Chapter 11

Injectable and Alternative Anesthetic Techniques

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Introduction

No injectable anesthetic produces all of the components of general anesthesia without depressing some vital organ function. Because the available drugs have rather selective actions within the central nervous system (CNS), combinations of drugs are necessary to provide surgical anesthesia without depressing vital functions. Other than ketamine, intravenous anesthetics generally provide only the mental depression of the anesthetic state. Additional analgesics, inhaled anesthetics, and/or muscle relaxants are required to provide and maintain all of the components of general anesthesia. Thus, drugs discussed in this chapter have been variously described as sedatives, hypnotics, anxiolytics, and incomplete anesthetics. The terms *sleep*, *hypnosis*, and *unconsciousness* have often been used interchangeably in describing the drug-induced sleep produced by these drugs. Characteristics of the ideal injectable anesthetic are listed in Table 11.1.

Injectable drugs are used to induce an unconscious state or are administered by repeated injection and infusion to maintain the mental depression necessary for anesthesia. In recent years, more specific and controllable compounds that provide hypnosis, analgesia, and muscle relaxation have been developed (e.g., propofol). Total intravenous anesthesia refers to the production of general anesthesia with injectable drugs only. The advantage of total intravenous anesthesia is its facility to provide each component of anesthesia with a dose of a specific drug. In contrast, inhalation anesthetics increase or decrease the intensity of all components of anesthesia (CNS depression, analgesia, and muscle relaxation) simultaneously, including their unwanted side effects. The search for new drugs and combinations with appropriate pharmacokinetic-pharmacodynamic profiles for use in domestic and wild animals is ongoing. In animals, unlike in people, a state approaching general anesthesia is not achievable with the use of opioids alone. Consequently, in veterinary anesthesia, opioids have been primarily used as analgesics perioperatively and as anesthetic adjuncts to induce a state of neuroleptanesthesia and are not employed alone as intravenous anesthetics. Because the dissociatives have such a widespread use in domestic, feral, and wild species, and are commonly combined with a variety of other drugs, they are discussed in Chapter 12.

Structure-Activity Relationships

Structure-activity relationships are descriptions of the way modifications of chemical structure affect pharmacological activity. The addition, modification, or removal of functional groups on the fundamental structure of a drug lends it physiochemical properties that alter its ability to access its site of action (receptor) and determines the effect it has on the receptor and cellular function (intrinsic activity). The structure-activity relationships of anesthetic induction drugs have been reasonably described.

Modification of the structure of barbituric acid converts the inactive compound into a hypnotic. The addition of aliphatic side chains in position 5 and 5′ produces hypnotic activity. The length of the side chains influences the duration of action, as well as potency. Replacement of the oxygen atom in position 2 of an active barbiturate with a sulfur atom produces a drug with a faster onset and a shorter action (e.g., thiopental or thiamylal). An active barbiturate methylated in position 1 produces a drug with a rapid onset and short action at the expense of excitatory side effects (e.g., methohexital). Generally, any modification that increases

Table 11.1. Characteristics of an ideal injectable anesthetic.

I. Physiochemical and pharmacokinetic
a. Water soluble
b. Long shelf life
c. Stable when exposed to light
d. Small volume required for induction of anesthesia
II. Pharmacodynamics
a. Minimal individual variation
b. Safe therapeutic ratio
c. Onset, one vein to brain circulation time
d. Short duration of action
e. Inactivated to nontoxic metabolites
f. Smooth emergence
g. Absence of anaphylaxis
h. Absence of histamine release
III. Side effects
a. Absence of local toxicity
b. No effect on vital organ function, except anesthetically desirable effects on the central nervous system

lipophilicity will increase a drug's potency and rate of onset and shorten its action.

Several imidazoles have hypnotic activity. This activity in such a molecule requires an alkyl branched carbon atom between the aryl moiety and the imidazole nitrogen and an ester moiety. Etomidate is the most widely used imidazole anesthetic derivative. Propofol is a diortho-substituted phenol with strong hypnotic actions. Sleep time increases with side-chain length. Potency increases with the length of the side chain up to a total of seven to eight carbon atoms. Longer chains decrease potency, while induction and recovery times are prolonged. The arylcycloalkylamines, of which ketamine is a derivative, derive their anesthetic activity from a cyclohexanone ring geminally substituted with an aromatic ring and a basic nitrogen. The potency of these compounds is influenced by substitution on the nitrogen, but their pharmacological activity is unaffected.

An often-overlooked aspect of structure-activity relationships is the role of stereoisomerism to biological activity. Except for the asymmetrical centers, the stereoisomers of a given molecule are physically and chemically identical. Nevertheless, activity is predicated on the active stereoisomer of a given neurotransmitter, hormone, or drug interfacing with the chiral active center of a receptor or enzyme. Because side effects are often caused by nonspecific action of drugs, the inactive stereoisomer can contribute to side effects of racemic mixtures. Some isomers may have the opposite effect on a receptor or enzyme than that of the active isomer. Several barbiturates have asymmetrical carbon atoms with isomers of varying potency. Nevertheless, all barbiturates are marketed as racemic mixtures. The (+) isomer of etomidate has hypnotic activity and is the only anesthetic to be marketed as a single active isomer. The stereoisomers of ketamine vary in their hypnotic and analgesic potency, with the (+) isomer being threefold more potent than the (−) isomer. The (−) isomer produces more untoward emergence reactions. Nevertheless, ketamine is marketed as a racemic mixture. Neither propofol nor the benzodiazepines have asymmetrical carbon atoms.[1]

Mechanisms of Action

The complexity of the CNS has contributed to the lack of a full understanding of the mechanisms of action of injectable anesthetic drugs. No drug has a single action. Some theories suggest that anesthetics alter cell membranes. Other theories emphasize interaction with neurotransmitter-receptor-ionophore systems. Considerable evidence suggests that most injectable anesthetics alter γ-aminobutyric acid (GABA)–mediated neurotransmission. GABA is an inhibitory neurotransmitter that activates postsynaptic receptors that, in turn, increase chloride conductance, thus hyperpolarizing and inhibiting the neuron. The specific mechanism of action of each injectable anesthetic will be described subsequently in this chapter.

Barbiturate Drugs

Barbituric acid was first prepared by Conrad and Gutzeit in 1882. In 1903, Fischer and von Mering introduced a derivative, diethyl barbituric acid (veronal or barbital), for use as a hypnotic. Fischer is believed to have named the drug veronal from the Latin *vera*, because he thought it to be the "true" hypnotic.

Chemical Structure

The barbiturates all contain a pyrimidine nucleus produced by the condensation of malonic acid and urea (Fig. 11.1). Barbituric acid itself has no hypnotic activity. Substituting alkyl or aryl groups on the R_1 or R_2 positions (Fig. 11.2) produces various compounds with hypnotic activity. Replacement of the oxygen atom in position X by a sulfur atom produces the ultra-short-acting thiobarbiturates.

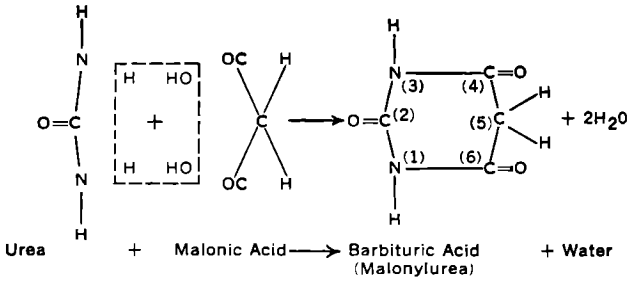

Fig. 11.1. Formation of barbituric acid from urea and malonic acid.

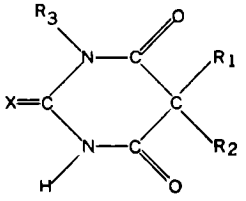

Fig. 11.2. General formula of the barbiturates.

Table 11.2. Names, status, chemical structures, duration of action, and excretion of the barbiturates

Barbiturate	Status	Commercial Names or Synonyms	R_1	R_2	R_3	X	Duration of Action	Organ of Degradation and/or Excretion
Allylbarbituric acid	NF	Sandoptal	allyl	isobutyl	H	O	Intermediate	III
Amobarbital	USP	Amytal	ethyl	isoamyl	H	O	Intermediate	III
Aprobarbital	NF	Alurate	allyl	isopropyl	H	O	Intermediate	II
Barbital	NF	Veronal Barbitone	ethyl	ethyl	H	O	Long	I
Butabarbital[a]	NNR	Butisol	ethyl	*sec*-butyl	H	O	Intermediate	—
Butallylonal[a]	NF	Pernoston	2-bromallyl	*sec*-butyl	H	O	Intermediate	II
Butethal	NF	Neonal	ethyl	*n*-butyl	H	O	Intermediate	II
Cyclobarbital	NF	Phanodorn	ethyl	cyclohexenyl	H	O	Short	II
Cyclopal	—	—	allyl	cyclopentenyl	H	O	Short	II
Diallylbarbituric acid	NF	Dial	allyl	allyl	H	O	Long	II
Hexethal[a]	NNR	Ortal	ethyl	*n*-hexyl	H	O	Intermediate	III
Hexobarbital[b]	NF	Evipal Hexobarbitone	methyl	cyclohexenyl	CH_3	O	Ultrashort	IV
Kemithal[b]	—	—	allyl	cyclohexenyl	H	S	Ultrashort	IV
Mephobarbital	NF	Mebaral	ethyl	phenyl	CH_3	O	Long	II
Pentobarbital	USP	Nembutal	ethyl	1-methylbutyl	H	O	Short	III
Phenobarbital	USP	Luminal Phenobarbitone	ethyl	phenyl	H	O	Long	I
Probarbital[a]	NF	Ipral	ethyl	isopropyl	H	O	Intermediate	III
Propallylonal	—	Nostal	isopropyl	2-bromallyl	H	O	Intermediate	III
Secobarbital[a]	USP	Seconal	allyl	1-methylbutyl	H	O	Short	III
Thiamylal[b]	NNR	Surital	allyl	1-methylbutyl	H	S	Ultrashort	IV
Thiopental[b]	USP	Pentothal	ethyl	1-methylbutyl	H	S	Ultrashort	IV
Vinbarbital[a]	NF	Delvinal	ethyl	1-methyl-1-butenyl	H	O	Intermediate	II

[a]Employed principally as the sodium salt.
[b]Used for intravenous anesthesia, as sodium salt.
I Mainly excreted by kidney.
II Degraded by liver and excreted by kidney.
III Degraded by liver.
IV Absorbed by body fat, degraded by liver, and excreted by kidney.
Adapted from Goodman and Gilman.[134]

Substituted R_1-R_2 derivatives of barbituric acid behave as weak acids and unite with fixed alkalies to form soluble salts. These salts hydrolyze in water to varying degrees and form alkaline solutions. Those commonly employed in veterinary medicine have a pH of 10 or above, and for this reason may cause severe tissue damage and slough if injected perivascularly in any appreciable quantity.

Classification

The barbiturates have been classified into four groups according to duration of action (Fig. 11.3 and Tables 11.2 and 11.3): long, intermediate, short, and ultrashort. All of those used for clinical anesthesia fall in the short or ultrashort classification, whereas those used for sedation or control of convulsions are of long or intermediate action.

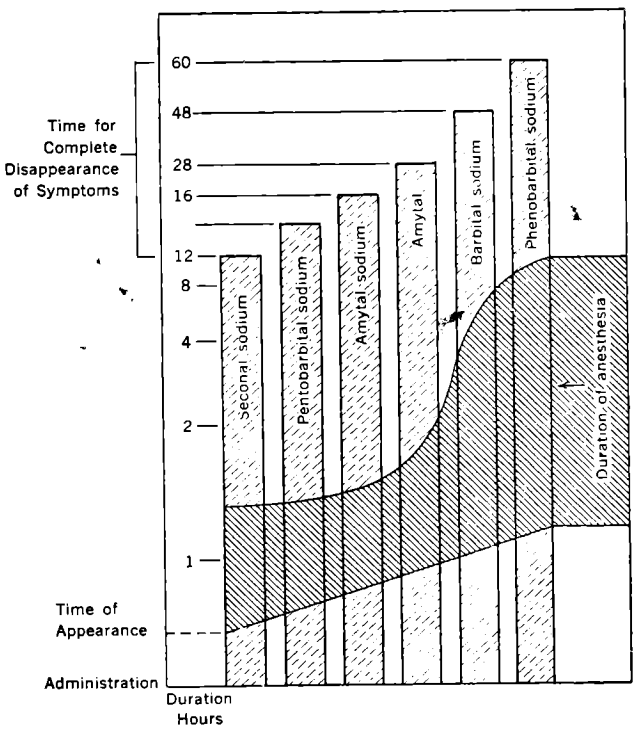

Fig. 11.3. Time of appearance, duration of anesthesia, and time needed for complete disappearance of symptoms after oral administration of equivalent single anesthetic doses in animals. From Jones et al.[139]

Table 11.3. Historical and clinical data of the oxybarbiturates and thiobarbiturates.

	Oxybarbiturates		
Agent Generic Name	**Pentobarbital**	**Secobarbital**	**Hexobarbital**
Trade name	Nembutal Sodium Registered by Abbott Laboratories	Seconal Sodium Registered by Eli Lilly	Evipal Sodium Registered by Parke, Davis
Chemical name	Sodium 5-ethyl-5(1-methylbutyl)-barbiturate	Sodium 5-allyl-5-(1-methylbutyl)-barbiturate	Sodium 1,5-dimethyl-5-(1-cyclohexenyl)-barbiturate
Formula	$C_{11}H_{17}N_2O_3$ Na	$C_{12}H_{17}N_2O_3$ Na	$C_{12}H_{15}N_2O_5$ Na
Discovery of compound	1930 by Volwiler	1930 by Shonle	1932 by Krepp and Taub
Discovery of anesthetic or relaxant properties	1930 by Volwiler and Tabern	1931 by Swanson	1932 by Weese and Scharpff
Type of compound	5-Substituted barbiturate	5-Substituted barbiturate	*N*-substituted barbiturate
Molecular weight	248.26	260.27	258.25
Buffer employed	None	None	None
Preservative or stabilizing agent used	None	Phenol, 0.25%, and polyethylene glycol 200, 50%	None
Thermostability	Precipitates on heating	Precipitates on heating	Free acid melts at 146°C
Chemostability	Solution stable indefinitely	Solution stable up to 18 months in sealed container; decomposes on exposure to air	Solution stable for 48 h if tightly stoppered
Onset of action	30–60 s	30–60 s	30–60 s
Duration of action	1–2 h	1–2 h	15–30 min
Route and/or organ of detoxification or elimination	Detoxified by the liver	Detoxified by the liver	Detoxified by the liver
Usual mode of administration	Intravenous, intrathoracic, intraperitoneal	Intravenous	Intravenous
Specific pharmacological antagonist	Yohimbine plus 4-aminopyridine will partially antagonize pentobarbital and probably other barbiturates. Oxygen administration and artificial respiration are recommended in respiratory arrest.		
Solution pH	6% mixture (10.0–10.3)	5% mixture (9.8–10.1)	2.5% mixture (8.5–10.5)

Adapted from data compiled by Dr. W. H. L. Dornette and published by the Ohio Chemical and Surgical Equipment Company.

General Pharmacology

Racemic mixtures of the barbiturates are used both as hypnotics and as general anesthetics. The principal effect of a barbiturate is depression of the CNS by interference with passage of impulses to the cerebral cortex. Barbiturates act directly on CNS neurons in a manner similar to that of the inhibitory transmitter GABA. At clinical drug concentrations, barbiturates have two mechanisms of action at $GABA_A$ receptors. At lower concentrations, barbiturates exert a GABA-mimetic effect by decreasing the rate of dissociation of GABA from the $GABA_A$ receptor.[2,3] At increasing drug concentrations, barbiturates directly activate the chloride-ion channel associated with the $GABA_A$ receptor.[4,5] The GABA-mimetic effects of barbiturates are thought to produce their sedative hypnotic effects, whereas the direct chloride-ion channel activation produces their anesthetic effects. Barbiturates also inhibit the synaptic actions of some excitatory neurotransmitters such as glutamate and acetylcholine.[6–8] The role of this action in the production of the anesthetic state remains uncertain.

Ganglionic transmission is approximately 20 times more sensitive to pentobarbital than is axonal conduction.[9] The fast excitatory postsynaptic potential (EPSP) is approximately 10 times more sensitive to pentobarbital than are the slow potentials (slow EPSP and slow inhibitory PSP). Phenobarbital also exerts some degree of selectivity toward the fast EPSP. Anesthetic concentra-

Oxybarbiturates (*cont.*)	**Thiobarbiturates**		
Methohexital	**Thiamylal**	**Thiopental**	**Thialbarbitone**
Brevital Registered by Eli Lilly	Surital Sodium Registered by Parke, Davis	Pentothal Sodium Registered by Abbott Laboratories	Kemithal Sodium Registered by Fort Dodge Laboratories
Sodium a-dl-1-methyl-5-allyl-5-(1-methyl-2-pentynyl)-barbiturate	Sodium 5-allyl-5-(1-methylbutyl)-2-thiobarbiturate	Sodium 5-ethyl-5-(1-methylbutyl)-2-thiobarbiturate	Sodium 5-allyl-5-(2-cyclohexenyl)-2-thiobarbiturate
$C_{14}H_{17}N_2O_3Na$	$C_{12}H_{17}N_2O_2SNa$	$C_{11}H_{17}N_2O_2SNa$	$C_{13}H_{15}N_2O_2SNa$
1955 by Doran	1929 by Dox	1929 by Taburn and Volwiler	1938 by Carrington
1955 by Gibson	1933 by Gruhzit	1933 by Tatum	1946 by Carrington and Raventos
N-5-substituted barbiturate	5-Substituted thiobarbiturate	5-Substituted thiobarbiturate	5-Substituted thiobarbiturate
284.0	276.33	264.23	286.3
Sodium carbonate	6% Sodium carbonate	6% Sodium carbonate	None
None	None	None	None
Deteriorates when boiled	Precipitates when boiled	Precipitates when boiled	Thermolabile
Solution stable at room temperature for 6 months	Solution stable for 48–72 h if tightly stoppered	Solution stable for 48–72 h if tightly stoppered	Solution stable 7 days; indefinitely, if frozen
10–30 s	20–30 s	20–30 s	20–30 s
5–15 min	10–15 min	10–15 min	15–45 min
Detoxified by the liver	Absorbed by fat and detoxified by the liver	Absorbed by fat and detoxified by the liver	Absorbed by fat and detoxified by the liver
Intravenous	Intravenous	Intravenous	Intravenous, intrathoracic, intraperitoneal
Yohimbine plus 4-aminopyridine will partially antagonize pentobarbital and probably other barbiturates. Oxygen administration and artificial respiration are recommended in respiratory arrest.			
5% mixture (10.4–11.4)	2.5% mixture (10.5–11.0)	2.5% mixture (10.5–11.0)	10% mixture (10.6)

tions of pentobarbital selectively block the fast EPSP. A selective postsynaptic block of the nicotinic action of acetylcholine also occurs and may account for the anesthetic-depressant effects of pentobarbital on ganglionic transmission. This selective depression on the nicotinic action of acetylcholine could occur by various molecular mechanisms, for example, by altering the binding of acetylcholine.

In hypnotic doses, the barbiturates have little effect on respiration, whereas, in anesthetic doses, respiration is depressed. Overdosage produces respiratory paralysis and death. With anesthetic doses, there is cardiovascular depression, both centrally and peripherally, with a fall in blood pressure. In hypnotic doses, barbiturates have little effect on the basal metabolic rate. With anesthetic doses, basal metabolism is depressed, resulting in lowered body temperature.

Following barbiturate administration, leukocyte counts decrease in normal and splenectomized dogs.[10] Packed cell volume also decreases in nonsplenectomized dogs, presumably owing to splenic sequestration of red blood cells. There is no significant change in the differential counts (Tables 11.4 and 11.5).

The oxidation of pentobarbital, hexobarbital, and amobarbital is noncompetitively inhibited by halothane, methoxyflurane, and diethyl ether.[11] Saturation of the enzyme system by the anesthetic appears responsible. Chloramphenicol, a microsomal in-

Table 11.4. Leukocyte counts and packed cell volumes (PCVs) in 12 dogs after barbiturate anesthesia.

	Pentobarbital		Thiopental		Thiamylal		Methohexital	
Time in minutes	Leukocytes × 10^3	PCV, %	Leukocytes × 10^3	PCV, %	Leukocytes × 10^3	PCV, %	Leukocytes × 10^3	PCV, %
−30	13.7 ± 1.5[a]	50 ± 1.2	12.4 ± 1.0	49 ± 1.2	12.5 ± 1.1	48.5 ± 1.5	13.4 ± 1.4	50 ± 1.4
Anesthesia begins	13.6 ± 1.5	48 ± 1.5	12.2 ± 0.9	47 ± 1.0	12.7 ± 1.0	48 ± 1.2	13.5 ± 1.4	49 ± 1.1
+30	10.8 ± 1.3	40 ± 1.2	10.8 ± 1.0	40 ± 1.4	10.8 ± 1.0	41 ± 1.2	10.9 ± 1.2	42 ± 0.7
+60	10.9 ± 1.3	40 ± 1.5	10.7 ± 0.9	40 ± 1.6	10.1 ± 1.0	41 ± 1.4	11.0 ± 1.4	42 ± 1.0
+120	10.7 ± 1.4	40 ± 1.4	10.9 ± 1.1	42 ± 1.6	10.3 ± 1.1	43 ± 1.2	11.1 ± 1.2	44 ± 1.0
+180	10.8 ± 1.3	41 ± 1.0	11.3 ± 1.2	42 ± 1.3	10.7 ± 1.1	43 ± 1.2	10.9 ± 1.4	44 ± 1.1

[a]Mean ± standard deviation.
From Usenik and Cronkite.[10]

Table 11.5. Leukocyte counts and packed cell volumes (PCVs) in six splenectomized dogs (two trials per dog) after pentobarbital anesthesia.

Time in Minutes	Leukocytes × 10^3	PCV, %
−30	14.2 ± 1.0[a]	46.5 ± 1.6
Anesthesia begins	13.9 ± 1.0	46 ± 1.9
+30	11.6 ± 1.1	45 ± 1.8
+60	11.2 ± 1.0	45 ± 1.8
+120	11.0 ± 1.1	45 ± 1.8
+180	11.0 ± 1.0	45 ± 1.9

[a]Mean ± standard deviation.
From Usenik and Cronkite.[10]

pK_a = dissociation constant
or
pH at which equal amount of drug is in ionized and unionized forms.

$$HA \rightleftharpoons H^+ + A^-$$

Barbiturate	*pK_a*
Thiopental	7.4
Secobarbital	7.9
Pentobarbital	8.0

Fig. 11.4. Dissociation of barbiturates.

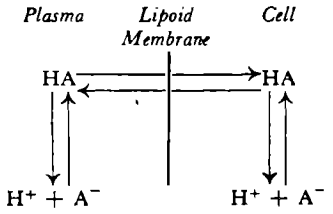

Fig. 11.5. Barbiturate dissociation. Cell membrane is permeable only to undissociated (nonionized) barbiturate.

hibitor, can markedly prolong recovery from pentobarbital anesthesia.

Barbiturates administered during the prenatal period can produce permanent alterations in sexual maturity of hamsters and rats,[12,13] and perhaps an increased incidence of congenital malformations in humans.[14,15]

Distribution

Barbiturates diffuse throughout the body, penetrating cell walls and crossing the placenta. The extent of ionization, lipid solubility (partition coefficient), and protein binding are the three most important factors in distribution and elimination of barbiturates.

Barbiturates are sodium salts of barbituric acid derivatives. When dissolved in water, they ionize. The degree of ionization is determined by the pH of the solution and the dissociation constant (p*Ka*) of the agent. This dissociation constant is the pH at which the compound exists in equal quantities in the dissociated (ionized or polar) and undissociated (nonionized or nonpolar) forms (Fig. 11.4). For a barbiturate to penetrate the lipoid layer of cell membranes, it must be in the undissociated or nonpolar form (Fig. 11.5). The more acidic the solution is containing the drug, the more undissociated form that exists and the greater the amount that can penetrate cell membranes to produce deeper anesthesia. The reverse is also true: The more alkaline the solution is, the greater the dissociation and the lesser the cell penetration.

At a blood pH of 7.4, a barbiturate assumes a "normal" distribution within the cells of the CNS and produces the desired degree of anesthesia. A change in blood pH, however, may lead to a change in the depth of anesthesia. An increase in acidity, such as commonly occurs with respiratory or metabolic acidosis, increases the depth. An increase in alkalinity, caused by hyperventilation or administration of alkalinizing agents, increases dissociation, and barbiturate migrates outward from the cells to the plasma, and anesthesia will lighten.[16] Alkalinization of the urine also decreases tubular reabsorption.

The undissociated form has a high affinity for nonpolar solvents. This varies between compounds, as shown in Table 11.6.

Table 11.6. Barbiturates: relation between physicochemical factors, distribution, and fate.

Barbiturate	Partition Coefficient[a]	Plasma Protein Binding[b]	Brain Protein Binding[c]	Delay in Onset of Activity[d]	Excreted by Kidney[e]	Degradation by Liver Slices[f]	p*Ka*[g]
Barbital	1	0.05	0.06	22	65–90	—	7.8
Phenobarbital	3	0.20	0.19	12	30	—	7.3
Pentobarbital	39	0.35	0.29	0.1	—	0.21	8.0
Secobarbital	52	0.44	0.39	0.1	—	0.28	7.9
Thiopental	580	0.65	0.50	—	—	0.38	7.4

[a](Concentration in methylene chloride): (concentration in aqueous phase) of the nonionized form at approximately 25°C.
[b]Binding of 0.001 M barbituric acid by 1% bovine serum albumin in M/15 phosphate buffer at pH 7.4; fraction bound.
[c]Fraction of barbiturate bound by rabbit brain homogenates.
[d]Minutes until anesthesia after intravenous injection in mice.
[e]Approximate percentage of total dose excreted unchanged in urine of humans.
[f]Fraction degraded in vitro by liver slices in 3 h.
[g]Ionization exponent at 25°C.
From Goodman and Gilman.[135]

Table 11.7. Rates of passage of drugs from bloodstream into the cerebrospinal fluid of dogs and degrees of ionization of drugs at pH 7.4.

Drug	% Nonionized at pH 7.4	Permeability Coefficient[a]	Heptane-Water Partition Coefficient of Unionized Form of Drug
Barbital	55.7	0.026	0.002
Thiopental	61.3	0.50	3.3
Pentobarbital	83.4	0.17	0.05

[a]The higher the permeability coefficient, the more rapid is the rate of entry into the CSF.
From Shanker.[136]

Table 11.8. Influence of carbon dioxide on penetration of brain by drugs.

Area	Concentration in the Brain		
	Hypercapnic Acidosis	Hypocapnic Alkalosis	Relative Penetration
Urea (1 h)			
Gray	0.40	0.16	2.50
White	0.12	0.05	2.40
Phenobarbital (1/2 h)			
Gray	1.20	0.72	1.67
White	1.08	0.40	2.70
Salicylic Acid (1 h)			
Gray	0.44	0.11	4.00
White	0.38	0.04	9.50

Concentration in brain is expressed as a fraction of levels in plasma (relative penetration is brain fractions under conditions of hypercapnia to brain fraction under conditions of hypocapnia). Note the disproportionate increase in penetration of white matter by salicylic acid under conditions of hypercapnia. Gray, cerebral cortex; white, cerebral white matter.
From Roth and Barlow.[137] Copyright 1961 by the American Association for Advancement of Science.

The highly lipid-soluble agents have a rapid onset and are short-acting. They are rapidly metabolized and also easily reabsorbed by the kidney tubules.

A reversible bond develops to plasma proteins, chiefly albumin, the degree of which agrees roughly with the partition coefficient. Because cerebrospinal fluid is practically protein free, it contains less barbiturate than does plasma (Table 11.7). Organ tissues contain a slightly higher level of barbiturate, whereas fat contains very high concentrations. Highly lipid-soluble compounds penetrate brain tissue quite rapidly, reaching equilibrium with two or three circulations of blood. Gray matter of the brain is penetrated rapidly, with white matter being slower to reach equilibrium (Table 11.8).

Barbiturate anesthesia is terminated by physical redistribution, metabolic degradation, and renal excretion. Again, the solubility coefficient dictates the chief route of elimination. Short-acting agents with a high solubility coefficient are largely reabsorbed from the kidney tubules. Their action ceases when they are metabolically transformed into inactive substances, principally in the liver. Long-acting agents with low lipid solubility are chiefly excreted through the kidneys. As much as 85% of barbital and phenobarbital may be recovered from the urine over several days following administration.[17] The short-acting barbiturates (pentobarbital, amobarbital, and secobarbital) are destroyed principally by the liver. Their rapid destruction in the body accounts for their shorter action. With anesthetic-inducing doses ultra-short-acting barbiturates are quickly redistributed, accounting for their short action. Thiobarbiturates are not metabolized more rapidly than the oxybarbiturates.

The "Glucose Effect"?

A unique reanesthetizing action, termed the *glucose effect*, has been observed in animals recovering from barbiturate anesthesia that were subsequently given glucose. A species variation in susceptibility to this effect has been demonstrated: Guinea pigs, chickens, pigeons, rabbits, and hamsters are susceptible; dogs are intermediate; and mice, rats, goldfish, and tadpoles are refractory or negative. Intermediates in the glycolysis of glucose and in the Krebs cycle have been shown to have the same effect. The glucose effect presumably occurs with most barbiturates and thiobarbiturates, but not with inhalation or other anesthetics. Glucose causes a decrease in activity of the components of the microsomal electron chain, resulting in decreased microsomal metabolism.[18] A study on the glucose effect on respiration and electroencephalogram in dogs following pentobarbital administration found no evidence of significant deepening of anesthesia as judged by cortical depression, decreasing rate or depth of respiration, or a decrease in minute volume.[19]

Epinephrine given intravenously (IV) to dogs or mice also causes a return of sleep on awakening from hexobarbital or chloral hydrate anesthesia. Norepinephrine is less effective in producing this effect.[20] This phenomenon presumably is caused by increased glucose levels in the blood and should be remembered when the use of epinephrine is considered in barbiturate-anesthetized dogs. The effect of glucose, sodium lactate, and epinephrine on thiopental anesthesia in dogs has also been studied (Table 11.9). The glucose effect does not appear to be of practical concern as long as these drugs are used in therapeutic doses.[21]

Table 11.9. Relative ability of glucose, sodium lactate, and epinephrine to cause anesthetic rebound[a] in dogs recovering from thiopental anesthesia.

Drug and Dosage	Dogs Given Injections (No.)	Dogs Rebounded (No.)	Dogs Rebounded %	Average Increase in Sleep Time (%)
Glucose, 600.0 mg/kg	18	2	11.1	47.9
Sodium lactate, 60.0 mg/kg	18	7	38.9	48.9
Epinephrine, 0.1 mg/kg	13	11	84.6	38.8
Saline solution, 1.0 mL/kg	12	0	0	0

[a]Apparent reanesthetization as indicated by loss of voluntary and involuntary movements and possible loss of pedal reflexes.

From Hatch.[21]

Therapeutic Uses

Barbiturates are used to induce sedation and hypnosis, as anticonvulsants, and as anesthetics. Their use as sedatives and hypnotics in low doses has been supplanted, in most instances, by tranquilizers. The ability of barbiturates to depress the motor cortex has been used to treat convulsions associated with poisoning, particularly strychnine, "running fits," distemper encephalitis, and overdosage of local anesthetics. In modern veterinary medicine, the thiobarbiturates are primarily used as induction agents or short-acting anesthetics, whereas pentobarbital is now used sparingly because of its propensity to cause prolonged, rough recoveries when administered in anesthetic doses.

Addiction

Although barbiturate addiction can be produced in animals, it is by its very nature self-limiting; however, in humans, repeated oral use of barbiturates as soporifics or sedatives may become habit forming. For this reason, legislation in many countries prohibits use of these drugs without a prescription. Veterinarians should be acquainted with applicable laws regarding the use and sale of barbiturates to avoid infraction and to prevent liability.

Oxybarbiturates

Phenobarbital Sodium

Phenobarbital was synthesized in 1912 in Germany and marketed under the trade name Luminal. It is a long-acting barbiturate, and advantage has been taken of its prolonged action in treating various convulsive disorders (Fig. 11.3). In control of convulsions caused by distemper encephalitis, it appears to be as effective as any of the newer drugs and considerably cheaper. Because it is excreted slowly in the urine, it tends to be cumulative. An oral loading dose should be administered first, followed by a daily maintenance dose. In average dogs (10 kg), this would be 60 mg initially, followed by 15 mg three times a day. Overdosage causes loss of motor coordination; when this occurs, the dose should be reduced. Serial assays on serum, saliva, and cerebrospinal fluid have shown considerable daily fluctuation in phenobarbital levels, even after several weeks of therapy. The phenobarbital concentration increases gradually in the three fluids up to doses of 9.0 mg/kg. Serum or saliva assays can accurately indicate the phenobarbital concentration in cerebrospinal fluid.[22]

In animals suffering from strychnine poisoning, phenobarbital solution may be given IV to effect in the same manner as one would administer pentobarbital sodium. Phenobarbital is a hepatic microsomal enzyme inducer. Concomitant administration of phenobarbital and digoxin can shorten the biological half-life of the latter by approximately 30%.[23]

Pentobarbital Sodium

This drug came into general use as an anesthetic agent for dogs and cats in the early 1930s and slowly supplanted ether administered by open-mask methods as the anesthetic of choice. By 1940, its use was widespread. Today, it has largely been replaced by inhalation and balanced anesthetic techniques.

Commercial preparations of pentobarbital are racemic mixtures. Administration of subanesthetic doses is often associated with CNS stimulation and preanesthetic excitation. The R-isomer of pentobarbital causes a transient period of hyperexcitability before depressing the CNS, whereas the S-isomer produces relatively smooth and progressively deeper hypnosis.[24] Evidence suggests the S-isomer is more potent, possibly because of increased uptake by the brain.[25,26]

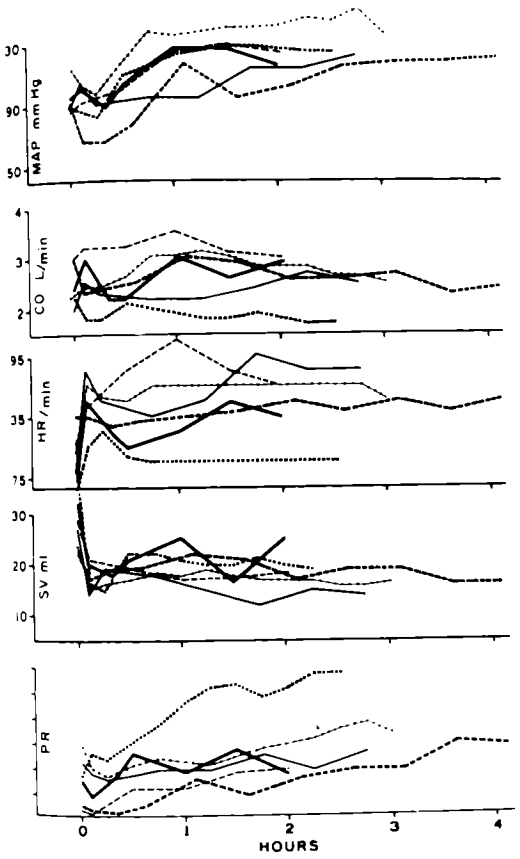

Fig. 11.6. Long-term changes from pentobarbital in six dogs. Note the large and abrupt increase in heart rate and decrease in stroke volume at the onset of the experiments. CO, cardiac output; HR, heart rate; MAP, mean arterial pressure; PR, peripheral resistance; and SV, stroke volume. From Olmsted and Page.[140].

Pentobarbital sodium occurs as a white powder or crystalline granules. It is freely soluble in water or alcohol. It forms a clear, colorless solution that is marketed under several trade names. Aqueous solutions have an alkaline pH and may precipitate on standing, but the drug can be redissolved by addition of an alkali such as sodium hydroxide. The calculated dose for dogs and cats is 30 mg/kg of body weight; however, it should be emphasized that pentobarbital is given *to effect*. Following a single intravenous dose of pentobarbital, arterial blood pressure decreases. The heart rate increases for 10 to 20 min and then stabilizes or decreases. Cardiac output is variable, whereas peripheral vascular resistance increases (Fig. 11.6).

The cardiovascular effects of prolonged pentobarbital (2.5 h) anesthesia in dogs have been assessed. Systolic blood pressure, initial ventricular impulse, stroke volume, pulse pressure, central venous pressure, arterial oxygen partial pressure, pH, and body temperature all decrease after anesthetic doses of pentobarbital. Heart rate, arterial carbon dioxide partial pressure, and peripheral resistance increased after 1.5 h. Cardiac output eventually decreases. Mean arterial pressure significantly decreases during induction, but usually returns to awake values in approximately 30 min (Table 11.10).[27] Intravenous pentobarbital administration alters myocardial function and distribution of blood flow. In dogs, it was found that intravenous pentobarbital decreases contractile force by 17.4%, arterial blood pressure by 4.8%, and renal blood flow by 8.4%, while increasing cardiac output by 4.8% and superior mesenteric artery flow by 14.1%. The decreased arterial blood pressure was believed to be caused by vasodilation of major vascular beds, and the increased cardiac output to be caused by increased venous return.[28] Respiration is initially depressed and gradually increases during recovery.[29]

Light pentobarbital anesthesia has little influence on renal hemodynamics. Deep anesthesia depresses renal function, both blood and urine flow, by circulatory depression and also by reflex vasoconstriction. Pentobarbital inhibits water diuresis by stimulating release of antidiuretic hormone.[30]

Leukopenia is found in dogs anesthetized with pentobarbital.[31] Leukocyte counts drop to 20% of control values (Fig. 11.7). Although the absolute differential white cell count decreases, there is a relative lymphocytosis that reaches its peak at 90 min and then returns to normal. Red cell numbers decrease also. Hemoglobin and hematocrit values show corresponding changes. Pentobarbital, amobarbital, and thiopental administration dilates the spleen, which presumably accounts for the decrease in erythrocytes via the sequestration of red blood cells.[32] Maximum dilation usually occurs 20 to 30 min after injection of the anesthetic. Sedimentation rate and coagulation time are both increased, whereas prothrombin time is decreased. Oral administration of pentobarbital sodium in sedative doses does not affect the blood constituents in the same fashion.

In some animals, the effect produced by high doses of pentobarbital is difficult to differentiate from shock. The size of the dose and method of its administration are the major factors in variation of response to pentobarbital. Individual variations undoubtedly exist. Roughly one of four animals given a dose of 30 mg/kg develops side effects that mimic some phase of shock.[33]

On intraperitoneal administration, the peak concentration in the blood is reached more slowly than with intravenous injection, and the portion of drug absorbed into the portal system is subjected to early destruction in the liver. When a 2.5% aqueous solution is given intraperitoneally in a dose of 30 mg/kg of body weight, anesthesia is not accompanied by impaired renal function, and arterial blood pressure increases.[34] When given radiolabeled pentobarbital orally, dogs excrete about 60% of the total dose in the urine during the first 24 h.[35] Over 92% is excreted as metabolic products derived from the drug, and only 3% is in the form of pentobarbital. Pentobarbital elimination from the blood of both intact and bilaterally nephrectomized dogs is similar because elimination is totally dependent on biotransformation of pentobarbital by the liver.[36] The absence of renal function per se does not seem to alter the pharmacokinetics of pentobarbital; however, the sensitivity of a patient to the action of barbiturates may be increased by uremia. This phenomenon is probably caused by the decreased capacity of plasma protein to bind acidic drugs.

Pentobarbital freely crosses the placental barrier and enters the fetus. For this reason, its use as a monoanesthetic (high dose) for

Table 11.10. Cardiovascular responses to pentobarbital anesthesia in 12 dogs.

Parameters	Control	Time After Pentobarbital Administration					
		0 h[a]	0.5 h	1 h	1.5 h	2 h	2.5 h
Systolic blood pressure	142 ± 3	116 ± 5[c]	123 ± 4[c]	121 ± 3[c]	122 ± 3[c]	124 ± 3[c]	130 ± 3[c]
(mm Hg)	100%[b]	82 ± 3	87 ± 3	86 ± 3	86 ± 2	88 ± 2	92 ± 2
Mean blood pressure	108 ± 4	95 ± 4[c]	104 ± 4	106 ± 3	108 ± 2	111 ± 3	117 ± 3
(mm Hg)	100%	89 ± 4	97 ± 4	99 ± 4	101 ± 3	104 ± 4	109 ± 4
Diastolic blood pressure	83 ± 3	80 ± 4	89 ± 4	93 ± 3[c]	95 ± 2[c]	90 ± 3[c]	105 ± 3[c]
(mm Hg)	100%	98 ± 5	109 ± 5	115 ± 6	117 ± 5	122 ± 6	127 ± 6
Pulse pressure (mm Hg)	59 ± 2.6	36 ± 2.4[c]	34 ± 1.9[c]	28 ± 2.2[c]	27 ± 1.9[c]	26 ± 1.3[c]	25 ± 1.4[c]
Central venous pressure (mm Hg)	+1.44 ± 0.7	+0.14 ± 0.4[c]	−0.4 ± 0.4[c]	−1.00 ± 0.5[c]	−1.25 ± 0.5[c]	−1.08 ± 0.5[c]	−1.55 ± 0.6[c]
Heart rate (beats/min)	96 ± 5	157 ± 5[c]	153 ± 7[c]	157 ± 8[c]	141 ± 7[c]	135 ± 7[c]	146 ± 10[c]
	100%	167 ± 9	165 ± 11	168 ± 9	155 ± 10	146 ± 11	157 ± 12
Initial ventricular	7 ± 0.4	9 ± 0.4[c]	9.8 ± 0.5[c]	10.1 ± 1[c]	12.5 ± 0.9[c]	13.8 ± 1[c]	14.7 ± 0.9[c]
impulse (angle in °)	100%	130 ± 6	142 ± 8	147 ± 15	180 ± 11	193 ± 11	212 ± 11
Cardiac output (L/min)	1.734 ± 0.15	1.834 ± 0.14	1.811 ± 0.09	1.502 ± 0.11[c]	1.324 ± 0.12[c]	1.195 ± 0.10[c]	1.172 ± 0.09[c]
	100%	111 ± 8	111 ± 8	90 ± 5	79 ± 6	71 ± 5	70 ± 5
Stroke volume	18.6 ± 2	11.8 ± 1[c]	12.3 ± 1[c]	10.1 ± 1[c]	9.5 ± 1[c]	9.4 ± 1[c]	8.9 ± 1[c]
(mL/beat)	100%	66 ± 4	68 ± 3	54 ± 2	51 ± 1	50 ± 3	47 ± 4
Total peripheral resistance	5287 ± 558	4574 ± 385	4819 ± 419	6200 ± 551	7370 ± 696[c]	8535 ± 942[c]	8864 ± 1928[c]
(dynes-s/cm^5)	100%	91 ± 7	95 ± 6	124 ± 11	142 ± 8	163 ± 10	168 ± 8
PaO_2 (mm Hg)	93.5 ± 3	60 ± 5[c]	70 ± 3[c]	73.5 ± 6[c]	70 ± 6[c]	77 ± 4[c]	75 ± 5[c]
	100%	61 ± 5	72 ± 4	75 ± 7	80 ± 6	79 ± 5	76 ± 6
$PaCO_2$ (mm Hg)	30.9 ± 0.8	40.9 ± 3[c]	44 ± 2[c]	41 ± 3[c]	38 ± 3[c]	38 ± 3[c]	38 ± 3[c]
	100%	132 ± 9	141 ± 5	133 ± 8	121 ± 7	123 ± 9	123 ± 7
pH arterial	7.38 ± 0.01	7.27 ± 0.03[c]	7.27 ± 0.03[c]	7.29 ± 0.03[c]	7.30 ± 0.02[c]	7.30 ± 0.03[c]	7.32 ± 0.03[c]
Temperature (°C)	38.8 ± 0.2	38.7 ± 0.2[c]	38.5 ± 0.2[c]	38.1 ± 0.2[c]	37.9 ± 0.2[c]	37.6 ± 0.2[c]	37.4 ± 0.2[c]

[a]0, time values taken 3 to 5 min after intravenous pentobarbital.
[b]Each value indicates mean ± standard error with percent of control ± standard error below.
[c]Denotes statistically significant changes with $P < 0.05$.
From Priano et al.[27]

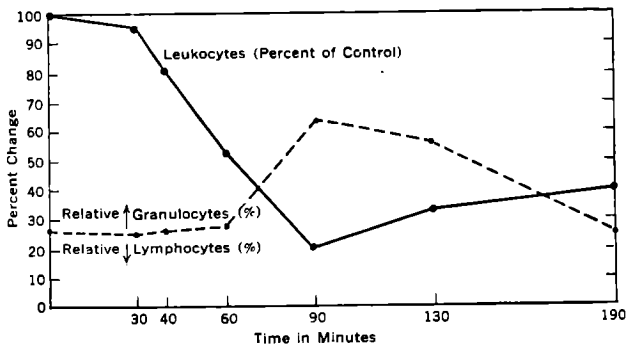

Fig. 11.7. The relative percentage change in white cell counts with intravenous pentobarbital sodium anesthesia in 12 dogs as compared with control levels in unanesthetized dogs. The relative percentage distribution of lymphocytes and granulocytes is shown on the same scale. From Graca and Garst.[31]

cesarean section causes high mortality among newborns. Neonates can be viable at birth, but usually do not recover from anesthesia and cannot nurse.

The duration of surgical analgesia with anesthetizing doses of pentobarbital varies widely with individual animals, averaging about 30 min. Complete recovery usually occurs in 6 to 18 h. Occasionally, animals, particularly cats, may not rouse for as long as 24 to 72 h.

Pentobarbital is no longer used in North America to produce anesthesia in most small companion animals, cattle, and horses, owing to the prolonged recovery period and marked respiratory depression. It has been administered by slow intravenous injection (15 to 30 mg/kg) in foals and young cattle. Because of prolonged recovery, pentobarbital should not be administered to animals younger than 1 month of age. In adult cattle, anesthesia has been induced with 14 mg/kg IV; half of the dose is injected rapidly, the animal is positioned on its sternum, and the remainder is injected slowly to effect.[37] Pentobarbital has also been administered with chloral hydrate or thiopental sodium to induce anesthesia in adult horses[38] and in goats before administration of inhalant anesthetics.[39]

The intravenous anesthetic dose in adult goats is 30 mg/kg, which maintains anesthesia for approximately 20 min. Anesthesia can be maintained by doses of 6 to 36 mg · kg^{-1} · h^{-1} of pentobarbital. The induction and intubation dose ranges from 10 to 42 mg/kg. A similar technique for intravenous pentobarbital in

Table 11.11. Effect of methohexital sodium on the horse after premedication with morphine, meperidine, or promazine (using four horses per treatment).

	Induction Time (s)		Duration (min)		Time to Stand (min)		
Premedication	**Mean**	**Range**	**Mean**	**Range**	**Mean**	**Range**	**Number of Horses and Type of Recovery[a]**
None	26	23–32	4	3–5.5	21	15–29	4 +++
Meperidine[b]	18	10–25	6	3–16	18	11–30	2 +++ 2 ++
Morphine[b]	16	10–20	5	2–9	19	10–27	2 +++ 1 ++ 1 +
Meperidine Morphine	20	20–21	5	2–7	17	10–34	2 +++ 1 ++ 1 +
Promazine[b]	32	25–35	9	7–10	12	9–16	4 +++
Promazine Meperidine	21	13–30	10	7–13	18	9–26	1 ++ 3 +
Promazine Morphine	24	20–30	7	4–9	27	22–30	1 ++ 3 +
Promazine Meperidine Morphine	27	21–35	8	6–11	17	5–30	1 ++ 3 +

[a]+, Hyperesthesia; ++, mild paddling; +++, severe paddling.
[b]The dose rates used in this trial were meperidine, 1 mg/lb body weight subcutaneously; morphine sulfate, 20 mg/100 lb body weight; promazine, 0.25 mg/lb body weight; methohexital sodium, 1 g/300 to 400 lb body weight.
From Grono.[42]

sheep has been described.[40] Like goats, sheep rapidly metabolize pentobarbital, and additional doses are required to maintain anesthesia for periods longer than 20 to 30 min. The anesthetic dose of pentobarbital sodium is approximately 25 mg/kg in adult sheep. In all ruminants, immediate intubation to prevent aspiration of regurgitated rumen contents is essential.

In swine, a 10- to 30-mg/kg dose of pentobarbital given IV provides anesthesia for 15 to 45 min. If anesthesia is induced until reflex response to surgical stimulation is abolished, respiratory depression is often severe, and apnea may occur.

Animals awakening from pentobarbital anesthesia tend to exhibit the same signs as when they are anesthetized, except in reverse order. These include crying, shivering, involuntary running movements, thrashing, increased respiratory movements followed by recovery of the righting reflex, and, later, ability to stand with a staggering gait. Because recovery is slow, without preanesthetic medication these actions may become so exaggerated that the animal injures itself through contact with the cage or stall or causes wound disruption. Greyhounds are notable for this effect. Show animals have been known to break teeth, much to the embarrassment of the veterinarian. Administration of a narcotic or a tranquilizer is indicated in cases of emergence excitement. Yohimbine plus 4-aminopyridine will incompletely antagonize pentobarbital-induced CNS depression in dogs preanesthetized with atropine-xylazine or atropine–acepromazine.[41]

Methohexital Sodium

This is an ultra-short-acting barbiturate that is unique in that it contains no sulfur atom. Its short duration owes more to redistribution than to rapid metabolism. Blood concentrations necessary to produce anesthesia are approximately one-half of those required with thiopental or thiamylal. According to the manufacturer, a double dose rapidly administered IV causes temporary apnea. The lethal dose is said to be approximately 2.5 times greater than the median anesthetic dose. Animals die of respiratory failure. Methohexital sodium is supplied as 500 mg of dry powder in glass vials. It is diluted with water or normal saline to form a 2.5% solution for injection. Solutions are said to be stable for as long as 6 months at room temperature. The dose for dogs or cats is 6 to 10 mg/kg of body weight. Half of the estimated dose is injected IV at a rapid rate, following which administration is continued to effect. Surgical anesthesia for 5 to 15 min is obtained by an initial injection. More prolonged anesthesia can be maintained by intermittent administration or continuous drip. Recovery is quick and may be accompanied by muscular tremors and violent excitement, which detract from the usefulness of the drug. Dogs are usually ambulatory 30 min after administration ceases.

Methohexital has been used alone and with several preanesthetics in horses (Table 11.11). Even with preanesthetic sedation, the recovery period is characterized by muscle tremors and strug-

gling.[42] For this reason, the anesthesia produced is undesirable except when followed by administration of an inhalant anesthetic. Under these circumstances, it proves to be a good drug for induction, because its effects are short-lasting. One injection provides just sufficient time for intubation and administration of the inhalant before its effect ceases, leaving horses anesthetized with only the inhalant. The induction dose in horses is approximately 6 mg/kg. It must be given rapidly or anesthesia will not be achieved.

Methohexital has been used to induce anesthesia in calves at the rate of 3 to 5 mg/kg. A smooth, rapid induction enabling endotracheal intubation is produced.[43] In adult cattle, the dose for induction is 6 mg/kg.[44]

A high percentage of the metabolites of methohexital is excreted in the bile of dogs and rats. Following administration of [^{14}C]methohexital to dogs and rats, 30.1% and 82.7% of the radioactivity is found in the feces, respectively. Dogs excrete 21.7% in bile and urine in the first hour and 52.4% in 8 h.[45]

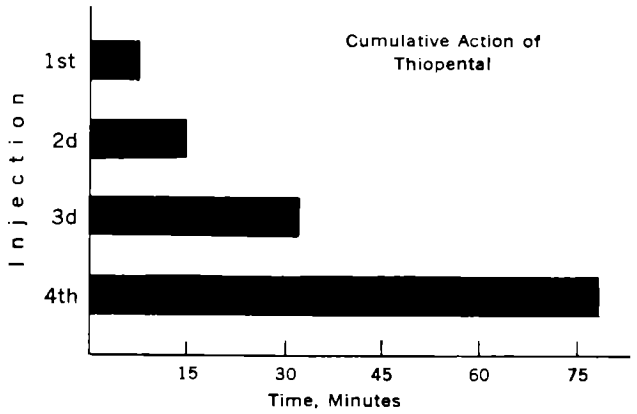

Fig. 11.8. The average duration of anesthesia after successive hourly intravenous injections of equal doses of thiopental to dogs. From Wyngaarden et al.[141]

Thiobarbiturates

Thiopental Sodium

Thiopental was the first thiobarbiturate to gain popularity as an anesthetic agent for animals. It is the thio analog of pentobarbital sodium, and differs only in that the number 2 carbon has a sulfur atom instead of an oxygen atom attached to it. Thiopental sodium is a yellow crystalline powder that is unstable in aqueous solution or when it is exposed to atmospheric air. For this reason, it is dispensed in sealed containers as a powder buffered with sodium carbonate. It is usually mixed with sterile water or saline to form 2.5%, 5.0%, or 10% solutions. Thiopental solutions should be stored in a refrigerator at 5° to 6°C (41° to 42°F) to retard deterioration. As solutions age, they become turbid and crystals precipitate, which results in progressive loss of activity, but does not increase its toxicity. Because the potency is decreased, larger quantities of solution must be used to produce the desired effect.[46]

The metabolism of thiopental is exceedingly complex. Following injection with thiopental containing radioactive sulfur (^{35}S), monkeys produce at least 12 different metabolic products that are excreted in the urine. About 86% is found in the urine within 4 days after intravenous injection; small amounts are also found in the tissues and feces.[47]

The initial toxic effect produced by thiopental is a marked depression of the respiratory centers. Both rate and amplitude are affected. By 5 min after administration of thiopental, heart rate, aortic pressure, peripheral vascular resistance, and left ventricular systolic and end-diastolic pressures increase.[48] Bigeminy is common. Cardiac arrhythmias associated with thiobarbiturate anesthesia can be accentuated by xylazine, halothane, methoxyflurane, and epinephrine.[49–52] Observed arrhythmias include sinus tachycardia, bigeminy, extrasystoles, ventricular tachycardia, multifocal ventricular tachycardia, and ventricular fibrillation. Administration of a lidocaine bolus concurrently with thiopental (11 mg/kg) reduces the cardiopulmonary depressive effects of the latter and has been advocated for anesthetic induction of patients predisposed to cardiac arrhythmias.[48]

During prolonged thiopental anesthesia, there is a pronounced hyperglycemia, increased lactic acid and amino acids in blood, and decreased liver glycogen.[53] Insulin either prevents a decrease or favors increased storage of liver glycogen. Repeated doses of thiopental have a cumulative effect, as shown in Figure 11.8. Prolonged periods of anesthesia may result from this effect if numerous doses are administered.

Thiopental has an ultrashort action because it is rapidly redistributed (e.g., into muscle tissue) and becomes localized in body fat.[54] As concentrations in the plasma, muscle, and viscera fall, the thiopental concentration in fat continues to rise. On the other hand, an appreciable amount is metabolized by the liver, and this contributes to the early rapid reduction of arterial thiopental concentration.[55] The same effect occurs after a fatty meal. A high chylomicron level in the blood reduces sleeping time significantly because thiopental is in more intimate contact with chylomicrons and a smaller diffusion distance is present. Blood fat is more potent than depot fat in decreasing thiopental sleeping time.[56] Leukopenia, hyperglycemia, elevated arterial partial pressure of carbon dioxide, and decreased arterial partial pressure of oxygen have been observed in thiopental-anesthetized horses (Table 11.12) and are comparable to changes observed with the use of other barbiturates and in other species.

For small animals, 1.25%, 2.5%, and 5.0% solutions of thiopental are used, depending on the animal's size. Whenever convenient, the more dilute solutions should be used, because overdosing is less likely and irritation is less in the event of accidental perivascular injection. As in other species, thiopental may be used in dogs and cats as the sole anesthetic or for induction prior to inhalation anesthesia. For rapid induction of anesthesia of short duration, the dose is 10 to 12 mg/kg. Should 10 to 20 min of surgical anesthesia be required, the dose range is 20 to 30 mg/kg. One-third of the estimated dose is injected rapidly within 15 s, and the remainder is administered slowly to effect. Additional doses may be administered to prolong anesthesia when required. Following large-dose administration, recovery (to standing) usually requires 1 to 1.5 h. Large doses will saturate the

Table 11.12. Mean values of the parameters listed below after a single intravenous anesthetic dosage of thiopental sodium in 8 horses[a].

		Minutes After Administering Anesthesia			
	Preanesthetic Value	5	15	25	Statistical Differences
Leukocyte count cell/mm^3	9700	7800	7500	6100	I
Packed-cell volume (vol %)	32	31	30.5	31	
Blood glucose (mg %)	82.1	85.0	91.2	103.1	I
Heart rate[b] (per min)	61	85	95	81	I
Blood pressure[c] (mm Hg)					
Systolic/diastolic	158/117	188/153	173/141	176/140	I
Respiratory rate[c] (per min)	29	8	14	21	I
Oxygen content of arterial blood (vol %)	19.2	19.0	18.2	18.4	II
Oxygen content of venous blood (vol %)	14.3	13.5	13.0	12.8	II
Carbon dioxide content of arterial blood ($PaCO_2$)	43.3	44.2	49.9	49.2	I
Arterial blood (pH)	7.39	7.31	7.21	7.22	I
Plasma level of thiopental sodium (mg/L)	—	49.3	37.1	35.8	I

[a]To produce surgical anesthesia, 9 to 17 mg/kg were required.
[b]Mean values in six horses because of equipment failure.
[c]Mean values in five horses because of equipment failure.
I Statistically significant difference at the 1% level before and after administration of thiopental sodium.
II Statistically significant difference at the 5% level before and after administration of thiopental sodium.
From Tyagi et al.[138]

tissues and cause a prolonged emergence. When induction is preceded by preanesthetic sedation, a dose range of 8 to 15 mg/kg is used. As in other species, too large a dose prior to inhalation anesthesia depresses respiration and impairs the uptake of inhaled gases. The use of thiopental is contraindicated in neonates and in feline porphyria.

Thiopental was commonly used for rapid induction of anesthesia in horses during the 1950s and early 1960s. After preanesthetic sedation with a suitable tranquilizer (e.g., xylazine or acepromazine), 6 to 10 mg/kg of thiopental are injected IV. If injected as rapidly as possible, 6 to 9 mg/kg are adequate. The smaller dose is used prior to the use of inhalant anesthetics, whereas the larger dose is used when a short period of surgical anesthesia is required. Thiopental is more commonly mixed with 5% guaifenesin when used for equine anesthesia. Two or three grams of thiopental are added to 1 L of 5% guaifenesin and administered rapidly IV to effect. It is often preceded by tranquilization with xylazine, detomidine, or acetylpromazine. The time of induction can be decreased by administering an additional 1 g of thiopental as an adult horse (400 to 500 kg) begins to relax. Once the horse is recumbent, the anesthesia can be maintained by continuing the infusion of thiopental and guaifenesin at a slower rate or by intubating and administering an inhalant anesthetic. The induction dose alone will produce anesthesia lasting 10 to 20 min. Total anesthesia time should be limited to less than 1 h when the combination of thiopental and guaifenesin is used as the maintenance anesthetic or recovery can be very prolonged and of poor quality. To minimize the recovery time when thiopental and guaifenesin are used for anesthetic maintenance, the amount of thiopental should be decreased by 50% in subsequent liters of the mixture.

Similar doses of thiopental alone (4 to 6 mg/kg) or with 5% guaifenesin in 5% dextrose in water may be given to induce anesthesia in cows. Once anesthesia is induced in cattle, endotracheal intubation is essential to prevent possible aspiration of rumen contents. The possibility of this is reduced by positioning animals so that the anterior thoracic and caudal cervical region is higher than any other part of the body. As in newborn foals, use of thiopental is contraindicated in the neonatal calves. Thiopental is also used in doses of 8 to 15 mg/kg in small ruminants. Rapid intravenous induction can be achieved with 8 to 12 mg/kg, whereas larger doses are given by slow intravenous injection to effect. The latter technique provides 10 to 20 min of surgical anesthesia.

The dose of thiopental required to induce anesthesia in swine is variable. The minimal dose required ranges from 4.0 to 8.0 mg/kg. Half the dose is injected rapidly, and the remainder more slowly over the next several minutes. Even during light anesthesia, respiratory depression, irregular breathing, and apnea commonly occur in swine.

Thiamylal Sodium

This is the thio analog of the barbiturate secobarbital sodium. It differs from thiopental sodium in that the ethyl radical of the latter (on R_1) is replaced by an allyl radical.[57] In dogs, the anesthetic potency of thiamylal is about 1.5 times that of thiopental.[58]

Administration

Barbiturates are administered by several routes, depending on the patient and the desired effect. For anesthesia, the intravenous route is preferable because the anesthetic can be given to effect. Because of wide variation in patient response, this type of dose

control is desirable. Intraperitoneal administration and intramuscular administration are not widely employed. The oral route is slow and unpredictable, and therefore is used chiefly when sedation is sought.

Care should be taken in selection of needles and syringes for administration. In large species of animals, 12- to 18-gauge 1.5- to 2.0-inch needles are used, depending on the quantity of anesthetic that must be injected rapidly to carry the patient through the excitement stage. When large quantities are to be injected, a vascular catheter is preferred. In smaller animals, 20- to 24-gauge needles aid in venipuncture and help slow the rate of injection. There is a careless tendency to use large syringes on very small animals. This is dangerous because the dose cannot be accurately controlled. A syringe size commensurate with the dose should always be employed; use of large syringes with small doses is an invitation to disaster.

In many practices, an indwelling venous catheter is inserted prior to anesthetic administration. This is used for anesthetic injection and subsequent fluid administration during surgery. It also helps ensure that inadvertent perivascular injection does not occur when animals are transported. In small animals (weighing less than 5 kg), it is advisable to dilute the anesthetic with sterile water. By making a 100% dilution, more accurate dose control is achieved.

When intravenous injection is to be made, hair over the vein may be removed with clippers and the skin prepared by swabbing with a suitable antiseptic. The latter procedure, in addition to cleaning the area, tends to distend the vein. For intravenous anesthesia, the cephalic vein on the anterior aspect of the forelimb is most commonly used in small animals. In dogs, the second choice is generally the saphenous vein on the lateral surface of the hind limb just proximal to the hock. In cats, the saphenous or femoral vein on the inner surface of the thigh is a good second choice. Other veins less frequently used are the jugular and the marginal vein of the ear. In large dogs already anesthetized, the lingual veins on the ventral surface of the tongue are easily accessible. These veins tend to bleed rather profusely, however. In horses, cattle, and sheep, the jugular vein is used almost exclusively. In swine, the marginal vein of the ear or the anterior vena cava is most commonly employed.

In dogs, if injection is to be made into the cephalic vein of the right foreleg, the assistant stands by the animal's left side with the left arm circling the dog's neck and the right arm extended over its back. The right hand grasps the right foreleg just below the elbow. The right index finger is extended over the dorsal surface of the limb, the thumb is held around the ventral surface of the leg, and, by compressing thumb and forefinger, the vein is occluded, causing it to distend with blood. The assistant turns his or her wrist slightly so that the skin covering the dorsal aspect of the foreleg and the cephalic vein is rotated outward. The veterinarian grasps the paw of the right foot with the left hand and, if the vein is not easily seen, by rapidly squeezing the paw several times, pumps blood from the paw to distend the vein. If the carpus is flexed acutely, the vein is stretched tightly over the underlying muscles and rolling is prevented. Good technique demands that the needle used for injection be threaded into the vein so that the hub is at the site of venipuncture. The leg and syringe are both held in the veterinarian's left hand during injection so they will move as a unit if the animal moves. This prevents accidental retraction of the needle from the vein.

Persons experienced with administration of barbiturates to dogs and cats usually estimate the weight of the animal and draw an excess of solution into a syringe. The first one-third to one-half of the dose is rapidly injected while watching the animal's facial expression closely. As injection is made, the animal often licks its lips as though tasting the drug. Frequently, dogs move the head from side to side as the anesthetic effect begins. These movements are seen early in the administration and indicate more drug must be given. The eyes begin to lose their alert expression, and the animal then relaxes. As injection is continued, the veterinarian can, with thumb and forefinger placed behind the canine teeth, open the animal's jaw. If in a light state of anesthesia, the patient will further open the jaw, curl the tongue, and simulate a yawn. At this point, the cornea and pedal reflexes are still present, and the animal is not in a state of surgical anesthesia. Administration of anesthetic should be continued cautiously and in small amounts, with careful attention paid to respiration and reflexes. Surgical anesthesia is reached when the pedal reflex is abolished. At this point, further administration of drug is not necessary.

Intraperitoneal Injection

This has been employed extensively in the past, but has the disadvantage that the dose cannot be as accurately controlled as it can by intravenous administration. Usually with this method, the animal is restrained in a vertical position against the assistant's body with the animal's abdomen facing outward. An area just lateral to the umbilicus is clipped and a suitable antiseptic applied. The needle is passed through the abdominal wall and the injection made. The dose for intraperitoneal administration is calculated in the same manner as the intravenous dose. The peak concentration in the blood is reached more slowly, and drug absorbed into the portal system is subject to early metabolism.[34] This technique is not recommended in the clinical practice of veterinary anesthesia and may be quite painful to the animal.

Intramuscular and Intrathoracic Injection

Under unusual circumstances, such as when wild animals are anesthetized, intramuscular or subcutaneous injection of barbiturates may be indicated. Because of their high alkalinity, there is a tendency for tissue necrosis to develop following this procedure. For moderate anesthesia, 30 mg/kg, and for surgical anesthesia of 1 to 2 h, 40 mg/kg of pentobarbital can be administered. Induction requires about 15 min, and anesthesia reaches its peak effect about 30 min after injection.

Although pentobarbital has been given intrathoracically using the same dose as for intravenous anesthesia, veterinarians should strongly oppose intrathoracic administration of anesthetic because there is risk of puncture to the heart, pericardium, and lung, and barbiturates irritate the serosal surfaces. The latter fact can be confirmed on necropsy of animals destroyed with intrathoracic barbiturates. Pleural thickening, bronchitis, and coagulative

necrosis of the lung have been observed on examination of experimentally injected cats.

In general, thiobarbiturates produce more respiratory depression on induction than do oxybarbiturates: Often one-third of the calculated dose causes the patient to collapse and respiration to stop. This transient apnea is alarming to those not aware of this reaction. When it occurs, injection of anesthetic should be suspended until spontaneous rhythmic respirations resume. This usually occurs as soon as the blood carbon dioxide level rises to stimulate respiration and rapid redistribution decreases CNS concentration.

Barbiturate Slough

Occasionally, animals may struggle during induction of barbiturate anesthesia, and some of the drug may be administered perivascularly. This should be avoided if at all possible because a tissue slough may develop. Experienced anesthetists prevent barbiturate slough by threading the needle into the vein. This procedure makes it unlikely that the needle will come out of the vein if the syringe is jarred or the animal moves. Sloughs caused by anesthesia require 2 to 4 weeks to heal and leave an unsightly scar. Nothing can infuriate owners more than development of a slough in their animal.

If it is suspected that barbiturate solution has been injected perivascularly, the area should be infiltrated with 1 or 2 mL of 2% procaine solution.[59] Lidocaine can also be used for this purpose. Local anesthetics are effective for two reasons. First, they are vasodilators and prevent vasospasm in the area, and thus aid in dilution and absorption of the barbiturate. Second, they are broken down in an alkaline medium, and this reaction neutralizes the alkali (barbiturate). The use of hot packs or hydrotherapy may be beneficial, as is infiltration of the area with saline to dilute the barbiturate further. Additionally, systemic anti-inflammatory drugs may be of benefit.

Barbiturate Euthanasia

All of the euthanasia solutions that are commercially available in the United States contain pentobarbital as their active ingredient. Some include other drugs, but the additional ingredients do not make the product a more effective euthanasia agent. The combination products are schedule III controlled substances compared with the schedule II products that contain only pentobarbital. The usual dose of pentobarbital for euthanasia of dogs and cats is 120 mg/kg for the first 4.5 kg of body weight and 60 mg/kg for each additional 4.5 kg. Large animals usually require 10 to 15 mL per 45 kg of body weight. Pentobarbital should not be used for euthanasia of animals intended for consumption by people or other animals, and carcasses should be disposed of in a manner that prevents consumption by domestic or wild animals. Pentobarbital can be administered orally as a sedative prior to euthanasia. The dose is approximately 60 mg/kg, and the time to lateral recumbency is approximately 60 min.

Nonbarbiturate Drugs

Although the barbiturates have been the most commonly used short-acting anesthetics, many other injectable drugs have been used to induce and maintain unconsciousness. Chloral hydrate alone and in combination with magnesium sulfate and pentobarbital sodium has been used for induction and maintenance of anesthesia in large domestic animals (i.e., horses and cows). Many drugs used to depress the CNS and immobilize laboratory animals do not find application in routine small animal clinical use. Among them are chloral hydrate, chloralose, urethan, metomidate, and magnesium sulfate. Newer drugs, such as etomidate and propofol, have been developed to provide short periods of unconsciousness from which recovery is rapid. These hypnotic drugs are most effective when given in combination with preanesthetics and analgesics to achieve anesthesia and analgesia. Several of these combinations have recently been developed and assessed for use in animal anesthesia.

Neurosteroids

This class of drugs was first evaluated as a combination of two steroids: alphaxalone and alphadolone acetate (Althesin or Saffan). The solubility of alphaxalone (9 mg/mL) is increased by alphadolone acetate (3 mg/mL) and by 20% wt/vol polyoxyethylated castor oil (Cremophor EL). The combination of the two steroids has an exceptionally high therapeutic index (30.6). It has little cumulative effect (Fig. 11.9), and the duration of anesthesia varies with species (Fig. 11.10). Administration of the combination before or after barbiturates is not advised, although adverse effects when used with other anesthetic drugs have not been reported. Evidence suggests the neurosteroid anesthetics work by enhancing GABA-mediated neurodepression.[60,61] In addition, the activation of centrally located inhibitory glycine receptors may be involved.[61]

A new neurosteroid product has been developed that is a 10-mg/mL solution of alphaxalone in 2-hydroxypropyl-ß-cyclodextrin (Alfaxan-CD; Jurox, Rutherford, Australia). This preparation does not appear to cause histamine release, which has been associated with the vehicle used in earlier neurosteroid preparations.[62]

In cats, the dose of Althesin is 9 mg/kg for intravenous administration and 12 to 18 mg/kg for intramuscular administration. Intravenous injection produces relaxation in approximately 9 s and surgical anesthesia in about 25 s. Intramuscular administration produces variable results, but may be useful in fractious animals. The onset occurs in 6 to 12 min and lasts for approximately 15 min. A quiet area for induction is desirable. In fractious cats, when drugs must be administered intramuscularly, ketamine is the drug of choice because Althesin is less reliable by this route.[63]

Althesin has a neutral pH and does not produce pain or inflammation when injected perivascularly or intramuscularly. Additional doses can be given to prolong anesthesia without cumulative effects, and recovery is rapid. In contrast to ketamine, Althesin produces good muscular relaxation. Althesin has a slightly protective effect against epinephrine-induced arrhythmias in cats.[64] Urination, defecation, muscle tremors, paddling, salivation, and hyperesthesia have been reported as side effects. Edema of the feet, ears, and muzzle occurs in approximately 25% of cats injected, but is usually transient and disappears within 2

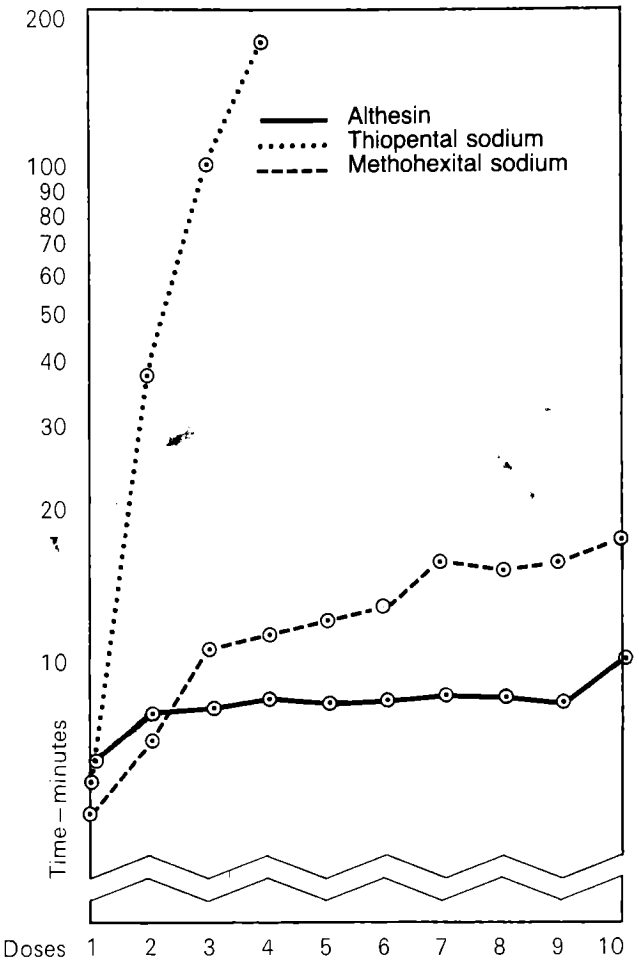

Fig. 11.9. Duration of loss of righting reflex in mice given repeated intravenous doses of Althesin and other anesthetics (five mice per group). Second and subsequent doses were given 30 s after return of the righting reflex. After Child et al.[65]

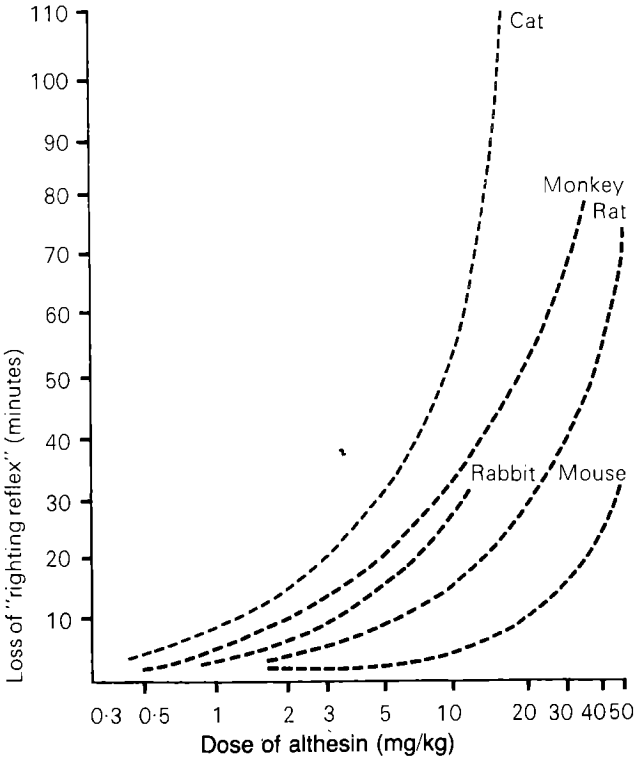

Fig. 11.10. Anesthetic activity of Althesin in different species. After Child et al.[65]

h. This condition apparently occurs in females more often than in males. Antihistamine administration reduces this occurrence.

In dogs and some other canidae, the use of polyoxyethylene derivatives of hexitol anhydride partial fatty acid esters produces an allergic response.[65] This response is manifested by a prolonged fall in blood pressure and a positive skin wheal if the drug is injected intradermally. Urticaria and erythema are believed to be caused by the release of histamine or histamine-like substances. Cremophor EL, a nonionic polyoxyethylated emulsifying agent used as the vehicle in Althesin, elicits the same response. Apparently, allergic reactions can be caused by the vehicle (polyoxyethylated castor oil). The reaction can be of the true-hypersensitivity type, which requires previous exposure to the drug, or of the complement-activation type, which requires no previous sensitization.[66]

Horses anesthetized with Althesin can develop violent paddling and galloping movements during recovery, which can be prevented by prior administration of xylazine (1 mg/kg).[67] The minimum dose of Althesin for induction of anesthesia is approximately 1.2 to 1.34 mg/kg in non-premedicated horses. Although xylazine administration lengthens the recovery time, its administration would appear prudent.

The dose of Althesin for sheep is approximately 2.2 mg/kg IV. This produces light surgical anesthesia for 8 to 15 min. The average maintenance dose to produce surgical anesthesia for a 3-h period is 0.23 mg · kg^{-1} · min^{-1}. Sheep given Althesin develop bradycardia, with a decrease in systolic and diastolic pressures of 20% to 35% of preinjection levels. Left ventricular end-diastolic pressure elevates, and cardiac output decreases. These parameters return to normal within 6 to 8 min of injection. Myocardial depression measured as a decrease in maximum *dp/dt* is produced.[67] Althesin has also been used to induce anesthesia prior to the administration of inhalants to maintain anesthesia in ruminants (goats, sheep, and young calves).[68] The dose of Althesin for pigs is approximately 6 mg/kg to produce 10 to 15 min of anesthesia. In pigs known to develop malignant hyperthermia under anesthesia, Althesin does not induce this reaction, and it has been used safely in animals known to be susceptible to this condition.[67]

Althesin decreases cerebral blood flow accompanied by a fall in intracranial pressure in baboons.[69] Neither of the two steroids is extensively protein bound by the serum of rats, cats, horses, or people. Approximately 60% to 70% of a radioactive dose of alphaxalone or alphadolone acetate is excreted as metabolic products in the feces during the 5 days following intravenous injection; the other 20% to 30% appears in the urine within the same period.[70]

Chloral Hydrate

Liebrich, who introduced chloral hydrate as a hypnotic in 1869, thought that, because it released chloroform in vitro, it would do the same in vivo. This has subsequently been proved a misconception. Chloral hydrate occurs as colorless translucent crystals that volatilize with an aromatic, penetrating odor on exposure to air. It has a bitter, caustic taste. One gram of the crystals dissolves in 0.25 mL of water. It may be administered orally, or solutions may be injected IV or intraperitoneally. It irritates the gastric mucosa and may cause vomiting if not diluted in water, but is readily absorbed from the gastrointestinal tract. A small amount of chloral hydrate is excreted unchanged in the urine. The greater portion is reduced to trichloroethyl alcohol, a less potent hypnotic, and this in turn is conjugated with glucuronic acid to form urochloralic (trichloroethylglucuronic) acid, which has no hypnotic property. The latter is excreted in the urine. In animals with liver damage, chloral hydrate may be found in larger quantities and urochloralic acid in smaller quantities in the urine.

Chloral hydrate depresses the cerebrum, with loss of reflex excitability. In subanesthetic doses, motor and sensory nerves are not affected. Chloral hydrate is a good hypnotic but a poor anesthetic; the amount needed to produce anesthesia approaches the minimal lethal dose, and it produces deep sleep that lasts for several hours. It has weak analgesic action. In hypnotic doses, the medullary centers are not affected. Anesthetic doses of chloral hydrate depress the vasomotor center severely, causing a fall in blood pressure. Hypnotic doses depress respiration, and anesthetic doses markedly depress the respiratory center. Death from chloral hydrate administration is caused by progressive depression of the respiratory center. The margin of safety is such that it is not a satisfactory surgical anesthetic.

Chloral hydrate is not used for small animal anesthesia and has lost most of its popularity as a general anesthetic in large animals. Its continued use in large animals depends on the simplicity of administration and on the duration of effect of the induction dose—an interval adequate for many routine procedures. It is relatively inexpensive and may be combined with barbiturates. It is an irritant when inadvertently injected outside the vein. Use of a vascular catheter obviates this hazard. The concentration of the chloral hydrate solution should not be too high: 7% to 12% wt/vol aqueous solutions are generally used.

Doses reported for intravenous chloral hydrate vary extensively, probably owing to the rate of administration and to varying interpretations of the depth of resulting anesthesia. The recommended intravenous dose for chloral hydrate in horses varies from 2 to 3 g/45 kg as a sedative and up to 10 g/45 kg when used alone for general anesthesia. When the drug is used to enhance xylazine or xylazine-butorphanol sedation, a dose of 0.6 to 1.2 g/45 kg is usually effective. A dose of 1.8 g/45 kg may be necessary. This mixture of drugs can be used to provide effective standing restraint during low epidural analgesia achieved with a local anesthetic in horses undergoing surgical correction of a rectovaginal fistula.

Chloral hydrate solution was once commonly administered at 15 to 30 g/min and was given until the horse was about to fall, at which time the intravenous tubing was disconnected and the animal restrained until recumbent. If necessary, additional solution was administered slowly until the desired degree of sedation or anesthesia was achieved. Because of conversion to trichloroethanol and slow passage across the blood-brain barrier, anesthetic depression increases for several minutes after initial induction. Therefore, additional doses should not be administered immediately. The chief disadvantage with chloral hydrate is that the dose required to induce general anesthesia prolongs recovery. For this reason, in modern practice, chloral hydrate is primarily used to induce a degree of narcosis or sedation, and analgesia is produced by means of local or regional anesthesia. Premedication with tranquilizers reduces the amount of chloral hydrate required, facilitates induction, and minimizes struggling during recovery.[71]

The time required for horses to stand after cessation of administration of anesthetic doses varies from 1 to 4 h and is similar in duration to that observed after chloral hydrate and magnesium sulfate administration. If anesthesia is maintained for a long period, recovery may also be prolonged. The nature of the recovery period can vary; if left undisturbed, horses often pass quietly into a hypnotic state, remaining thus until they are ready to stand. Excitement and struggling during recovery are not uncommon and can be minimized by use of tranquilizers.

Chloral hydrate is also occasionally used to induce narcosis or anesthesia in cattle and swine. In the former, it has been largely replaced by xylazine. The chloral hydrate dose required is similar to that for horses. In cattle, premedication with atropine sulfate and early intubation are indicated. Chloral hydrate may also be administered to horses and cattle by stomach tube to induce varying degrees of sedation or narcosis (3 to 6 g/45 kg of body weight).

Chloral hydrate has been combined with magnesium sulfate or with magnesium sulfate and pentobarbital sodium for anesthesia in horses and cattle (Fig. 11.11). Investigators claimed that these drug combinations produced a more rapid and excitement-free induction, an increased anesthetic depth, a smoother emergence, a wider margin of safety, and less irritation than does anesthesia achieved with chloral hydrate alone. Nevertheless, with the advent of rapid-onset, short-acting, and safer drugs, there seems to be little merit in the use of chloral hydrate alone or in combination with other drugs to induce and maintain anesthesia in any species.

Chloralose

This is prepared by heating anhydrous glucose and trichloroacetaldehyde (anhydrous chloral) in a water bath. Both α-chloralose and ß-chloralose are formed, with the α form being active. Chloralose has been advocated for use in cardiovascular studies because it produces minimal depression and maintains more active reflexes than other anesthetics.[72]

Chloralose is usually prepared as a 1.0% aqueous solution. Heat is necessary to dissolve the drug, but solutions should not be boiled. The intravenous anesthetic dose of α-chloralose is approximately 110 mg/kg in dogs and 80 mg/kg in adult cats.[73] α-Chloralose appears to depress neuronal function of the cortex and routes of afferent input less than pentobarbital. Many investigators still consider chloralose a valuable drug for maintenance of unconsciousness for long, nonsurvival, surgical experiments.[74]

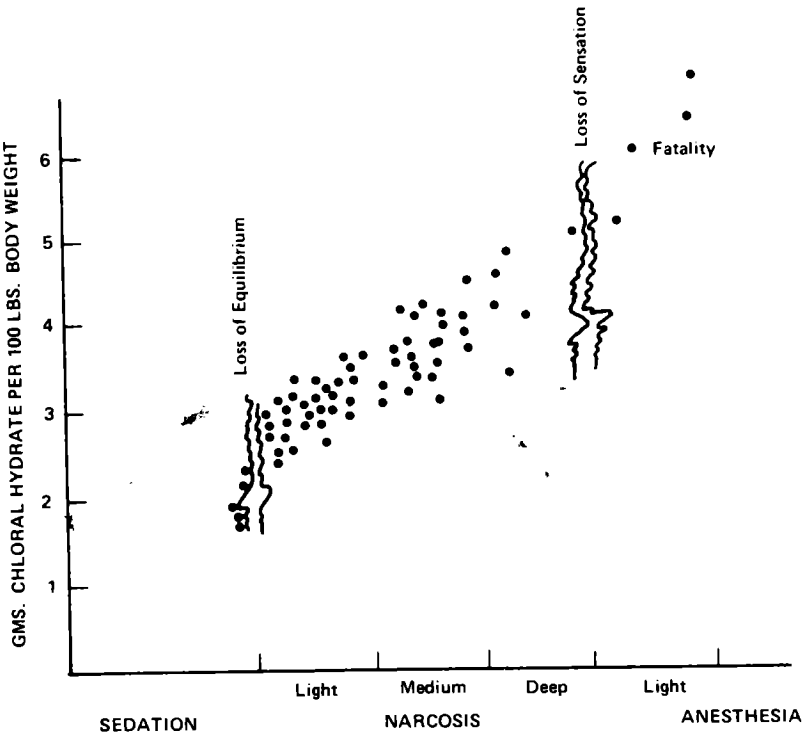

Fig. 11.11. Chloral hydrate and magnesium sulfate anesthesia (2:1) in horses: dose of chloral hydrate used and degree of anesthesia obtained in clinical cases.

Urethan

This is prepared by heating urea with alcohol under pressure or by warming urea nitrate with alcohol and sodium nitrite. The drug is marketed in the crystalline state. One gram dissolves in 0.5 mL of water, the aqueous solution being neutral. It is most often used as an anesthetic in laboratory animals and fish. The lethal intravenous dose for rabbits is 2.0 g/kg. The dose for dogs and cats is 0.6 to 2.0 g/kg. Up to 0.5 g/kg may be used as a hypnotic dose.

Urethan is mutagenic, carcinostatic, and carcinogenic.[75] Mice given urethan develop an exceptionally high incidence of lung tumors, regardless of the route of administration. Tumors also develop in treated rats and rabbits. Concern over the health of individuals in prolonged contact with urethan or its solutions is justified.[76] For this reason, urethan is no longer commonly used in any species.

Magnesium Sulfate

A saturated solution of magnesium sulfate has been used for euthanasia. However, it should be administered only after animals have been rendered unconscious with a barbiturate or another rapid-acting anesthetic. In small animals, anesthesia has been achieved with dilute solutions of magnesium sulfate; however, the CNS is globally depressed and respiratory arrest often occurs at anesthetic doses. Animals will become excited just prior to collapse. Respiratory arrest likely is caused by complete neuromuscular block and paralysis of the muscles of respiration rather than being a consequence of CNS depression. Therefore, one cannot be assured that magnesium sulfate administered alone is a humane method for achieving anesthesia or euthanasia. Magnesium sulfate is better thought of as a muscle relaxant and CNS depressant than as a stand-alone anesthetic and is not recommended as such.

Metomidate

Metomidate hydrochloride is a hypnotic with muscle relaxant properties. Its hypnotic effect is exerted on mammals, birds, reptiles, and fish. Given alone, it induces sleep without analgesia. General anesthesia can be produced by combining it with neuroleptics or analgesics. It is available in powdered form, which dissolves readily in water to make 1% or 5% solutions. These solutions have a pH of 2.9 and 2.4, respectively. Combined with the butyrophenone tranquilizer azaperone, metomidate produces anesthesia in swine for approximately 2 h. Respiration slows and deepens. With rapid intravenous injection, apnea may occur. The cardiovascular system remains stable. It is often used as a sedative-anesthetic for fish.

Etomidate

This is an imidazole derivative that was synthesized in 1965 and first used for induction of anesthesia in people in 1975. It is a congener of metomidate and contains 2 mg/mL of the drug in 35% propylene glycol. Etomidate appears to work in a fashion similar to that of propofol and the barbiturates in that it enhances the action of the inhibitory neurotransmitter GABA.[77,78] Single injections produce relatively brief hypnosis. In dogs, doses of 1.5 and 3.0 mg/kg last 8 ± 5 and 21 ± 9 min, respectively.[79] The duration of hypnosis is dose related. Etomidate is rapidly hy-

drolyzed in the liver and excreted in the urine. The pharmacokinetics of a 3-mg/kg intravenous dose of etomidate in cats are best described as a three-compartment open model similar to those determined in people and rats. Induction and recovery are rapid, with a brief period of myoclonus early in the recovery period.[80]

Etomidate in powder and injectable forms has been used as an anesthetic for exotic species of animals. It was introduced in the United States as an induction agent for poor-risk human patients because it does not depress the cardiovascular and respiratory systems or release histamine. When used alone in dogs, it produces no change in heart rate, blood pressure, or myocardial performance.[79] Neonates born to mothers anesthetized with etomidate have minimal respiratory depression. Etomidate does not trigger malignant hyperthermia in susceptible swine.[81] Etomidate qualifies as a good induction drug for neurosurgical procedures. It decreases cerebral metabolic rate of oxygen consumption ($CMRO_2$) and has anticonvulsant properties. It may have brain-protective properties following episodes of global ischemia associated with cardiac arrest.

Etomidate inhibits adrenal steroidogenesis in dogs, suppressing the usual increase in plasma cortisol observed during surgery. A single induction dose of etomidate may depress adrenal function for up to 3 h. However, the lack of a stress response to surgery does not have deleterious effects, and it has been argued that attenuation of metabolic and endocrine responses to surgery actually reduces morbidity and may make this unique action of etomidate beneficial to overall patient outcome. Attention has been given to the development of Addisonian crisis produced by etomidate-induced blockade of corticosteroid production during prolonged infusion to maintain sedation in intensive care patients. Consequently, long-term infusion is not recommended.[82,83] Etomidate (2 mg/kg) can cause acute hemolysis. The mechanism of hemolysis appears to be propylene glycol, which causes a rapid osmolality increase that causes red cell rupture.[84]

Etomidate is compatible with other common preanesthetic agents. Venous pain is common on injection in humans, and myoclonia may occur if premedication is not administered. Nausea and vomiting are troublesome, especially after the use of multiple doses, and can occur at recovery, as well as induction. For the most part, these side effects can be prevented by adequate preanesthetic sedation. In summary, etomidate may be one of the better induction drugs in traumatized patients and those with severe myocardial disease, cardiovascular instability, cirrhosis, or intracranial lesions, or in patients requiring cesarean section surgery.[81]

Propofol

Propofol (2,6-diisopropylphenol) is unrelated to barbiturates, euganols, or steroid anesthetics. It is only slightly soluble in water and is marketed as an aqueous emulsion containing 10 mg of propofol, 100 mg of soybean oil, 22.5 mg of glycerol, and 12 mg of egg lecithin/mL. Sodium hydroxide is added to adjust the pH. It is available in sterile glass ampules and contains no preservatives. Propofol emulsion can support microbial growth and endotoxin production.[85] Because of the potential for iatrogenic sepsis, unused propofol remaining in an open ampule should be discarded and not be kept overnight for use the next day. Some formulations contain bacterial growth inhibitors to slow the growth rate of contaminants after a vial is opened, but these additives will not completely inhibit bacterial growth, so any unused propofol should still be discarded 6 h after a vial or ampule is opened. The growth inhibitors used are 0.005% disodium edentate or 0.025% sodium metabisulfite.

The pharmacokinetics of propofol in dogs fit a two-compartment open model. Rapid onset of action is caused by rapid uptake into the CNS. The short action and rapid smooth emergence result from rapid redistribution from the brain to other tissues and efficient elimination from plasma by metabolism.[86] Propofol has a large volume of distribution, as would be expected from its lipophilic nature. It is metabolized primarily by conjugation, but propofol's rapid disappearance from plasma is greater than hepatic blood flow, suggesting extra hepatic sites of metabolism.[87] The pharmacokinetics of propofol have not been reported in cats, but its anesthetic action is similar to that in dogs.[88] In general, after a single bolus injection, propofol induces a rapid, smooth induction followed by a short period of unconsciousness.[89] In people, recovery is rapid and free of emergence excitement after constant infusion or repeated bolus administration. In dogs, especially greyhounds, recoveries may be prolonged after continuous infusion of propofol exceeding 30 min.[90]

Propofol is usually injected as a single bolus for induction of general anesthesia in dogs and cats to enable intubation and initiation of inhalation anesthesia.[89] It should be remembered that propofol is a sedative-hypnotic and has only minimal analgesic action at a subanesthetic dose. As with other hypnotics, even when an animal is rendered unconscious with propofol, it will respond to painful stimuli unless analgesic drugs such as the opioids or α_2-agonists are administered concurrently. If administration is preceded by a preanesthetic such as morphine or medetomidine, the induction dose of propofol can be decreased substantially. The dose for induction of anesthesia in nonpremedicated dogs ranges from 6 to 8 mg/kg IV, whereas the dose in sedated animals may be as low as 2 to 4 mg/kg IV.[85,86] Following a single dose of 6 mg/kg IV, recovery in dogs is complete in approximately 20 min. A similar dose given to cats provides about 30 min of anesthesia to complete recovery. The incidence of postanesthetic side effects, such as vomiting, sneezing, or pawing, is about 15%, but can be decreased with acepromazine or α_2-agonist premedication. When a patient is premedicated with 0.02 to 0.04 mg/kg of acepromazine, the induction dose of propofol is decreased by approximately 30% to 40%. Propofol can be used for maintenance of anesthesia in dogs either by intermittent bolus or continual infusion.[91,92] The rate of administration depends on the adjunctive drugs administered and the degree of surgical stimulation.[92] The continuous infusion rate ranges from 0.15 to 0.4 mg $\cdot$ kg^{-1} $\cdot$ min^{-1}. When using an intermittent-bolus technique, doses of 0.5 to 2 mg/kg are administered as needed. If the bolus dose used is kept constant, the interval between bolus administrations will stabilize and remain constant after 1 to 2 boluses are administered.

Propofol induces depression by enhancing the effects of the inhibitory neurotransmitter GABA and decreasing the brain's

metabolic activity.[93] Propofol decreases intracranial and cerebral perfusion pressures. It transiently depresses arterial pressure and myocardial contractility similar to the ultra-short-acting thiobarbiturates. Hypotension is primarily the result of arterial and venous vasodilation.[94] Propofol enhances the arrhythmogenic effects of epinephrine, but is not inherently arrhythmogenic.[95]

Propofol is a phenolic compound and, as such, can induce oxidative injury to feline red blood cells when administered repeatedly over several days. This toxicity is likely the result of the cat's reduced ability to conjugate phenol. Heinz bodies form, and clinical signs of anorexia, diarrhea, and malaise can result.[96] Brief apnea may occur after induction with propofol. Animals breathing spontaneously may experience hypercapnia for a short period after rapid bolus injection.[97] Propofol is primarily metabolized in the liver by conjugation pathways to form inactive metabolites, which are then excreted in the urine and, to a much lesser extent, in bile.[98] Evidence suggests a variability in the capacity of the hepatic cytochrome P-450 enzyme system involved in propofol metabolism among dog breeds.[99] This may explain some of the breed variability in recovery times seen after propofol administration (e.g., the slower recoveries seen in greyhounds). Propofol has been used for cesarean section surgery with generally good results.[89,100] Because puppies have good conjugation enzyme activity, there is minimal fetal depression among neonates delivered from mothers anesthetized with propofol.

Complaints of pain by people injected with propofol IV are common. Pain likely occurs in small animals, but the prevalence appears to be much less. Pain can be minimized by premedication with an opioid or α_2-agonist and/or injection into larger vessels. Propofol, unlike barbiturates, does not damage tissue when injected perivascularly or intra-arterially. When combined with an opioid, acepromazine, or an α_2-agonist, propofol provides dependable short anesthesia for procedures such as castrations, ear flushes, exploration for foxtails, ultrasound examinations, biopsies, and suturing of small lacerations. Additionally, the advantage of rapid smooth recovery is beneficial in patients with chronic respiratory disease or those undergoing bronchoscopy or transtracheal aspiration procedures. Light propofol anesthesia has been advocated for patients undergoing upper-airway examination.[101]

Propofol is a satisfactory drug for immobilization of neonatal foals when given in combination with 0.5 mg/kg of xylazine IV. Immobilization is induced with 2 mg/kg propofol IV and maintained with 0.33 mg $\cdot$ kg^{-1} $\cdot$ min^{-1} IV. Cardiovascular changes are characterized by decreased pressure and cardiac output, and a decrease in respiration rate.

Propofol anesthesia has been used in full-sized horses, as well. It is usually employed in conjunction with an α_2-agonist such as detomidine or xylazine and can be used to maintain, as well as induce, general anesthesia. The induction dose of propofol is 2 to 4 mg/kg administered IV to premedicated horses.[102–104] Limited data on maintenance of propofol anesthesia suggest an infusion rate of approximately 0.2 mg/kg/min is acceptable.[104] The quality of the induction and recovery seen with the use of propofol in horses is acceptable.[102–105]

Alternative Methods of Anesthesia and Analgesia

Hypothermia

As the body temperature of warm-blooded animals falls, their metabolism is reduced, and therefore the need for oxygen is diminished. Oxygen uptake in dogs is reduced by approximately 50% at 30°C and 65% at 25°C.[106] The metabolic rate of isolated slices of rat heart is reduced 90% by lowering the temperature to 10°C.[107] The potassium-arrested heart at 37°C used four times as much glycogen and produced three times as much lactic acid as the heart at 17°C.[108] Thus, the heart, brain, liver, or other vital organs can survive at a low temperature for a considerably increased period when deprived of all or a portion of their blood supply. Hypothermia may be artificially produced in the entire body or in only a portion, such as the heart or head. It has found its greatest usefulness in surgery of the heart and CNS.[109]

The colder an animal becomes, the less oxygen is required by a given organ. It has been shown, however, that the reduction of oxygen consumption varies for different organs. For example, the work done by the heart at 26° to 27°C is a little less than that at normal temperature, and while the general oxygen uptake by the body at this temperature is reduced to 40% of normal, that of the heart is still 50%. In monkeys, little change in cerebral oxygen uptake occurs until a temperature of 31°C is reached.[110] At this point, it falls sharply, and through the next 4°C there is a drop of about 25%. Below 27°C, oxygen consumption continues to fall, but at a much slower rate. The relationship of cerebral oxygen consumption to temperature is sigmoid rather than linear (Fig. 11.12).

Several species of warm-blooded animals have been subjected to drastic hypothermia. Small laboratory animals can be cooled to 0°C, and even lower, and still recover. Between 80% and 100% of rats recovered after being cooled to temperatures just above the freezing point with cardiac and respiratory arrest for 1 h.[111] Golden hamsters have been kept on ice with circulatory arrest for up to 7 h. These animals even survived supercooling to $-5°$ or $-6°$C.[112] When the circulation is maintained with a pump-oxygenator, dogs have survived cooling to 1.5°C.[113]

To induce the hypothermic state as quickly as possible, shivering must be controlled, because it is an important mechanism in protection against cold. Shivering is induced by an increased temperature gradient between cold receptors in the skin and centers in the hypothalamus.[114] Even without visible shivering, there is general hypertonicity of the skeletal muscles, which results in increased metabolic, heart, and respiratory rates. Shivering can be prevented by deep anesthesia or by light anesthesia with curarization or tranquilization with a phenothiazine. The latter drugs exert their effect through a peripheral action on muscle fibers and on the hypothalamic temperature control center.

Moderate hypothermia produces a rectilinear decrease in anesthetic requirements (minimum alveolar concentration [MAC]) for cyclopropane, diethyl ether, fluroxene, halothane, and methoxyflurane (Fig. 11.13).[115] Moderate hypothermia also reduces the concentration of anesthetic required to produce apnea. There is little difference between halothane, pentobarbital, and

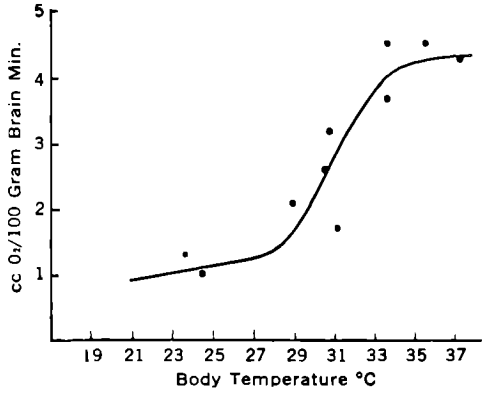

Fig. 11.12. Relation of oxygen uptake by the brain to temperature. From Bering et al.[110]

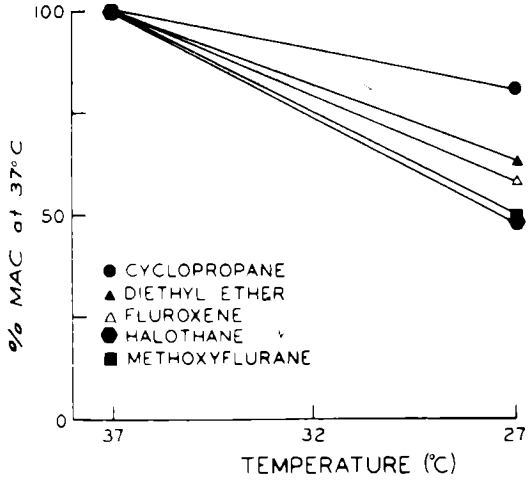

Fig. 11.13. The percentage decline between 37° and 27°C of the minimum alveolar concentration (MAC) required for anesthesia. Cyclopropane, the least oil-soluble agent, declines least, and halothane and methoxyflurane, the most oil-soluble agents, decline most. From Regan and Eger.[115]

chloralose in their effects on whole-body oxygen consumption during surface cooling in dogs (Fig. 11.14).[116]

Three methods of whole-body cooling have been used: surface, body cavity, and extracorporeal. *Surface cooling* is usually accomplished by directly immersing the unprotected body in ice water or by placing the body on a mattress through which ice water is circulated. Hyperventilation is maintained throughout the procedure to keep the blood pH on the alkaline side of normal. This has been shown to reduce cardiac arrhythmias and fibrillation. Below 28°C (82.4°F), no anesthetic is needed, and the patient is maintained on artificial ventilation alone. Active cooling is stopped when approximately two-thirds of the desired temperature fall has been accomplished. Otherwise, the temperature continues to drop once the desired degree of hypothermia has been reached.

Body cavity cooling is accomplished by pouring cold saline solution into the open thoracic cavity.[117] This method has the disadvantage of being slow and requiring large volumes of saline solution.

Extracorporeal cooling can be accomplished by running blood from a cannulated artery through a heat exchanger using cold tap water as the cooling medium. A pump is required to force the blood through the system. Thrombosis is prevented by administration of heparin. Extracorporeal cooling has been used to lower the brain temperature below that of the general body temperature, but carries with it the dangers of hemolysis, interference with the blood coagulation mechanism, and thrombosis. The most obvious advantage is that it provides the best control over body temperature, and rewarming can be performed quickly and efficiently by running warm water through the heat exchanger. Warming also may be accomplished by covering the patient with electric blankets or by using warm-water baths. Microwave rewarming has been used experimentally.[116]

Since hypothermia is a form of general anesthesia, it carries the risks of profound depression of the CNS and vital organs. In addition, it has its own hazards for the circulatory system, skin and internal organs, and metabolism. Blood pressure falls during hypothermia, owing to decreased cardiac output, whereas peripheral vascular resistance increases. Occasionally, blood pressure may drop severely. The fall in heart rate seen with hypothermia is caused by depression of the sinoatrial node and the bundle of His. These conduction changes are manifested by a prolonging of the PR interval, spreading of the QRS complex, and lengthening of the ST interval. In dogs, a cardiac crisis occurs between 23° and 15°C. This is characterized by cessation of sinus rhythm, intense bradycardia, ventricular extrasystoles, and ventricular fibrillation or standstill. As expected, atropine does not relieve the bradycardia. Ventricular fibrillation has been shown to occur most often when the temperature of the heart muscle is below

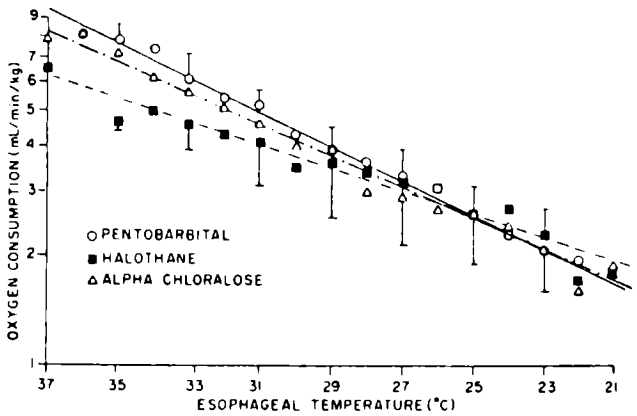

Fig. 11.14. Whole-body oxygen consumption compared with esophageal temperature during surface cooling in dogs. The least-squares best-fit lines are shown for three anesthetics: pentobarbital, halothane, and α-chloralose. Each point represents the mean, and each bar 1 SD. From Westenskow et al.[116]

28°C and when the heart is manipulated. Fibrillation rapidly depletes cardiac muscle energy stores. It occurs less frequently in young animals than in adults. Hypercapnia with acidemia, hyperkalemia, and myocardial hypoxia also appears to cause fibrillation. The incidence of spontaneous ventricular fibrillation has been shown to vary with the anesthetic used to initiate hypothermia. For example, administration of pentobarbital produces a higher incidence than does use of thiopental or ether.[118]

Several cardioplegic solutions have been used to stop the heart and to prevent fibrillation. Hypothermia plus cardioplegia is more protective of cardiac tissue than is hypothermia alone.[119,120] Combined with deep hypothermia, cardioplegia solutions have provided 30 min of cardiac arrest without heart-lung bypass.

During hypothermia, clotting time is prolonged. In addition, the platelet count decreases, hemoconcentration occurs with sludging, and eosinophil and leukocyte counts decrease, accompanied by a fall in the mean corpuscular hemoglobin concentration.

Prolonged periods of hypothermia have detrimental effects on patients.[121–123] In dogs held at 29°C for 24 h, cardiac output and whole-body oxygen consumption decreased progressively to 7% and 28% of control, respectively. Cerebral blood flow and cerebral oxygen consumption responded similarly. On rewarming, cardiovascular collapse with severe tissue hypoxia and metabolic acidosis occurs. Cerebral blood flow becomes grossly inadequate, with depletion of brain energy stores. Hypothermia severely damages the liver, kidneys, and adrenal glands in dogs when temperatures of around 25°C are maintained for several hours.[124] Short periods (1 to 2 h) of cooling, however, do not appear to cause demonstrable damage.

Hypothermia has been used for surgery of the heart and great vessels, brain, and spinal cord, and in some other surgical procedures. It also has been advocated in treatment of shock, stroke, and cerebral and spinal contusion, and in prevention of brain damage following a severe hypoxic episode. The chief factor limiting its use alone in heart surgery is the danger of hypoxic brain damage. For this reason, older patients and those with cardiac defects requiring extensive repair should be managed with heart-lung bypass. Hypothermia has also been used in dogs to remove heartworms and to repair cardiac anomalies, but its use is not widespread. This is probably because many veterinarians are unaware of the simplicity of the technique and do not appreciate its potential.

Induction

To produce hypothermia in dogs, a phenothiazine tranquilizer may be given IV as a preanesthetic agent. A thiobarbiturate is injected for general anesthesia, following which an endotracheal catheter is inserted and an inhalant anesthetic is used for maintenance. A slow intravenous drip of Ringer's lactate solution or 5% dextrose is started, and a muscle relaxant is given in the drip tubing to abolish respirations. Controlled ventilation is then initiated. Unless a cooling mattress is available, the animal is positioned in a sink, bathtub, or other container, with its head above water. Electronic thermometer probes are placed in the esophagus at heart level and in the rectum, and electrodes of an electrocardiograph are attached to the feet. From this point, constant monitoring of the electrocardiogram on an oscilloscope is desirable, because cardiac fibrillation may occur at any time during the cooling period and requires immediate corrective measures.

Ice water is used for rapid cooling. It should be constantly agitated by hand or with a pump. The dog should be removed from the bath before the desired body temperature is reached, because temperature will continue to decline even after the dog's removal from the water.

After removal, the dog should be dried with towels and placed on an inactive heating pad during the operative period. Rewarming can then be started as soon as closure of the surgical wound is begun. As anesthesia is discontinued and shivering commences, the body temperature quickly begins to rise. If the operation is short, rewarming in a water bath may be necessary, along with administration of atropine and neostigmine to reverse the effects of the muscle relaxant.

Electronarcosis and Immobilization

Electric stimulation of the brain can activate either opioid or nonopioid pain-control pathways or both.[125] Passage of electricity through the brain to produce anesthesia has been investigated for many years. In the veterinary field, clinical trials were conducted by Sir Frederic Hobday in England as early as 1932. Despite extensive research, much remains to be learned about this technique. Early work documented the occurrence of respiratory depression, hyperthermia, convulsions, and fatalities. Electronarcosis may be of greatest use in situations where prolonged anesthesia is required for experimental purposes.

Most instruments deliver the current through needle electrodes applied to the head. Direct, pulsating direct, and alternating current have been used to produce electronarcosis. Alternating current of 700 cycles, 35 to 50 mA, and approximately 40 V has been employed.[126] Others have used combined direct and alternating current, modified to produce a rectangular wave for 1.0 to 1.4 ms, with a frequency of 100 waves/s.[127] Continuous electrode contact is important to maintain electronarcosis anesthesia. Individual variation among animals requires that the current be adjusted for each according to the response observed.

Electronarcosis is characterized by convulsions on induction unless a muscle relaxant is first administered. An exception to this is the method employing direct current for induction and then both direct and alternating current.[127] Profuse salivation develops on induction and continues throughout. This can be counteracted by using atropine. Endotracheal intubation should always be performed. Hyperthermia, probably caused by disturbance of the thermoregulatory center in the hypothalamus, is commonly seen. The electroencephalogram immediately following anesthesia is decreased in amplitude and increased in frequency, but returns to normal within 30 min. Brain lesions have been found following electronarcosis,[128] and skin burns from the electrodes have been reported.[129]

Electronarcosis appears to produce severe stress, as evidenced by an increased plasma level of hydroxycorticoids, epinephrine, and norepinephrine (Fig. 11.15). The blood pressure rises sharply and then gradually falls to near normal levels (Fig. 11.16). The clotting time, sedimentation rate, hemoglobin, hematocrit, and

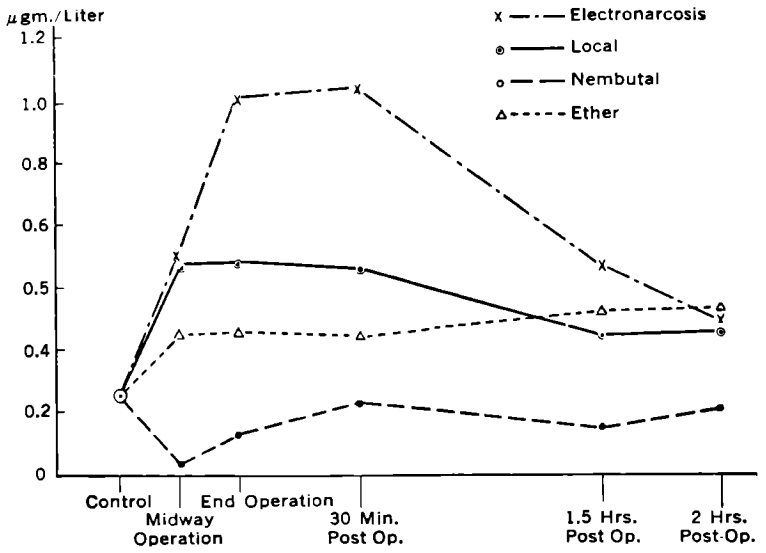

Fig. 11.15. Epinephrine secretion in response to a standard laparotomy: a comparison of different agents for anesthesia. The points on each curve represent the average values from seven dogs. Electronarcosis and laparotomy produced the greatest rise in epinephrine secretion, with response to procaine and to ether next in order, respectively. Nembutal (pentobarbital) depressed the epinephrine level of plasma despite the associated surgery. From Hardy et al.[142]

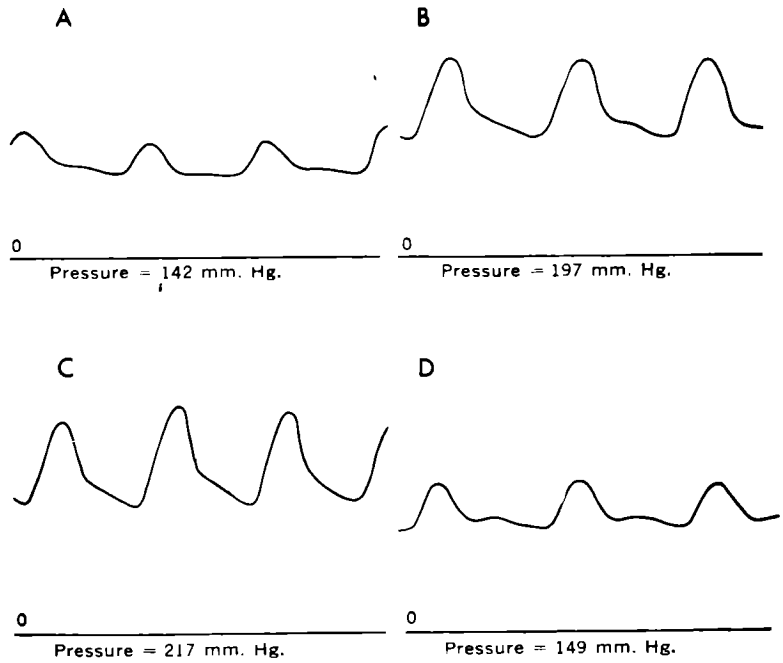

Fig. 11.16. Mean femoral artery blood pressure in a dog under electronarcosis: preinduction **(A)**, induction **(B)**, beginning surgical anesthesia **(C)**, and 15 min after onset of surgical anesthesia **(D)**. Courtesy of Dr. R.A. Herin, Colorado State University, Fort Collins, Colorado.

total and differential white blood cell counts do not differ from preinduction values.[130] There is little effect on arterial oxygen partial pressure; carbon dioxide content and pH decrease, whereas blood glucose rises. It was originally thought that electronarcosis, which produces an uninhibited response of the adrenal medullary and cortical systems, may be more desirable than drug-induced anesthesia, which usually depresses this response.[131] This is in contrast to the modern concept of anesthesia, which endeavors to minimize sympathetic nervous system response associated with the production of general anesthesia. Consequently, there has been a loss of interest in electronarcosis and immobilization as humane alternatives for producing general anesthesia.

In addition to questionable humaneness, it is difficult to assess the depth of unconsciousness achieved by electronarcosis. Muscle relaxation varies from adequate to poor. Pain induced by surgery may cause body movements in animals that appear unconscious. The photomotor reflex is probably the best means of determining the depth of anesthesia if a large dose of atropine has not been used. Early investigators indicated that analgesia persists for several minutes after removal of the current and the animal often appears hypnotized. A slight stimulus may then cause complete arousal, and the patient resumes all normal activities.

In the mid-1980s, electroimmobilization was advocated and

used by sheep and cattle producers and some veterinarians for restraint and processing of food animals. This technique was recommended for minor surgery, although strong evidence exists that electroimmobilization is aversive and does not eliminate pain. Amnesia and unconsciousness are not achieved with the manufacturer's recommended electrode placement and electric current application, and this technique may induce pain and dysphoria. Consequently, electroimmobilization is no longer widely used, nor can it be recommended as a humane method of animal restraint.[132]

Acupuncture

This technique has been advocated for providing analgesia during the operative and postoperative periods, to treat chronic pain, and even to treat selected disease states. Charts for people and farm animals (horses, cattle, and pigs) can be commonly found in the Oriental literature. Acupuncture points can be stimulated in many different ways, including needling, injection of saline, electric stimulation, and metal implantation. It has been shown that electroacupuncture minimally decreases halothane MAC in dogs. Although the mechanism of action of acupuncture has been suggested to be the activation of the endogenous opioid neurotransmitter system, the administration of opioid antagonists does not reverse acupuncture-induced decreases in halothane MAC. Some investigators have indicated that acupuncture induces surgical analgesia. However, there appear to be three reasons why acupuncture should not be solely relied upon for surgical anesthesia: lack of restraint, inadequate analgesia, and lack of adequate information on acupuncture points to be used for specific surgical sites. These factors—along with the disadvantages of unfamiliarity, time-consuming methods of application, and inconsistent effects—have made acupuncture an unreliable and nonviable method of producing general anesthesia. Acupuncture may be best used for treatment of chronic pain in animals. Treatment of laminitis and chronic back pain in horses has reportedly been effective.[133] See Chapter 24 for further discussion.

Physiological Hypnosis

Certain species of animals are highly susceptible to hypnosis (immobility reflex). These include arthropods, amphibians, reptiles, birds, guinea pigs, and rabbits. This modality is seldom used in animal anesthesia because of a lack of analgesia associated with the state of physiological hypnosis. Hypnosis should be viewed as a legitimate method of producing immobilization, not anesthesia.

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