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**Long Acting Neuroleptic Drugs** (15-Mar-2002)

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The term "long-acting neuroleptic" is used to describe a member of a group of tranquilizers that has been used in wildlife over the past 20 years. Tranquilizers comprise one of many groups of pharmacologically active agents that have their primary effect by modulating neurotransmitter activity within the central nervous system [1]. There are five main neurotransmitters that are involved in behavior modification: acetylcholine, dopamine, norepinephrine, serotonin, and γ-aminobutyric acid (GABA). Tranquilizers, also referred to as neuroleptics, act as antipsychotics through their action as dopamine antagonists.

**Tranquilizers**

The antipsychotic action of dopamine antagonists is achieved by blocking dopamine receptors and increasing turnover of dopamine in the limbic system of the brain, producing a state of "ataxia" or behavioral quieting that is characterized by decreased emotional reactivity and aggression, and relative indifference to stressful situations [1-3]. Tranquilizers do not cause profound cortical depression (unconsciousness), but will suppress spontaneous movements while sparing spinal reflexes and unconditioned pain reflexes [1,4]. These drugs are used in people as antipsychotics, and are used primarily for the treatment of acute psychoses such as schizophrenia. Typically, these agents work best for treatment of conditions that manifest with episodes of hallucinations, delusion, agitation, and unresponsive behavior [1].

Tranquilizers can be categorized according to their potency (minor or major, based on the incidence of side-effects), structural similarities (phenothiazine, benzodiazepine, or butyrophenone), and duration of action (short-acting or long-acting). Minor phenothiazine tranquilizers are familiar to most practitioners and include the agents (i.e., promazine, acepromazine) that have historically been used for sedation and anesthesia in domestic species. Typically, the minor tranquilizers produce a greater degree of sedation, while having a higher incidence of anticholinergic and cardiovascular side-effects, and fewer extrapyramidal side-effects [1]. Major tranquilizers produce less sedation and fewer anticholinergic effects, but have a higher incidence of extrapyramidal side-effects [1].

All long-acting neuroleptics used in wildlife are phenothiazine derivatives and share structural similarities to the prototypical antipsychotic, chlorpromazine. In addition, all are classified as major tranquilizers based on their side-effect profiles [1,4]. The different neuroleptics that have been evaluated in animals have all been developed for use in people and are not licensed for veterinary use. These formulations were developed with the specific goal of achieving prolonged tranquilization of the patient, without the need for frequent, repeated injections that would be required with the traditional agents [5]. Prolonged duration of drug action can be accomplished through several mechanisms, including: slow release of active drug from the site of injection, slow absorption of active drug or metabolite(s) into the blood, slow metabolism of active drug once absorbed, or slow elimination of the active drug or metabolite(s) from the body [4,5]. The challenge of achieving prolonged duration of effect has been met with these agents by creating a fatty acid ester of the active drug ingredient, and then dissolving this entity in a vegetable or medicinal oil [5-7]. When this formulation is injected intramuscularly, it forms a depot at the site of injection. With the slow breakdown of the oil solvent, the ester diffuses out of the depot into muscle. Once absorbed into the blood, the ester is then hydrolyzed and the active ingredient is able to exert its clinical effect. They are all metabolized in the liver, and their metabolites are excreted in the feces.

**Side-Effects**

There are several important side effects that can occur with the use of long-acting neuroleptics. As mentioned, these agents act primarily as antipsychotics by blocking dopamine receptors in the limbic system [1,4]. As expected, it is often difficult to titrate an injectable agent to effect, and excessive blockade of dopamine receptors in the basal ganglia can result in extrapyramidal signs, and hormonal side-effects may result from excessive blockade in the hypothalamus [4]. In people, oral formulations are often used to establish tolerance and to determine individual responses prior to the depot injection being
given [1]. In wildlife, this is rarely possible, and the injectable neuroleptic is frequently given when the animal is first handled. As a result, the potential for side-effects in animals is greater, and it is important to understand how the side-effects can manifest, how to recognize them, and how to treat them if they do occur.

As members of the phenothiazine family of tranquilizers, all neuroleptics have the potential to cause mild anticholinergic effects, peripheral alpha-adrenergic receptor blockade, and to impair thermoregulation [4]. They may also interfere with several hormones, including increasing prolactin secretion, and inhibiting luteinizing hormone, anti-diuretic hormone and oxytocin secretion [4]. Fortunately, these effects are considered to be less of a risk with major tranquilizers, and are therefore less likely to occur with use of the long-acting neuroleptics [1].

Extra-pyramidal signs (EPS) encompass a large group of clinical manifestations of overdose or individual sensitivity to a drug. They are believed to occur when there is excessive dopamine blockade in the basal ganglia [2,4]. EPS occur commonly in people being treated with long-acting neuroleptics, and have been observed and reported in animals. There are three main categories of EPS: pseudoparkinsonism, dystonic reactions, and akathisia [1]. Parkinsonism is characterized by motor stiffness, difficulty initiating movements, shuffling, stiff gait, resting tremors, and reduced facial movements. Dystonic reactions are acute, involuntary spasms of the muscles of the face (eyes, tongue) and back, manifesting as eye rolling, tongue protrusion and opisthotonus. Akathisia is motor restlessness and manifests as pacing, rocking, and generalized agitation. Prolonged EPS may result in the animal losing condition from inappetance and exhausting itself from pacing, and disturbance of other animals in the group [7].

EPS have been reported with the use of long-acting neuroleptics in wildlife and domestic species [2,3,8-10]. Mild EPS in animals include continuous licking and chewing of objects [8,10] while severe signs include restlessness, circling, recumbency, paddling, and altered levels of consciousness [2,3,9]. EPS have been found to manifest in wildlife when animals that were already tranquillized were further stressed with hyperthermia, sudden loud noises, and increases in activity associated with transportation [8].

Treatment of EPS in animals is generally symptomatic. Several drugs have been used in attempt to limit the excitatory signs that are seen, including sedatives such as xylazine, butorphanol and acepromazine, as well as anticonvulsants such as diazepam and the barbiturates [2,3]. Short-term relief (< 2 hours) of EPS can be achieved with these agents, but with variable success. In people, EPS are treated with antiparkinsonian drugs such as diphenhydramine and benztrapine [1,2]. It is thought that the EPS may be the result of an imbalance between dopamine and acetylcholine in the striatum, and that diphenhydramine acts to restore this balance [3]. In the one successful reported treatment of EPS in a horse, 0.7mg/kg diphenhydramine IV resulted in resolution of signs within 3 minutes, and lasted 18 hours [3]. One additional dose was required at 18 hours when EPS returned, and no further doses were necessary. Continued efforts should be made to report successful treatments of EPS in wildlife, since the available literature is lacking this important information.

**Use of Long-Acting Neuroleptics in Wildlife**

Long-acting neuroleptics were initially evaluated for use during translocation of wildlife in southern Africa in the 1980’s [5]. Several excellent references are available, which review the initial findings and the rational behind the investigational use of these drugs during wildlife translocations [4,5,7]. Briefly, with the increased capture and handling involved in conservation and game-farming efforts in southern Africa during this time, it quickly became apparent that there was a need to improve management during the translocation of large numbers of animals [11]. Captured and confined animals showed high degrees of excitement and stress, and frequently injured themselves or others in the group during struggle or when attempting to escape [6-8,12,13]. Further, the inability to adapt to confinement often resulted in exhaustion from constant pacing and marked loss of condition due to refusal to eat and drink resulting from unfamiliar food and water delivery systems [7,14]. Mortalities were extremely high in some cases (> 50 - 60%) [5].

Clearly, there was a need to suppress the alarm reaction, to reduce the effects of psychological stress and physical exertion, and to facilitate handling and translocation [8]. Since long-acting neuroleptics were used in people to reduce emotional reactivity, aggression, and spontaneous motor activity, and to create relative indifference to stressful situations, it was hypothesized that they might cause these same effects in wildlife. Shorter acting tranquilizers such as acepromazine, chlorpromazine, and azaperone were already being used as tranquilizers and as adjuncts to chemical immobilization, and although they were found to be useful in aggressive and anxious animals, the desired effects only lasted a few hours [6,11]. It was hoped that the longer-acting formulations of these compounds could also be used effectively during translocation operations.
In the literature, there are differing definitions of "long-acting" as pertains to these drugs. Some authors use this term to
describe formulations that provide effects for at least 3 days [7], while others limit use of the term to describe only agents
where a single dose will give effects for greater than a week [4]. Irrespective of the definition used, there are neuroleptics
available for use in wildlife that will produce a duration of effect ranging from 3 to 30 days, depending on the active drug, the
structure of the ester, and the type of oil base [4].

The Drugs - Long-Acting Neuroleptics
Zuclopenthixol - This is a thioxanthine derivative, and shares general properties with the other phenothiazines [4]. There are
two formulations of zuclopenthixol that have been used in wildlife, the shorter-acting acetate ester, and the longer-acting
decanoate ester. As with other long-acting neuroleptics, dissolution in an oil delays absorption of drug from the site of
injection, and esterification delays metabolism and release of the active component [4]. This drug must be administered
intramuscular (IM), and never intravenous. Zuclopenthixol acetate causes a nonspecific sedation within a few hours of
administration, and its effects last three to four days. The decanoate ester requires several days for onset, but its clinical
effects last up to three weeks [4]. Zuclopenthixol acetate can be used alone for short duration tranquilization, or it can be used
in combination with longer-acting agents to provide "loading" effects prior to the clinical onset of the slower-acting agent [4].

Zuclopenthixol acetate has been used successfully in a variety of species of wildlife. Several authors have examined both
subjective and objective effects of this drug, in attempt to describe its usefulness. Its effects have been recently evaluated in
red deer [15], bison [16], Nile lechwe [17], wapiti [18], and white-tailed deer [10], in addition to numerous historical
references. It has been used alone [17,18] and in combination with other tranquilizers such as azaperone [10,16] and
perphenazine [15]. In all cases, clinical effects were observed within a few hours, and lasted 3 - 4 days. In three studies
[15,17,18], treated animals were administered the drug and were compared to controls when challenged with different
degrees of stressors including proximity to people and handling for blood collection. In all cases, treated animals were easier
to handle and manipulate, their flight distances were reduced, and they appeared subjectively less stressed during and after
handling. Treated animals were observed to spend more time eating, drinking and performing normal behaviors than were the
controls in each study. Treated animals spent more time lying down and less time pacing. Objective measures of stress such as
heart rate, temperature, and blood parameters were more variable, but tended to suggest less stress in the treated animals
than in controls. No side effects of the drug were observed in any of the animals in these studies, given a dose of 1 mg/kg IM
[15,17,18], however extrapyramidal signs have been reported to occur early in treatment or at higher doses [4]. In one report
[10], apparent extrapyramidal signs were observed in two white-tailed deer, manifesting as continuous self-grooming and
facial movements. These animals had been administered an estimated dose of 1mg/kg IM 24 hours previously. The signs
resolved without treatment with no ill-effects to the animals.

Zuclopenthixol acetate is an excellent short-term tranquilizer for repeated handling or captivity over 3 - 4 days. Its use allows
animals to acclimate to new surroundings, and it is very effective for "taming" animals prior to handling. It has also been
reported to remove the "background" stress associated with handling, allowing assessment of two analgesic techniques for
antler removal in wapiti [19]. In this report, by minimizing the physiologic alterations from the stress of handling, the
investigators were better able to differentiate two analgesic methods by measuring the changes in heart rate and direct blood
pressure that resulted from a painful stimulus.

Perphenazine enanthate - This is a phenothiazine derivative dissolved in a sesame oil vehicle. The onset of action is slow,
taking 12 - 16 hours in some cases. Peak effects are reached at three days, and clinical effects may last 7 - 10 days [4,6]. As
with other long-acting neuroleptics, perphenazine must be administered IM.

Use of perphenazine has been reported in several species, including impala [6,14,20], red deer [15], and equids such as
domestic horses [9], and Przewalski’s horses [21]. Flight distance was reduced in the red deer and impala, and animals were
subjectively easier to handle [6,14,15]. Treated animals also spent more time eating, and were able to maintain better body
condition than controls [6,15]. In the case of the Przewalski’s horses, perphenazine was used as part of a protocol to establish
a bachelor herd of mature males [21]. Usually an aggressive species when new animals are mixed, the animals showed
minimal excitement and aggression while establishing a dominance hierarchy over a week, resulting in no significant injury
to any of the individuals.

Pipothiazine palmitate - This is also a phenothiazine derivative dissolved in a sesame oil, and must be administered IM. It is
reported to have action similar to perphenazine. It has a markedly delayed onset of up to three days, and a prolonged duration
of two to four weeks [4].
Although its use in wildlife has been described in a variety of references [4,5,7], it has only been critically evaluated in impala [6,14], cane rats [22], and wallabies [23]. Impala showed decreased flight distance and were easier to handle. Wallabies and cane rats demonstrated marked decreases in stress-related behaviors during handling, and clinical effects lasted two to four weeks in both cases. Higher doses were used in these studies than are required in hoofstock, however these doses were determined through pilot-studies in both of these species as those that were required to produce a clinical effect. No extra-pyramidal side-effects were observed in any of these studies, although appetite suppression has been reported in a group of impala after administration of pipothiazine [14].

Treatment of EPS in animals is generally symptomatic. Several drugs have been used in attempt to limit the excitatory signs that are seen, including sedatives such as xylazine, butorphanol and acepromazine, as well as anticonvulsants such as diazepam and the barbiturates [2,3]. Short-term relief (< 2 hours) of EPS can be achieved with these agents, but with variable success. In people, EPS are treated with antiparkinsonian drugs such as diphenhydramine and benztropine [1,2]. It is thought that the EPS may be the result of an imbalance between dopamine and acetylcholine in the striatum, and that diphenhydramine acts to restore this balance [3]. In the one successful reported treatment of EPS in a horse, 0.7mg/kg diphenhydramine IV resulted in resolution of signs within 3 minutes, and lasted 18 hours [3]. One additional dose was required at 18 hours when EPS returned, and no further doses were necessary. Continued efforts should be made to report successful treatments of EPS in wildlife, since the available literature is lacking this important information.

### Table 1. Characteristics of Long-Acting Neuroleptics

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Trade Name</th>
<th>Time to Initial Effect</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zuclopenthixol acetate</td>
<td>Clopixol-Acuphase</td>
<td>1 hr</td>
<td>3 - 4 days</td>
</tr>
<tr>
<td>Zuclopenthixol decanoate</td>
<td>Clopixol</td>
<td>1 wk</td>
<td>10 - 21 days</td>
</tr>
<tr>
<td>Perphenazine enanthate</td>
<td>Trilafon-LA</td>
<td>12 - 16 hr</td>
<td>7 - 10 days</td>
</tr>
<tr>
<td>Pipothiazine palmitate</td>
<td>Piportil</td>
<td>3 days</td>
<td>2 - 4 weeks</td>
</tr>
</tbody>
</table>

### Table 2. Reported Use of Long-Acting Neuroleptics in Wildlife

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Trade Name</th>
<th>Route of Administration</th>
<th>Doses Reported (mg/kg)</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zuclopenthixol acetate</td>
<td>Clopixol-Acuphase</td>
<td>IM</td>
<td>0.6</td>
<td>- wood bison [16] - red deer[15], Nile lechwe[17], wapiti[10], white-tailed deer[18]</td>
</tr>
<tr>
<td>Zuclopenthixol decanoate</td>
<td>Clopixol</td>
<td>IM</td>
<td>10</td>
<td>- red-necked wallabies[23]</td>
</tr>
<tr>
<td>Pipothiazine palmitate</td>
<td>Piportil</td>
<td>IM</td>
<td>4 - 4.5 10 25</td>
<td>- impala[6,14] - red-necked wallabies[23] - cane rats[22]</td>
</tr>
</tbody>
</table>

### The Drugs - Short-Acting Neuroleptics

There are two drugs that have been successfully used to provide shorter-term tranquilization in wildlife. **Azaperone** - This is a member of the butyrophenone family of tranquilizers, and has been found to be useful in cases requiring fast onset and a short duration of clinical effect. Azaperone has been found to be very useful on its own for short-term tranquilization for transportation, and minimally interferes with thermoregulation compared to the phenothiazines [7]. This agent may be administered intravenous or intramuscular, and it has been used in combination with immobilizing agents to facilitate chemical capture [10]. One added benefit of using it in this way, is that not only does it assist in immobilizing the animal initially, but it maintains its tranquilizing effects after the other immobilizing agent has worn off or been antagonized. Azaperone can also be used in combination with other, longer-acting agents to "load" the initial effects while the longer-acting agent begins to be absorbed and hydrolyzed [4,10,16].
Haloperidol - This is also a member of the butyrophenone tranquilizers. As with other drugs in this group, haloperidol does not cause significant hypotension through peripheral alpha-adrenergic blockade, and it does not cause hypothermia [8]. It has a similar onset time to azaperone, but its duration of action is prolonged (the longest of any clinically used butyrophenones). Given intravenous or intramuscular, haloperidol provides beneficial tranquilization for up to 10 - 12 hours [8].

Haloperidol has been used successfully in a number of species. It appears to be most useful in small and medium sized antelope species, and its results can be variable in larger species such as Sable and roan antelope [8]. Some authors report that paradoxical excitement can be seen when higher doses are used in larger ungulates such as gemsbok, and that haloperidol is more useful in these species at lower doses [5,7]. During the initial research with this drug in wildlife, several animals did experience extra-pyramidal side-effects which were described as rare and transient [8]. These signs manifested when the animals were further stressed with hyperthermia, noise, and excitement during transportation. For this reason, careful management must still be used even after clinical effects of the drugs are seen.

Haloperidol is unique among the other tranquilizers in that it may also be administered orally. Two cases have been reported whereby bongo antelope and Przewalski’s horses were administered haloperidol in the feed prior to a stressor being applied [21,24]. The bongo could be approached and handled safely without struggle, and several male Przewalski’s horses were introduced into a new herd without aggression and serious injury. In the case of the bongo, animals received 1mg/kg orally every 24 hours for 28 days without complications [24]. Peak behavioral effects appeared 2 hours after feeding, while peak serum levels were attained at 10 hours. Clearly, this method of administration could be useful in a number of situations, and its use should be evaluated further in other species.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Time to Onset</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azaperone</td>
<td>&lt; 10 min IV</td>
<td>&lt; 6 hr</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>&lt; 5 min IV, 10 - 15 min IM</td>
<td>10 - 12 hr</td>
</tr>
</tbody>
</table>

### Table 3. Characteristics of Short-Acting Neuroleptics

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Trade Name</th>
<th>Time to Onset</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azaperone</td>
<td>Stresnil</td>
<td>&lt; 10 min IV</td>
<td>&lt; 6 hr</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Haldol</td>
<td>&lt; 5 min IV, 10 - 15 min IM</td>
<td>10 - 12 hr</td>
</tr>
</tbody>
</table>

### Table 4. Reported Use of Short-Acting Neuroleptics in Wildlife

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Trade Name</th>
<th>Route of Administration</th>
<th>Doses Reported (mg/kg)</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azaperone</td>
<td>Stresnil</td>
<td>IV or IM</td>
<td>0.3</td>
<td>- white-tailed deer[10]</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Haldol</td>
<td>oral</td>
<td>0.3</td>
<td>- Przewalski’s horse[21]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>- bongo antelope[24]</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Haldol</td>
<td>IV or IM</td>
<td>0.1 - 0.15</td>
<td>- Impala [6,8], tsessebe [8], blesbok [8]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.2 - 0.25</td>
<td>- kudu [8], springbok [8]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>.3 - 0.4</td>
<td>- zebra [8], sable [8], gemsbok[8]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.45</td>
<td>- duiker [8], steenbok [8]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.4 - 0.6</td>
<td>- dik dik [8]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.7 - 0.8</td>
<td>- hartebeest [8]</td>
</tr>
</tbody>
</table>

### Drug Availability in North America

In Canada, several of these drugs are available for off-label use in animals by veterinarians. Zuclopenthixol acetate, zuclopenthixol decanoate and pipothiazine palmitate are all available for mid- to long-duration tranquilization. Perphenazine enanthate is not available. Azaperone and haloperidol (injectable and oral formulations) are both available for shorter duration effects.

### Considerations

Long-acting neuroleptics have proven to be a valuable tool for use during wildlife management. Translocation operations frequently involve chemical capture, confinement, transport, relocation and adaptation to a new environment [5], and these are unnatural, traumatic, and stressful events in the lives of the animals. Ebedes [5,7] has reviewed the considerations that should be made prior to the use of these agents. First, these drugs may be used to facilitate wildlife management and should never be used as a substitute for poor handling practices. Every procedure should be conducted in a humane and efficient
manner with the use of appropriate equipment and trained personnel. The primary goal of every operation should be to minimize discomfort to the animals.

Second, prior to the use of long-acting neuroleptics, several decisions must be made [5]. Is there a need for tranquilizers? What is the desired speed of onset and duration of effect? Is there a discrete end point for the desired tranquilization (i.e., time of planned release from captivity)? Is there available information for the particular scenario (previous use in the species, doses known, side effects reported)? Are other aspects of the operation satisfactory? Based on the answers to these questions, specific agents can be selected for use, either alone or in combination.

After capture, the animals should be tranquilized as soon as possible. Each treated animal should be identified to prevent redosing, and risking overdose and side effects. Depending on the situation, it is usually only necessary to tranquilize the mature animals in a group, since their lack of activity will often calm the immature animals [7]. If this is not the case, all members of a group should be tranquilized. Tranquilized animals should never be mixed with untranquilized animals that might become hostile, aggressive and gain advantage over the tranquilized individuals [5,7].

Used correctly, long-acting neuroleptics have been found to be extremely effective for decreasing handling stress, anxiety, and motor activity in wildlife. They cause a general calming effect, loss of interest in surroundings and people, and reduce aggressive and dominant behavior within a group. Overall, their judicious use has contributed to captured wildlife adapting to captivity sooner, and they have been found to decrease mortality associated with wildlife translocation operations. As wildlife management continues to intensify in the coming years, we must strive to provide the best care for the animals in our keep. This mandate includes continuing to conduct controlled clinical research, and the thoughtful and timely reporting of the results, not only as pertains to long-acting neuroleptics, but to all aspects of wildlife management.

References


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