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Management and Treatment of Toxicosis in Cattle

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Intoxications in domestic livestock continue to confront practitioners with therapeutic and prophylactic problems. The current widespread and necessary use of pesticides in American agriculture continues to cause accidental intoxications in animals. Because of the continued likelihood of intoxications in animals, it is imperative that veterinarians continue their attempt to educate their clients to use proper handling and storage techniques. Only when the actual users and applicators of toxic chemicals control these chemicals properly will the incidence of intoxications be lowered.

The increased incidence of intoxications in domestic animals makes necessary the continued emphasis on treating disease conditions caused by toxicants. Consequently, the purpose of this communication is to briefly identify some of the more common toxicants which cause intoxications in animals, and describe the therapeutic and management procedures which should be instituted to treat the resulting disease states.

Basic Concepts of Intoxication Therapy

The primary goals of therapy in cases of intoxication are:

1. Emergency intervention and prevention of further exposure.

2. Establishment of a tentative diagnosis upon which to base rational therapeutic measures.
3. Delay further absorption.
4. Application of specific antidotes and remedial measures.
5. Hastening elimination of the absorbed toxicant.
6. Supportive therapy.
7. Determine the source of the toxicant.
8. Educate the client.

When initiating therapy for intoxications, the veterinary clinician should direct his efforts toward treating the signs exhibited by the affected animal(s) unless the correct diagnosis is obvious. Pre-existing conditions and the diagnosis should be determined following stabilization of the patient.

It is important that neither the client nor the clinician waste time. The animal should be brought to the veterinarian (or the veterinarian summoned) as soon as possible. The owner should be instructed to bring suspected materials or their containers with the animal to aid in the proper diagnosis. The client should be advised to place the specimens in clean, sealed jars or plastic containers. The client should be cautioned not to contaminate the material because the suspected material may be important from a medico-legal aspect.

The most important aspect of treatment of intoxications is to ensure adequate physiologic function. This may include establishment of a patent airway, artificial respiration, cardiac massage and perhaps the application of defibrillation techniques. Following the stabilization of vital signs, the clinician may proceed with subsequent therapeutic measures.

The stabilized animal may be treated in the following steps, in any order:

Delaying Absorption

Preventing the animal from absorbing additional intoxicant is a major factor in treating cases of intoxication. In many instances the intoxication may be prevented in this manner if the animal was actually observed ingesting or being in contact with suspect material. Removal of the animal from the affected environment is a necessary first step to prevent further absorption. Hopefully, bringing the animal to the veterinary clinic or hospital will suit this purpose. It also may entail washing the animals's skin to remove the noxious agent. If an external toxicant is involved caution must be exercised to avoid the contamination of all persons handling the case. Protective clothing, such as rubber aprons and gloves, is a necessity in these cases. In addition, the judicious use of absorbants and cathartics will further aid in the prevention of further absorption of toxic materials that are ingested. Also absorption may be retarded by precipitation, inactivation, neutralization, oxidation and chelation. Several of the mechanisms may be accomplished by carefully chosen locally-acting chemical anitdotes (Table 1).

Absorbants

Activated charcoal is probably the best absorbing agent available to the practitioner. Although it does not detoxify toxicants, it will effectively prevent absorption of a toxicant if properly utilized. Activated charcoal can be effectively utilized with emetics, gastric lavage techniques, or by itself.

The proper type of activated charcoal for treatment in intoxication is of vegetable, not mineral or animal origin. There are several commercial types of activated charcoal available (Norit R-American Norit, Nuchar CR- West Virginia Pulp and Paper, Darco G-60R-Atlas Chemical). The proper technique for utilizing activated charcoal is as follows: 1) Make a slurry of the charcoal using water. The proper dose is 1-4 gm/lb of body weight in a concentration 1 gm charcoal/3-5 ml of water. 2) Administer the charcoal by a stomach tube. 3) Thirty minutes following administration of the charcoal, a cathartic of sodium sulfate should be administered. Some charcoal should remain in the stomach and should be followed by a cathartic to prevent desorption of the toxicant.

Activated charcoal is highly absorptive for many toxicants including mercuric chloride, strychnine, many other alkaloids including morphine and atropine, barbiturates and ethylene glycol. It is ineffective against cyanide.

Cathartics

Sodium sulfate is a more efficient agent for evacuation of the bowel than magnesium sulfate and is the preferable agent to use, especially with activated charcoal. There is also some danger of CNS depression due to the magnesium ion. The dose of sodium sulfate is 1 gm/kg. Either agent may be used in an emergency.

Mineral oil or vegetable oil are of value if lipid soluble toxicants are involved. Mineral oil (liquid petrolatum) is inert and unlikely to be absorbed. Vegetable oil, however, is more likely to be absorbed and therefore may be contraindicated. Regardless of the types of oil utilized, it should be followed by a saline cathartic in 30 to 40 minutes.

Elimination of Absorbed Toxicants

Absorbed toxicants are generally excreted via the kidneys. Some toxicants may be excreted by other routes (bile-feces, lung, other body secretions). Renal excretion can be manipulated in many instances. Urinary excretion of toxicants may be enhanced by the use of diuretics or altering the pH of the urine.

The use of diuretics to enhance urinary excretion of toxicants requires adequate renal function and hydration of the affected animal. Once these facts are established, diuretics are indicated. Monitoring of urinary out-put is essential in these animals and a minium urinary flow of 0.1 ml/kg/min is necessary. The diuretics of choice are mannitol and furosamide (Lasix R). Both of these agents are very potent diuretics. The dosage of mannitol is 1 gm/lg/hr and for furosamide is 2 mg/lb.

Alteration of urinary pH to expedite the excretion of toxicants and foreign chemicals is a classical pharmacologic technique. The technique relies on the physio-chemical phenomenon that ionized compounds do not readily traverse cell membranes and hence are not reabsorbed by the renal tubules. Consequently, acid compounds such as acetylsalicylic acid (aspirin) and some barbiturates remain ionized in acidic urine. As a result, urinary excretion of many toxic ompounds may be enhanced by modifying the urine pH. Some bicarbonate may be used as an alkalinizing agent.

Peritoneal dialysis is indicated in small animals, but is difficult in large animals when an intoxicated animal exhibits oligunia or anuria. It is a rather time-consuming but effective technique in many conditions. The procedure requires the use of two separate solutions and the solutions should be exchanged every 30 to 60 minutes. Two dialyzing solutions which may be used are: 5% dextrose in 0.45% NaCl with 15 mEq/L of potassium as potassium chloride and 5% dextrose in water with 44.6 mEq of bicarbonate and 15 mEq of potassium added. Other dialyzing solutions may be utilized.

The process of peritoneal dialysis involves the infusion of 10 20 ml/kg of the one dialyzing solution into the peritoneal cavity, waiting the prescribed length of time, withdrawing the first dialyzing solution and infusing the second solution. The infusion and withdrawal cycles with alternating solutions should be maintained for 12 to 24 hours or until normal renal function is restored. The pH of the dialyzing solutions may be altered to maintain the ionized state of the offending compound.

In cattle a rumenotomy is an excellent means of rapidly emptying the rumen.

Supportive Measures

Supportive measures are very important in intoxications. These measures include control of body temperature, maintenance of respiratory and cardiovascular function, control of central nervous signs and control of pain.

Body Temperature Control

Hypothermia may be controlled with the use of blankets and keeping the animals in a warm, draft-free stall. Infra-red lamps should be used with caution and under constant observation.

Hyperthermia is controlled through the use of ice bags, cold water baths, cold water enemas or cold peritoneal dialysis solutions. Regardless of the type of temperature control required, it is vitally important that the animal's body temperature be constantly monitored to insure that over correction does not occur.

Respiratory Support Measures

Adequate respiratory support requires the presence of an adequate patent airway. A patent airway may be obtained either with a cuffed

endotracheal tube in an unconscious animal or a tracheostomy performed under local anesthesia. An emergency tracheostomy tube may be made from a cuffed endotracheal tube which has been shortened to reduce the dead-space.

A respirator is of great value in cases of respiratory depression, however, an anesthetic machine may be utilized with manual compression of the bag. A mixture of 50% oxygen and 50% room air is generally adequate unless there is a thickened respiratory membrane, in which case 100% oxygen is necessary.

The use of analeptic drugs in cases of severe respiratory depression or apnea is questionable due to the short duration of their effects, and other undesirable side effects. Positive-pressure ventilatory support is of greater value. The use and dosage of several analeptic drugs are presented in a later section on CNS depression.

Cardiovascular Support

Cardiovascular support requires the presence of an adequate circulating volume, adequate cardiac function, adequate tissue perfusion and adequate acid-base balance. Volume and cardiac activity are of immediate concern, while perfusion and acid-base balance, though of no lesser importance, are not of immediate concern.

In the presence of hypovolemia due to loss of both cells and volume, whole blood is the necessary agent. A good rule of thumb is to give a sufficient quantity of whole blood to raise the packed cell volume up to 75% of the animal's estimated normal.

Hypovolemia due to fluid loss alone can be treated with the administration of lactated Ringer's solution or plasma expanders. Central venous pressure should be monitored in these cases to prevent overloading the heart with too much volume, too rapidly.

Tissue perfusion should also be monitored periodically to determine the adequacy of the replacement therapy. In some cases it may be necessary to administer massive doses of corticosteroids intravenously to restore adequate tissue perfusion (Dexamethasone - Azium^{R}, 2-10 mg/kg).

Cardiac activity can be aided by the application of closed-chest massage for immediate requirements, but the administration of pharmaceutical agents which can stimulate inotropic and chronotropic activity must also be undertaken in most instances. One of these agents is calcium gluconate infused very slowly I.V. This agent is also reported as being a good nonspecific measure in many toxicities. Other agents include glucogon - 25 to 50 ug/kg, I.V. and digoxin - 0.2 to 0.6 mg/kg, I.V. Care must be taken not to overdose animals with cardio-active agents as they are highly toxic to the myocardium.

Acid-Base Imbalance

Control of acid-base balance problems is primarily one of physiologically maintaining an animal in a homeostatic condition. The most common acid-base disturbance seen in animals is acidosis, mainly of metabolic origin. However, acidosis or alkalosis may occur in cases of intoxication.

In correcting acidosis, not of respiratory origin, sodium bicarbonate administered I.V., at a dosage rate of 2 to 4 mEq/kg every 15 minutes is the drug of choice. Other alkalinizing solutions include 1/6 Molar sodium lactate - 16 to 32 ml/kg; lactated Ringer's solution - 120 ml/kg; and THAM buffer - 300 mg/kg. Bicarbonate is generally the easiest to administer volume-wise and requires no metabolic conversion. Caution must be exercised with all alkalinizing agents against the induction of alkalosis.

Alkalosis, unless drug induced, does not generally occur in animals. However, if alkalosis is present, the I.V. administration of 0.9% NaCL (Physiological Saline) - 10 mg/kg, is usually suficient for initial therapy. This should be followed by the oral administration of ammonium chloride - 200 gm/kg/day in divided dosages. As in the case of acidosis, the clinician should be cautioned about the overtreatment of the alkalotic patient.

Central Nervous System

Management of central nervous disorders, in cases of intoxication, is simple in appearance but complex in actuality. The type of therapy will depend upon the presence of depression or hyperactivity. Either disorder can easily be turned into the opposite problem by overzealous therapeutic measures.

CNS Depression

CNS depression can also be considered respiratory depression as the management of the two conditions is very similar. Although analeptic agents such as doxapram (Dopram^{R}) - 5-10 mg/kg, bemegride (Mikedimide) - 10-20 mg/kg, or pentylenetetrazol (Metrazol) - 6-10 mg/kg, are reported as efficacious when administered I.V. in these conditions, their actions are short-lived and CNS depression can return if the animals are not monitored continuously. Another disadvantage is that analeptics can induce convulsions. Artificial respiration or respiratory support is of greater value in animals exhibiting CNS depression and may be the treatment of choice for most CNS depression syndromes.

CNS Hyperactivity

Cases of CNS hyperactivity including convulsions can be managed by the administration of CNS depressants or tranquilizers. Pentobarbital sodium is generally the agent of choice for convulsions and hyperactivity. Care must be taken since in many cases a respiratory-depressing dose may be required to alleviate the signs. In these cases, respiratory support is mandatory.

Inhalant anesthetics have been reported as excellent for long-term management of CNS hyperactivity, but this removes the machine from surgery room use for extended periods. Central-acting skeletal muscle relaxants and minor tranquilizers have been reported for use with convulsant intoxicants. Some of these include methocarbamol (Rubaxin^{R}), 110 mg/kg, I.V.; glyceryl guaiacolate (Geocolate^{R}), 110 mg/kg, I.V.; and diazepam (VAlium^{R}), 0.5 to 1.5 mg/kg, I.V. or I.M. In other cases of CNS stimulation due to amphetamines and some hallucinogens such as LSD and phencyclidine, phenothiazine tranquilizers have produced adequate control. Regardless of the regimen of therapy for CNS hyperactivity, the animals should be placed in a quiet, dark room or stall to prevent additional stimulation due to auditory or visual stimuli.

Systemic and Specific Antidotes

When a poison has been absorbed, use of a systemic antidote, if available, is indicated. In most situations, it is advisable to treat immediately with a systemic antidote, promote elimination (excretion) and apply supportive therapy. However, specific antidotes are available for only a few poisons.

Available systemic and specific antidotes, and the dosages for each, are presented in Table 2. The dosage and duration of treatment given in the table are to serve as guidelines only and must be adjusted according to the severity of the poisoning and condition of the animal.

Systemic antidotes possessing specific actions for their antidotal activity are classified by the following mechanisms:

1. Complexing with a poison, rendering it inert (e.g., dimercaprol for arsenic poisoning).
2. Accelerating the metabolic conversion of a toxic to a nontoxic product (e.g., thiosulfate for cyanide poisoning).
3. Blocking the metabolic formation of a poison from a nontoxic precursor (e.g., monoacetin for fluoracetate poisoning).
4. Specifically accelerating the excretion of a poison (e.g., chloride for bromide poisoning).
5. Competing with a poison for essential receptors (e.g., vitamin Kl for coumarin-derivative poisoning).
6. Blocking receptors responsible for toxic effects (e.g., atropine for cholinesterase inhibition).
7. Restoring normal function by repairing or by-passing the effects of a poison (e.g. methylene blue for methemoglobinemia).

It must also be noted that a number of drugs, poisons and other chemicals can either cause a toxic reaction when used to inhibit drug (or poison) metabolism, or cause a state of tolerance by stimulating the activity of the liver microsomal drug-metabolizing enzymes. Great species differences and genetic variations in drug or poison metabolism also exist.

A discussion of therapeutic measures for some of the more common intoxications in cattle is presented in the following paragraphs.

Specific Therapeutic Measures

Warfarin

Transfusion of whole blood constitutes the single most effective treatment since it provides prothrombin as well as red blood cells and fluid lost by the patient. A citrated whole blood mixture consisting of 100 ml of an aqueous solution containing 2 gm sodium acid citrate and 2.5 gm dextrose, to which is added 300 ml whole blood, may be used. This mixture may be stored at refrigerator temperatures for a maximum of 14 days. In cases of poisoning, a minimum volume of 9 ml/lb should be administered. Half the estimated volume should be given if the mucous membranes still appear pallid.

The administration of vitimin K_1 is indicated to promote the production of prothrombin and other clotting factors by the liver. The dose is 0.5 mg/kg I.V. in 5% dextrose at a rate of 10 mg/min. One should not use synthetic vitamin K_1 analogs as numerous studies have shown them to be clearly inferior to vitamin K_1 in decreasing blood clotting time.

Cyanide

Perhaps the most commonly used and most effective of the cyanide antidotes is the combination of nitrite and thiosulfate. Therapy is directed at splitting of the cytochrome-cyanide bond and subsequent rapid removal of a cyanide complex. The cyanide-cytochrome complex is broken by the addition of sodium nitrite with the formation of methemoglobin which competes with cytochrome oxidase for the cyanide ion, and cyanmethemoglobin is formed. Thiosulfate then reacts with cyanide under influence of the enzyme rhodanase, to form thiocyanate, which is readily excreted in the urine. A recommended therapeutic regimen is the intravenous administration of a mixture of 1ml of 20% sodium nitrite and 3 ml of 20% sodium thiosulfate, giving 4 ml of this mixture per 45 kilograms body weight. Commercial solutions for treatment of prussic acid poisoning are available.

$$MetHb{:}CN^- + S_2O_3^= \xrightarrow[SCN\ ox.]{rhodanase} SCN^- + SO_3 + MetHb.$$

Care must be taken in administration of the nitrite so as not to form too much methemoglobin and compromise O_2 -carrying ability too much. Some beneficial effect has been shown for cobalt salts administered for cyanide poisoning. However, the nitrate and thiosulfate remain most effective.

Nitrate-Nitrite

Therapy is aimed at restoring the iron in hemoglobin to the divalent state. To do this, methylene blue is added to the system. It is rapidly reduced to leukomethylene blue and then serves as the reducing agent to convert methemoglobin (Fe^{+3}) to hemoglobin (Fe^{+2}) as follows:

NADPH	Methylene Blue (Ox.)	Hemoglobin (Fe^{+2})
NADP	Leukomethylene Blue (Red.)	Methemoglobin (Fe^{+3})

It may be seen that overpowering the system with methylene blue will also produce methemoglobinemia. The suggested dosage is 2 mg/lb body weight administered in a 2% to 4% solution. This may need to be repeated, since absorption of nirate-nitrite from a full rumen can continue. Mineral oil given via a stomach tube will counteract the caustic action of nitrate salts and help speed elimination. For forage nitrate poisoning, purging with saline cathartics and control of bacterial nitrate reduction with intraruminal antibiotics and 3-5 gallons of cold water may be beneficial.

Urea and Ammonium Ion

The best treatment for urea and ammonium ion poisoning is to give several gallons of cold water orally. As much as 5-10 gallons should be given to an adult cow.

If 6% acetic acid or vinegar is available, up to 3 gallons should be given along with the cold water. The rationale is that water lowers the rumen temperature and dilutes the reacting medium while the acetic acid lowers rumen pH (preventing ammonia absorption) and also supplies carbon skeletons needed by rumen bacteria. Urea intoxicated animals should be watched closely for at least 14 hours after treatment or apparent recovery, since an occasional relapse of clinical signs may occur.

Lead

Prior to the advent of lead-chelating agents, treatment consisted mainly in attempts to induce the deposition of lead in bone, such as the administration of large quantities of calcium phosphate and vitamin D. Dimercaprol (BAL) initially increases urinary excretion of lead quite markedly; but the effect wanes rapidly and the amount of lead mobilized is negligible. Apparently only the lead in the blood can be chelated by dimercaprol. The lead in bone and soft tissues is too firmly bound to be mobilized. In animals dimercaprol gives unpredictable results and may add the toxicity of the lead which is bound to it.

The discovery of the efficacy of calcium disodium edetate in the treatment of lead poisoning added greatly to the successful management of plumbism. Nevertheless edetate proved to have certain short-comings in addition to its own toxic potentialities and the necessity for its intravenous administration for maximal efficacy. In the treatment of lead encephalopathy, edetate may exacerbate the syndrome during the first day of therapy. Acute cases in farm animals are usually encountered too late for most forms of treatment to be efficacious. Attempts should be made to remove the lead by giving saline purgatives and emetics and by gastric lavage. Chemical antidotes in the form of soluble sulphates (sodium sulphate, magnesium sulphate), milk and egg-white, or tannic acid are recommended to immobilize lead in the gut by precipitating it as insoluble sulphate, albuminate or tannate, respectively. Sedatives may be used to control the convulsions.

The treatment recommended for cattle consists of intraperitoneal or subcutaneous administration of 1-2% (weight/volume) solution of CaEDTA in 5% dextrose at the rate of 110 mg/kg. This should be given twice daily for two days, the treatment withheld for two days followed by two more days of therapy. Success is best achieved when the blood lead is less than 1 ppm. Cattle require 10 to 14 days to recover and may require several series of treatments in severe cases. Supportive therapy of forced feeding and oral fluids is very important since these animals are frequently anorectic, emaciated, and dehydrated. Excessive quantities of fluids should not be given since water loading will compound the brain edema. Oral magnesium sulphate may be of some value in limiting further absorption of lead in animals as well as serving as a purge. Animals with neurologic involvement are accorded a poor prognosis.

Chlorinated Hydrocarbon Insecticides

Treatment must control the violent seizures, remove the offending material, and maintain body fluid and electrolyte balance. The barbiturates, particularly pentobarbitol sodium, are the sedatives of choice, using care in dosage to prevent further depression of the respiratory system.

Since chlorinated hydrocarbon compounds are stored in the fat, the clinical course may be somewhat protracted. Maintenance of a normal or nearly normal state of nutrition and hydration is mandatory. Maintaining adequate urine formation is especially important as the chlorinated hydrocarbons are excreted by the kidneys. Since cerebral edema has been described as a post mortem change, dexamethasone (1 mg per pound of body weight) and/or mannitol (1 gm per kg) might be beneficial. Dietary fat should be avoided as it encourages chlorinated hydrocarbon absorption. Calcium gluconate (2 to 4 ml of a 10% solution) has been recommended but its efficacy is disputed.

Organophosphate and Carbamate Insecticides

Atropine sulfate is the pharmacologic antidote for organosphosphorus and carbamate poisoning. Although atropine is highly effective as an antidote, it is important to realize that it has no effect on the fundamental biochemical lesions. Atropine acts only to block or counteract come of the more important effects of acetylcholine accumulation. Animals poisoned

by cholinesterase inhibitors have an increased tolerance to atropine and the dosage should be greater than is usually recommended. For ruminants, an average of 0.5 mg/kg body weight should be administered. About one fourth of the dosage should be given intravenously and the remainder subcutaneously or intramuscularly. Improvement in the animal's condition should be seen within a few minutes. It may be necessary to repeat the dosage every 3 to 4 hours for one to two days, depending upon the response of the animal. With each successive treatment, however, the response becomes less and less apparent.

The development of specific antidotes for organophosphorus poisoning shows promise in the hydroximic acids and oximes. Compounds such as 2-PAM (pralidoxime) and TMB-4 act competitively breaking down the phosphorylated enzyme complex, freeing acetylcholinesterase and at the same time tying up the organophosphate, making it available for hydrolysis and excretion. Dosages of approximately 20 mg/kg body weight have been effectively used in animals. The oximes may not be effective in the treatment of carbamate poisoning. In those cases of massive oral exposure, especially in ruminants, the use of both atropine and the oximes may be ineffective because of the continued absorption of the insecticide from the rumen. Animals may make a transient recovery only to relapse into more severe poisoning than was initially observed.

A number of drugs should be avoided in treating poisoning by organophosphorus compounds. These include morphine, succinylcholine, and penothiazine.

Herbicides and Fungicides

Treatment of most poisonings caused by herbicides or fungicides is symptomatic and supportive in nature because of the lack of specific antidotes. The recommendations in the introductory chapter on treatment of poisonings should be followed in treating animals poisoned by these agents.

Animals poisoned by sodium chlorate, a methemoglobin former, should be given methylene blue (1%) solution, 1 ml/kg body weight. The methylene blue must be given slowly, and the animal must be closely observed because methylene blue in an overdose is also a methemoglobin former. Because sodium chlorate is not rapidly biotransformed, a poisoned animal may have to be retreated for one to two days to insure proper recovery. Other supportive measures such as fluid and eletrolyte therapy should also be instituted.

In poisonings caused by organic mercurial fungicides, signs may not become apparent until permanent nerve damage has occurred. BAL, as used for arsenical poisonings, may be of value along with other supportive measures.

Adverse Drug Reactions

Drugs are developed for the beneficial effects that may be achieved by their proper use. However, all drugs have side effects, and the therapeutic effect of drugs may be modified by many factors including: gastrointestinal absorption (modification of microflora); feed; the xenobiotics (insecticides, cleaning agents, cosmetics, inhalants, etc.); genetic variation in drug metabolism (susceptibility, idiosyncrasy); species; sex (hormonal effect); age (difference in drug-metabolizing ability); nutritional status; body temperature; dosage; route of administration and pathophysiologic factors modifying drug response (enzyme deficiency, liver or kidney disease, etc.). The decrease in drug effectiveness or increased action up to the toxic level caused by these many factors has become a major concern in modern therapeutics.

Normal doses of a single drug tolerated by the majority of people or animals (in any one species) may cause some adverse reactions in some individuals. Many of these reactions are due to: 1) hypersensitivity; 2) idiosyncrasy; 3) allergy; 4) drug resistance; 5) tolerance and tachyphylaxis, and physical dependence; and 6) drug and bioactive environmental chemical toxicity (acute or chronic effects, including mutagenesis, teratogenesis and tumorigenesis).

In vitro drug incompatibilities may properly be classified as iatrogenic drug interactions. There may be some justifiable reasons for extemporaneous mixtures of drugs, including economy of time, convenience and avoiding multiple injection sites. However, the reasons for not mixing drugs *in vitro* should be given serious consideration. Certainly, an important reason for refraining from extemporaneous drug mixtures is the possibility of inactivating one or more of the active ingredients. Visible signs of *in vitro* incompatibility or inactivation include colloidal formation, color changes or gas formation. It should be remembered that some reactions may occur that are invisible but nevertheless may render an active ingredient inactive. For instance, certain sulfonamides and penicillins are incompatible due to the fact that the high pH of sulfas will inactivate the penicillins. Unfortunately, this interaction is not grossly observable in the vial. It would be advantageous to consult with a pharmacist before mixing drugs *in vitro*.

Allergic Drug Reactions

Hypersensitivity reactions, or allergic drug reactions, are those based on immunological responses, and are the result of antigen-antibody combination. Other types of adverse effects such as direct toxicity, overdosages, side effects, or interaction between drugs, are not caused by immune mechanisms.

Predispositions to Drug Reactions

The factors contributing most significantly to the incidence of side effects and interactions are:

1. The great number of potent drugs available to practitioners.
2. The practice of administering more than one drug to a patient.
3. Availability of potent drugs without prescription.
4. Animal exposure to pollutants from the environment (e.g., insecticides, pesticides, fertilizers, etc.).
5. Lack of knowledge concerning the pharmacology, pharmacokinetics and chemistry of the drug used.
6. Failure to set a therapeutic end point, producing overdose effect (e.g., digitalis therapy).
7. Lack of precise diagnosis followed by administration of useless drugs.
8. Lack of knowledge of predisposing factors in both health and disease, which contributes to poor prescription practices.

Difficulties in Recognizing Drug Reactions

Frequently a series of clinical accidents due to drug reactions has led to discovery of the underlying toxicologic mechanisms. However, in many situations drug reactions are not recognized because of the following reasons:

1. Apparent proximate cause and long-term effects of some drugs are lacking (e.g., phenothiazines concentrate in the retina and may cause later damage).
2. Use of multiple drugs which are not needed.
3. Poor documentation of drug reactions (minimizing some toxic effects).
4. Lack of concern about potential toxicity of many drugs; reluctancy of practitioners to think that treatment may aggravate the patient's condition.
5. Occult drug toxicity.
6. Emergency treatment often contributes to irrational use of drugs.

How To Minimize The Occurence of Adverse Drug Effects In Practice

1. **Where possible, avoid multiple drug therapy. The knowledgeable use of a single drug in pharmacotherapy is superior to the blind administration of a series of drugs with no regard to how they may influence one another.**
2. **Avoid combination products. As a matter of policy, we do not include combination products in our Veterinary Medical Teaching Hospital Formulary.**
3. **Avoid simultaneous use of drugs which may be antagonistic.**
4. **Try to minimize your personal formulary to the point that you are thoroughly familiar with each drug. Today there is a greater danger from overtreatment than from undertreatment of most cases.**
5. **Limit intravenous infusion solutions to only one drug additive to avoid incompatibilities.**
6. **Always have on hand appropriate drugs with which to treat acute allergic reactions. If dispensing drugs for administration by the owner,**

explain how to recognize and treat an anaphylactic reaction. Penicillin allergy in cattle is being seen more commonly today.

7. **When in doubt consult your local pharmacist. By training he is an excellent source of information on drug incompatibilities, interactions and adverse effects.**
8. **Finally, it may be concluded that some adverse reactions are inevitable. The number, however, can be reduced if a correct doagnosis can be made initially and only the proper drug administered, and if an old principle in therapy is always observed:** *primum non nocere* (first of all-do no harm.

Table 2-1 Systemic Antidotes and Dosages

Toxic Agents	Systemic Antidotes*	Dosage and Method For Treatment
Amphetamines	Chlorpromazine	1 mg/kg, IM, IP, IV; administer only half dose if barbiturates have been given; blocks excitation.
Ammonia (urea)	Acetic acid** gamma-Aminobutyric acid**	2% solution; give large animals 1 ml/lb. IV; repeat as needed; protective effect on experimental ammonia intoxication in rats.
Arsenic, mercury and other heavy metals except silver, selenium and thallium	Dimercaprol (BAL)	10% solution in oil; 2.5-5 mg/kg. IM every 4 hours for 2 days, 3 times a day on 3rd day, and then twice a day for the next 10 days or until recovery. Note: 5 mg/kg dosage should be given only first day in severe acute poisoning
	Sodium thiosulfate (only for arsenic poisoning)	20% solution; give large animals 30-40 mg/kg IV or orally (double dose for oral administration) two to three times daily until recovery (usually 3-4 days).
	N-Acetyl-D.L.-Penicillamine** (only for mercury poisoning).	Developed for chronic mercury poisoning, now seems most promising drug; no reports on dosage in animals. Dosage for man is 250 mg orally, every 6 hrs for 10 days.
Barbiturates	Pentylenetetrazol	10% solution; give 10-20 mg/kg IV or IM, repeat at 15-30 min. intervals as needed. Give large animals total IV dose of 1000-3000 mg.
	Doxapram	2% solution; give 3-5 mg/kg., IV only; repeat as necessary.
	Bemegride	3% solution; give 5-10 mg/kg, IV only, by slow infusion or in intermittent doses.
	Amphetamine	5% solution; give 0.5-1 mg/kg, SC, IV or IP, not to be repeated within 60 min. Give large animals 100-300 mg SC. Note: All of the above are reliable only when depression is mild; in deeper levels of depression, artificial respiration (and oxygen) is preferable.
Bromides	Chlorides (sodium or ammonium salts)	0.5-1 Gm. daily for several days; hasten excretion.
Bracken fern	DL-batyl alcohol	10% solution in olive oil. Give cows 10 ml SC, daily for 5 days. Blood tranfusion may be helpful.
Carbon monoxide	Oxygen	Pure oxygen at normal or high pressure, or oxygen with 5% carbon dioxide; artificial respiration, blood transfusion.
Cholinergic agents	Atropine sulfate	0.02 mg-0.04 mg/kg as needed.
Cholinsterase inhibitors	Atropine sulfate	Dosage for large animals is 0.2 mg/kg., repeated as needed for atropinization. Treat cyanosis (if present) first. Blocks only muscarinic effect. Atropine in oil may be injected for prolonged effect during the night.
Cholinergic agents Cholinsterase inhibitors (organophosphates, some carbamates; but not carbaryl, dimetilan or carbomoyloxime, etc.)	Pralidoxime chloride (2-PAM)	For large animals: 10% solution; give 25-50 mg/kg (cows) IV during 6-min. period; maximum dose is 100 mg/kg via drip technic. 2-PAM alleviates nicotinic effect and regenerates cholinesterase. Morphine, succinylcholine,

TOXIC AGENTS	SYSTEMIC ANTIDOTES*	DOSAGE AND METHOD FOR TREATMENT
		and phenothiazine tranquilizers are contraindicated.
Copper	D-Penicillamine	Dose for animals not established. Dose for man is 1-4 gm daily in divided doses (250 mg tablets).
	Molybdenum	For chronic poisoning in sheep: 100 mg ammonium molybdate and 0.3-1 gm sodium sulfate, orally, daily for 3 weeks.
Curare (tubocurarine)	Neostigmine methylsulfate	Solution: 1:2000 or 1:500 (1 ml = 0.5 mg or 2 mg). Dose for small animals is 0.1 mg/10 lb SC. Dose for large animals is 1 mg/100 lb SC or IV; if given IV, administer very slowly and follow with IV injection of a 1% solution of atropine (9.04 mg/kg).
	Edrophonium	1% solution; give small animals 0.05-1 mg/kg IV.
Coumarin-derivative anticoagulants	Vitamin K1	5% stable emulsion; give large animals 0.5-1 mg/kg IM or IV in 5% solution of glucose at the rate of 10 mg vitamin K per min; maximum effect occurs within 50-60 minutes. Give 5 mg/kg IM for 3 days.
	Whole blood or Plasma	Blood transfusion; for large animals, 2-4 L/500 kg.
Cyanide	Methemoglobin (sodium nitrate is used as former of methemoglobin)	1% solution of sodium nitrate; dosage is 16 mg/kg IV for both large and small animals.
	Sodium thiosulfate	Follow with: 20% solution at dosage of 30-40 mg/kg IV. If treatment is repeated, use only sodium thiosulfate. Note: Both of the above may be given simultaneously as follows: 20 ml/50 kg of combination consisting of 10 gm sodium nitrate, 15 gm sodium thiosulfate, and distilled water q.s. 250 ml. Dosage may be repeated once if further treatment is required, give only 20% solution of sodium thiosulfate at level of 10-20 ml/50 kg IV.
Digitalis glycosides	Potassium chloride	0.5-2 gm orally in divided dose, or as diluted solution given IV by slow drip (ECG control is essential).
	Propranolol (beta blocker)	0.5-1 mg/kg IV or IM as needed to control cardiac arrhythmias.
	Atropine sulfate	0.02-0.04 mg/kg as needed for cholinergic control.
Fluoroacetate (1080)	Glyceryl monoacetin**	0.1 to 0.5 mg/kg IM hourly for several hours (total 2-4 mg/kg); or diluted (0.5-1%) IV (danger of hemolysis). Monoacetin is available only from chemical supply houses.
	Acetamide*	Animal may be protected if acetamide is given prior to or

TOXIC AGENT	SYSTEMIC ANTIDOTES*	DOSAGE AND METHOD FOR TREATMENT
		simultaneously with 1080 (experimental).
Fluoride	Calcium borogluconate	Large animals: 23% solution, 250-500 mg IV, at body temperature and by very slow injection (danger of heart block). Small animals: 5-10% solution, 3-10 ml.
Heparin	Protamine sulfate	1% solution; give 1-1.5 mg to antagonize each 1 mg of heparin; slow IV injection. Reduce dose as time increases between heparin injection and start of treatment (after 30 min, give only 0.5 mg).
	Hexadimethrine	1 mg for each 1 mg heparin, by slow IV injection. Hexadimethrine is a synthetic product, causes fewer side effects than protamine.
Iron Salts	Desferrioxamine (deferoxamine)**	Dose for animals not yet established. Dose for man is 5 gm of 5% solution given orally, then 20 mg/kg IM every 4 hours. In case of shock, dose is 40 mg/kg by IV drip over 4 hour peroid; may be repeated in 6 hours, then 20 mg/kg by drip every 12 hours.
Lead	Calcium disodium edetate (EDTA), EDTA and BAL	DOSAGE: Maximum safe dose is 75 mg/kg/24 hours (only for severe case). EDTA is available in 20% solution; for IV drip, dilute in 5% glucose to 0.5%; for IM, add procaine to 20% solution to give 0.5% concentration of procaine. BAL is given as 10% solution in oil. TREATMENT; 1) In severe case (CNS) involvement or >100 mg Pb/100 gm whole blood) give 4 mg/kg BAL only as initial dose; follow after 4 hours, and every 4 hours for 3 or 4 days, with BAL and EDTA at separate IM sites; skip 2 or 3 days and then treat again for 3 to 4 days. 2) In subacute case or 100 mg Pb/100 gm whole blood, give only 50 mg EDTA/kg/ 24 hours for 3 to 5 days.
Methanol and Ehylene glycol	Ethanol	Give IV, 0.75 mg/kg of 25% solution; then give 0.5 mg/kg every 4 hours for 4 days. To prevent or correct acidosis, use sodium bicarbonate IV.
Methemoglobinemia-producing agents (nitrates, chlorates, etc.)	Methylene blue	1% solution (maximum concentration); give by slow IV injection, 8.8 mg/kg; repeat if necessary. To prevent fall in blood pressure in cases of nitrite poisoning, use a sympathomimetic drug (ephedrine, epinephrine, etc.).
Morphine and Related Drugs	Nalorphine hydrochloride	Give IV to each dog, 1-2.5 mg of solution containing 5 mg nalorphine per ml. Do not repeat if respiration is not satisfactory.
	Levallorphan tartrate	Give IV to each dog, 0.1-0.5 mg of solution containing 1 mg per ml.

TOXIC AGENTS	SYSTEMIC ANTIDOTES*	DOSAGE AND METHOD FOR TREATMENT
		Note: Use either of the above antidotes only in acute poisoning. Artificial respiration may be indicated.
Molybdenum	Copper Sulfate	Prophylaxis: 1-5% in salt, or orally.
	Cobalt	1 gm copper sulfate and 1 mg/100 lb body weight of cobalt carbonate per cow, daily at weekly intervals for 4 to 6 weeks. Supplement ration with phosporus.
	Copper glycinate	Solution containing 60 mg/ml: inject into dewlap; 1 ml for calves; 2 ml for cows; repeat once or twice during a season.
Oleander Glucosides	Atropine sulfate	0.04 mg/kg IV or IM; repeat as needed. Controls cholinergic effects.
	Propranolol	0.5 mg/kg IV or IM; repeat as needed. Controls cardiac arrhythmias.
Oxalates	Calcium	TREATMENT: 23% solution of calcium borogluconate IV. Give large animals 250-500 ml. Give small animals 3-20 ml (to control hypocalcemia). PROPHYLAXIS: 25% dicalcium phosphate in usual salt ration, or 10% in alfalfa cubes.
Phenothiazine Derivatives	Methylamphetamine	For horses: 0.1-0.2 mg/kg IV; also blood transfusion.
Phytotoxins and Botulinus	Antitoxins	As indicated for specific antitoxins. Examples of phytotoxins; ricin, abrin, robin, curcin, crotin.
Red Squill	Atropine Sulfate Propranolol	As for oleander poisoning.
Selenium and its analog (Selenocystathionine)	Cystine** Methionine** Vitamin E**	Application is still experimental and dosages of these drugs have not been established.
	Arsenic	Alkali-type disease: Give large animals 25 ppm sodium arsenite in salt, or 5 ppm in drinking water. Arsanilic acid (0.02%) in the ration of calves and pigs has protected against as much as 10 ppm of selenite in the body; increasing the protein content of the ration seems to help with detoxification.
	Strychnine	Blind staggers-type in cattle: Give 4-6 mg strychnine sulfate/600-800 lb body weight every 2 hours for 3 to 4 doses. In the early stages, administer 1-3 gallons tepid water every 3 hours for 1 or 2 days.
	Neostigmine	1-2 mg/100 lb body weight IM, with glucose IV; give daily for 3 to 4 days.
Strychnine and Brucine	Pentobarbital	Small animals; give IP or IV to effect. A higher dose is usually required than is required for anesthesia. If necessary, repeat with lower dose. Place animal in warm, dark, quiet room.
	Amytal	Give by slow IV injection to effect. Duration of sedation is usually 4-6 hours.

TOXIC AGENT	SYSTEMIC ANTIDOTES*	DOSAGE AND METHOD FOR TREATMENT
	Methocarbamol	10% solution; average first dose for dogs is 149 mg/kg IV (range: 40-300 mg) to effect; repeat half dose as needed.
	Chloral hydrate	As commonly given to large animals.
Strontium	Calcium salts	Usual dose of calcium boroglu-conate IV.
	Ammonium chloride	Small animals: 0.2-0.5 gm orally in water, 3 to 4 times daily. Large animals: 5-30 gm in divided doses.
Thallium	Diphenylthio-carbazone**	Dog: 70 mg/kg orally, 3 times a day for 6 days. Hastens elim-ination, but is potentially toxic.
	Cysteinamine and Cystine**	Has some chelating properties; dose not established.
	Potassium chloride	Give simultaneously with thio-carbazone. Dose is 2-6 gm orally, daily in divided doses.

* Boldface type indicates specific antidote.
** Experimental drug; practical efficacy not well established.

Table 1-1 Locally-Acting Antidotes Against Unabsorbed Poisons, and Some Principles of Treatment.

POISON	ANTIDOTE AND DOSE OR CONCENTRATION
Acids, Corrosive	Magnesium Oxide solution Large Animals ..... 20-30 Gm. Milk of Magnesia Large Animals ..... 30-300 ml.
Alkali, Caustic	Weak acid: Vinegar (diluted 1:4), 1% Acetic Acid or Lemon Juice given orally
Alkaloids	Potassium Permanganate (1:5000 to 1:10,000) for lavage and/or oral administration. Tannic Acid or Strong Tea, except in cases of poisoning by cocaine, nicotine, phy-sostigmine, atropine or morphine. Large Animals ..... 5-25 Gm. in 0.5-1 gallon of water. Purgative should be used for prompt removal of tannates.
Arsenic*	Sodium Thiosulfate: 10% solution given orally. Large Animals ..... 20-30 Gm. Protein: evaporated milk, egg whites, etc. Tannic Acid or Strong Tea.
Barium Salts	Sodium Sulfate and Magnesium Sulfate (20% solution given orally) Large Animals ..... 250-1000 Gm.
Bismuth Salts	Acacia or Gum Arabic as mucilage.
Carbon Tetrachloride	Empty stomach; high protein and carbohydrate diet; maintain fluid and electrolyte bal-ance. Hemodialysis is indicated in anuria. Epinephrine is contraindicated (ventricular fibrillation).
Copper	Albumin Magnesium Oxide (as for acid)
Detergents, Cationic (Chlorides, iodides, etc.)	Soap (Castile, etc.) dissolved in 4 times its bulk of hot water.
Detergents, Anionic (Na, K, NH4 salts)	Milk or Water followed by demulcent (oils, acacia; gelatin, starch, egg white, etc.)
Fluoride*	Calcium (milk, lime water or powdered chalk mixed with water) given orally.
Formaldehyde	Ammonia Water (9.2% orally) or Ammonium Acetate (1% for lavage). Starch: 1 part to 15 parts hot water added gradually. Gelatin soaked in water for ½ hour. Sodium Thiosulfate (as for arsenic).
Iron*	Sodium Bicarbonate: 1% for lavage. Deferoxamine as 5% solution given orally (0.5-1.5 Gm. for dogs).
Lead*	Sodium or Magnesium Sulfate given orally (500-1000 Gm. for large animals). Sodium Ferroxyahide Tannic Acid (as for alkaloids). Albumin
Mercury*	Protein: milk, egg whites Magnesium Oxide (as for acid). Sodium Formaldehyde Sulfoxylate: 5% solu-tion for lavage. Activated Charcoal Large Animals ..... 250-500 Gm.
Oak (Shin Oak)	Hydrated Lime (calcium hydroxide) fed pro-phylactically; formula: 1080 lb cotton-seed meal, 600 lb dehydrated alfalfa, 120 lb vegetable oil, 200 lb hydrated lime. Feed 4 lb/day. Note: Treatment is not affective for kidney damage.
Oxalic Acid*	Calcium: Calcium Hydroxide as 0.15% solution. Other alkalies are contraindicated because their salts are more soluble. Chalk or other calcium salts. Magnesium Sulfate as cathartic. Maintain diuresis to prevent calcium oxalate deposition in kidney.
Petroleum Distillates (aliphatic hydrocarbons)	Olive Oil or other Vegetable Oil given orally. After ½ hour, Magnesium Sulfate as cathartic.
Phenol and Cresols	Soap-and-Water or Alcohol lavage of skin. Sodium Bicarbonate (0.5%) dressings. Activated Charcoal and/or Mineral Oil given orally.
Phosphorus	Copper Sulfate (0.2-0.4% solution) or Potassium Permanganate (1:5000 solution for lavage). Turpentine (preferably old oxidized) in gela-tin capsules or floated on hot water. small animals, give 2 ml. four times at 15 min. intervals. Potassium Permanganate Activated Charcoal Do not give vegetable oil cathartic. Removal all fat from diet.
Silver Nitrate	Normal Saline for lavage. Albumin
Urea*	Acetic Acid (5% solution in 20% glucose) given orally. For large animals, given 1-4 liters. Vinegar diluted!!! May be used for large cows. Give 1 gallon orally and repeat in 1-2 hours.
Unknown	Activated Charcoal (replaces universal antidote) Large Animals - 0.25 to 0.5 kg per head. ..... In case of chlorinated hydrocarbon intoxi-cation, give up to 1 kg/head/day. Follow by cathartic and repeat charcoal dosage.

* Systemic antidote also available. (See Table 2).