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**EVALUATION OF CARFENTANIL AND XYLAZINE FOR
IMMOBILIZATION OF WHITE-TAILED DEER**

A Thesis

Presented for the

Master of Science Degree

University of Tennessee, Knoxville

Bradley F. Miller

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DEDICATION

I dedicate this thesis to my father and grandfather, Al Miller and Edd Miller, for their roles in encouraging my love for the outdoors, and to my mother and stepmother, Brenda Hoskins and Susan Dowling-Miller for their encouragement and support, and to my wife April for her love and patience during my time in graduate school.

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ABSTRACT

From October 2001 until January 2002 captive wild white-tailed deer (*Odocoileus virginianus*) held at the University of Georgia Daniel B. Warnell School of Forest Resources Whitehall Deer Research Facility were immobilized with a combination of carfentanil (carfentanil citrate) and xylazine (xylazine hydrochloride) to 1) determine and evaluate an optimum and safe dose for carfentanil/xylazine in white-tailed deer and 2) compare immobilization parameters and physiological effects of carfentanil/xylazine to Telazol[®]/xylazine. Animals were given intramuscular injections of 10 mg of xylazine and one of four different levels of carfentanil 0.5, 1.0, 1.5, and 2.0 mg. A carfentanil dose of 1.2 mg (mean = 23.0 μ g/kg) and 10 mg xylazine (mean = 0.19 mg/kg) was selected to compare with a combination of 230 mg of Telazol[®] (mean = 4.41 mg/kg) and 120 mg xylazine (mean = 2.3 mg/kg) based on induction times and previously published reports. Time until first drug effects and time until deer dropped to the ground without rising were significantly longer in deer treated with carfentanil/xylazine than Telazol[®]/xylazine ($p < 0.01$). Hyperthermia was common in deer immobilized with carfentanil, but heart rate, respiration rate, and hemoglobin saturation were within acceptable levels. Quality of anesthesia of deer immobilized with Telazol[®]/xylazine was superior to deer immobilized with carfentanil/xylazine. The combination of 120 mg of naltrexone and 6.5 mg of yohimbine provided rapid and complete reversal (mean = 1.9 min.) of carfentanil/xylazine immobilization. Animals immobilized with

Telazol[®]/xylazine had long recovery times with occasional resedation after antagonism with 6.5 mg of yohimbine. The combination of carfentanil and xylazine at the doses tested did not provide reliable induction or immobilization of white-tailed deer even though drug reversal was rapid and safe using naltrexone and yohimbine.

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CHAPTER 1

INTRODUCTION, JUSTIFICATION, AND OBJECTIVES

The research and management of white-tailed deer (*Odocoileus virginianus*) often requires capture of live animals using chemical immobilization. Physical restraint by hand or with chute systems is usually not possible in field research, and increases the risk of injury to animals and personnel. In addition, some procedures may require a completely anesthetized animal to prevent unnecessary discomfort or stress.

Several criteria must be met for effective and efficient chemical immobilization. An ideal capture drug must be safe. Although researchers try to use caution in field situations, accidents from excitement, inexperience, and unstable darting conditions may result in accidental human exposure. Second, an ideal capture drug should have a short induction time. Short induction times limit flight distance, which increases the likelihood of recovering the animal and reduces the chance of negative interactions with the public when capture situations occur near urban/suburban areas. Third, an ideal capture drug should have a wide safety margin. It is difficult to assess the size and condition of an animal and prepare the proper drug dose in a field situation. Fourth, an ideal capture drug should have no long-term effects. Chemical immobilization should not affect an animal's long-term behavior or future health. Fifth, an ideal capture drug should be deliverable in a small volume. Low volumes reduce the time a dart must stay in an animal for complete delivery of the drug. Low volumes also

reduce the weight of a dart, which reduces chance of penetration injuries or broken bones at the injection site. Lighter darts are also ballistically superior to heavy darts for remote injection. Sixth, an ideal capture drug should be completely reversible. Following handling, animals must be returned to the wild in a fully coordinated and alert state. Residual drug effects may increase mortality through predation, adverse environmental conditions, or intraspecific fighting. Finally, an ideal capture drug should not be cost prohibitive. At this time, there are no published reports of a capture drug for white-tailed deer that meets all of these criteria.

The most commonly used drug combination for remote immobilization of wild white-tailed deer is Telazol[®] (tiletamine and zolazepam) and xylazine (xylazine HCl) (Kreeger, 1996; Kilpatrick and Spohr, 1999). The combination of Telazol[®] and xylazine has been very effective and safe in field conditions (Kilpatrick and Spohr, 1999; Murray et al., 2000). Drug reversals, however, may require an extended recovery time for animals (Millspaugh et al., 1995; Nielsen, 1999).

Carfentanil (carfentanil citrate), an ultra-potent opioid, combined with xylazine has shown potential for chemical immobilization of cervids. This combination has demonstrated short induction times, wide safety margins, and low volumes in some species (Kock and Berger, 1987; Haigh 1991; Miller et al., 1996). Furthermore, it is rapidly and completely reversible with naltrexone (naltrexone HCl) and yohimbine (yohimbine HCl) (Meuleman et al., 1984; Haigh, 1991; Miller et al., 1996).

This study 1) determined and evaluated an optimum and safe dose for carfentanil/xylazine in white-tailed deer and 2) compared immobilization parameters and physiological effects of carfentanil/xylazine to Telazol[®]/xylazine.

CHAPTER 2

LITERATURE REVIEW

Hall et al. (1953) described some of the first injectable chemical immobilizing agents and equipment for cervids. They tested curare (d-tubocurarine hydrochloride pentahydrate) and Flaxedil[®] (tri-(diethylaminoethoxy) benzene triethyliodide). Both were effective for immobilizing deer, but had serious limitations for use in the field. Curare, one of the first immobilization drugs, had such a narrow safety margin that slight miscalculation of animal weights resulted in death. Flaxedil[®], a synthetic curare, did not exert its maximum paralytic effect for 20-40 minutes. There have been tremendous advances in immobilizing drugs and remote delivery equipment (Kilpatrick et al., 1996), but no single drug or combination of drugs is best for all situations or species.

NEUROMUSCULAR BLOCKING DRUGS

One of the earliest groups of drugs used for chemical immobilization were neuromuscular blocking (NMB) drugs. There are two classes of NMB drugs that have been used on cervids: depolarizing and ganglionic.

Depolarizing NMB drugs

The most commonly used depolarizing NMB drug for cervids is succinylcholine (succinylcholine chloride). Succinylcholine depolarizes postsynaptic membrane receptors in skeletal muscles, which mimics the endogenous neurotransmitter acetylcholine (Kreeger, 1996). Succinylcholine has

no central nervous system (CNS) or analgesic properties. An animal treated with succinylcholine chloride is fully conscious and sensitive to stress, pain, and stimulation. Succinylcholine has a narrow safety margin and is not reversible. Pistey and Wright (1961) described the action of succinylcholine in white-tailed deer, however, because of major disadvantages, succinylcholine is no longer recommended for general use.

Ganglionic NMB drugs

The ganglionic class of NMB drugs includes two derivatives of tobacco. Nicotine salicylate and nicotine alkaloid cause paralysis by initial stimulation and consequent depression of the autonomic ganglia (Nielsen, 1999). These nicotine derivatives have been used to immobilize white-tailed deer (Crockford, 1957; Behrend, 1965). However, several disadvantages have been reported: 1) narrow safety margin, 2) nonreversible, 3) rough immobilization, and 4) danger to humans (Behrend, 1965; Kreeger, 1996). Nicotine derivatives are no longer recommended for immobilizing any wildlife.

DRUGS AFFECTING THE CENTRAL NERVOUS SYSTEM

Centrally acting drugs are most commonly used today for chemical immobilization work. This group of drugs depresses or modulates the CNS causing sedation to anesthesia (Lumb and Jones, 1996). There are five classes of CNS drugs used in immobilization of cervids: α_2 -adrenergic agonists, butyrophenones, ultra- potent opioids, benzodiazepines, and cyclohexamines.

Alpha₂-adrenergic agonists

Alpha₂-adrenergic agonists are potent CNS depressants with sedative, muscle relaxant, and some analgesic properties (Adams, 2001). Alpha₂-agonists are commonly used in combination with cyclohexamines or opioids for immobilization of white-tailed deer (Klein and Klide, 1989). The effects of alpha₂-agonists may last for several hours in white-tailed deer (Hsu and Shulaw, 1984; Mech et al., 1985). However alpha₂-agonists are reversible. Respiratory depression, hyperthermia, and bradycardia have been documented with use of alpha₂-agonists (Hsu and Shulaw, 1984; Wallingford et al., 1996)

Xylazine (xylazine HCl) is one of the most widely used alpha₂-agonists. Roughton (1975) and Wallingford et al. (1996) used xylazine alone to immobilize white-tailed deer caught in box traps and drop-nets, respectively. However, xylazine alone is unreliable for remote immobilization (Roughton, 1975; Hsu and Shulaw, 1984). Xylazine is most commonly used in combination with cyclohexamines or opiates and can be used on a wide range of species. Overdosing of xylazine may result in respiratory depression (Klein and Klide, 1989).

Detomidine (detomidine HCl) is an alpha₂-agonist that was recently developed. It has been used primarily in horses, and is approximately 10 times as potent as xylazine in horses (Klein and Klide, 1989). Galka et al. (1999) describe detomidine use in fallow deer (*Cervus dama*). In fallow deer, detomidine alone caused recumbency with minimal sedation. Detomidine combined with Telazol[®]

caused sufficient anesthesia for surgery (Galka et al., 1999).

Medetomidine (medetomidine HCl) is the latest α_2 -agonist approved for veterinary use (Nielsen, 1999). It has a greater affinity and selectivity for the α_2 receptor than the other α_2 -agonists (Jalanka and Roeken, 1990; Klein and Klide, 1989). Jalanka and Roeken (1990) reported that using medetomidine alone resulted in incomplete immobilization of captive white-tailed deer. The successful use of medetomidine in combination with cyclohexamines has been reported for mule deer (*Odocoileus hemionus*) and mule deer $\times$ white-tailed deer hybrids (Caulkett et al. 2000), white-tailed deer (Jalanka and Roeken, 1990), sika deer (*Cervus Nippon*) (Tsuruga et al., 1999; Suzuki et al., 2001), reindeer (*Rangifer tarandus tarandus*) (Ryeng et al., 2001), and fallow deer (Fernandez-Moran et al., 2000).

Butyrophenones

Butyrophenones are neuroleptics with an affinity for the dopamine D-₂ receptor subfamily (Gross, 2001). They have wide safety margins in normal dosages, and cause no substantial negative effects on cardiovascular or thermoregulatory systems (Nielsen, 1999). There are no known antagonists for butyrophenones.

Azaperone is a butyrophenone that has been used in many European countries for nearly 20 years (Gross, 2001). It is also commonly used in Canada and New Zealand. Azaperone has been used alone and in combination with opioids for immobilization of many species. Wilson et al. (1996a, 1996b)

combined azaperone with an α_2 -agonist and an ultra-potent opioid for immobilization of red deer (*Cervus elaphus*) and red $\times$ wapiti (*Cervus canadensis*) deer. De Vos (1978) reports the addition of azaperone can control some negative side effects associated with the use of ultra-potent opioids.

Ultra-potent opioids

Ultra-potent opioids are CNS drugs characterized by sufficient analgesic but limited muscle relaxation properties (Nielsen, 1996). Opioids are oripavine derivatives of the juice of the poppy (*Papaver somniferum*) or 4-amino-piperidine derivatives (Haigh, 1990; Kreeger, 1996). They bind to specific opioid receptors (delta, kappa, mu, sigma) causing CNS modulation and depression (Branson and Gross, 2001) They have a wide safety margin, and are reversible. Ultra-potent opioids are very potent, and most animals require only a small volume of drug for successful immobilization. Many are used in combination with α_2 -agonists.

Major side effects of opioids include: excitability prior to induction, loss of thermoregulatory capabilities, respiratory depression, muscle rigidity, bradycardia in high doses, vomiting, defecation, temporary endocrine changes, and potential for narcotic recycling (Haigh, 1990; Kreeger, 1996; Nielsen, 1999). Narcotic recycling can occur when the action of an opioid antagonist decreases to ineffective levels before the agonist is eliminated from the body, resulting in resedation (Roffe et al., 2001).

Ultra-potent opioids are extremely potent to humans and should be used only if an antagonist is readily available. Opioids are schedule II narcotics which

require a much more extensive application process than other drugs. The Drug Enforcement Administration is the federal agency that reviews all applications and issues drug licenses.

Etorphine (etorphine HCl) is one of the most commonly used opioids. Presnell et al. (1973) found that white-tailed deer given intramuscular injections of etorphine (0.02 mg/kg of body weight) and xylazine (0.4 mg/kg) were satisfactorily immobilized for up to 90 minutes. Kreeger et al. (1987) immobilized white-tailed deer with intramuscular injections of etorphine only (0.05-0.07 mg/kg). These trials were considered unsuccessful due to long induction times characterized by hyperactivity and high mortality rates (two of three animals died). Xylazine (0.5-0.8 mg/kg) was then combined with etorphine (0.05-0.07 mg/kg) and injected into additional deer. This combination resulted in complete but not rapid immobilization. Mean ($\pm$ SD) induction times were 15.7 ± 2.0 minutes ($n = 10$).

Fentanyl (fentanyl citrate) is an opioid that has been used on many cervid species. It is less potent than etorphine, and the currently available solutions of fentanyl are too dilute for larger species (Nielsen, 1999). Wilson et al. (1996a, 1996b) evaluated its use on red deer and red $\times$ wapiti deer. A combination of xylazine/fentanyl citrate/azaperone was used to effectively immobilize the animals, but was not adequate for humane velvet antler removal. Kocan et al. (1981) used fentanyl only to immobilize captive white-tailed deer for collection of blood samples. Mean ($\pm$ SD) induction times for the deer ($n = 10$) averaged 4.5 ± 1.7 minutes.

Carfentanil (carfentanil citrate) is the most potent opioid available (De Vos, 1978; Meuleman et al., 1984; Haigh, 1990). A derivative of fentanyl, it is approximately 10,000 times more potent than morphine in rats and three times more potent than etorphine in elk (O’Gara, 1987; Nielsen, 1999). Carfentanil has successfully immobilized ungulates with doses as low as 1.0 $\mu\text{g/kg}$ (Meuleman et al., 1984; Bailey et al., 1985). Carfentanil has demonstrated a wide safety margin in some cervids (Bailey et al., 1985; Allen, 1989). De Vos (1978) used carfentanil or carfentanil/xylazine to successfully immobilize 20 species of free-ranging African herbivores. Carfentanil also has been used to successfully immobilize black bears (*Ursus americanus*) (Ramsay et al., 1995), polar bears (*Ursus maritimus*) (Haigh et al., 1983), moose (*Alces alces*) (Meuleman et al., 1984; Seal et al., 1985; Delvaux et al., 1999; Roffe et al., 2001), elk (*Cervus elaphus*) (Meuleman et al., 1984; Bailey et al., 1985; Haigh, 1991; Miller et al., 1996), American bison (*Bison bison*) (Kock and Berger, 1987), wood bison (*Bison bison athabasca*) (Haigh and Gates, 1995), mule deer (Jessup et al., 1984; Caulkett et al., 2000), mule deer $\times$ white-tailed deer hybrids (Caulkett et al., 2000), and pronghorns (*Antilocapra americana*) (O’Gara, 1987). However, there has been no substantial testing of its effectiveness for chemical immobilization of white-tailed deer.

Thiafentanil (A-3090) is another potent opioid that has been used for chemical immobilization of wildlife. Thiafentanil is approximately 6,000 times more potent than morphine (Kreeger et al., 2001). Thiafentanil alone has been

used to immobilize elk (Stanley et al., 1988; Smith et al., 1993) and pronghorns (Kreeger et al., 2001). The addition of xylazine did not demonstrate any additional benefit for immobilizing pronghorns (Kreeger et al., 2001). In elk, induction times for thiafentanil are comparable to those of carfentanil, but its effects are not as long lasting as those of carfentanil (Stanley et al., 1988). Kreeger et al. (2001) reported pronghorns injected with thiafentanil had shorter induction times than pronghorns from the same population immobilized with carfentanil in an earlier study. The use of thiafentanil for chemical immobilization of white-tailed deer has not been reported.

Benzodiazepines

Benzodiazepines are used in combination with other drugs for sedation and analgesia. Normally they will not produce anesthesia when used alone (Hall et al., 2001). Benzodiazepines depress the limbic system and inhibit internuncial neurons at spinal levels to induce sedation and muscle relaxation, respectively (Hall et al., 2001). Benzodiazepines have no significant effects on heart rate, blood pressure, but may produce minimal cardiovascular depression (Klein and Klide, 1989; Nielsen, 1999). Benzodiazepines are reversible.

Zolazepam is a benzodiazepine that is combined with tiletamine hydrochloride (a cyclohexanone dissociative anesthetic agent) in a 1:1 ratio to form Telazol® (Haigh et al., 1985; Millspaugh et al., 1995; Kilpatrick and Spohr, 1999; Murray et al., 2000). Zolazepam combined with tiletamine improves muscle relaxation, counters convulsions often associated with cyclohexane

immobilization, and facilitates a smoother induction, with a more uneventful recovery (Nielsen, 1999; Murray et al., 2000). Zolazepam is only sold in combination with tiletamine.

Cyclohexamines

Cyclohexamines typically produce dissociative anesthesia, analgesia, and immobilization in treated animals (Nielsen, 1999). Cyclohexamines act by causing a functional and an electrophysiological dissociation between the thalamo-neocortical and limbic systems (Hall et al., 2001). Cyclohexamines are usually used in conjunction with a sedative due to the potential to cause convulsions, rough inductions, and rough recoveries when used alone (Kreeger, 1996). Cyclohexamines also may cause copious salivation, and a variety of hematological, serum chemical, and endocrine alterations (Kreeger, 1996).

Phencyclidine (phencyclidine HCl) was the first cyclohexamine used for chemical immobilization (Nielsen, 1999). Dean et al. (1973) described its effectiveness for chemical immobilization of captive and free-ranging black-tailed deer (*Odocoileus hemionus columbianus*), mule deer, and white-tailed × black-tailed hybrids. Because of illegal human use, it was taken off the market in 1978 (Nielsen, 1999).

Ketamine (ketamine HCl) is a cyclohexane structurally related to phencyclidine (Nielsen, 1999). The combination of ketamine and xylazine is commonly used for chemical immobilization of white-tailed deer (Kreeger et al., 1986; DeNicola and Swihart, 1997; Kilpatrick and Spohr, 1999; DelGiudice et al.,

2001). Ketamine is effective for immobilizing white-tailed deer, however it requires a large volume that makes remote immobilization difficult (Murray et al., 2000). The lyophilized form of ketamine only can be reconstituted to 200 mg/cc (Kilpatrick and Spohr, 1999). A 45.0 kg white-tailed deer requires 297.0 mg of ketamine (6.6mg/kg). Therefore, the combination of ketamine and xylazine requires large darts with poor ballistics. In addition, Kilpatrick and Spohr (1999) reported deer darted with ketamine/xylazine traveled greater distances than deer darted with Telazol[®]/xylazine. There are no known antagonists for ketamine.

Tiletamine (tiletamine HCl) is a cyclohexanone dissociative anesthetic agent that is combined with zolazepam in a 1:1 ratio to form Telazol[®] (Haigh et al., 1985). Telazol[®] has a duration of action approximately three times longer than ketamine (Branson, 2001). In many species, the induction time for Telazol[®] is faster than the induction time of ketamine (Millspaugh et al., 1995; Nielsen, 1999). Telazol[®] is typically used in combination with xylazine for immobilization of white-tailed deer (Millspaugh et al., 1995; Kilpatrick and Spohr, 1999; Murray et al., 2000). Telazol[®] is more highly concentrated than ketamine. The powdered form of Telazol[®] can be reconstituted up to 500mg/cc, which is an advantage for remote injection (Kilpatrick and Spohr, 1999). The tiletamine component of Telazol[®] is not reversible, but there is an antagonist for the zolazepam component (Spelman et al., 1997; James et al., 1999).

ANTAGONISTS

Antagonists are drugs capable of blocking the effects of the agonist (Novotny, 2001). There are antagonists for three classes of immobilizing drugs: alpha₂-adrenergic agonists, opioids, and benzodiazepines.

Alpha₂-adrenergic antagonists

Alpha₂-adrenergic antagonists are used to reduce the effects of alpha₂-adrenergic agonists that may last several hours in white-tailed deer (Hsu and Shulaw, 1984; Mech et al., 1985). When using an alpha₂-adrenergic agonist in combination with a cyclohexamine, immediate administration of an alpha₂ antagonist may reveal the negative qualities of the cyclohexamine (Kreeger, 1996; Kilpatrick and Spohr, 1999). Therefore, sufficient time to allow metabolism of the cyclohexamine should occur before the administration of the alpha₂-adrenergic antagonist.

Nielsen (1999) stated yohimbine (yohimbine HCl) was the first alpha₂ antagonists used for reversal of xylazine. Yohimbine acts by blocking central and peripheral alpha₁ and alpha₂ receptors (Klein and Klide, 1989). This permits resumption of neural transmission (Nielsen, 1999). Although newer alpha₂ antagonists have virtually no pharmacological effects when given alone, yohimbine has demonstrated behavioral and cardiovascular actions in some species (Klein and Klide, 1989). Successful antagonism of xylazine in white-tailed deer has occurred with intramuscular injection of yohimbine (Wallingford et al., 1996). However, intravenous injection may provide a more rapid recovery

(Mech et al., 1985; Murray et al., 2000).

Tolazoline (tolazoline HCl) has the least α_2 -adrenoreceptor specificity of all the α_2 antagonists (Kreeger et al., 1986; Nielsen, 1999). Tolazoline has histaminergic activity that has caused negative side effects in some species (Kreeger et al., 1986; Dew, 1988; Kreeger, 1996), but tolazoline has been effective in antagonizing xylazine in white-tailed deer (Kreeger et al., 1986; Dew, 1988; DelGuidice et al., 1989).

Atipamezole is more potent and selective than tolazoline or yohimbine (Jalanka and Roeken, 1990; Arnemo et al., 1993; Kreeger, 1996). Overdosing of atipamezole may cause excitability and overalertness, and underdosing may result in resedation (Jalanka and Roeken, 1990; Nielsen, 1999). Atipamezole is the α_2 -antagonist primarily used for reversal of medetomidine because medetomidine is a specific agonist. Ancrenaz (1994) reported atipamezole was not able to reverse all of the effects of xylazine immobilization in captive Arabian oryx (*Oryx leucoryx*). Xylazine affects α_1 -receptors and α_2 -receptors and atipamezole is only specific for α_2 -receptors. However, Arnemo et al. (1993) reported complete reversal of xylazine induced immobilization in axis deer (*Axis axis*) with no relapse into sedation, and only one animal of eight showed signs of overalertness. Nicholls et al. (1996) reported grey duikers (*Sylvicapra grimmia*) immobilized with ketamine/xylazine showed variable reversal of sedation with atipamezole. Tsuruga et al. (1999) reported the use of atipamezole on sika deer immobilized with medetomidine and ketamine resulted in smooth and rapid reversal.

Opioid antagonists

Modern opioid antagonists give researchers the ability to return immobilized animals to a normal state with their natural functions and reflexes intact (Nielsen, 1996). Diprenorphine (diprenorphine HCl) and nalorphine (nalorphine HCl) are two of the earlier antagonists used to reverse the effects of fentanyl and etorphine (Kreeger, 1996; Nielsen, 1999). Diprenorphine and nalorphine act as an antagonist on the mu receptor, while displaying agonistic characteristics on other opioid receptors (Haigh, 1990). Overdosing with these drugs may result in continued immobilization (Haigh, 1990). Use of diprenorphine and nalorphine has decreased with the development of new opioid antagonists.

Naloxone (naloxone HCl), naltrexone (naltrexone HCl), and nalmeferone (nalmeferone HCl) are opioid antagonists with no agonistic properties (Haigh, 1990; Kreeger, 1996; Nielsen, 1999). Nalmeferone in a ratio of 100 mg nalmeferone : 1 mg carfentanil has been used successfully to antagonize carfentanil in a variety of nondomestic ungulates; however, narcotic recycling was more likely to occur with nalmeferone than with naltrexone given at the same ratio (Allen, 1989 and 1996).

Haigh (1991) reports that a mean ratio of 48.5 mg naloxone : 1 mg carfentanil was effective in antagonizing carfentanil induced immobilization in elk. Carfentanil induced immobilization in bison and polar bears has also been reversed completely by naloxone, but naloxone has a shorter duration of activity

than naltrexone and has resulted in higher rates of narcotic recycling in many species (Haigh et al., 1983; Bailey et al., 1985; Kock and Berger, 1987; Haigh, 1991).

The reported use of naltrexone in a ratio of 100 mg naltrexone : 1 mg carfentanil has demonstrated rapid and complete antagonism of carfentanil in elk, black bears, and many nondomestic ungulates (Allen, 1989; Haigh, 1993; Ramsay et al., 1995; Allen, 1996; Miller et al., 1996). A ratio of 125 mg naltrexone : 1 mg carfentanil has been effective in antagonizing carfentanil and preventing narcotic recycling in moose and wood bison (Haigh and Gates, 1995; Roffe et al., 2001). Carfentanil antagonism by naltrexone based on body weight, not dose of carfentanil, has been effective in dama gazelles (*Gazella dama*), moose, mule deer, and mule deer × white-tailed deer hybrids (Schumacher et al., 1997; Delvaux et al., 1999; Caulkett et al., 2000). Designating a portion of the antagonist for injection either intramuscularly or subcutaneously while delivering the rest intravenously may reduce the chance of narcotic recycling (Haigh et al., 1983; Ramsay et al. 1995; Miller et al., 1996; Delvaux et al., 1999).

Benzodiazepine antagonists

Flumazenil is an antagonist that effectively reverses benzodiazepines (Nielsen, 1999). Flumazenil has a great affinity for benzodiazepine receptors and reverses all actions of benzodiazepines without any side effects (Lumb and Jones, 1996). Recovery time of river otters (*Lutra canadensis*) immobilized with tiletamine/zolazepam (Telazol[®]) was shortened with the use of flumazenil

(Spelman et al., 1997). Anesthesia of babirusa (*Babyrussa babyrussa*) immobilized with xylazine and tiletamine/zolazepam (Telazol[®]) also was reversed with the combination of yohimbine and flumazenil (James et al., 1999). However, the effectiveness of flumazenil for antagonizing the zolazepam portion of Telazol[®] immobilization in white-tailed deer has not been reported.

There are many classes of immobilization drugs, each with its own positive and negative attributes. No single drug or drug combination is best for all situations or species. The development of new drugs with fewer negative qualities is necessary to improve chemical restraint of white-tailed deer.

CHAPTER 3
A COMPARISON OF CARFENTANIL/XYLAZINE
WITH TELAZOL/XYLAZINE FOR
IMMOBILIZATION OF WHITE-TAILED DEER

MATERIALS AND METHODS

All research was conducted at the University of Georgia Daniel B. Warnell School of Forest Resources Whitehall Deer Research Facility (33°53'N, 83°21'W). The mean weight ($\pm$ SD) of tested animals was 52.1 ± 8.7 kg. Animals were housed in large outdoor pens with food and water available *ad libitum*. Deer were moved to three by six meter stalls for 24-36 hours prior to treatments. Food was withheld 12-16 hours before immobilization.

Animals were randomly assigned to treatments administered in a squeeze chute via intramuscular (IM) injection in the hindquarter. After drug injection, animals were immediately released into a 15x20 m observation pen where observers recorded time for first noticeable drug effect (e.g., stumbling, change in movement pattern and behavior) and induction time (when deer dropped to the ground without rising). Following lateral recumbency, each deer was moved, treated with ophthalmic ointment (Paralube[®] Vet Ointment, Pharmaderm, Melville, New York, USA) to prevent corneal drying, masked, and weighed. Heart rate (determined by auscultation), respiration rate (observed by thoracic movements), rectal temperature (digital thermometer, B-D Digital Fever Thermometer, Becton Dickinson, Franklin Lakes, New Jersey, USA), and

hemoglobin saturation (pulse oximeter with probe on the tongue, Ohmeda Biox 3700, Ohmeda, Louisville, Colorado, USA) were recorded at 5-10 and 15-20 minutes after induction. The maximum temperature measurable by the thermometer was 42.2°C. Therefore temperatures $\geq 42.2^{\circ}\text{C}$ were recorded as 42.2°C.

Approximately 30 minutes after induction, each animal was taken to an individual stall for antagonist administration. All animals were periodically checked for signs of resedation for 24 hours following antagonist administration. To avoid arousing any resedated animals, all night checks were made in complete darkness with the use of night vision equipment (ITT Night Quest Model 160, ITT, Roanoke, Virginia, USA). Time periods from injection of agonists until induction (C/X and T/X treated deer) and time periods from injection of antagonist until standing (C/X treated deer) were videotaped for further evaluation.

Regression analysis for general linear models was used to evaluate the relationship between induction times, physiological measurements, and carfentanil dose. Relationships between ambient temperatures and rectal temperatures were examined by correlation. Differences between groups were analyzed using paired t-tests and the Wilcoxin Signed Rank test for non-normal data (SAS Institute, Cary, North Carolina, USA). If no significant differences were detected between time periods, values were combined and used to test for differences between drug treatments.

Optimization of carfentanil dose

Nineteen captive white-tailed deer (≥ 1.5 yrs old; 10 males, 9 females) were immobilized with carfentanil (3 mg/ml; Wildnil[®], Wildlife Laboratories, Inc., Fort Collins, Colorado, USA) and xylazine (Cervizine[®], Wildlife Laboratories, Inc., Fort Collins, Colorado, USA) between 8-31 October 2001. Ten of the 19 deer were immobilized on two separate occasions with a three week washout period between treatments. Deer were randomly assigned to one of four treatment groups. Four males and four females were given a carfentanil dose of 0.5, 1.0, or 1.5 mg. Three males and three females were given a carfentanil dose of 2.0 mg. Each dose of carfentanil was combined with 10 mg xylazine. Immobilization was reversed with naltrexone (50 mg/ml, Trexonil[®], Wildlife Laboratories, Inc., Fort Collins, Colorado, USA) administered at 100 times the carfentanil dose (Allen, 1996) and 5 mg yohimbine (5 mg/ml, Antagonil[®], Wildlife Laboratories, Inc., Fort Collins, Colorado, USA). The actual yohimbine dosage ranged from 0.08-0.14 mg yohimbine/kg body weight. After yohimbine was given intravenously (IV), naltrexone was given half IV and half subcutaneously (SC). Time from injection of naltrexone until the deer was standing was recorded to the nearest second.

Duration and safety of carfentanil/xylazine effect without antagonist treatment

Two male and two female deer, ≥ 1.5 yrs old, were immobilized on 22 January 2002 with 1.2 mg carfentanil and 10 mg xylazine. After induction,

physiological measurements were recorded at 5-10 and 15-20 minutes as before, and then heart rate, respiration rate, and rectal temperature were taken approximately every 30 minutes until the animals were unapproachable. Duration of immobilization was recorded as the time from induction until the deer was standing. Ambient temperatures ranged between 10-15 °C during trials.

Comparison of carfentanil/xylazine to Telazol[®]/xylazine

On 20 December 2001, 16 deer, ≥ 1.5 yrs old were randomly assigned to drug treatment groups (eight males and eight females). Eight deer were immobilized with a combination of 1.2 mg of carfentanil (19.9-29.9 $\mu\text{g/kg}$) and 10.0 mg of xylazine (0.15-0.25 mg/kg) (C/X) and eight deer were immobilized with a combination of 230 mg Telazol[®] (3.4-5.7 mg/kg) (100 mg/ml, Fort Dodge Animal Health, Fort Dodge, Iowa, USA) and 120 mg of xylazine (1.8-3.0 mg/kg) (T/X). The drug treatment groups were reversed in each deer 2.5 weeks later.

Immobilization was reversed using naltrexone (100 times the carfentanil dose) combined with 6.5 mg yohimbine in a single syringe for C/X deer, and 6.5 mg yohimbine for T/X-treated deer. All reversal drugs were given half IV and half SC. Any T/X-treated deer that showed no signs of reversal after 120 minutes were given an additional 10 mg yohimbine (half IV and half IM). Time of reversal was recorded to the nearest second for C/X-treated deer and to the nearest minute for T/X-treated deer.

RESULTS

Optimization of carfentanil dose

A combination of (0.5-2.0 mg) carfentanil (7.75-46.84 $\mu\text{g/kg}$) and 10 mg xylazine (0.16-0.27mg/ kg) was evaluated with 29 immobilizations on 19 deer. Time to first noticeable drug effects occurred from 0.7-3.5 minutes and included stumbling and changes in gait patterns. Excitability was observed in most animals. Deer ran around the observation pen in circles, often unconcerned or unaware of the presence of nearby human observers. Hind-end ataxia was common prior to induction. Two animals violently flipped on their backs from loss of control in the hind legs; however, they suffered no ill effects. Generalized muscle fasciculations lasting 5-10 minutes post induction were common in sternally or laterally recumbent animals. Urination and penile erections were observed in males on two occasions.

Induction times ranged from 2.2-8.7 minutes. Linear regression of carfentanil dose verses induction time was statistically significant ($p < 0.05$). However, due to variability of induction times, the linear model was a poor predictor of the relationship ($r^2 = 0.17$; Fig. 1). Quality of immobilization was not consistent. Similar doses of carfentanil caused varied levels of sedation. Some animals were completely immobilized while others were responsive to noise or touch.

Carfentanil dose of 1.2 mg (23.0 $\mu\text{g/kg}$) combined with 10 mg of xylazine was chosen for all further testing. Lower carfentanil doses resulted in poor

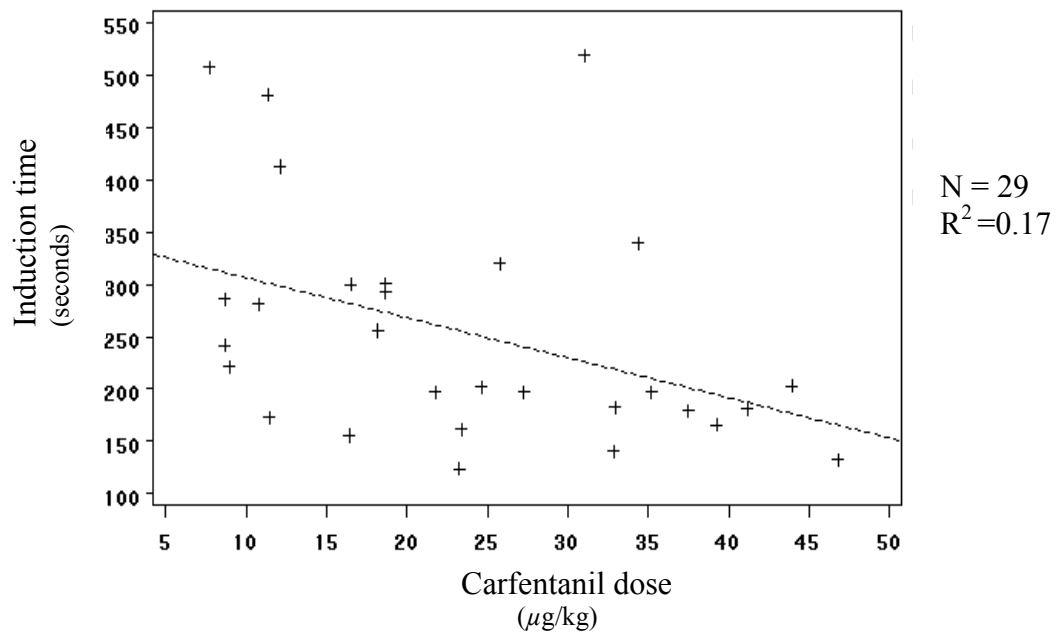


FIGURE 1. Induction times of white-tailed deer immobilized with intramuscular 0.5-2.0 mg carfentanil (7.75-46.84 $\mu\text{g/kg}$) and 10 mg xylazine (0.16-0.27 mg/kg)

induction times, and higher doses did not show improvement in induction times (Fig. 1). All reversals were rapid. Mean ($\pm$ SD) reversal times were 2.6 ± 1.7 minutes. Only one animal showed signs of narcotic recycling. A female that received a carfentanil dose of $34.4 \mu\text{g/kg}$ appeared drowsy and reluctant to rise 1.5 hours after reversal. All other animals appeared alert and fully coordinated following antagonist administration.

One animal sustained a lower lip avulsion after colliding with a fence, and required sutures. Hyperthermia (rectal temperatures $\geq 41.1^\circ\text{C}$) was observed in 13 of 29 immobilizations. All other physiological parameters were considered acceptable. No health complications resulting from immobilization and reversal of C/X were observed in the animals within three months post-immobilization treatment.

Carfentanil/xylazine immobilization without antagonist treatment

Mean ($\pm$ SD) duration of immobilization for C/X-treated deer was 3.5 ± 0.8 hours. Three to 5 observations per deer were taken during immobilization. There was no significant relationship between heart rate (24-66 beats/min), or respiration rate (7-30 breaths/min) and duration of immobilization ($p > 0.05$). Rectal temperatures were negatively related with duration of immobilization ($p < 0.05$) (Fig. 2). One animal that fractured its mandible during induction was euthanized after recovery from immobilization. All remaining animals recovered normally.

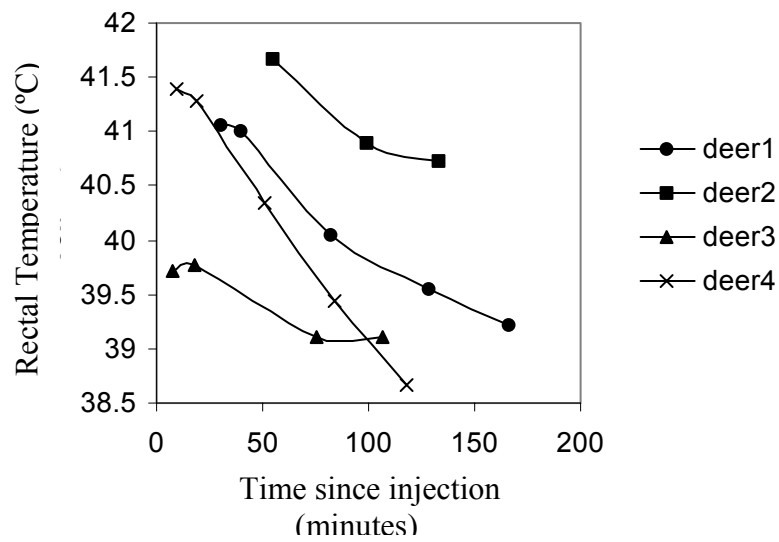


FIGURE 2. Rectal temperatures^a of white-tailed deer immobilized with 1.2 mg of carfentanil and 10 mg of xylazine (C/X).

^a The maximum temperature measurable by the thermometer was 42.2°C.

No observations were recorded until temperatures fell to measurable levels.

Comparison of carfentanil/xylazine to Telazol[®]/xylazine

All deer injected with C/X or T/X were successfully immobilized. All deer were hand-injected in the squeeze chute except one, this deer was physically restrained by two people for injection. Time until first noticeable drug effect and induction time were significantly ($p<0.01$) shorter with T/X-treated deer than C/X-treated deer (Table 1).

Quality of immobilization was not consistent among the 16 C/X-treated deer. One male had to be reversed before all physiological measurements could be taken due to an insufficient level of anesthesia. Four other C/X-treated deer were responsive to sound or touch, however all measurements were obtained. All T/X-treated deer demonstrated excellent immobilization.

Physiological data are presented in Table 2. Respiration rates, heart rates, and rectal temperatures did not differ significantly between the two time periods measured for C/X-treated deer or T/X-treated deer. Respiration rates and heart rates did not significantly differ ($p>0.05$) between C/X and T/X immobilized deer.

Rectal temperatures were higher ($p<0.01$) in C/X-treated deer than T/X-treated deer. Nine of 16 deer immobilized with C/X had rectal temperatures $\geq 41.1^{\circ}\text{C}$; however, only two of 16 deer immobilized with T/X had rectal temperatures $\geq 41.1^{\circ}\text{C}$. No correlation was found between ambient temperature at time of agonist injection and rectal temperature 15-20 minutes post induction for C/X-treated deer ($r=0.08$, $p>0.05$) or T/X-treated deer ($r=-0.28$, $p>0.05$).

Hemoglobin saturation did not differ between the two time periods for

Table 1. Chemical immobilization of 16 white-tailed deer using 1.2 mg carfentanil and 10 mg xylazine (C/X) and 230 mg Telazol® and 120 mg of xylazine (T/X) and reversal by 120 mg of naltrexone and 6.5 mg of yohimbine (N/Y) and 6.5 mg yohimbine (Y).

Agonist	<u>C/X</u>	<u>T/X</u>
	mean ± SD (<i>n</i>)	mean ± SD (<i>n</i>)
	(range)	(range)
Time to first effect (min)	1.8 ± 0.6 (16) (0.4-3.0)	1.4 ± 0.3 (16) (0.9-2.1)
Induction time (min)	4.7 ± 3.3 (16) (0.5-11.7)	2.4 ± 0.7 (16) (1.1-4.6)
Antagonist	<u>N/Y</u>	<u>Y</u>
	mean ± SD (<i>n</i>)	mean ± SD (<i>n</i>)
	(range)	(range)
Reversal time (min)	1.9 ± 1.1 (16) (0.6-5.0)	165.5 ± 66.4 (13) ^a (69-259)

^a Ten animals still immobilized after 120 minutes were given an additional 10 mg yohimbine.

Table 2. Physiological data from 16 white-tailed deer immobilized with 1.2 mg of carfentanil and 10 mg xylazine (C/X) and 230 mg Telazol[®] and 120 mg xylazine (T/X).

	<u>C/X</u>		<u>T/X</u>	
	mean ± SD (<i>n</i>)		mean ± SD (<i>n</i>)	
	(range)		(range)	
Time post				
Induction (min)	5-10	15-20	5-10	15-20
<u>Parameter</u>				
S _p O ₂	90.3 ± 3.1 (13)	90.6 ± 4.1(14)	84.5 ± 7.8 (14)	86.9 ± 5.4 (15)
	(85-95)	(79-95)	(72-94)	(75-92)
Heart rate	66.6 ± 24.9 (16)	66.6 ± 26.0 (15)	65.5 ± 16.0 (16)	65.9 ± 29.8(16)
	(40-125)	(40-126)	(48-112)	(40-172)
Respiration	30.8 ± 22.3 (16)	29.5 ± 27.3 (15)	28.3 ± 22.5 (16)	33.3 ± 30.5 (16)
Rate	(11-102)	(9-112)	(8-102)	(8-122)
Rectal	41.1 ± 1.0 (16) ^a	40.9 ± 1.2 (15)	40.1 ± 1.1 (16)	40.0 ± 1.1 (16)
temperature (°C)	(39.3-42.2)	(39.0-42.2)	(38.5-42.2)	(38.6-42.2)

^a Temperatures $\geq$ 42.2°C were recorded as 42.2°C

C/X-treated deer ($p>0.05$), however hemoglobin saturation for T/X-treated deer was higher ($p<0.05$) in the second time period. Hemoglobin saturation was not different ($p=0.07$) in the first time period between C/X-treated deer and T/X-treated deer. Hemoglobin saturation was higher ($p<0.05$) in the second time period for C/X-treated deer than for T/X-treated deer.

Reversals of C/X-treated deer were rapid (mean = 1.9 min.), compared to reversals of T/X-treated deer (mean = 165.5 min)(Table 1). Due to injection errors, 2 C/X-treated deer did not receive the full subcutaneous dose of naltrexone and yohimbine, however reversal times were normal (1.0 and 1.8 min.) and there were no signs of narcotic recycling. Narcotic recycling was not present after antagonist administration in any of the C/X-treated deer, however at least five of the sixteen T/X-treated deer were found partially or fully immobilized 1-4 hours after initial standing.

One C/X-treated animal sustained a laceration on its leg, and another sustained a lower lip avulsion. Both recovered normally with only superficial treatments. One female injected with T/X ate from a feeder located in the release pen before succumbing to drug effects and regurgitated while being carried to a stall. She died 3 weeks later from probable aspiration pneumonia. No other animals exhibited any health complications within one month post treatment.

DISCUSSION

The 1.2 mg of carfentanil (19.9-29.9 $\mu\text{g/kg}$) combined with 10.0 mg of xylazine (0.15-0.25 mg/kg) was not reliable for producing short induction times in

captive white-tailed deer. Induction times did not decrease with higher dosages, and there was an increased risk of narcotic recycling with higher dosages (Haigh, 1990). Additionally, Jessup et al. (1984) reported a mean carfentanil dose of 30.0 $\mu\text{g/kg}$ was effective for remote immobilization of captive mule deer (*Odocoileus hemionus*) and Caulkett et al. (2000) reported an intramuscular injection of carfentanil 10.0 $\mu\text{g/kg}$ was effective for immobilizing captive mule deer and mule deer/white-tailed deer hybrids.

Short induction time is one of the most important characteristics of a remote immobilization drug. The risk of injury and hyperthermia increased with prolonged induction times. In field situations, long induction times increase flight distance and reduce the chance of recovering an animal.

Not all field procedures would be possible when using the tested dosages of C/X as an immobilization drug combination for white-tailed deer because of variability of drug effect. The level of immobilization in all C/X-treated animals was adequate for minimal handling; however, complex or invasive procedures would not have been possible in some animals.

Safe chemical immobilization should not cause adverse effects to normal physiological function. Respiratory depression is a concern with opioids and xylazine (Klein and Klide, 1989; Haigh, 1990). However, hemoglobin saturation was not different in the first time period between C/X-treated deer and T/X-treated deer, although it was almost significantly higher for C/X-treated deer ($p=0.07$), and hemoglobin saturation for C/X-treated deer was significantly higher

than T/X-treated deer in the second time period. Hyperthermia was common in C/X-treated deer. C/X should only be used to immobilize white-tailed deer if adequate means to decrease body temperature are available. Heart rates and respiratory rates were considered acceptable for C/X-treated deer.

Jessup et al. (1984) reported rectal temperatures, heart rate, respiration rate, and blood pressure of a mule deer increased to unsafe levels as duration of carfentanil immobilization increased. Because some animals immobilized in the field are not recovered, the relationships between certain physiological parameters and duration of immobilization were investigated. Since no relationship between heart rates or respiration rates and duration of immobilization was found, and rectal temperatures returned to normal as duration of immobilization increased, the recovery from C/X immobilization, using the dosages investigated, without reversal does not increase the risks associated with carfentanil in white-tailed deer.

Immobilization with carfentanil/xylazine is effectively and rapidly reversed using naltrexone and yohimbine in white-tailed deer. Animals were alert and fully coordinated within minutes of antagonist administration, with little risk of renarcotization. This ability to completely reverse immobilization may be extremely beneficial in field situations.

The combination of Telazol[®] and xylazine also effectively immobilized white-tailed deer. Induction times were rapid, and immobilization was excellent for all animals. In addition, all physiological parameters remained satisfactory.

Reversal times for deer immobilized with the combination of Telazol[®] and xylazine were prolonged. The sluggish and uncoordinated demeanor of animals after yohimbine administration suggested residual xylazine effects. The 0.125 mg/kg yohimbine dose recommended by Kreeger (1996) appeared to insufficiently antagonize the effects of xylazine.

Immobilization drugs should not be cost prohibitive. Costs to immobilize animals with 1.2 mg of carfentanil and 10 mg of xylazine were \$15.05 per animal. Reversal using 120 mg of naltrexone and 6.5 mg of yohimbine was \$23.33 per animal. Therefore, total cost per deer was \$38.38. Immobilization with 230 mg of Telazol[®] and 120 mg of xylazine was \$12.08 per animal. Reversal with 6.5 mg of yohimbine was \$2.93 per deer. Therefore, total cost was \$15.01 per deer. Although use of carfentanil and xylazine to immobilize deer, and its reversal with naltrexone and yohimbine was more than twice the cost of the other treatment, the ability to rapidly reverse immobilization may increase the number of possible immobilizations each day and reduce overall costs.

Major drawbacks for the use of carfentanil are its risk to human personnel and its classification as a schedule II narcotic. Carfentanil is extremely toxic to humans and should never be used in the absence of a syringe containing an emergency antagonist. All ultra-potent opioids are classified as schedule II narcotics. The Drug Enforcement Administration requires strict license and usage requirements for schedule II narcotics.

Additional dose evaluations of carfentanil and xylazine should be

conducted to reduce induction times and improve reliability of anesthesia in white-tailed deer. Furthermore, research of yohimbine and other alpha-2 antagonists and benzodiazepam antagonists should be conducted to decrease the long recovery times associated with Telazol[®] and xylazine immobilization.

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CHAPTER 4

CONCLUSIONS

The combination of carfentanil (carfentanil citrate) and xylazine (xylazine hydrochloride) has been an effective drug combination in cervids. However this study demonstrated that the combination of 23.0 $\mu\text{g/kg}$ of carfentanil and 10.0 mg of xylazine (C/X) was not effective for rapid induction and immobilization of white-tailed deer. Inductions were prolonged in some animals. Animals with long induction times have an increased risk of injury or hyperthermia, or not being found in field settings.

Quality of immobilization was variable for animals treated with C/X. Some animals given similar doses displayed very different levels of anesthesia. Most measured physiological parameters for animals immobilized with C/X were within acceptable levels. However, hyperthermia was common in animals immobilized by C/X.

Reversal of C/X immobilization with naltrexone (naltrexone hydrochloride) and yohimbine (yohimbine hydrochloride) was rapid and complete. Narcotic recycling was not common in white-tailed deer immobilized with C/X.

Carfentanil's complete reversibility, and low volume make it an attractive drug for remote immobilization of white-tailed deer. However, additional research evaluating doses of carfentanil and xylazine is necessary before C/X can be used for remote immobilization of white-tailed deer in the field.

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