Kirk-Othmer Encyclopedia of Chemical Technology.

VETERINARY DRUGS

The use of pharmaceuticals (qv) in the treatment and prevention of animal diseases has expanded greatly since the 1960s. The modern veterinarian, whether in companion-animal practice, equine service, feedlot medicine, swine and poultry dairy work, zoo management, or any animal medical or surgical specialty, has a wide range of products from which to choose. These products may generally be classified as one of the following: antimicrobial agents (see Antibacterial agents, synthetic; Antibiotics; Growth regulators–animal); antiinflammatory agents (see Analgesics, antipyretics, and antiinflammatory agents); parasiticides (see Antiparasitic agents); hormones (qv); anesthetics (qv) and tranquilizers (see Hypnotics, sedatives, anticonvulsants, and anxiolytics); cancer chemotherapeutics (see Chemotherapeutic agents, anticancer); or production enhancers (eg, BGT), reproductive hormones, and growth promoters (eg, steroids).

All drugs used for veterinary purposes are subject to governmental regulations. In the United States, pharmaceuticals are regulated by the Center for Veterinary Medicine of the FDA. Vaccines and many immunotherapeutics are classified as biologicals, and thus, are regulated by the USDA. Topical insecticides and growth regulators are regulated by the EPA.

1. Governmental Regulations

The exact requirements for regulatory approval of a given product for veterinary purposes, whether prescription or over-the-counter, vary from country to country. Product development often takes a minimum of eight to ten years and usually requires large ($>\$10 \times 10^6$) sums of money.

In general, the following information must be provided:

Acute toxicity in laboratory animals and target species, including eye and skin irritation and toxicity.

Subacute toxicity in laboratory animals by 28- and 90-day feedings.

Chronic toxicity in laboratory animals by two-year or lifetime feedings in two species of laboratory animals, multiple-generation teratogenicity, and, not always required, one-year feeding of dogs.

Specialized *in vitro* mutagenicity tests.

Overdose or extended treatment studies in the target species.

Efficacy to justify label claims.

Drug stability studies to determine rate of compound degradation and incompatibilities with other compounds or feed ingredients according to the anticipated conditions of use.

Metabolism studies to identify site of metabolism and principal metabolites.

Tissue residues in food-producing animals to document persistence in edible tissues.

Manufacturing methods to assure product consistency and the safety of personnel exposed to the drug or process intermediates.

Environmental effects, including effect on methanogenic and nitrifying bacteria, persistence in the environment, and projections of possible liability to relevant ecosystems.

Comprehensive labeling and directions.

2. Antimicrobial Agents

The use of drugs to control infection is considerably older than the recognition of the causes of infection or the complex physiological responses to the infectious agent. Historically such unlikely and diverse agents as vinegar (qv) (wine), copper salts, and honey, not to mention various natural plant products, were used to combat a recognized infection. The discoveries of sulfanilamide and penicillin in the 1930s and 1940s, however, ushered in the golden age of antimicrobial therapy, in which the use of antimicrobial agents came to be based on the knowledge of specific causative organisms and their corresponding activities.

The selection of the most appropriate antimicrobial agent depends on an accurate diagnosis and identification of the offending organism. *In vitro* culture and sensitivity testing of isolated organisms are routine methods for determining the antimicrobial of choice. The spectrum of activity of most antibiotics is broadly described in terms of activity against gram-positive or gram-negative organisms. This classification is based on staining characteristics with a blue primary stain of crystal violet with iodine and a red counterstain, usually safranin. The biochemical foundation for an organism retaining the blue, gram-positive color or not is related to the physical and chemical characteristics of the cell wall or cytoplasmic membrane. Empirically, the functional activity of many antibacterials correlates to some degree with the gram-staining reaction. The medical trend is toward use of relatively narrow-spectrum therapeutics having strong activity against specific organisms, as opposed to use of broad-spectrum agents without the supporting diagnostics. When the time factor is critical, as in life-threatening conditions, therapy using a broad-spectrum agent may be started before the culture and sensitivity testing. In addition to organism identification, consideration is given to whether an agent kills or inhibits the organism or its growth. The route of administration, dosage rate, frequency of treatment, and overall duration of treatment must also be considered. Microbes are constantly undergoing genetic change. Some variant strains have the ability to deactivate certain antimicrobials or grow in the presence of antimicrobials to which earlier generations were sensitive. Under antimicrobial therapy, the resistant strains may survive and render the agent less effective. Because of this phenomenon of selection, several agents representative of structurally different antimicrobial families may be used consecutively or, less often, concurrently for an evolving microbial population.

Antimicrobial agents are also used as prophylactics during surgery or at generally lower levels of administration to promote an animal's ability to withstand pathogenic challenge when under stress. In addition to the various families of drugs discussed herein, antimicrobial agents include carbadox [6804-07-5], the cephalosporins, nitrofurans, oxytetracycline [79-57-2], cefluofor, tilmecosen, trimethoprim sulfa, florfenicol [73231-34-2], [76639-94-6], and tylosin [1401-69-0].

2.1. Sulfonamides

The sulfonamides (sulfas) are derivatives of *para*-aminobenzenesulfonamide [63-74-1]. These agents are active against a broad spectrum of gram-positive and gram-negative organisms. Their mode of action is by competitive antagonism of *para*-aminobenzoic acid (PABA), a folic acid precursor. Because mammalian cells do not synthesize folic acid, as do the bacteria that are sensitive to the sulfas, mammalian toxicity is low. The antibacterial activity of the sulfas can be augmented by concurrent use of trimethoprim [738-70-5], which blocks another step in folic acid synthesis.

Although the antibacterial spectrum is similar for many of the sulfas, chemical modifications of the parent molecule have produced compounds with a variety of absorption, metabolism, tissue distribution, and excretion

characteristics. Administration is typically oral or by injection. When absorbed, they tend to distribute widely in the body, be metabolized by the liver, and excreted in the urine. Toxic reactions or untoward side effects have been characterized as blood dyscrasias; crystal deposition in the kidneys, especially with insufficient urinary output; and allergic sensitization. Selection of organisms resistant to the sulfonamides has been observed, but has not been correlated with cross-resistance to other antibiotic families (see Antibacterial agents, synthetic–sulfonamides).

2.2. Penicillins

Since the discovery of penicillin in 1928 as an antibacterial elaborated by a mold, *Penicillium notatum*, the global search for better antibiotic-producing organism species, radiation-induced mutation, and culture-media modifications have been used to maximize production of the compound. These efforts have resulted in the discovery of a variety of natural penicillins differing in side chains from the basic molecule, 6-aminopenicillanic acid [551-16-6]. These chemical variations have produced an assortment of drugs having diverse pharmacokinetic and antibacterial characteristics (see Antibiotics, β-lactams).

The mechanism of antibacterial activity is through inhibition of gram-positive bacterial cell-wall synthesis; thus, the penicillins are most effective against actively multiplying organisms. Because mammalian cells do not have a definitive cell-wall structure as do bacteria, the mammalian toxicity of the penicillins is low. Allergic phenomena in patients following sensitization may occur.

The penicillins as natural and semisynthetic agents are used primarily against susceptible *Pasteurella* sp., staphylococci, streptococci, clostridia, and *Corynebacterium* sp. Penicillin is widely used for therapeutic purposes against these organisms and in animal feeds as a growth promoter. The latter effect is considered to be a result of subtle and reversible effects on the gastrointestinal microflora.

2.3. Aminoglycosides

The aminoglycosides, such as streptomycin [128-46-1], neomycin [119-04-0], kanamycin [59-01-8], and gentamycin [1403-66-3], have a hexose nucleus joined to two or more amino sugars (see Antibiotics, aminoglycosides). These all tend to be poorly absorbed from the gastrointestinal tract but are absorbed well following parenteral administration. They are rapidly bactericidal by inhibiting intracellular protein synthesis. The active transport mechanism which allows intracellular access strongly depends on pH, divalent cations, osmolality, and oxygen tension. The latter renders many anaerobes resistant to the aminoglycosides, which typically have very broad activity spectra, with greater activity against gram-negative bacteria. For this reason, a penicillin may be complementary to an aminoglycoside and provide, overall, a broader spectrum. Toxicity following exaggerated or prolonged dosage schedules is characterized by renal failure or damage to the eighth cranial nerve (auditory) with auditory- or vestibular-balance dysfunction.

2.4. Tetracyclines

The tetracyclines, including chlortetracycline [57-62-5] and oxytetracycline [79-57-2], are produced as fermentation products (see Antibiotics, tetracyclines). These have a broad antibacterial spectrum including gram-positive and gram-negative organisms, rickettsiae, *Chlamydia* sp., and *Mycoplasma* sp. In addition, the tetracyclines are commonly employed at low dosages as growth promoters in the main food-producing species. Most tetracyclines are incompletely absorbed following oral administration and are antagonized through chelatin primarily with divalent cations. The mechanism of action is, like the aminoglycosides, by intracellular inhibition of protein synthesis. Toxicity is rare. Although seldom of clinical significance, the tetracyclines are incorporated into metabolically active calcified tissues, resulting in discoloration. This phenomenon is most prominent in rapidly growing bone, eg, fetal or juvenile skeletal and dental systems.

2.5. Growth Promoters

The tetracyclines and penicillin, when administered to food-producing species (poultry, swine, and cattle) during active growth, improve the rate of weight gain and efficiency of feed utilization significantly (see Feeds and feed additives). Other antibacterials are also used for this purpose, including avoparcin [37332-99-3], monensin [17090-79-8], bacitracins, virginiamycin [11006-76-1], lincomycin [154-21-2], tylosin, and flavomycin [11015-37-5]. These effects are not related specifically to prevention or treatment of bacterial diseases, but to subtle shifts in enteric processes (1) (see Growth regulators, animal).

2.6. Antifungal Agents

Fungi and related organisms are encountered most commonly in superficial infections of the skin, and less commonly as systemic or deep mycoses affecting internal organs (see Antiparasitic agents–antimycotics). Superficial lesions may range from minor hair loss (ringworm) to severe, generalized hair loss and marked pathological changes in the skin, with secondary bacterial infections. The systemic diseases are typically refractory to most therapeutics and are frequently fatal. Many of the mycotic infections have, to some highly variable degree, zoonotic potential. Because they tend to be spore-forming organisms, mycoses also tend to be periodically recurrent or persistent in a given environment.

Favorable responses of the superficial infections have been observed following exposure to sunlight or administration of vitamin A [68-26-8] (qv). Some infections remit spontaneously as a young animal matures. More often, topical application of an antifungal such as nystatin [34786-70-4] or cuprimyxin [28069-65-0] or systemic griseofulvin [126-07-8] over six to 12 weeks is justified. The systemic mycoses are sensitive to very few therapeutic agents. Some, such as actinomycosis and actinobacillosis of cattle, respond to sulfa therapy, but others (cryptococcosis, blastomycosis, etc) may show response only to amphotericin B [1397-89-3], a relatively toxic antibiotic, or itraconazole [84625-61-6] (dogs and cats). Animals having systemic infections are frequently euthanized because of the history of limited therapeutic success and the zoonotic disease potential.

3. Parasiticides

Parasiticides can be roughly divided according to parasites, host species, or chemical classification (see Antiparasitic agents–anthelmintics; Antiparasitic agents–antiprotozoals). By any classification, these are ubiquitous in the management and control of parasites of both companion and food-producing animals (2, 3).

3.1. Organophosphates and Carbamates

The main pharmacologic action of organophosphates and carbamates is the inhibition of the cholinesterase enzymes, primarily acetylcholinesterase (AChE) (see Enzyme inhibitors). Generally, acetylcholine (ACh) is responsible for transmission of neutral impulses at voluntary neuromuscular junctions, at the sympathetic ganglia synapses, and throughout the parasympathetic system (see Choline). Under normal conditions, it is rapidly hydrolyzed and inactivated by AChE. In the presence of AChE inhibitors, the enzyme is phosphorylated, with the consequent pharmacologic and toxic actions produced by excessive accumulations of ACh. Because ACh is an integral part of insect and helminth physiology, the antiparasitic utility spectrum of the drug family is immense.

Organophosphates and carbamates are typically lipid-soluble and are, as a consequence, rapidly absorbed following inhalation or oral, parenteral, or topical administration. Once absorbed, metabolism is primarily by hepatic hydrolysis or oxidation. Various organophosphates (O–Ps) and carbamates are used against virtually all animal parasites. The use of O–Ps and carbamates is widespread, both as animal antiparasiticides and as

agricultural and home-use pesticides (see Insect control technology). In addition, concurrent exposure to more than one agent results in cumulative physiologic effect, and therefore the incidence of toxic effect is relatively high. Atropine is an excellent antidote by virtue of its blocking the action of ACh within the parasympathetic nervous system. It is neither a complete antagonist nor does it modify the rate at which the enzyme is regenerated. Pralidoxime chloride is another antidote frequently used as an adjunct to atropine specifically for O–P toxicity. It acts by regenerating the enzyme throughout the system, but may exacerbate toxicity in cases of reversible carbamate–esterase bonding.

3.2. Avermectins

The avermectins [65195-52-0, 65195-58-6] are fermentation products derived from *Streptomyces avermitilis* (see Antiparasitic agents, avermectins). They are macrocyclic lactones having a very broad spectrum of insecticidal and anthelmintic activity. First commercially available in 1981, abamectin [71751-41-2] (avermectin B_1) and ivermectin [70288-86-7] are highly active at doses of ca 0.2 mg/kg body weight against the internal parasites of cattle and horses, respectively, as well as against lice, internally migrating fly larvae (warbles), and mites. They are active in dogs against larval stages of heartworm disease and intestinal parasites, with the exception of tapeworms. Milbemycin, sulfar, and metronidazole [443-48-1] are used in small-animal practice.

3.3. Levamisole

The racemic mixture of the *d* and *l* isomers of tetramisole [6649-23-6] was first described in 1966. It is used as an anthelmintic against a wide variety of nematodes, including lungworms, of ruminants, swine, horses, dogs, and poultry. Anthelmintic activity resides in the *l*-isomer, levamisole [14769-73-4], the form used.

3.4. Benzimidazoles

The benzimidazoles include a large family of anthelmintics, eg, thiabendazole [148-79-8], albendazole [54965-21-8], cambendazole [26097-80-3], fenbendazole [43210-67-9], mebendazole [31431-39-7], oxfendazole [53716-50-0], and oxibendazole [20559-55-1]. Administration is oral, and the spectrum of activity is broad against nematode parasites of the intestinal tract. The usual dosage of thiabendazole is 50–110 mg/kg body weight. Dosage of other benzimidazoles are 2–30 mg/kg. The activity of the individual compound varies against specific parasite species; none, however, is effective against lungworms. Benzimidazoles have the advantage of a low mammalian toxicity, ca 10–30 times the recommended dosage. Absorption is rapid, parent compound and metabolites are excreted in the urine. There has been some indication of teratogenic effects with use of albendazole and cambedazole.

3.5. Other Parasiticides

The parasiticides described below have a relatively limited usage owing to a narrow spectrum of antiparasitic activity or because of the introduction of inherently safer or more effective products.

Immiticide (melarsonine hydrochloride) is now the drug of choice in dogs against the adult stage of heartworm infection.

Carbon disulfide (qv) is used, in combination with other orally administered anthelmintics, by stomach tube for bots (*Gastrophilus sp*. larvae) and ascarids (roundworms) of horses.

3.6. Coccidiosis

Coccidiosis, caused by protozoans of the genera Eimeria and Isospora, may be present in any domesticated animal species but is ubiquitous in the poultry industry, with serious consequences (see Antiparasitic agents,

antiprotozoals). The life cycle involves both asexual and sexual intracellular parasitic stages characterized by a rapid development and multiplication of infective stages with consequent destruction of, primarily, the intestinal lining of the host. This leads to growth retardation and, when severe, a high mortality. Anticoccidial agents are added routinely as feed components through the life of broiler chickens. A partial list of additives includes amprolium [121-25-5], ethopabate [59-06-3], robenidine [25875-50-7], arprinocid [55779-18-5], monensin, lasalocid [25999-31-9], chlortetracycline [57-62-5], and the sulfa compounds. The most widely used additives are representatives of the ionophore antibiotics, ie, monensin and lasalocid. Historically, the appearance of resistance by the coccidia to anticoccidial agents has been rapid, frustrating efforts aimed at control. This resistance has not yet been observed to any notable degree with the ionophores even after more than a decade of extensive use. A program of rotation, where anticoccidials with differing modes of action are used in succession minimizes the impact of resistance.

Diethylcarbamazine [98-89-1] is a piperazine derivative which is given daily as a prophylactic for canine heartworm disease (*Dirofilaria immitis*) or as a therapeutic for roundworms. *D. immitis* is transmitted only by mosquitoes, and therefore the period of administration varies geographically, depending on temperatures and humidity which regulate the mosquito life cycle.

Phenothiazine [58-37-7] (thiodiphenylamine) is used orally against intestinal nematodes of ruminants and horses. It is used with occasional gastrointestinal upset, hemolytic processes, and photosensitivity. It is used routinely at low concentrations on horse farms to suppress the egg production of intestinal parasites (strongyles) and thus limit pasture contamination and transmission (4).

Hexachloroethane [67-72-1] has, like carbon tetrachloride [56-23-5], been used to remove liver flukes from ruminants. Also used are albenzadole, previously mentioned as a benzimidazole, and clioxanide [144327-41-3], oxychozanide [2277-92-1], or rafoxanide [22662-39-1]. Ciba's Ivomect is used for fluke control in Europe.

Niclosamide [50-65-7] (2′,5-dichloro-4′-nitrosalicylanilide) has been commonly used against tapeworms in small animals (5). Although tapeworms (cestodes) are frequently refractory to anthelmintics highly active against other intestinal parasites, they are sensitive to niclosamide as well as praziquantel [55268-74-1] and epsirantel. Pyrantel pamoate [22204-24-6] is probably the most common animal wormer used in the 1990s.

4. Antiinflammatory Agents

Inflammation is a defense mechanism of the body that plays a key role in righting disease and initiating wound healing. It is clinically characterized by local redness, swelling, pain, and heat. Because of these symptoms, inflammation can be more detrimental than beneficial to normal body function and at such times the practitioner chooses to slow it down. This group of compounds is used on an individual animal basis and tends to be used more in the companion-animal and equine specialities (4) (see Analgesics, antipyretics, and antiinflammatory agents).

The classic example of an antiinflammatory drug is aspirin [50-78-2], acetosalicylic acid, an effective analgesic for many years. It is well tolerated by the dog and the horse, but is relatively toxic to cats. Under the proper clinical circumstances, it can be used for prolonged therapy in chronic inflammatory diseases such as arthritis. Rimadyl is presently used.

Pyrazolone derivatives, specifically phenylbutazone [50-33-9] and, for limited conditions, dipyrone [5907-38-0], are very popular with equine practitioners and are particularly useful in managing cases of lameness and controlling inflammation after trauma or surgery (4). Dipyrone is an analgesic for cases of equine colic. Phenylbutazone is an effective antiinflammatory drug, but is more toxic than the salicylates, which limits its long-term use. For short-term usage, its ease of administration as injectable or oral preparations makes it a popular product for the equine or small-animal specialist. However, ketoprofen [22071-15-4] is a new drug of choice.

The most widely used group of antiinflammatory drugs are the corticosteroids and their synthetic analogues. This group of compounds has several physiologic actions, including effects on sodium retention and liver glycogen deposition as well as inhibitory effects on wound healing and, more recently recognized, proliferation of cancer cells.

The natural compounds cortisol [50-23-7], cortisone [53-06-5], and corticosterone [50-22-6] vary only slightly in structures and pharmacologic properties (see Steroids). The synthetic analogues in more modern practice, prednisolone [52438-85-4], dexamethasone [50-02-2], triamcinolone [124-94-7], and betamethasone have greater antiinflammatory potency, and their effects on sodium retention tend to be less severe.

The uses of corticosteroid antiinflammatory drugs in veterinary medicine are many and varied. In the intact animal, the glucocorticoids and mineralcorticoids are produced in the adrenal glands. Exogenous compounds are, therefore, used for their glucogenic physiologic effect in cases where the animal is unable to produce sufficient quantities of these compounds. When given at pharmacologic dosage, their effects include antiinflammatory aspects useful in controlling healing and inflammation following trauma or surgery; controlling inflammation in severe dermatologic cases, thereby improving effective treatment of the cause of the problem; and in helping to control allergic reactions. On a cellular level, these compounds exert less well-defined effect in helping to preserve cell-membrane integrity and improve cellular metabolism. These effects, in addition to the effects on the microcirculation, are the basis for corticosteroid use in shock-syndrome therapy, which is, however, controversial.

5. Hormones

Hormones (qv) as naturally occurring, semisynthetic, or synthetic compounds are used to regulate reproductive cycles, gestation, and parturition. They are also used as therapeutics for hormonal imbalances and responsive physical or physiological abnormalities, or as growth promoters in ruminants (see Growth regulators, animal). The application of other than sex-related hormones is not as complex as in human therapy because of the relatively short life spans of animals and high cost.

Hormones can either delay or induce estrus. The therapeutic manipulations of normal, or abnormal, estrus sequences are based on the intricate biological feedback relationship between the pituitary gland and the gonads. In broad terms, follicle-stimulating hormone [9034-38-2] releases estrogens. The estrogens cause a decrease in FSH and an increase in luteinizing hormone [9002-67-9] (LH) which causes ovulation and formation of an ovarian corpus luteum (CL). The CL releases natural progesterone, the level of which either helps maintain pregnancy or, at some point, reinitiates the cycle. The therapeutic applications are based on adjusting or creating the normal sequence of events. Administration of progesterone [57-83-0] or progestogens (mibolerone [3704-09-4] or megestrol acetate [3562-63-8]) simulates the hormonal action of the corpus luteum and, in so doing, delays the onset of an estrus. Estrus can be terminated with progesterone, LH, or some prostaglandins (qv), with a resulting fertile ovulation. Stilbestrol is used in female dogs for estrogen-responsive incontinence. An artificial estrus, which does not produce a fertile ovulation, can be induced by exogenous estrogens such as diethylstilbestrol [56-53-1]. Pregnant mare serum, a functional gonadotrophin, the chorionic gonadotrophins and FHS create superovulation with an increased number of developed ova. The estrogens are frequently used to prevent zygote implantation and thus pregnancy, when given shortly after an unintended mating. Estradiol cypronate is used for mismating in dogs. Oxytocin [50-56-6] of pituitary origin stimulates sensitive uterine muscle at parturition. Oxytocin and prolactin [12585-34-1] facilitate milk production and let-down in lactating animals. For fertility control and estrus synchronization, the following are used: prostaglandins as lukeolytic agent ($PGF_{2\alpha}$;, both natural and synthetic) in cattle; GNRH (aptorellin and Factrel) in cattle; FSH for superovulation in cattle and sheep and in embryo-transfer work; and anabolic steriods, eg, Winstrol-V (stanozolal). Cases of enlarged prostate glands in males are frequently responsive to estrogen therapy. The progestins, notably megestrol acetate, have been used successfully in the management of a variety of

dermatitides and behavioral problems in small animals, and discrete clinical syndromes are associated with estrogen and testosterone imbalances in both males and females. Medical therapy, in light of the multisystem effects of these compounds, is always conservative, and adverse effects related to feminization of males or aggressive masculinization of females is frequent. Therapy is often an adjunct to surgical ovariectomy or castration.

Estrogens, testosterone [58-22-0], or compounds such as zeranol [26538-44-3] or trenbolone [10161-33-8] which can mimic their effects, have shown utility in accelerating the rate of weight gains and decreasing the amount of feed required to produce these gains in food-producing animals (6). The potential for human consumption of these compounds via the food supply has come under severe regulatory scrutiny and most of the drugs used for this purpose are administered as an implant or pellet in a part of the body, usually the ear, which is discarded at the time of slaughter. Extended withdrawal periods between the time of administration and the allowable date of slaughter depend on the release characteristics of the implant and may range from zero to one year. Dosages are relatively low, allowing drug release of 2–5 mg/d (see Controlled release technology; Drug delivery systems).

6. Tranquilizers and Anesthetics

Tranquilizers find their niche in veterinary medicine in the management of excitement in individual animals (7) (see Psychopharmacological agents). This group of compounds allows the practitioner to examine the frightened or injured patient with less chance of further damage or injury to the animal, the owner, and the veterinarian. Tranquilizers are also useful in the management of stress to avoid injury during the shipping of animals (see also Anesthetics; Hypnotics, sedatives, anticonvulsants and anxiolytics).

Acepromazine [61-00-7], a phenothiazine, is used in most animal species in both oral and injectable forms. It can be used at varying dosages to provide the state of tranquilization desired by the veterinarian. The product has a good margin of safety and has been used successfully by the veterinary profession for many years. Xylazine hydrochloride [23076-35-9] is another product used for both large and small animals. A thiazine compound unrelated to the phenothiazines, it acts primarily as a sedative. This compound is especially useful in examining fractious horses under field conditions (4). Both acepromazine and xylazine can be combined with other anesthetics for varying degrees of anesthesia or tranquilization. Detonimide is more potent than tylazine.

Tranquilizers are employed for restraint in minor surgical procedures. The cardiovascular system, respiratory system, and blood chemistry are all greatly altered by general anesthesia. In larger animals, such as cattle and horses, the weight of the animal's body alone resting on its side can be a physiologically adverse stress on the heart and lower lung field that the veterinarian would prefer to avoid. If the surgery is of a confined or local nature, such as the repair of a superficial laceration, the animal can be tranquilized and analgesics provided to the wound area by use of a specific nerve block or by infiltrating the area around the site with a local anesthetic. The latter are synthetic nonnarcotic substitutes for cocaine, the first anesthetic ever used. The synthetic substitutes include procaine hydrochloride [51-05-8], tetracaine hydrochloride [136-47-0], lidocaine [137-58-6], and mepivacaine hydrochloride [1722-62-9]. Lidocaine is preferred in veterinary medicine.

These agents are often combined with a vasoconstrictant such as epinephrine [51-43-4]. By using such a combination, the local anesthetic is held in the area for a longer period of time and its effect extended; hemorrhage is minimized, blood loss prevented, and a better surgical repair obtained.

A drug combination in popular use in dogs is a mixture of fentanyl [437-38-7], a narcotic analgesic, and droperidol [548-73-2], a butyrophenone tranquilizer. This combination produces a state of neuroleptanalgesia in which sedation and analgesia are achieved. The mixture is sold commercially and can be administered by both subcutaneous and intramuscular injection. Because the combination contains a narcotic, it has the

advantage of being rapidly reversible with narcotic antagonists such as naloxone [465-65-6] and nalorphine [62-67-9] once the effects are no longer needed.

Another injectable anesthetic widely used in feline and primate practice is ketamine hydrochloride [1867-66-9]. Ketamine, a derivative of phencyclidine, can be chemically classified as a cyclohexamine and pharmacologically as a dissociative agent. Analgesia is produced along with a state that resembles anesthesia but in humans has been associated with hallucinations and confusion. For these reasons, ketamine is often combined with a tranquilizer. The product is safe when used in accordance with label directions, but the recovery period may be as long as 12–24 h.

Another group of anesthetics is comprised of barbiturates. By substituting various side chains on the basic structure, anesthetic activity can be greatly altered with regard to onset and duration of action. Short-acting barbiturates, such as thiopental [77-27-0], often provide only a few minutes of sedation. These products are useful for induction to other types of general anesthesia, trachea intubation, and minor manipulations, examinations, and procedures. Pentobarbital [57-33-0] is longer-acting and can be useful in more extensive or time-consuming surgery or in procedures requiring an extended sedation. Long-acting barbiturates, such as barbital and phenobarbital, have a prolonged effect in the animal, but also have a delayed onset of activity. These have generally been replaced in veterinary medicine by inhalation anesthetics. Phenobarbital [50-06-6], phenytan [57-41-0], and primidone [125-33-7] are used as anticonvulsants.

In veterinary medicine, the list of inhalation anesthetics generally includes only two agents, halothane [151-67-7] and methoxyflurane [76-38-0]. Although ether (ethyl ether) is used extensively in experimental work with laboratory animals, the risks associated with its use and the advantages of halothane and methoxyflurane have removed ether from general use by the practitioner.

Halothane and methoxyflurane are volatile and are used in a vaporizer and delivered to the animal via an oxygen carrier. Both agents can be delivered with nitrous oxide [14522-82-8], a mild anesthetic that when combined with halothane or methoxyflurane can induce anesthesia faster than halothane or methoxyflurane alone. The recovery is faster because of the low solubility of nitrous oxide in the blood. Nitrous oxide can also be used alone, but must be supplemented with a barbiturate or a narcotic. At present, isoflurane [26675-46-7] is the most commonly used and preferred gas anesthetic in veterinary medicine.

It must be remembered that all anesthetics and tranquilizers are used by the practitioner following a risk–benefit evaluation. General anesthesia, even being administered by an experienced practitioner, can result in death through cardiac or respiratory depression. The veterinarian is acutely aware of these risks and chooses the drug and method of administration considering the patient's health status, the nature of and need for the procedure, and the likelihood of success.

7. Cancer Chemotherapy

In the veterinary as in the human patient, neoplasms are often metastatic and widely disseminated throughout the body. Surgery and irradiation are limited in use to well-defined neoplastic areas and, therefore, chemotherapy is becoming more prevalent in the management of the veterinary cancer victim (see Chemotherapeutics, anticancer). Because of the expense and time involved, such management must be restricted to individual animals for which a favorable risk–benefit evaluation can be made and treatment seems appropriate to the practitioner and the owner. In general, treatment must be viewed not as curative, but as palliative.

The purpose of cancer chemotherapy, most briefly put, is to kill specific cells. The compounds are most active against rapidly growing and dividing cells, ideally the neoplastic cells, but all dividing cells can be attacked. For this reason, toxic signs such as alopecia, anemias and leukopenias, anorexia, vomiting, and other gastrointestinal signs may be indicative of undesirable effects of therapy. Periods of rest are often built into the treatment regimen to allow the animal's body a chance to recover and reestablish normal function.

Chemotherapeutic agents are grouped by cytotoxic mechanism. The alkylating agents, such as cyclophosphamide [50-18-0] and melphalan [148-82-3], interfere with normal cellular activity by alkylation deoxyribonucleic acid (DNA). Antimetabolites, interfering with complex metabolic pathways in the cell, include methotrexate [59-05-2], 5-fluorouracil [51-21-8], and cytosine arabinoside hydrochloride [69-74-9]. Antibiotics such as bleomycin [11056-06-7] and doxorubicin [23214-92-8] have been used, as have the plant alkaloids vincristine [57-22-7] and vinblastine [865-21-4].

These compounds vary in their specific mechanism of action and often have different effects on the individual patients. Thus, they are generally used in combinations, eg, corticosteroids with an alkylating agent, or an antimetabolite with a plant alkaloid in a rotating schedule.

8. Immunostimulation

The body's immune mechanism, both humoral and cell-mediated, affords a primary defense against invasion by foreign substances, ie, exogenous entities that the body may encounter, including viruses, bacteria, chemicals, drugs, grafts, and transplants. The reaction by the immune system kills, neutralizes, or rejects the entity. The mechanisms involved in this complex system are under intense investigation, and a better understanding of the immune system will, in the future, permit the control of disease by means only speculated about today.

Human and veterinary practitioners have been manipulating the immune system for many years with bacterins and virus vaccines, in order to induce a response in the immune system. The animal forms antibodies which destroy the antigen. When the same or similar antigen is encountered again, as during exposure to the disease organism, the immune system is activated more quickly through an anamnestic response, thereby preventing the disease. Vaccines and bacterins are widely used in veterinary medicine for most domestic and exotic species (8) (see Immunotherapeutic agents; Vaccine technology).

The prophylactic stimulation of the immune system using vaccines and bacterins is time-consuming. Of even greater value would be the ability to activate the system to combat a disease attack already underway, or to be able to increase the response to abnormal cells and neutralize neoplasia in any organ of the body. Several compounds, some unique entities and some already in use for other purposes, have shown potential utility as such nonspecific immune stimulants.

In 1971, levamisole, an anthelmintic compound widely used in cattle and swine, was shown to improve the effects of an experimental *Brucella abortus* vaccine in mice. Since that time, the veterinarians and physicians have explored the effects of levamisole in such diverse areas as arthritis, lupus erythematosis, cancer therapy, respiratory diseases, Newcastle disease, foot-and-mouth disease, mastitis, and vaccine potentiation. Although the exact mechanism of action has as yet not been determined there is substantial evidence that, under defined circumstances, levamisole can augment the animal's natural immune response (9). New immunostimulants include *Staph Lysate acemannon, MAB-31*.

Discovered in 1957, a group of natural substances called interferons has been the subject of therapeutic interest. Interferons are glycoproteins synthesized by cells that are under attack by a virus. Interferon seems to be an integral part of the body's basic defense mechanism, but more recent work indicates broad therapeutic activity and the possibility of cross-species efficacy. Human interferons are used in cats with FIV and FetV. Feline interferon has been approved. In Japan, cyclosporine [59865-13-3] is used in organ transplantation. Prednisone [53-03-2] is approved for topical application in treatment of autoimmune ocular disease. The emergence of recombinant DNA technology might allow sufficient quantities of interferon to be produced at a reasonable cost and thus may make interferon therapy a practical reality (see Genetic engineering, animals).

BIBLIOGRAPHY

"Veterinary Drugs" in *ECT* 2nd ed., Vol. 21, pp. 241–254, by A. L. Shor and R. J. Magee, American Cyanamid Co.; in *ECT* 3rd ed., Vol. 23, pp. 742–753, by D. M. Petrick and R. B. Dougherty, American Cyanamid Co.

Cited Publications

1. *Feed Additive Compendium*, Miller Publishing Co., Minneapolis, Minn., 1982, published annually.
2. O. H. Siegmund, *The Merck Veterinary Manual*, 5th ed., Merck and Co., Inc., Rahway, N.J., 1979.
3. J. R. Georgi, *Parasitology for Veterinarians*, 3rd ed., W. B. Saunders Co., Philadelphia, Pa., 1980.
4. E. J. Catcott and J. F. Smithcors, *Equine Medicine and Surgery*, 2nd ed., American Veterinary Publications, Inc., Wheaton, Ill., 1972.
5. R. W. Kirk, *Current Veterinary Therapy, Small Animal Practice*, 7th ed., W. B. Saunders Co., Philadelphia, Pa., 1980.
6. J. L. Howard, *Current Veterinary Therapy, Food Animal Practice*, W. B. Saunders Co., Philadelphia, Pa., 1981.
7. L. R. Soma, *Textbook of Veterinary Anesthesia*, The Williams and Wilkins Co., Baltimore, Md., 1971.
8. S. Krakowka, *Mod. Vet. Pract.* **62**, 447 (1981).
9. J. Symoens and M. Rosenthal, *J. Reticuloendothel. Soc.* **21**, 175 (1977).

Related Articles

Vaccine technology; Antibacterial agents; Antibiotics; Analgesics, antipyretics, and anti-inflammatory agents; Antiparasitic agents; Hormones; Anesthetics; Hypnotics, sedatives, anticonvulsants, and anxiolytics; Chemotherapeutic agents, anticancer; Growth regulators, animal; Controlled release technology; Drug delivery systems