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PHARMACOLOGICAL REVIEW OF CHEMICALS USED FOR THE CAPTURE OF ANIMALS

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ABSTRACT: A review of the literature reveals that over 60 chemicals have been used for the capture of wild animals, but only 30 of the most widely used chemicals are discussed in the present paper. For practical considerations these chemicals can be classified as being either (l) neuromuscular blocking agents, or (2) central nervous system (CNS) depressants. Some common neuromuscular blocking agents are d-tubocurarine, gallamine, succiny1choline, and nicotine. M99 and its derivatives, phencyclidine, and xylazine are some of the more commonly used CNS depressants. Neuromuscular blocking agents have a relatively rapid onset and short duration of action but they do not possess sedative, analgesic, or anesthetic properties. CNS depressants do produce desirable sedative, analgesic, and anesthetic effects, and frequently a combination of CNS depressants results in more desirable immobilization characteristics.

INTRODUCTION

It is beyond the scope of this paper to give a comprehensive review of the pharmacology of all chemicals used for the capture of animals. Only the more widely used chemicals are presented and discussions on the sites and mechanisms by which these chemicals manifest their effects have not been stressed. The textbook by Goodman and Gilman (1975) gives a thorough pharmacological evaluation for most of the chemicals. Harthoorn (1965) discusses application of chemicals in wildlife management programs, and an annotated bibliography, with 150 references, summarizes the use of chemicals to immobilize mammals (Denny and Gill, 1970). Although the present paper primarily emphasizes chemicals to capture mammals, the reader interested in avian species is referred to the publication by Schafer and Cunningham (1972).

Before 1960, neuromuscular blocking agents were the chemicals most commonly used. Generally speaking, the neuromuscular blocking agents are potent in many animals but they have less desirable immobilizing characteristics than the central nervous system depressants that were developed in the 1960's.

NEUROMUSCULAR BLOCKING AGENTS

The neuromuscular junction is a specialized anatomical area where a nerve fiber supplies a skeletal muscle fiber. At this junction, a nerve impulse liberates acetylcholine from the nerve terminal. Acetylcholine combines with receptor substances in the muscle membrane to initiate a chain of electrical events which lead to muscle contraction (Ganong, 1963). The mechanism of action of drugs at the neuromuscular junction is described as being either (a) competitive or nondepolarizing, or (b) depolarizing. Competitive or nondepolarizing neuromuscular blocking agents prevent acetylcholine from coming in contact with the receptor sites in the muscle membrane. Without the availability of acetylcholine, skeletal muscle contractions cease to function. Depolarizing blocking agents act like acetylcholine and produce a persistent depolarization at the neuromuscular junction. Initially, depolarizing blocking agents produce visible muscle fasciculations throughout the body before paralysis develops. In contrast, competitive blocking agents do not produce this effect.

Competitive or Nondepolarizing Agents

d-Tubocurarine

Centuries before the use of chemicals in wildlife management programs, Indians of South America used poisoned arrows to kill animals for food. The poison was called curare which is a generic term that applies to many poisonous plant extracts. Curare is obtained from species of Strychnos and Chondodedron and crude preparations contain several closely related chemicals that have similar pharmacological effects (Mclntyre, 1972). One of the active ingredients in curare is d-tubocurarine which has been structurally identified

*Use of trade names in this publication does not imply endorsement of commercial products by the Federal Government.

(Everett et al., 1970). Although d-tubocurarine has not been used extensively to capture animals in recent times, some aspects of its pharmacology will be discussed because it serves as the prototype by which other neuromuscular blocking agents are evaluated.

There is a sequential characteristic order of flaccid muscle paralysis in animals poisoned by d-tubocurarine and other competitive blocking agents (Koelle, 1975). Small, short, rapidly moving muscles of the eyes, ears, toes and fingers are affected first. Muscles of the limbs, neck, and trunk then become paralyzed. Next, the intercostal muscles and finally the diaphragm become affected. Death is caused by peripheral respiratory paralysis and mild terminal asphyxial convulsions may occur. In doses that produce complete muscle paralysis, d-tubocurarine does not have any significant central nervous system stimulant, depressant, or analgesic effects (Smith et_al_., 1947). d-tubocurarine causes the release of histamine which results in hypotension, bronchospasm, and excessive salivary and bronchial secretions.

Gallamine Triethiodide

Gallamine triethiodide is a synthetic chemical that acts in a manner similar to d-tubocurarine at the neuromuscular junction. There are fewer side effects with a paralyzing dose of gallamine than with a paralyzing dose of d-tubocurarine (Mushin et_al., 1949). Gallamine does not produce ganglionic blockade nor hypotension. Its duration of action is reported to be shorter than that of d-tubocurarine (Post, 1959).

Depolarizing Agents

Succinylcholine

Succiny1choline is an important blocking agent of the depolarizing type and has been widely used for the capture of wild animals. It is a synthetic chemical and may be described as consisting of two molecules of acetylcholine linked together. One advantage of succiny1choline is a rapid onset of action and short duration. However, there is no effective antidote and there is a narrow safety margin between doses that produce immobilization and those that produce respiratory paralysis.

The short duration of action of succinylcholine is due to its rapid metabolism by pseudocholinesterase found in the liver and plasma. The initial metabolic product, succinylmonocholine, is further metabolized to succinic acid and choline. Succinylmonocholine has a weak neuromuscular blocking action. Succinylmonocholine, succinic acid, and choline can decrease the rate of destruction of succiny1choline by pseudocholinesterase. Genetic factors, liver damage or changes in nutritional states may reduce the synthesis of pseudocholinesterase. Under these conditions, the action of succinylcholine may be prolonged (Chagas et_ al_., 1972).

Nicotine

From a pharmacological standpoint nicotine is classified as a ganglionic stimulating agent (Voile and Koelle, 1975), but in the doses employed for the capture of wild animals it causes neuromuscular blockade which produces a cataleptoid ("waxy rigidity" of the muscles) or flaccid state of muscular paralysis. It first stimulates, and at higher doses blocks the action of autonomic ganglia. As a result of this dual action, nicotine has varied and widespread effects in the body. Major side effects include salivation, nausea, emesis, disturbed vision and hearing, and mental confusion. Its action on the central nervous system results in tremors and convulsions. Death results from respiratory failure due to both central nervous system and respiratory muscle paralysis.

In 14 species of animals tested intramuscularly, the safety factor between effective and lethal doses ranged from 1.5 (rat and monkey) to 3.3 (dog) (Feurt et al_., 1958). Transitory excitement preceded muscular paralysis in white-tailed deer (0docoileus virginianus) and the animals became immobilized in 2.5 to 15 minutes after receiving 200-300 mg nicotine salicylate intrasmuscularly (Crockford et_ al_., 1957). Recovery time ranged from 15 to 60 minutes.

CENTRAL NERVOUS SYSTEM DEPRESSANTS

Central nervous system (CNS) depressants can produce effective sedative, analgesic, narcotic, and anesthetic properties which are highly desirable characteristics for the

capture, restraint, and treatment of animals. These chemicals can produce signs and symptoms ranging from "taming" behavior to psychomotor stimulation and convulsions, sometimes within a single species. A particular effect depends upon the chemical, dose, and species of animal. In general, the CNS depressants are safer to use than the neuromuscular blocking agents because: (1) they exhibit a greater safety margin, and (2) many of the CNS depressants have effective antidotes that reverse the immobilized condition within a matter of minutes.

Site and mode of action of the CNS depressants are extremely complex. The majority of CNS depressants can be more conveniently classified according to chemical class, rather than by mode of action as is true of the neuromuscular blocking agents.

Barbiturates

A wide range of desirable applications including sedation, hypnosis, anticonvulsant activity, and anesthesia can be obtained from chemicals known as barbiturates. Barbiturates reversibly depress many cellular functions and are known as general depressants. They depress the activity of cardiac, smooth, and skeletal muscles, nerves, and the brain. Experimental evidence indicates that the reticular activating system located in the brain stem is a primary site of action of barbiturates (Rosner and Clark, 1973). The cause of death in acute barbiturate poisoning is cessation of respiration. Barbiturates have a curare-like effect at the neuromuscular junction and can enhance the neuromuscular blocking effects of d-tubocurarine (Thesleff, 1956).

Barbiturates alone are not considered to be effective intramuscular immobilizing agents because of prolonged induction times (up to 1-1/2 hours). Intramuscular injections of thiopental of up to 200 mg/kg in northern fur seals (Callorhinus ursinus) produced only slight ataxia after 30 minutes (Peterson, 1965). Thiopental, hexobarbital, and pento-barbital produced anesthesia within 5 minutes when administered intravenously to white-tailed deer (Severinghous, 1950; Piperno, 1965). Intraperitoneal injections of pento-barbital have been used to anesthetize trapped black bear (Ursus americanus)(Erickson, 1957).

Gaseous Anesthetics - Ether and Chloroform

Effective use of gaseous anesthetics can only be achieved when they are administered in a closed environment. Black bear caught in a culvert-type trap have been anesthetized by applying ether to the confines of the trap. Bear caught in steel traps have been anesthetized by administering ether through a cone placed over the muzzle (Erickson, 1957)-Black et al. (1959) have used chloroform to anesthetize black bear.

Ether has a curare-like action at the neuromuscular junction and can potentiate neuromuscular blocking agents. Marked salivation occurs during the induction and recovery phases of ether anesthesia.

Xylazine

Xylazine, first synthesized in 1962, produces sedation, analgesia, and muscular relaxation (Chemagro Corporation, 1970). Bauditz (1972) has made a comprehensive review on the use of xylazine in captive and free-ranging wild animals. In the majority of mammals, xylazine has pronounced sedative and muscle relaxant properties, accompanied by good analgesia and immobilization, with minimal excitement. Xylazine has at least an 8-fold safety margin in captive white-tailed deer (Roughton, 1975). His data also indicate that highly stressed deer are more quickly immobilized than unstressed deer. With intramuscular doses ranging from 0.89 to 8.0 mg/kg, induction times ranged from 1 to 22.5 minutes. Immobilization times ranged from 22 to 466 minutes. Only transitory, minimal side effects such as increased heart rate and panting were noted. Regurgitation did not occur.

The Arylcycloalkylamines

The better known chemicals in this class are phencyclidine, ketamine, tiletamine, and CI-744 (a mixture of tiletamine and zolazepam). These chemical analogs produce a cateleptoid condition in animals characterized by "waxy rigidity" of the muscles so that animals tend to remain in any position in which they are placed. They also produce marked analgesic and anesthetic effects without the loss of protective reflexes such as coughing and swallowing. Some side effects of these chemicals include salivation, hyperthermia, excitement, and convulsions. The use of these chemicals, complete with dosage charts, for several animal species has been reviewed by Beck (1972).

Phencyclidine

Gross behavior of animals given phencyclidine varies considerably among species. Mice and rats exhibit excitatory symptoms. In dogs, cats, and monkeys, sedation is evident at lower doses, while convulsions may be precipitated at higher doses (Domino, 1964). The majority of the common adverse effects (hypertonicity of the muscles, hyperthermia, salivation) of phencyclidine can be successfully eliminated by combination with other CNS depressants.

The benefits of phencyclidine combined with promazine have been reported in a number of species of animals (Seal and Erickson, 1969). Harthoorn (1962, 1963) has used phencyclidine in combination with morphine or diethy1thiambutene, and hyoscine (scopolamine). This combination produced a large increase in the margin of safety and better immobilization characteristics in elephant, rhinoceros, hippopotamus, giraffe, and buffalo.

Ketamine

Ketamine differs from phencyclidine in that it is weaker in potency (amount of chemical to obtain a desired effect), has a faster onset and shorter duration of action, and a lower incidence of convulsant activity (Chen et al., 1966).

Tiletamine

In general, the potency, onset and duration of action, and convulsant activity of tiletamine is intermediate between that of phencyclidine and ketamine. Like phencyclidine, it produces good anesthesia in primates and the domestic cat (Chen et_ al_., 1969).

CI-744

CI-744 is the code number of a compound that contains a 1:1 combination of tiletamine hydrochloride and zolazepam. Tiletamine is classified as a cataleptoid anesthetic with marked central nervous system depressant properties. When used by itself, tiletamine produces a high incidence of convulsions in cats and dogs. However, zolazepam has anticonvulsant and antianxiety properties and when used in conjunction with tiletamine, convulsions are eliminated. In fact, the two chemicals potentiate one another and the resultant effect is better muscle relaxation and anesthesia (Parke-Davis and Company, 1974).

The Dithienylalkenylamines

Several chemicals in this class which have analgesic potencies comparable to that of morphine have been synthesized (Adamson, 1950).

Thiambutene

In dogs, thiambutene produces mild sedation, analgesia, and narcosis (Owen, 1955)- Nalorphine is an effective antidote. Thiambutene has had only limited application in capturing wild animals because of the large amount required to be effective and slow onset of action. A combination of thiambutene, phencyclidine, and scopolamine has been used in four topi (Damaliscus korrigum) and two hippopotami (Hippopotamus amphibus). Usually it required at least 30 minutes for the animals to become immobilized. (Royal Veterinary College of East Africa Expedition, 1963).

Morphine and Its Derivatives

The immobilizing characteristics of these chemicals include stupor or insensibility, loss of fear and anxiety, and marked analgesia. Frequently, animals stand with heads drooped, and if they fall to the ground they lie in sternal recumbency. These chemicals have a wide safety margin and severe side effects *are* minimal. Effective antagonists are available which quickly reverse the immobilization effects. Overdoses produce respiratory depression which is the cause of death.

Morphine

Morphine is a natural chemical obtained from opium, which is the dried juice of the poppy plant, Papaver somniferum. The chemical structure of morphine was established in 1925 and since that time many derivatives have been synthesized. By itself, morphine has been used to only a limited extent. It is more effective when used in conjunction with

other chemicals, such as phencyclidine. Morphine potentiates the analgesic activity of phencyclidine and renders an animal more tractable. Effective immobilization of an animal by morphine and phencyclidine can be partially antagonized by administering nalorphine (Harthoorn, 1962; 1963).

M99-Etorphine

Several morphine derivatives with analgesic activities ranging up to 10,000 times greater than morphine have been described by Bentley and Hardy (1963); and Bentley et al. (1965). One of these chemicals, etorphine, has been used extensively for capturing animals (Harthoorn and Bligh, 1965; Wallach, 1966; Woolf, 1970; Al ford et al., 1974; Roussel and Patenaude, 1975). The effective immobilization potency of etorphine is reported to be about 1,000 times that of morphine (Harthoorn, 1966). Underdoses of etorphine are more stressful to animals than overdoses because they cause hyperexcitabi1ity and struggling. Promazine has been used to reduce the struggling in white-tailed deer, but the combination of etorphine with other CNS depressants is generally not considered necessary (Woolf, 1970; Alford et al., 1974.)

Nalorphine, cyprenorphine (M285), and diprenorphine (M50-50) are effective antidotes to the narcotic effects of etorphine. Diprenorphine is the most potent of the three and results in less residual central nervous system depression (King and Klingel, 1965; Alford et al., 1974).

The Phenothiazines

When used alone, phenothiazine derivatives such as chlorpromazine, promazine, and acetylpromazine are not effective immobi1izing agents because they have a slow onset of action and prolonged recovery periods. They are best used in combination with other CNS depressants to produce potentiation of more desirable immobilizing characteristics. They are effective sedatives and can be used to transport animals. These phenothiazines do not have analgesic properties. Hypotension and hypothermia are common side effects.

The Benzodiazepines

These chemicals can produce a "taming" effect in animals, but like the phenothiazines, they have limited application and are usually combined with other CNS depressants to achieve desirable immobilization characteristics. As already stated, zolazepam is combined with tiletamine to reduce the incidence of convulsions in cats and dogs.

In feeding studies with penned cowbirds (Molothrus ater) and coturnix quail (Coturnix coturnix), chlordiazepoxide was somewhat more effective than sodium pentobarbital in producing narcosis (Peek, 1966). Diazepam incorporated into a tab and fastened to jaws of a steel trap, produces sedation in trapped animals when they chew the tab. Foot damage is reduced and animals can be removed from the trap more easily (Balser, 1965).

Miscellaneous CNS Agents

Tribromoethanol and Alpha-chloralose

Tribromoethanol is a hypnotic drug that produces anesthesia. It has been used for the capture of wild turkeys (Meleagris gallopava) (Evans et al., 1975). Successful capture ranged from 50% to 92% with a mortality rate of 0% to 22% for the dosages employed. Alpha-chloralose is another hypnotic drug which can produce long periods of anesthesia. It has also been used for the capture of wild turkeys (Williams, 1966) and Canada geese (Branta canadensis) (Crider and McDaniel, 1967).

Atropine and Scopolamine

Both atropine and scopolamine are anticholinergic drugs and are used frequently to antagonize side effects of salivation and cardiovascular disturbances such as decreased heart rate and low blood pressure. Scopolamine has a more sedative effect than atropine. Combination of scopolamine with a morphine narcotic produces less respiratory depression than does the morphine narcotic by itself.

SUMMARY

Several major advances have been made in the use of chemicals for the capture of wildlife. These include mechanical improvements in delivery systems such as the projectile syringe (Crockford et. al., 1958), and the development of potent, relatively safe chemicals that can be used in a variety of species. From the time when only a few neuromuscular blocking agents were of practical use, many central nervous system drugs have come into widespread application. The centrally acting drugs are the chemicals of choice in most situations. Mortality rates from the use of neuromuscular blocking agents range from 10 to 20% whereas the mortality rate with the centrally acting drugs is less than 3%.

Many of the CNS drugs are regulated by the Drug Enforcement Administration (DEA), U.S. Department of Justice, and investigators are required by law to have a DEA registration number for their possession. Authorization and clearance from the Food and Drug Administration, U.S. Department of Health, Education, and Welfare is highly recommended for the use of any drug, especially if the target animal is likely to become a source of food for humans.

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