures are not seen when potent m agonists are used to produce anesthesia.

Naloxone is more potent in antagonizing convulsions produced by some opioids (*e.g.,* morphine, methadone, and *d*-propoxyphene) than those produced by others (*e.g.,* meperidine). The production of convulsant metabolites of the latter agent may be partially responsible (*see* below). Anticonvulsant agents may not always be effective in suppressing opioid-induced seizures.

Respiration: Morphine-like opioids depress respiration, at least in part by virtue of a direct effect on the brainstem respiratory centers. The respiratory depression is discernible even with doses too small to disturb consciousness and

increases progressively as the dose is increased. In human beings, death from morphine poisoning is nearly always due to respiratory arrest. Therapeutic doses of morphine in human beings depress all phases of respiratory activity (rate, minute volume, and tidal exchange) and may also produce irregular and periodic breathing. The diminished respiratory volume is due primarily to a slower rate of breathing, and with toxic amounts the rate may fall to 3 or 4 breaths per minute. Although respiratory effects can be documented readily with standard doses of morphine, respiratory depression is rarely a problem clinically in the absence of underlying pulmonary dysfunction. However, the combination of opiates with other medications, such as general anesthetics, tranquilizers, alcohol, or sedative-hypnotics, may present a greater risk of respiratory depression.

Maximal respiratory depression occurs within 5 to 10 minutes after intravenous administration of morphine or within 30 or 90 minutes following intramuscular or subcutaneous administration, respectively. Maximal depressant effects occur more rapidly with more lipid-soluble agents. Following therapeutic doses, respiratory minute volume may be reduced for as long as 4 to 5 hours. The primary mechanism of respiratory depression by opioids involves a reduction in the responsiveness of the brainstem respiratory centers to carbon dioxide. Opioids also depress the pontine and medullary centers involved in regulating respiratory rhythmicity and the responsiveness of medullary respiratory centers to electrical stimulation. Hypoxic stimulation of the chemoreceptors still may be effective when opioids have decreased the responsiveness to CO_2, and the inhalation of O_2 may thus produce apnea. After large doses of morphine or other m agonists, patients will breathe if instructed to do so, but without such instruction they may remain relatively apneic.

Because of the accumulation of CO_2, respiratory rate and sometimes even minute volume can be unreliable indicators of the degree of respiratory depression that has been produced by morphine. Natural sleep also produces a decrease in the sensitivity of the medullary center to CO_2, and the effects of morphine and sleep are additive. Numerous studies have compared morphine and morphine-like opioids with respect to their ratios of analgesic to respiratory- depressant activities. Most studies have found that, when equianalgesic doses are used, the degree of respiratory depression observed with morphine-like opioids is not significantly different from that seen with morphine. However, the partial agonist and agonist/antagonist opioids are less likely to cause severe respiratory depression and are far less commonly associated with death caused by overdosage.

High concentrations of opioid receptors, as well as of endogenous peptides, are found in the medullary areas believed to be important in ventilatory control. As mentioned previously, respiratory depression may be mediated by a subpopulation of m receptors (m_2), distinct from those that are involved in the production of supraspinal analgesia (m_1). Severe respiratory depression is less likely after the administration of large doses of selective k agonists.

Nauseant and Emetic Effects: Nausea and vomiting produced by morphine-like drugs are unpleasant side effects caused by direct stimulation of the chemoreceptor trigger zone for emesis, in the area postrema of the medulla. Certain individuals never vomit after morphine, whereas others do so each time the drug is administered. Nausea and vomiting are relatively uncommon in recumbent patients given therapeutic doses of morphine, but nausea occurs in approximately 40% and vomiting in 15% of ambulatory patients given 15 mg of the drug subcutaneously. This suggests that a vestibular component also is operative. Indeed, the nauseant and emetic effects of morphine are markedly enhanced by vestibular stimulation, and morphine and related synthetic analgesics produce an increase in vestibular sensitivity. All clinically useful m agonists produce some degree of nausea and vomiting. Careful, controlled clinical studies usually demonstrate that, in equianalgesic dosage, the incidence of such side effects is not significantly lower than that seen with morphine. Drugs that are useful in motion sickness are sometimes helpful in reducing opioid-induced nausea in ambulatory patients; phenothiazines are also useful.

Fentanyl

Description: Fentanyl is an opioid analgesic. Fentanyl interacts predominately with the opioid mu- receptor. These mu-binding sites are discretely distributed in the human brain, spinal cord, and other tissues. In clinical settings, fentanyl exerts its principal pharmacologic effects on the central nervous system. Its primary actions of therapeutic value are analgesia and sedation. Fentanyl may increase the patient's tolerance for pain and decrease the perception of suffering, although the presence of the pain itself may still be recognized.

In addition to analgesia, alterations in mood, euphoria and dysphoria, and drowsiness commonly occur. Fentanyl depresses the respiratory centers, depresses the cough reflex, and constricts the pupils. Analgesic blood levels of fentanyl may cause nausea and vomiting directly by stimulating the chemoreceptor trigger zone, but nausea and vomiting are significantly more common in ambulatory than in recumbent patients, as is postural syncope.

Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. The resultant prolongation in gastrointestinal transit time may be responsible for the constipating effect of fentanyl. Because opioids may increase biliary tract pressure, some patients with biliary colic may experience worsening rather than relief of pain. While opioids generally increase the tone of urinary tract smooth muscle, the net effect tends to be variable, in some cases producing urinary urgency, in others, difficulty in urination. At therapeutic dosages, fentanyl usually does not exert major effects on the cardiovascular system. However, some patients may exhibit orthostatic hypotension and fainting. Histamine assays and skin wheal testing in man indicate that clinically significant histamine release rarely occurs with fentanyl administration. Assays in man show no clinically significant histamine release in dosages up to 50 mcgm/kg.

Fentanyl, in small (2 to 5 mg/kg) or anesthetic (10 to 100 mg/kg) doses, infrequently causes significant decreases in arterial blood pressure when given alone, even in patients with poor left ventricular function (LVF). Most evidence indicates that fentanyl produces little or no change in myocardial contractility, although a few investigators have reported a negative inotropic effect. Virtually all hemodynamic variables, including heart rate, arterial blood pressure, cardiac output, systemic and pulmonary vascular resistance, and pulmonary artery occlusion or wedge pressure, remain unchanged after large (anesthetic) doses of fentanyl.

Anesthetic induction with fentanyl is associated with the least change in mean arterial pressure and myocardial performance. While sufentanil does not produce hemodynamic instability, it does cause myocardial depression. Perhaps fentanyl is preferred over sufentanil in patients with poor left ventricular function. On the other hand, other investigators have found better hemodynamic stability, less hypotension, and less ventricular stroke work after sufentanil than after fentanyl in patients undergoing valvular heart surgery.

Hypotension after fentanyl is often related to associated bradycardia and can be prevented or treated with anticholinergics, ephedrine, or even pancuronium. Patients with high sympathetic tone are more likely to experience hypotension after fentanyl.

Usage: Used in surgical procedure as perioperative analgesic.

Dosage and Administration: Fentanyl is 100 times more potent than morphine. The onset of the drug is immediate when it is given IV and the duration of action is 30 to 60 min after a single IV dose of 100 micrograms. Following IM injection the onset is 7 to 8 min and the duration is 1 to 2 hr. It is distributed as Sublimaze by Janssen Pharmaceutica. Dosage 0.05-0.15 milligram / kg IM or SQ.

Sufentanil

Sufentanil, which is 7 to 10 times as potent as fentanyl, causes hypotension with equal or greater frequency as compared with the latter. Since sufentanil is available in concentrations similar to those of fentanyl (50 mg/ml) one obvious possible cause of hypotension is relative overdose. Sufentanil does not produce increases in plasma histamine but does cause vagal-induced bradycardia. As with fentanyl, mild to no depression of cardiac index and

pump function is usually observed after sufentanil in humans. Ablation of sympathetic tone and enhanced parasympathetic tone are the most likely mechanisms for sufentanil-associated hypotension. Sufentanil-induced hypotension may also be mediated by a direct depression of vascular smooth muscle.

Several studies suggest that sufentanil not only is more potent than fentanyl but also is closer to a "complete anesthetic." These claims are supported by greater MAC reduction during coadministration of inhalation anesthetics in laboratory animals and less hemodynamic responses to stimuli such as intubation in humans 180 as compared with fentanyl. Sufentanil can cause more hypotension than equipotent doses of fentanyl. It is found that sufentanil (5 mg/kg) produces lower mean arterial blood pressures than fentanyl (25 mg/kg) during induction of anesthesia in patients undergoing coronary artery surgery. It has been also shown that although sufentanil (15 mg/kg) attenuated the hemodynamic response to endotracheal intubation better than fentanyl (75 mg/kg), it impaired myocardial function and depressed systolic blood pressure more.

Usage: Analgesic used during and after surgical procedures.

Dosage and Administration:. Dosage 8 ug/kg.

Buprenorphine

Description: Distributed as Buprenex. Duration of action is 8-12 hours. Peak action at 3 hours. Side effects include respiratory depression, which will manifest itself as a gradual slowing of breathing and increased intracranial pressure. Buprenorphine is a thebaine derivative, which is similar to morphine in structure but approximately 33 times as potent. Buprenorphine is a partial mu-receptor agonist and also binds to delta and kappa receptors, but its activity at the latter two sites is relatively insignificant. 91 Although buprenorphine is highly lipophilic, its opiate receptor association and dissociation are slow. Whereas fentanyl disassociates rapidly from mu receptors (t½ 6.8 minutes), buprenorphine, which has a higher affinity, takes much longer (t½ 166 minutes). Thus, plasma levels do not parallel CNS effects. Buprenorphine's onset of action is slow, and its peak effect may not occur until 3 hours, and the duration of its effect is prolonged (up to 10 hours). Metabolism occurs in the liver, with biliary excretion of most metabolites. The metabolites of buprenorphone, buprenorphone-3-glucuronide, and norbuprenorphine are significantly less potent and have lower affinities for the mu receptor. Their accumulation in patients with renal failure is unlikely to cause significant pharmacologic activity. Buprenorphine's volume of distribution is 2.8 L/kg and its clearance is 20 ml/kg/min. The recommended initial analgesic dose is 0.3 to 0.4 mg.

The subjective effects (e.g., euphoria) of buprenorphine are similar to those of morphine, although they occur less frequently. Nausea and vomiting are the most common side effects. Buprenorphine produces respiratory depression, with a ceiling after 0.15 to 1.2 mg in adults. Higher doses do not produce further respiratory depression and may actually result in increased ventilation (predominance of antagonistic actions). Nonetheless, at some doses respiratory depression is impressive after buprenorphine. Reversal with naloxone is limited owing to buprenorphine's high affinity for and slow dissociation from the mu opiate recovery; very large doses of naloxone and/or doxapram may be required for full reversal. Buprenorphine (0.6 mg IV) reverses troublesome fentanyl-induced postoperative respiratory depression as well as does naloxone (0.4 mg) and better preserves analgesia. Dopram should be administered if Narcan does not reverse the respiratory depression.

Buprenorphine has been successfully used for premedication (0.3 mg IM), as the analgesic component in balanced anesthesia (4.5 to 12 mg/kg), 771 and for postoperative pain control (0.3 mg IM). Sublingual administration (0.4 mg) has also proved effective. Like the other agonist-antagonist compounds, buprenorphine is not acceptable as a sole anesthetic, and its receptor kinetic profile restricts its usefulness if other mu-receptor agonists are used concurrently. On the other hand, in large doses buprenorphine might be of value as an alternative to methadone for maintenance therapy in opiate addicts. The hemodynamic effects of buprenorphine are similar to those of morphine. Opioid withdrawal symptoms develop slowly (5 to 10 days) after buprenorphine is discontinued following chronic use. In contrast to other opioid compounds (antagonists, agonists, and agonist-antagonists) buprenorphine produces minimal effects in methadone-maintained opioid abusers.

Usage: Analgesic used during and after surgical procedures.

Dosage and Administration: 0.01-0.03 mg/kg IM or SC every 8-12 hrs.

Naloxone

Description: Narcan, a narcotic antagonist, is a synthetic congener of oxymorphone. It antagonizes the opioid effects by competing for the same receptor sites. thus reversing narcotic depression resulting from opioid overdose. Its duration of action is approximately 4 hours; therefore, it may need to be administered more than once. It is distributed as Narcan by Du Pont. When using Narcan against Buprenex you may need to use 10X the normal dose

Usage: To reverse the effects of possible overdose of narcotics. Note that Naloxone is not effective against respiratory depression due to non-opioid drugs. Reversal of buprenorphine-induced respiratory depression may be incomplete. If an incomplete response occurs, respirations should be mechanically assisted using AMBU.

Dosage and Administration: . Dosage 0.01-0.05 mg/kg IM or IV We usually use the 0.4 mg/kg concentration. For this concentration and for an average "dosage" of 0.03 mg/kg the dosage is: 0.075 ml/kg.

Non-Opioid Analgesics

Acetaminophen

Description: Distributed as Tylenol. Given prior to and following surgery for 48 hours, often in conjunction with other analgesics. Provides mild to moderate analgesia. Can be found in variety of size tablets. Often it is convenient to use children's Tylenol because of the smaller number of milligrams per tablet. Tylenol can be also found in a syrup form.

Usage: For mild analgesia.

Dosage and Administration: 10mg/kg P.O. 2 times daily.

Other Drugs

Antibiotics

Antibiotics are substances produced by various species of microorganisms (bacteria, fungi, actinomycetes) that suppress the growth of other microorganisms and eventually may destroy them. However, common usage often extends the term *antibiotics* to include synthetic antibacterial agents, such as the sulfonamides and quinolones, which are not products of microbes. Hundreds of antibiotics have been identified, and many have been developed to the stage where they are of value in the therapy of infectious diseases. Antibiotics differ markedly in physical, chemical, and pharmacological properties; antibacterial spectra; and mechanisms of action. We use them:

1. For systemic infections or illnesses
2. For pre and post surgical profylaxis
3. For the maintenance of implants

Agents of the first category will only be always selected for use by the designated veterinarian. No person in the laboratory should ever administer antibiotics to the monkeys without previously consulting the veterinarian.

Specific agents of the other two categories are routinely used for the maintenance of implants, or before and after the surgery. The following describes the properties, dosages, and types of administration of the antimicrobial drugs used in the lab:

Ampicillin

Description: Ampicillin is a semisynthetic penicillin derived from the basic penicillin nucleus, 6-amino-penicillanic acid. Ampicillin is not only bactericidal against the gram-positive organisms usually susceptible to penicillin G, but also against the gram-negative bacteria. It is, however, ineffective for organisms which produce penicillinase, including the penicillin G resistant strains of staphylococci. We use it for the treatment of skin and skin-structure infections caused by beta-lactamase producing strains of *Staphylococcus aureus*, *E. coli, Klebsiella spp.,* and *Proteus mirabilis*; microbes commonly found in monkeys with implants. It can be also given for infections caused by meningococcus, pneumococcus, gonococcus.

Usage: Local application in chambers used for surface cortical recordings. Ampicillin should be used if the susceptibility test shows sensitivity of the cultured pathogens to this drug.

***Dosage and Administration*:** Locally ca. 0.5 ml after each cleaning of the chamber. Systemically, the dosage is 20 mg/kg every 8 hours. It is administered intramuscularly.

Bacitracin Ophthalmic Ointment

Description: Bacitracin zinc (or polymyxin B sulfate) ophthalmic ointment is a sterile antimicrobial ointment for ophthalmic use. Each gram contains: bacitracin zinc equivalent to 500 bacitracin units, polymyxin B sulfate equivalent to 10,000 polymyxin B units, and white petrolatum. Bacitracin zinc is the zinc salt of bacitracin, a mixture of related cyclic polypeptides (mainly bacitracin A) produced by the growth of an organism of the Licheniformis group of Bacillus Subtilis var Tracy. It has a potency of not less than 40 bacitracin units per mg. Polymyxin B sulfate is the sulfate salt of polymyxin B1 and B2 which are produced by the growth of Bacillus Polymyxa (Prazmowski) Migula (Fam. Bacillaceae). It has a potency of not less than 6,000 polymyxin B units per mg, calculated on an anhydrous basis.

Usage: A wide range of antibacterial action is provided by the overlapping spectra of bacitracin and polymyxin B sulfate. Bacitracin is bactericidal for a variety of gram- positive and gram-negative organisms. It interferes with bacterial cell wall synthesis by inhibition of the regeneration of phospholipid receptors involved in peptidoglycan synthesis. Polymyxin B is bactericidal for a variety of gram-negative organisms. It increases the permeability of the bacterial cell membrane by interacting with the phospholipid components of the membrane. Bacitracin zinc and polymyxin B sulfate together are considered active against the following microorganisms: Staphylococcus Aureus, streptococci including Streptococcus Pneumoniae, Escherichia Coli, Haemophilus Influenzae, Klebsiella/Enterobacter species, Neisseria Species, and Pseudomonas Aeruginosa. The product does not provide adequate coverage against Serratia Marcescens. Bacitracin is indicated for the topical treatment of superficial infections of the external eye and its adnexa caused by susceptible bacteria. Such infections encompass conjunctivitis, keratitis and keratoconjunctivitis, blepharitis and blepharoconjunctivitis.

Dosage and Administration: Apply the ointment every 3 or 4 hours for 7 to 10 days, depending on the severity of the infection.

Bacitracin-neomycin-polymyxin

Description: Commonly referred to as “triple antibiotic”, this ointment is for external use only. Do not apply to the eye.

Usage: We use this around the headpost after it has been cleaned and postoperatively on the surgical wounds to prevent infections.

Dosage and Administration: Apply as needed directly upon the infected area. Usually once a day.

Bactrim

Bactrim (trimethoprim and sulfamethoxazole) IV Infusion, is a sterile solution for intravenous infusion only. It is a synthetic antibacterial combination product. Each 5 mL contains 80 mg trimethoprim (16 mg/mL) and 400 mg sulfamethoxazole (80 mg/mL) compounded with 40% propylene glycol, 10% ethyl alcohol and 0.3% diethanolamine; 1% benzyl alcohol and 0.1% sodium metabisulfite added as preservatives, water for injection, and pH adjusted to approximately 10 with sodium hydroxide.

Excretion of trimethoprim and sulfamethoxazole is primarily by the kidneys through both glomerular filtration and tubular secretion. Urine concentrations of both trimethoprim and sulfamethoxazole are considerably higher than are the concentrations in the blood. The percent of dose excreted in urine over a 12- hour period following the intravenous administration of the first dose of 240 mg of trimethoprim and 1200 mg of sulfamethoxazole on day 1 ranged from 17% to 42.4% as free trimethoprim; 7% to 12.7% as free sulfamethoxazole; and 36.7% to 56% as total (free plus the N4-acetylated metabolite) sulfamethoxazole. When administered together as Bactrim, neither trimethoprim nor sulfamethoxazole affects the urinary excretion pattern of the other. Both trimethoprim and sulfamethoxazole distribute to sputum and vaginal fluid; trimethoprim also distributes to bronchial secretions, and both pass the placental barrier and are excreted in breast milk. Sulfamethoxazole inhibits bacterial synthesis of dihydrofolic acid by competing with Para-aminobenzoic acid (PABA). Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the required enzyme, dihydrofolate reductase. Thus, Bactrim blocks two consecutive steps in the biosynthesis of nucleic acids and proteins essential to many bacteria.

Usage: Bactrim IV Infusion is indicated in the treatment of Pneumocystis Carinii pneumonia in humans or monkeys, and treatment of enteritis caused by susceptible strains of Shigella Flexneri and Shigella Sonnei. Bactrim IV Infusion is also indicated in the treatment of severe or complicated urinary tract infections due to susceptible strains of Escherichia Coli, Klebsiella species, Enterobacter species, Morganella Morganii and Proteus species, when oral

administration of Bactrim is not feasible and when the organism is not susceptible to single- agent antibacterials effective in the urinary tract. We use Bactrim both locally in chambers and systemically.

Dosage and Administration: 15 to 20 mg/kg per day in three or four equally divided doses every 6 to 8 hours for up to 14 days. For Pneumonia the total daily dose is 15 to 20 mg/kg (based on the trimethoprim component) given in 3 or 4 equally divided doses every 6 to 8 hours for up to 14 days. For severe urinary tract infections the total daily dose is 8 to 10 mg/kg (based on the trimethoprim component) given in 2 or 4 equally divided doses every 6, 8 or 12 hours for up to 14 days for severe urinary tract infections and 5 days for shigellosis. The maximum recommended daily dose is 60 mL per day.

Note that Bactrim IV Infusion must be diluted. Each 5 ml should be added to 125 ml of 5% dextrose in water. After diluting with 5% dextrose in water the solution should not be refrigerated and should be used within 6 hours. If a dilution of 5 mL per 100 mL of 5% dextrose in water is desired, it should be used within 4 hours. If upon visual inspection there is cloudiness or evidence of crystallization after mixing, the solution should be discarded and a fresh solution prepared.

Baytril

Description: Baytril is the brand name for the substance **enrofloxacin**. Enrofloxacin is a synthetic chemotherapeutic agent from the class of the quinolone carboxylic acid derivatives. It is a DNA gyrase inhibitor, whereby gyrase is a synthesis promoting enzyme, essential for bacteria. It has antibacterial activity against a broad spectrum of Gram negative and Gram positive bacteria, including Pseudomonas aeruginosa, Klebsiella spp., Clostridium perfringens, E. coli, Enterobacter spp., Staph. (coag. +), and Strep. (alpha hemol.).

Usage: Enrofloxacin is one of the most important antibiotics for our lab, not only because it has a broad range of activity, but also because it penetrates all tissues and body fluids, including the brain. Moreover, it is very effective for treating dermal infections caused by susceptible strains of *Escherichia coli* and *Staphylococcus aureus*, the 2 most common bacteria around the implants. We use it systemically if an animals has infected tissues around its implants.

***Dosage and Administration*:** Enrofloxacin is one of the very few drugs we have that can be administered once a day, thereby eliminating the need of injecting the animal multiple times daily. It should be used whenever mild to moderate infections are noticed, and definitely before and after every surgical operation. The dosage is 5mg/kg/day or 1.5mg/kg 2 wise a day. If possible (if the animal is anesthetized) the dosage can be divided in two injections daily. Injection should be given intramuscularly (IM).

Cephalothin

Description: Cephalothin is a broad-spectrum antibiotic acting against streptococci, staphylococci, Klebsiella, salmonella. It should be reserved for serious infections.

Usage: Drs. Neil Lipman and Robert Marini, the veterinarians at MIT, suggested this drug strongly for meningitis. It should be used with caution, as it is as dangerous as the chloramphenicol. It is distributed as Keflin by Eli Lilly and as Seffin by Glaxo. In ointment it can be also used for the eye, if a corneal ulcer is present. In the latter case do not use a steroid-based ophthalmic solution or ointment. If in doubt, get veterinarian to examine eye. Do not confuse Cephalothin with the regular triple antibiotics (that cannot be applied on the eye).

Dosage and Administration: The ointment can be applied to the eye 3-4 times daily. Dosage 20-35 mg/kg IV, IM, SQ, two or three times per day. We usually use Keflin (100 mg/ml). For this concentration the dosage during surgery is 0.30 ml/kg Bacitracin-neomycin-polymyxin-hydrocortisone

Chloramphenicol

Description: Chloramphenicol is a very potent antibiotic that should be reserved for serious infections caused by susceptible organisms. It enters the cerebrospinal fluid even in the absence of meningeal inflammation, appearing in

concentrations about half of those found in the blood. Serious and fatal blood dyscrasias are known to occur after the administration of chloramphenicol. It must not be used when less potentially dangerous agents will be effective. This substance should be administered with gloves on. It is distributed as Chloromycetin by Parke-Davis.

Usage: We use it mainly when meningitis is suspected.

Dosage and Administration: 50 mg/kg per day in divided doses IV only.

Cleocin

Description: Cleocin phosphate Sterile Solution in vials contains Clindamycin phosphate, a water soluble ester of Clindamycin and phosphoric acid. Each mL contains the equivalent of 150 mg Clindamycin, 0.5 mg disodium edetate and 9.45 mg benzyl alcohol added as preservative in each mL.

Usage: Clindamycin is an antibiotic used in the treatment of infections caused by susceptible anaerobic bacteria as well as for infections caused by streptococci, staphylococci and pneumococci. Anaerobic bacteria are responsible for certain serious respiratory tract infections, serious skin and soft tissue infections, septicemia. Clindamycin is particularly indicated when penicillin is inappropriate. Since Clindamycin does not diffuse adequately into the cerebrospinal fluid, the drug should not be used in the treatment of meningitis. It should be noted that Clindamycin therapy has been associated with severe colitis which may end up being fatal. It is distributed as Clindamycin by Upjohn.

Dosage and Administration: 20 to 40 mg/kg/day (IM or IV) in 3 or 4 equal doses. The higher doses would be used for more severe infections. As an alternative to dosing on a body weight basis, monkeys may be dosed on the basis of square meters body surface: 350 mg/M(squared)/day for serious infections and 450 mg/M(squared)/day for more severe infections. Parenteral therapy may be changed to oral cleocin. Treatment should be continued for at least 10 days.

Erythromycin

Description: Erythromycin is mainly an orally effective antibiotic, and the IV injection is indicated only when oral administration is impossible. It does not penetrate the blood-brain barrier, but it diffuses readily into intracellular fluids, and antibacterial activity can be achieved at essentially all the other sites. It can be used for minor streptococcal and staphylococcal infections

Usage: Used in the chambers or systemically, according to the veterinarian's instructions.

Dosage and Administration: Erythromycin lactobionate 10-20 mg/kg I.V. per day. It must be administered by continuous infusion. Erythromycin ethylsuccinate suspensions may be administered without regard to meals in a dosage 10-20 mg/kg/day in equally divided doses. For severe infections this dosage may be doubled.

Genoptic Ointment and Solution (Gentamycin Ophthalmic)

Description: Genoptic is a sterile, topical anti-infective agent for ophthalmic use. Gentamicin sulfate is a water-soluble antibiotic of the aminoglycoside group. Gentamicin is obtained from cultures of Micromonospora Purpurea. It is a mixture of the sulfate salts of gentamicin C1, C2, and C1A. All three components appear to have similar antimicrobial activities. Gentamicin sulfate occurs as a white to buff powder and is soluble in water and insoluble in alcohol. Each mL contains gentamicin sulfate equivalent to 3 mg (0.3%) gentamicin base with: Liquifilm (r) (polyvinyl alcohol) 14 mg (1.4%); benzalkonium chloride, edetate disodium, sodium phosphate, dibasic; sodium chloride; hydrochloric acid and/or sodium hydroxide to adjust the pH; and purified water. The solution is an aqueous, buffered solution with a pH of 7.2- 7.5. Each gram of Genoptic ointment contains gentamicin sulfate, USP (equivalent to 3.0 mg gentamicin) in a base of white petrolatum, with methylparaben (0.5 mg) and propylparaben (0.1 mg) as preservatives.

Usage: In Vitro gentamicin sulfate is active against many strains of the following microorganisms: Staphylococcus Aureus, Staphylococcus Epidermidis, Streptococcus Pyogenes, Streptococcus Pneumoniae, Enterobacter Aerogenes, Escherichia Coli, Haemophilus Influenzae, Klebsiella Pneumoniae, Neisseria Gonorrhoeae, Pseudomonas Aeruginosa, and Serratia Marcescens. Genoptic ointment and solution are indicated in the topical treatment of ocular bacterial infections including conjunctivitis, keratitis, keratoconjunctivitis, corneal ulcers, blepharitis, blepharoconjunctivitis, acute meibomianitis, and dacryocystitis, caused by susceptible strains of the following microorganisms: Staphylococcus Aureus, Staphylococcus Epidermidis, Streptococcus Pyogenes, Streptococcus Pneumoniae, Enterobacter Aerogenes, Escherichia Coli, Haemophilus Influenzae, Klebsiella Pneumoniae, Neisseria Gonorrhoeae, Pseudomonas Aeruginosa, And Serratia Marcescens.

Dosage and Administration: Genoptic solution: Instill one or two drops into the affected eye(s) every four hours. In severe infections, dosage may be increased to as much as two drops every hour. Genoptic ointment: Apply a small amount (about 1/2 inch) to the affected eye two to three times a day.

Neosporin Ophthalmic Ointment

Description: Neosporin Ophthalmic Ointment (neomycin and polymyxin B sulfates and bacitracin zinc ophthalmic ointment) is a sterile antimicrobial ointment for ophthalmic use. Each gram contains: neomycin sulfate equivalent to 3.5 mg neomycin base, polymyxin B sulfate equivalent to 10,000 polymyxin B units, bacitracin zinc equivalent to 400 bacitracin units, and special white petrolatum, q.s. Neomycin sulfate is the sulfate salt of neomycin B and C, which are produced by the growth of Streptomyces Fradiae Waksman (Fam. Streptomycetaceae). It has a potency equivalent of not less than 600 mcgm of neomycin standard per mg, calculated on an anhydrous basis. Polymyxin B sulfate is the sulfate salt of polymyxin B1 and B2 which are produced by the growth of Bacillus Polymyxa (Prazmowski) Migula (Fam. Bacillaceae). It has a potency of not less than 6,000 polymyxin B units per mg, calculated on an anhydrous basis. Bacitracin zinc is the zinc salt of bacitracin, a mixture of related cyclic polypeptides (mainly bacitracin A) produced by the growth of an organism of the Licheniformis group of Bacillus Subtilis var Tracy. It has a potency of not less than 40 bacitracin units per mg.

Usage: A wide range of antibacterial action is provided by the overlapping spectra of neomycin, polymyxin B sulfate, and bacitracin. Neomycin is bactericidal for many gram-positive and gram-negative organisms. It is an aminoglycoside antibiotic which inhibits protein synthesis by binding with ribosomal RNA and causing misreading of the bacterial genetic code. Polymyxin B is bactericidal for a variety of gram-negative organisms. It increases the permeability of the bacterial cell membrane by interacting with the phospholipid components of the membrane. Bacitracin is bactericidal for a variety of gram- positive and gram-negative organisms. It interferes with bacterial cell wall synthesis by inhibition of the regeneration of phospholipid receptors involved in peptidoglycan synthesis. Neomycin sulfate, polymyxin B sulfate, and bacitracin zinc together are considered active against the following microorganisms: Staphylococcus Aureus, streptococci including Streptococcus Pneumoniae, Escherichia Coli, Haemophilus Influenzae, Klebsiella/Enterobacter species, Neisseria species, and Pseudomonas Aeruginosa. The product does not provide adequate coverage against Serratia Marcescens.

Neosporin Ophthalmic Ointment is indicated for the topical treatment of superficial infections of the external eye and its adnexa caused by susceptible bacteria. Such infections encompass conjunctivitis, keratitis and keratoconjunctivitis, blepharitis and blepharoconjunctivitis.

Dosage and Administration: Apply the ointment every 3 or 4 hours for 7 to 10 days, depending on the severity of the infection.

Panalog

Dosage: Panalog cream combines nystatin, neomycin sulfate, thiostrepton, and triamcinolone acetonide (potent corticosteroid).

Usage: It provides four basic therapeutic effects: anti- inflammatory, antipruritic, antifungal and antibacterial. Do not use if pus is present since the drug may allow the infection to spread.

Dosage and Administration: For mild inflammations, application may range from once daily to once a week. For severe conditions Panalog Cream may be applied as often as 2 to 3 times daily, if necessary.

Polytrim (trimethoprim & polymyxin)

Description: Polytrim Ophthalmic Solution (trimethoprim sulfate and polymyxin B sulfate) is a sterile antimicrobial solution for topical ophthalmic use. Each mL contains trimethoprim sulfate equivalent to 1 mg trimethoprim and polymyxin B sulfate 10,000 units. Trimethoprim is a synthetic antibacterial drug active against a wide variety of aerobic gram- positive and gram-negative ophthalmic pathogens. Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the enzyme dihydrofolate reductase. This binding is very much stronger for the bacterial enzyme than for the corresponding mammalian enzyme. For that reason, trimethoprim selectively interferes with bacterial biosynthesis of nucleic acids and proteins. When used topically, trimethoprim and polymyxin B absorption through intact skin and mucous membranes is insignificant. Vitro studies have demonstrated that the anti-infective components of Polytrim are active against the following bacterial pathogens that are capable of causing external infections of the eye: Staphylococcus Aureus and Staphylococcus Epidermidis, Streptococcus Pyogenes, Streptococcus Faecalis, Streptococcus Pneumoniae, Haemophilus Influenzae, Haemophilus Aegyptius, Escherichia Coli, Klebsiella Pneumoniae, Proteus Mirabilis (indole-negative), Proteus Vulgaris (indole- positive), Enterobacter Aerogenes, and Serratia Marcescens. polymyxin B: Pseudomonas Aeruginosa, Escherichia Coli, Klebsiella Pneumoniae, Enterobacter Aerogenes and Haemophilus Influenzae.

Usage: Polytrim Ophthalmic Solution is indicated in the treatment of surface ocular bacterial infections, including acute bacterial conjunctivitis, and blepharoconjunctivitis, caused by susceptible strains of the following microorganisms: Staphylococcus Aureus, Staphylococcus Epidermidis, Streptococcus Pneumoniae, Streptococcus Viridans, Haemophilus Influenzae and Pseudomonas Aeruginosa.

Dosage and Administration: Clinical studies have shown Polytrim to be safe and effective for use in children over two months of age. The dosage regimen is the same as for adults.

Tribrissen

Description: Tribrissen is a combination of 40 mg trimethoprim and 200 mg sulfadiazine in 30 ml of 24% aqueous suspension for subcutaneous administration. It is active against a wide spectrum of bacterial pathogens, both gram-negative and gram-positive. Tribrissen therapy is indicated in animals where potent systemic antibacterial action against sensitive organisms is required. Tribrissen is distributed by Burroughs Wellcome. Tribrissen is the antibiotic most frequently used before and after surgery in this laboratory.

Usage: It is indicated during treatment of wound infections and abscesses, acute respiratory infections, acute septicemia due to streptococcus zooepidemicus etc.

Dosage and Administration: 0.1 ml of 24% solution per kg per day. For severe infections, the initial dose may be followed by one-half the normal daily dose every 12 hours. Administer IM or subcutaneously 15 mg/kg 2 times a day (total of 30 mg/kg).

Adrenergic Drugs

Epinephrine

Description: Epinephrine is a sympathomimetic drug. It is the most potent alpha receptor activator. It is given as an emergency dose for failing circulation or extremely congested respiration. It is not used in cardiac failure or in hemorrhagic, traumatic, or cariogenic shock. It is also used as hemostatic agent.

Usage: Epinephrine is used in cardiac asystole or in cases where a pressor effect is needed immediately to counter decreases in blood pressure. Phenylephrine can also be used to elevate blood pressure. It is distributed as Adrenaline injection by Parke-Davis and as Epinephrine injection by Astra, Elkins-Sinn and Astra. We generally use it with saline irrigation fluid, since it constricts blood vessels and therefore decreases bleeding.

Dosage and Administration: 0.01 mg/kg IV or IM for irrigation: 1ml/200ml saline.

Antiarrhythmics

Brevibloc

Description: Brevibloc (esmolol HCL) is an antiarrhythmic drug that can be used when ever short term control of ventricular rate with a short-acting agent is desirable. Brevibloc is relatively selective beta blocker (beta-1 blocker). Note that if you give a nonselective beta blocker like propranolol, you will cause both a drop in HR but also a drop in blood pressure, which is sometimes dangerous for the monkey. Monkeys have on average 145/85 blood pressure. Blood pressure above 150/95 is considered to be hypertension. Brevibloc is indicated for the rapid control of ventricular rate in animals with atrial fibrillation or atrial flutter. For example, Brevibloc is indicated for the treatment of tachycardia and hypertension (it will do some things against high pressure as well…. Selective but not specific) that occur during induction and tracheal intubation, during surgery, on emergence from anesthesia, and in the postoperative period. Yet, usage of the drug for preventing such events is not recommended.

Warnings: In clinical trials 20-50% of human patients treated with Brevibloc have experienced hypotension, generally defined as systolic pressure less than 90 mmHg (in monkeys this is about 80 mmHg) and/or diastolic pressure less than 50 mmHg. Hypotension can occur at any dose but is dose-related so that doses beyond 0.2 mg/kg/min are not recommended. All animals treated with Brevibloc must be closely monitored. Do not leave your monkey in the recovery room alone or do not get involved in activities that are guaranteed to interfere with your attending the animal. If the animal is anesthetized and the drug is being infused, termination of the infusion reverses the effects of Brevibloc within 30 minutes. Keep in mind that continued depression of the myocardium with beta blocking agents over a period of time can, in some cases, lead to cardiac failure. Stop the administration of the drug immediately if you notice an abnormality in the animal's ECG.

Usage: Use this drug with great caution in the following cases: (a) Tachycardia during tracheal intubation. (b) Tachycardia during surgery. First check, whether anesthesia is appropriate. If tachycardia persist despite appropriate anesthesia, and despite the absence of any painful surgical manipulation, then administer Brevibloc (0.5 mg/kg/min loading dose), slowly. (c) Hypertension during surgery. (d) Postsurgical arrhythmias

Dosage and Administration: Brevibloc can be purchased as Ampul or a multi-dose vial. The vial has diluted Brevibloc (0.2mg/ml) and can be used as is. The 2.5 g Ampul, however, is not for direct intravenous injection. This dosage form is a concentrated, potent drug which must be diluted prior to its infusion. Brevibloc should not be admixed with sodium bicarbonate. Brevibloc should not be mixed with other drugs prior to dilution in a suitable intravenous fluid. To dilute, aseptically prepare a 10 mg/mL infusion, by adding one 2.5 g Ampul to a 250 mL container, of a compatible intravenous solution. Brevibloc injection was found to be compatible with the following solutions and was stable for at least 24 hours at controlled room temperature or under refrigeration:

1. Dextrose (5%) Injection, USP
2. Dextrose (5%) in Lactated Ringer's Injection
3. Dextrose (5%) in Ringer's Injection
4. Dextrose (5%) and Sodium Chloride (0.45%) Injection, USP
5. Dextrose (5%) and Sodium Chloride (0.9%) Injection, USP

6. Lactated Ringer's Injection, USP
7. Potassium Chloride (40 mEq /liter) in Dextrose (5%) Injection, USP
8. Sodium Chloride (0.45%) Injection, USP
9. Sodium Chloride (0.9%) Injection, USP
10. Brevibloc injection **is not compatible** with Sodium Bicarbonate (5%) Injection, USP.

Antiemetics

Inapsine (Droperidol)

Description: Inapsine (droperidol) is a neuroleptic (tranquilizer) agent available in ampoules and vials. Each milliliter contains 2.5 mg of droperidol in an aqueous solution adjusted to pH 3.4 +/- 0.4 with lactic acid. Inapsine in 10 mL multidose vials also contains 1.8 mg of methylparaben and 0.2 mg propylparaben. Droperidol is chemically identified as 1-(1-(3-(p-fluorobenzoyl) propyl)- 1,2,3,6-tetrahydro- 4-pyridyl)-2-benzimidazolinone with a molecular weight of 379.43. For chemical structure(s), click here, or use the button on the toolbar. Inapsine is a sterile, non-pyrogenic aqueous solution for intravenous or intramuscular injection.

Inapsine (droperidol) produces marked tranquilization and sedation. It allays apprehension and provides a state of mental detachment and indifference while maintaining a state of reflex alertness. Inapsine produces an antiemetic effect as evidenced by the antagonism of apomorphine in dogs. It lowers the incidence of nausea and vomiting during surgical procedures and provides antiemetic protection in the postoperative period. Inapsine potentiates other CNS depressants. It produces mild alpha-adrenergic blockade, peripheral vascular dilatation and reduction of the pressor effect of epinephrine. It can produce hypotension and decreased peripheral vascular resistance and may decrease pulmonary arterial pressure (particularly if it is abnormally high). It may reduce the incidence of epinephrine- induced arrhythmias, but it does not prevent other cardiac arrhythmias. The onset of action of single intramuscular and intravenous doses is from three to ten minutes following administration, although the peak effect may not be apparent for up to thirty minutes. The duration of the tranquilizing and sedative effects generally is two to four hours, although alteration of alertness may persist for as long as twelve hours.

Usage: Inapsine (droperidol) is indicated: to produce tranquilization and to reduce the incidence of nausea and vomiting in surgical and diagnostic procedures. For premedication, induction, and as an adjunct in the maintenance of general and regional anesthesia. in neuroleptanalgesia in which Inapsine is given concurrently with an opioid analgesic, such as Sublimaze (fentanyl citrate) Injection, to aid in producing tranquility and decreasing anxiety and pain.

Dosage and Administration: Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used and the surgical procedure involved. Vital signs should be monitored routinely. For monkeys a dose as low as 1.0 to 1.5 mg (0.4 to 0.6 mL) per 20 to 25 pounds is recommended for premedication or for induction of anesthesia.

Promethazine

Prevention and control of vomiting, as an adjunct to analgesics for the control of postoperative pain. It is contraindicated following administration of large doses of barbiturates or narcotics. It is distributed as Phenergan by Wyeth. Dosage 25 mg IM single dose every 6 hours.

Respiratory Stimulants

Dopram-V

Description: Dopram is a brand name of Doxapram Hydrochloride. Doxapram is 1-ethyl-4-(2-morpholinoethyl)-3,3-diphenyl-2-pyrrolidinone hydrochloride hydrate. Doxapram stimulates primarily respiration by an effect on the brain stem, since sectioning of reflex pathways do not abolish its action. The detection of increased electrical activity in both the inspiratory and expiratory centers of the medulla, at doses as low as 0.2 mg/kg constitutes confirmation of this type of action. Only after high doses were other parts of the brain and spinal cord stimulated. Doxapram does not produce convulsions as readily as other stimulants. Excessive does may produce to hyperventilation which may lead to respiratory alkalosis.

The respiratory stimulant effects of doxapram are not blocked (at least in dogs) by anesthetic doses of the following: phenobarbital sodium, pentobarbital sodium, thiopental sodium, halothane, methoxyflurane. It stimulates respiration that was depressed severely by morphine or meperidine. The action of doxapram is rapid usually beginning in a few seconds. The duration and intensity of response depends upon the does, the conditions of the animal at the time the drug is administered, and depth of anesthesia. Dopram is available in 20mL-multiple dose vials of the sterile solution. The concentration is 20 mg/mL.

Usage: In cases of respiratory arrest due to overdose with barbiturates.

Dosage and Administration: The dosage of doxapram must be adjusted for depth of anesthesia, respiratory volume and rate. Dosage can be repeated in 15 to 20 minutes, if necessary. Dopram is administered intravenously (IV) only. Dosage for barbiturate anesthesia is 2.5 - 5 mg/kg. Dosage for gas anesthesia is 0.5 mg/kg.

Anti-inflammatory Agents

Decadron (Dexamethasone)

Description: Decadron (Dexamethasone sodium phosphate), a synthetic adrenocortical steroid, is a white or slightly yellow, crystalline powder. It is freely soluble in water and is exceedingly hygroscopic. Each milliliter of decadron Phosphate injection, 4 mg/mL, contains dexamethasone sodium phosphate equivalent to 4 mg dexamethasone phosphate or 3.33 mg dexamethasone. Inactive ingredients per mL: 8 mg creatinine, 10 mg sodium citrate, sodium hydroxide to adjust pH, and Water for Injection q.s., with 1 mg sodium bisulfite, 1.5 mg methylparaben, and 0.2 mg propylparaben added as preservatives. Each milliliter of decadron Phosphate injection, 24 mg/mL, contains dexamethasone sodium phosphate equivalent to 24 mg dexamethasone phosphate or 20mg dexamethasone. Inactive ingredients per mL: 8 mg creatinine, 10 mg sodium citrate, 0.5 mg disodium edetate, sodium hydroxide to adjust pH, and Water for Injection q.s., with 1 mg sodium bisulfite, 1.5 mg methylparaben, and 0.2 mg propylparaben added as preservatives.

Decadron Phosphate injection has a rapid onset but short duration of action when compared with less soluble preparations. Because of this, it is suitable for the treatment of acute disorders responsive to adrenocortical steroid therapy. Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs, including dexamethasone, are primarily used for their potent anti-inflammatory effects in disorders of many organ systems. Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli. At equipotent anti-inflammatory doses, dexamethasone almost completely lacks the sodium-retaining property of hydrocortisone and closely related derivatives of hydrocortisone.

Usage: Preoperatively, and in the event of serious trauma or illness, in patients with known adrenal insufficiency or when adrenocortical reserve is doubtful Shock unresponsive to conventional therapy if adrenocortical insufficiency exists or is suspected.

Dosage and Administration: Decadron Phosphate injection, 4 mg/mL--For Intravenous, Intramuscular, Intra- articular, Intralesional, And Soft Tissue Injection. Decadron Phosphate injection, 24 mg/mL--For Intravenous Injection Only. Decadron Phosphate injection can be given directly from the vial, or it can be added to Sodium Chloride Injection or Dextrose Injection and administered by intravenous drip. Solutions used for intravenous administration or further dilution of this product should be preservative-free when used in the neonate, especially the premature infant. When it is mixed with an infusion solution, sterile precautions should be observed. Since infusion solutions generally do not contain preservatives, mixtures should be used within 24 hours.

Neodecadron

Description: The Ophthalmic Ointment Neodecadron contains in each gram: dexamethasone sodium phosphate equivalent to 0.5 mg (0.05%) dexamethasone phosphate and neomycin sulfate equivalent to 3.5 mg neomycin base. Inactive ingredients: white petrolatum and mineral oil. Corticosteroids suppress the inflammatory response to a variety of agents, and they probably delay or slow healing. Since corticosteroids may inhibit the body's defense mechanism against infection, a concomitant antimicrobial drug may be used when this inhibition is considered to be clinically significant in a particular case.

When a decision to administer both a corticosteroid and an antimicrobial is made, the administration of such drugs in combination has the advantage of greater patient compliance and convenience, with the added assurance that the appropriate dosage of both drugs is administered, plus assured compatibility of ingredients when both types of drug are in the same formulation and, particularly, that the correct volume of drug is delivered and retained. The relative potency of corticosteroids depends on the molecular structure, concentration, and release from the vehicle. The anti-infective component in Ophthalmic Ointment Neodecadron is included to provide action against specific organisms susceptible to it. Neomycin sulfate is active In Vitro against susceptible strains of the following microorganisms: Staphylococcus Aureus, Escherichia Coli, Haemophilus Influenzae, Klebsiella/Enterobacter species, and Neisseria species. The product does not provide adequate coverage against: Pseudomonas Aeruginosa, Serratia Marcescens, and streptococci, including Streptococcus Pneumoniae.

Usage: For steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where bacterial infection or a risk of bacterial ocular infection exists. Ocular steroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe where the inherent risk of steroid use in certain infective conjunctivitis is accepted to obtain a diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical, radiation, or thermal burns, or penetration of foreign bodies. The use of a combination drug with an anti- infective component is indicated where the risk of infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye. The particular anti-infective drug in this product is active against the following common bacterial eye pathogens:

- Staphylococcus Aureus
- Escherichia Coli
- Haemophilus Influenzae
- Klebsiella/Enterobacter species
- Neisseria species
- The product does not provide adequate coverage against:
- Pseudomonas Aeruginosa
- Serratia Marcescens

- Streptococci, including Streptococcus Pneumoniae

Dosage and Administration: The duration of treatment will vary with the type of lesion and may extend from a few days to several weeks, according to therapeutic response. Apply a thin coating of Ophthalmic Ointment Neodecadron three or four times a day. When a favorable response is observed, reduce the number of daily applications to two, and later to one a day as maintenance dose if this is sufficient to control symptoms.

Solu-Medrol (Methylprednisolone)

Description*:* Solu-Medrol Sterile Powder contains methylprednisolone sodium succinate as the active ingredient. Methylprednisolone sodium succinate, USP, occurs as a white, or nearly white, odorless hygroscopic, amorphous solid. It is very soluble in water and in alcohol; it is insoluble in chloroform and is very slightly soluble in acetone. Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs are primarily used for their potent anti-inflammatory effects in disorders of many organ systems. Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli. Methylprednisolone is a potent anti-inflammatory steroid synthesized in the Research Laboratories of The Upjohn Company. It has a greater anti- inflammatory potency than prednisolone and even less tendency than prednisolone to induce sodium and water retention. Methylprednisolone sodium succinate has the same metabolic and anti-inflammatory actions as methylprednisolone. When given parenterally and in equimolar quantities, the two compounds are equivalent in biologic activity. The relative potency of Solu-Medrol Sterile Powder and hydrocortisone sodium succinate, as indicated by depression of eosinophil count, following intravenous administration, is at least four to one. This is in good agreement with the relative oral potency of methylprednisolone and hydrocortisone.

Usage*:* In cases of brain injury due to electrodes or to implanted guide tubes. Note that convulsions have been reported with concurrent use of methylprednisolone and cyclosporin. Drugs that induce hepatic enzymes such as phenobarbital, phenytoin and rifampin may increase the clearance of methylprednisolone and may require increases in methylprednisolone dose to achieve the desired response. Drugs such as troleandomycin and ketoconazole may inhibit the metabolism of methylprednisolone and thus decrease its clearance. Therefore, the dose of methylprednisolone should be titrated to avoid steroid toxicity. Methylprednisolone may increase the clearance of chronic high dose aspirin. This could lead to decreased salicylate serum levels or increase the risk of salicylate toxicity when methylprednisolone is withdrawn. Aspirin should be used cautiously in conjunction with corticosteroids in patients suffering from hypoprothrombinemia. The effect of methylprednisolone on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulant when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effect.

Dosage and Administration*:* When high dose therapy is desired, the recommended dose of Solu-Medrol Sterile Powder is 30 mg/kg administered intravenously over at least 30 minutes. This dose may be repeated every 4 to 6 hours for 48 hours. In general, high dose corticosteroid therapy should be continued only until the patient's condition has stabilized; usually not beyond 48 to 72 hours. Although adverse effects associated with high dose short-term corticoid therapy are uncommon, peptic ulceration may occur. Prophylactic antacid therapy may be indicated. In other indications initial dosage will vary from 10 to 40 mg of methylprednisolone depending on the clinical problem being treated. The larger doses may be required for short-term management of severe, acute

conditions. The initial dose usually should be given intravenously over a period of several minutes. Subsequent doses may be given intravenously or intramuscularly at intervals dictated by the patient's response and clinical condition. Corticoid therapy is an adjunct to, and not replacement for conventional therapy. Dosage may be reduced for infants and children but should be governed more by the severity of the condition and response of the patient than by age

or size. It should not be less than 0.5 mg per kg every 24 hours. For strokes we use 0.5 mg/kg 2 times a day IM for 7-10 days.

Dosage must be decreased or discontinued gradually when the drug has been administered for more than a few days. If a period of spontaneous remission occurs in a chronic condition, treatment should be discontinued. Routine laboratory studies, such as urinalysis, two-hour postprandial blood sugar, determination of blood pressure and body weight, and a chest X-ray should be made at regular intervals during prolonged therapy. Upper GI X-rays are desirable in patients with an ulcer history or significant dyspepsia. Solu-Medrol may be administered by intravenous or intramuscular injection or by intravenous infusion, the preferred method for initial emergency use being intravenous injection. To administer by intravenous (or intramuscular) injection, prepare solution as directed.
Anticoagulants and Anticoagulant-Antidotes

Anti-coagulants

Heparin

Description: Heparin Sodium Injection, USP is a sterile solution of heparin sodium derived from bovine lung tissue, standardized for anticoagulant activity. Heparin is a heterogeneous group of straight-chain anionic mucopolysaccharides called glycosaminoglycans having anticoagulant properties, that is preventing blood clotting.

Full-dose heparin therapy usually is administered by continuous intravenous infusion. The **USP unit** of heparin is the quantity that prevents 1.0 ml of citrated sheep plasma from clotting for 1 hour after the addition of 0.2 ml of 1% $CaCl_2$. Treatment is initiated with a bolus injection of 5000 U, followed by 1200 to 1600 U per hour delivered by an infusion pump. Therapy routinely is monitored by the aPTT. A clotting time of 1.5 to 2.5 times the normal mean aPTT value (usually 50 to 80 seconds) is therapeutic. The risk of recurrence of thromboembolism is greater in patients who do not achieve this level of anticoagulation within the first 24 hours. Initially, the aPTT should be measured and the infusion rate adjusted every 6 hours; dose adjustments may be aided by use of a nomogram. Once a steady dosage schedule is established, daily monitoring is sufficient.

Subcutaneous administration of heparin can be used for the long-term management of patients in whom warfarin is contraindicated (*e.g.*, during pregnancy). A total daily dose of about 35,000 U administered as divided doses every 8 to 12 hours usually is sufficient to achieve an aPTT of 1.5 times the control value (measured midway between doses). Monitoring generally is unnecessary once a steady dosage schedule is established.

Low-dose heparin therapy sometimes is used prophylactically to prevent deep venous thrombosis and thromboembolism in susceptible patients, *e.g.*, postoperatively. A suggested regimen for such treatment is 5000 U of heparin given subcutaneously every 8 to 12 hours. Laboratory monitoring is unnecessary, since this regimen does not prolong the aPTT.

Usage: We use it in sterile saline to flush IV catheters. We also use it in the rinse solution for a perfusion.

Dosage and Administration: Dosage is 2 units / ml saline We usually use the 1,000 units/ml concentration. For this concentration the dosage is 0.5 ml / (250 ml saline [0.9% sodium chloride]). Heparin is to be administered IV or by deep subcutaneous routes.

Protamine

Description: Protamines are simple proteins of low molecular weight, rich in arginine and strongly basic. This strongly basic nature accounts for their antiheparin effect which makes it a useful antidote to heparin overdose. It is distributed as such by Eli Lilly.

Usage: In cases of Heparin Overdose (Should never happen!)

Dosage and Administration: It should be given IV very slowly; not more than 50 mg in every 10-minute period. Each mg protamine neutralizes 90 USP units of heparin.

Diuretics

Furosemide

Description: Furosemide is a potent diuretic which is effective 5-10 minutes after IV administration.

Usage: We use it for the control of intracranial pressure. It is distributed as Lasix by Hoechst-Roussel.

Dosage and Administration: 2-8 mg/kg IV.

Antidiarrheal Compounds

Lomotil

Description: Lomotil (Searle & Co) is an antidiarrheal compound. It is a combination of diphenoxylate (2.5mg) and atropine (0.25mg) The etiology of the problem should be determined before using this drug.

Usage: In cases of severe diarrhea.

Dosage and Administration: 2 mg (adults), 1 mg (infants) ¼-1/2 tablet.

Replacement Fluids

Lactated Ringer's Solution

Description: Polyionic, isotonic solution for fluid therapy. For the monkey the water loss in terms of body weight is (1) Respiratory/cutaneous losses 15ml/kg, (2) Fecal 10 ml/kg, and (3) Urinary 20 ml/kg per day, with total loss of approx. 40-50 ml/kg/day or 2 ml/kg/hr. The exact drip rate should be adjusted for each procedure. A water-deprived animal should be given replacement fluids along with maintenance fluids.

Usage: In all surgeries for maintaining the monkey's fluid requirements during the operative period. During surgery water is also lost from the surgical site, from the vascular effects of anesthetic agents, and from sequestration of interstitial fluids from surgical trauma. Total loss is approx. 2.5 ml/kg/hr. For maintenance use isotonic Lactated Ringer's (0.18%) with 4% Dextrose, or plain Lactated Ringer's (0.9%). Our IV drips (pediatric) give 60 drops/ml (Drp/ml). Drops per minute (dpm) are computed based on: dpm = (Drp/ml)*(ml/kg/hr)*Weight/60

Dosage and Administration: 3-15 ml/kg/hr.

Summary of Drugs for Macaques

Drug Dosage-Charts for MPIK

Drugs	*Dosage*	*Duration*
Anticholinergics		
Atropine	0.02-0.05 mg/kg IM	
Glycopyrrolate	0.005-0.01 mg/kg IM	
Dissociatives		
Ketamine	5-20 mg/kg IM	15 – 30 min
Ketamine & xylazine	7 mg/kg & 0.6 mg/kg IM	15 – 30 min
Ketamine & xylazine	10 mg/kg & 0.25-2 mg/kg IM	45 – 138 min
Tiletamine & zolazepam	1.5-3.0 mg/kg IM & 4-6 mg/kg IM	45 – 60 min
Barbiturate Anesthetics		
Pentobarbital	20-30 mg/kg IV (induction)	30 – 60 min
Pentobarbital	8 mg/kg if 15 mg/kg Ketamine used	
Thiopental	5 -7 mg/kg IV (induction)	
Non-barbiturate Anesthetics		
Propofol	2.5-5 mg/kg IV (induction)	5 – 10 min
Propofol	0.3-0.4 mg/kg/min (infusion)	
Neuroleptanalgesics		
Fentanyl-droperidol (Innovar-Vet)	0.1-0.3 ml/kg IM	
Fentanyl-fluanisone (Hypnorm)	0.3 ml/kg IM	
Opioid Analgesics		
Fentanyl	0.003 mg/kg IV	15 min
Sufenta	0.01 mg/kg	
Sufenta mite	0.01 mg/kg	
Morphine	1-2 mg/kg IM	4 hr
Oxymorphone	0.15 mg/kg IM	4-6 hr
Meperidine	2 mg/kg IM	4 hr
Buprenophrine	0.01 mg/kg IM	6-8 hr
Non-Opioid Analgesics		
Aspirin	325 mg PO	
Aspiring rectal suppositories	125 mg/5kg	
Ketorolac	15-30 mg IM	

Drugs	*Dosage*
Muscle Relaxants	
Pancuronium	0.08-0.1 mg/kg IV followed by 03 ug/kg/min
Vecuronium	0.04-0.06 mg/kg IV followed by 0.4 ug/kg/min
Atracurium	0.25-0.3 mg/kg IV followed by 1.5 ug/kg/min

Anticholinesterases

Neostigmine	0.05 mg/kg

Inhalation Anesthetics

Nitrous Oxide	Addition of 30% reduces MAC
	Halothane from 1.15 to 0.75%
	Enflurane from 1.84 to 1.46%
Halothane	1 MAC = 0.89 – 1.15%
Isoflurane	1 MAC = 1.28%
Enflurane	1 MAC = 1.84%
Desflurane	1 MAC = 6.4 % if no Fentanyl is used
Desflurane	1 MAC = 3.5 % if Fentanyl is used

Miscellaneous

Valium	5 mg
Brevibloc	0.05 mg/kg
Dopram	5 mg/kg
Naloxon	0.04 mg/kg