Determination of optimal immobilizing doses of a medetomidine hydrochloride and ketamine hydrochloride combination in captive reindeer

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Objective—To establish optimal immobilizing doses of medetomidine hydrochloride (MED) with ketamine hydrochloride (KET) for hand- and dart-administered injections in captive reindeer.

Animals—12 healthy 6- to 9-month-old reindeer (Rangifer tarandus tarandus).

Procedure—An optimal dose was defined as a dose resulting in an induction time of 150 to 210 seconds, measured from the time of IM injection until recumbency. Initially, each stalled reindeer was immobilized by hand-administered injection. If the induction time was > 210 seconds, the dose was doubled for the next immobilization procedure. If it was < 150 seconds, the dose was halved for the next immobilization procedure. This iteration procedure was continued for each reindeer until an optimal dose was found. Later the reindeer was placed in a paddock and darted with its optimal dose as determined by hand-administered injection. Adjusting to a linear relationship between dose and induction time, optimal darting doses for each reindeer were predicted and later verified.

Results—The established mean optimal hand- and dart-administered doses were 0.10 mg of MED/kg of body mass with 0.50 mg of KET/kg, and 0.15 mg of MED/kg with 0.75 mg of KET/kg, producing mean induction times of 171 seconds and 215 seconds, respectively. The mean induction time after darting was 5 seconds greater than the upper limit of the predefined time interval.

Conclusions and Clinical Relevance—The higher dose requirement of MED-KET administration outdoors, compared with indoors, was explained by factors inherent in the darting technique and the different confinements. The iteration and the prediction methods seem applicable for determination of optimal doses of MED-KET in reindeer. The iteration and the prediction procedures may be used to reduce the number of experimental animals in dose-response studies in other species. (Am J Vet Res 2001;62:119–126)

In zoo and wildlife medicine, recommended doses of immobilizing agents are often empirically determined or extrapolated. To our knowledge, no clinically controlled studies have been reported on the optimal dose of MED-KET in reindeer.

Several factors are known to influence the effects of immobilizing drugs and thereby the dose required. The sensitivity to a drug or drug combination may vary among species or subspecies, among animals within a species or subspecies, and even within the same animal. Physiologic factors such as age, sex, and reproductive status, season, as well as the animal’s physical condition, health, and size may have influence. Furthermore, important modifying factors to be considered at the time of drug administration are the amount of stress and excitement. While in contact with humans, a higher amount of stress can be anticipated in wild free-ranging animals, compared with captive wild animals that are tamed. The lowest amount of such stress may be anticipated in domestic animals. Wild free-ranging animals may require higher doses of immobilizing drugs than captive animals of the same species. We also need to consider the injection site, type of remote injection system, and the method of drug administration. Doses established for hand-administered injection to cause a successful immobilization may not be comparable to the dose required for dart-administered injection in the same species.

Controlled studies in wild animals must be performed on captive members of the species to determine the optimal doses of immobilization drugs. However, in nondomestic species, the number of animals available for such studies is often limited. For animal welfare and economic reasons, there is a need for new trial designs to ensure reliable results with a limited number of experimental animals.

Dose-response studies in domestic animals have traditionally involved the testing of different doses in each animal. A consequence of using different animals, however, is that the procedures and the results may be influenced by the biological variation among animals. The Aitken procedures are mathematic models that are based on iteration. Such repeated procedures can be used in clinical research using each experimental animal as its own control. With this approach, the number of experimental animals required to determine an effective dose will be reduced. To the best of our knowledge, the principles of the Aitken iteration procedures have not been used as a method in clinical research. An important aspect when evaluating a new method is the repeatability of the results obtained. A method producing results with poor repeatability will hardly be reliable.
The purposes of the study presented here were to determine and verify optimal hand-administered injection doses of MED-KET in stalled reindeer using the iteration design and to use these doses for the determination of optimal darting doses for reindeer kept in paddocks.

Materials and Methods

Animals—Twelve sexually immature reindeer, 10 males and 2 females, were included in the study. The reindeer were brought from a semidomestic reindeer herd in Finnmark County to the Department of Arctic Biology, University of Tromso (69 N, 19 E), in October 1996. During the first 3 weeks, reindeer were kept separately in adjacent semidoor paddocks of approximately 100 m² each and adapted to a commercially available pelleted ration. The following 2 weeks prior to the trials, the reindeer were placed indoors in a ventilated room in a research facility. In this room, reindeer were kept separately in adjacent stalls, which were separated from each other by 7-m wooden walls. Reindeer were allowed to adapt to indoor feeding and handling. A part of the handling adaptation was to approach and touch the reindeer on the thigh every day to mimic IM injection.

The indoor experiments were conducted in 2 periods, separated by a 3-week period of rest. In the first period, lasting 6 weeks, reindeer were darted in a number of times in accordance with an iteration procedure to establish an optimal dose. The washout period between immobilization procedures for the same reindeer was 7 days. In the second period, lasting 3 days, reindeer were darted once again with the established optimal dose. At the beginning of the trials, the reindeer were 6 to 7 months old. Reindeer were weighed the day before each immobilization procedure. The initial mean body mass was 35.0 (range, 29.0 to 40.0) kg, increasing to 36.7 kg (range, 29.5 to 45.5) the last time reindeer were darted, lasting 3 days, reindeer were darted once again with the established optimal dose. At the beginning of the trials, the reindeer were 6 to 7 months old. Reindeer were weighed the day before each immobilization procedure. The initial mean body mass was 35.0 (range, 29.0 to 40.0) kg, increasing to 36.7 kg (range, 29.5 to 45.5) the last time reindeer were darted, lasting 3 days, reindeer were darted once again with the established optimal dose.

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in an induction time of < 150 seconds and \( D_1 \) (\( k \leq 1 \)) represented the dose with the shortest induction time > 210 seconds, the next dose was \( D_{1.2} = (D_{1.1} + D_2)/2 \).

**Prediction method, outdoor experiments**—On the basis of the iteration procedure, an optimal hand-administered injection dose was determined for each reindeer. Each dose was given to the same reindeer when they were darted the first time in the paddocks.

On the basis of the assumption that the curve describing the relationship between dose and induction time for darted reindeer in paddocks lies in parallel above the curve for stalled reindeer that received a hand-administered injection (Fig 1), optimal darting doses could be calculated from a mathematical expression for the relationship between 2 hyperbolic curves. However, to reduce the complexity we made a linear adjustment, assuming that the optimal darting dose is proportional to the established optimal hand-administered injection dose. Then, the ratio between indoor and outdoor doses is equal to the ratio between indoor and outdoor injection dose. The process for predicting the darting dose for reindeer is explained using the following description: \( D_0 \) = optimal hand-administered injection dose indoors; \( D_x \) = optimal darting dose outdoors; \( I_y \) = induction time caused by \( D_0 \); \( I_x \) = induction time caused by \( D_x \) when darted; and, \( I_z \) = induction time caused by \( D_0 \). The predicted optimal darting dose is given by the following formula:

\[
D_x = D_0 \frac{I_z - I_y}{I_y - I_x}
\]

The optimal darting doses (\( D_x \)) were predicted after measuring the individual induction times (\( I_x \)) produced when reindeer were darted in the paddocks with the same doses that were optimal when given with a hand-administered injection indoors (\( D_0 \)). The amounts of MED and KET were transferred to 2-ml sterile syringes for outdoor experiments, using 0.5-ml insulin syringes with 0.4-35-mm collared needles. The biceps femoris muscle in the heavy musculature of the hind limb using 0.8 \( \times \) 40-mm needles. Sterile water was then used to achieve a total injection volume of 2 ml. All reindeer were monitored throughout the immobilization period. The ATI was injected IM in the opposite thigh 45 minutes after administration of MED-KET. If a reindeer had signs of drug overdose during immobilization, it was to be treated IV with ATI.

**Results**

The iteration procedure was successfully conducted in all reindeer. In 2 reindeer, the initial dose was optimal. In 3 reindeer, the optimal doses were determined within 2 immobilization procedures. Four reindeer were immobilized 3 times to identify the optimal doses (Fig 2). In these reindeer the initial dose was doubled for the second immobilization procedure. The second dose resulted in an induction time of < 150 seconds. The third immobilization procedure with 0.09 mg of MED and 0.45 mg of KET/kg resulted in an induction time within the predefined interval of 150 to 210 seconds.

Four immobilization procedures were required in another 2 reindeer to identify an optimal dose, which was lower than the initial dose for 1 of the reindeer. In this reindeer the initial dose resulted in an induction time of 128 seconds (Fig 2). Following the iteration procedure, the initial dose was halved for the next immobilization procedure. This dose and the dose used for the third attempt were too low, whereas the fourth immobilization procedure with 0.05 mg of MED and 0.26 mg of KET/kg resulted in an induction time within the predefined limits.

One reindeer received a total of 6 immobilization procedures (Fig 2). The initial dose was doubled twice, first to 0.12 mg of MED and 0.60 mg of KET/kg and then to 0.24 mg of MED and 1.20 mg of KET/kg before an induction time of < 150 seconds was achieved. The fourth immobilization procedure with 0.18 mg of MED and 0.9 mg of KET/kg resulted in an induction time just outside the upper limit of the predefined window. The fifth immobilization procedure resulted in an induction time just outside the lower limit, before the sixth resulted in an induction time within the predefined window. The mean optimal hand-administered injection dose was 0.10 mg of MED with 0.50 mg of KET/kg, and...
the median dose was 0.09 mg of MED/kg and 0.45 mg of KET/kg. However, a considerable dispersion among reindeer was detected (Table 1). The mean induction time was reduced by 166 seconds (95% CI, 19 to 314) when the initial dose of 0.06 mg of MED with 0.3 mg of KET/kg was changed to the optimal dose (Table 2).

No significant difference was found between the first and the repeated immobilization procedures in terms of the induction time for optimal hand-administered injection doses, although the dispersion for the repeated immobilization procedure was significantly larger (Table 2, Fig 3). The mean difference in induction time between the first and the repeated immobilization procedures with the optimal hand-administered injection doses was 4 seconds (95% CI, -29 to 36; Table 3). However, the induction time range for the repeated immobilization procedure was larger than the predefined optimal time interval.

Only 1 reindeer had a difference in induction time between the first and the repeated immobilization procedures that was outside the agreement limits (Fig 3), and the agreement index was sufficiently positive (Table 3). However, a significant negative correlation was found between the difference in the 2 induction times and the mean of the same 2 measurements. This negative correlation was, however, caused by 1 outlier and reduced to $r = -0.20$ by excluding data from the reindeer concerned.

All dart-administered injections were evaluated as IM injections. When darting reindeer with their optimal hand-administered injection dose, the induction times varied from 177 to 504 seconds. The mean induction time increased from 171 seconds when the dose was given repeatedly with a hand-held syringe (Table 2) to 306 seconds (95% CI, 237 to 375) when the same dose was given by dart-administered injection. The mean and the median predicted optimal darting dose for reindeer in paddocks was 0.15 mg of MED/kg and 0.75 mg of KET/kg.

The predicted optimal darting doses created a mean induction time 5 seconds greater than the upper limit of the predefined interval. Additionally, the induction time range was larger than the set interval (Table 2). The mean induction time caused by the predicted optimal darting dose was slightly, but not significantly, greater than the mean induction time measured for the repeated indoors immobilization procedure with the optimal hand-administered injection dose. The mean difference between these induction times was 44 seconds (95% CI, -16 to 104; Table 3). The linear relation between the 2 induction times was not significantly different from the line of equality (Fig 3). The difference in induction time between immobilization procedures with the optimal hand-administered injection dose given indoors and the predicted optimal darting dose was not outside the agreement limits for any of the reindeer. The agreement index was positive. A positive, but not significant, correlation between the differences in induction time between the 2 situations was detected.

During the iteration procedure, 2 reindeer had signs of drug overdose when they received an injection of 0.12 mg of MED and 0.6 mg of KET/kg. Arterial oxy-

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**Figure 2**—Relationship between induction time and dose of medetomidine hydrochloride to determine optimal hand-administered injection dose of medetomidine and ketamine hydrochloride (MED-KET) in captive reindeer. The predefined induction time was 150 to 210 seconds (horizontal lines in graphs), and the initial dose of MED-KET was 0.06 mg of MED/kg and 0.3 mg of KET/kg. Panel A: graph of the most common situation in which the optimal dose is higher than the initial dose (determined from 3 immobilization procedures). Panel B: graph of data from the reindeer with an optimal dose that was lower than the initial dose (determined from 4 immobilization procedures). Panel C: graph of data from the reindeer with the highest optimal dose (determined from 6 immobilization procedures).
Figure 3—Panel A: induction times of the first optimal hand-administered injection dose (OPT) versus repeated optimal hand-administered injection doses (REP OPT); and Panel B: induction times of REP OPT versus the predicted optimal darting dose (OPT DART) in 12 captive reindeer. Data are plotted around the lines of equality. Each dot represents 1 reindeer. Differences between the induction times for OPT versus REP OPT (panel C) and between the induction times for REP OPT versus OPT DART (panel D) are plotted against the mean of the same 2 measurements. The mean difference and the agreement limits are given as dotted lines. Each dot represents 1 reindeer.

Table 1—Established optimal immobilizing hand-administered injection and darting doses of medetomidine hydrochloride and ketamine hydrochloride in twelve 6- to 9-month-old captive reindeer

<table>
<thead>
<tr>
<th>Variables</th>
<th>MED (mg/kg)</th>
<th>KET (mg/kg)</th>
<th>MED (mg/kg)</th>
<th>KET (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>0.10 (0.04)</td>
<td>0.50 (0.20)</td>
<td>0.15 (0.04)</td>
<td>0.75 (0.22)</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.065–0.125</td>
<td>0.325–0.625</td>
<td>0.122–0.178</td>
<td>0.63–0.91</td>
</tr>
<tr>
<td>Range</td>
<td>0.0525–0.195</td>
<td>0.2625–0.375</td>
<td>0.085–0.211</td>
<td>0.425–1.055</td>
</tr>
</tbody>
</table>

MED Medetomidine hydrochloride. KET Ketamine hydrochloride. CI Confidence interval.

Table 2—Comparisons of induction times after injection of the initial dose, the optimal hand-administered injection doses, the optimal hand-administered injection doses when repeated, and the predicted optimal darting doses of MED-KET in twelve 6- to 9-month-old captive reindeer

<table>
<thead>
<tr>
<th>Variables</th>
<th>INI</th>
<th>OPT</th>
<th>REP OPT</th>
<th>OPT DART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>341 (243)</td>
<td>175 (18)</td>
<td>171 (50)</td>
<td>215 (66)</td>
</tr>
<tr>
<td>95% CI</td>
<td>187–496</td>
<td>164–186</td>
<td>139–203</td>
<td>173–257</td>
</tr>
<tr>
<td>Range</td>
<td>128–920</td>
<td>150–208</td>
<td>132–317</td>
<td>90–328</td>
</tr>
</tbody>
</table>

INI Initial dose. OPT Optimal hand-administered injection doses. REP OPT Repeated optimal hand-administered injection doses. OPT DART Predicted optimal darting doses. See Table 1 for key.

Table 3—Agreement regarding induction time of MED-KET between OPT and REP OPT and between REP OPT and OPT DART in twelve 6- to 9-month-old captive reindeer

<table>
<thead>
<tr>
<th>Variables</th>
<th>OPT vs REP OPT</th>
<th>REP OPT vs OPT DART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean difference (s)</td>
<td>4</td>
<td>44</td>
</tr>
<tr>
<td>SD of the difference (s)</td>
<td>51</td>
<td>94</td>
</tr>
<tr>
<td>Mean induction time (s)</td>
<td>173</td>
<td>193</td>
</tr>
<tr>
<td>Agreement index</td>
<td>0.41</td>
<td>0.03</td>
</tr>
<tr>
<td>No. of agreement limit outliers (%)</td>
<td>1 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Correlation* (r value)</td>
<td>0.79</td>
<td>0.28</td>
</tr>
</tbody>
</table>

*Correlation between the mean and mean difference in induction times. See Table 2 for key.
gen saturation decreased in both reindeer. At the same time, their respiratory effort became shallow. Both reindeer were treated IV with ATI and retained in the study. No other signs of drug overdose were seen during the study, and the established optimal doses were determined to be clinically acceptable.

**Discussion**

From an animal welfare point of view, the induction time, or the time elapsed from administration of the drug until the reindeer is immobilized, should be short so that the reindeer can be found, handled, and clinically monitored within a reasonable period. An extended induction time may allow the reindeer to become unnecessary excited and run for long distances, increasing the chances for injuries, hyperthermia, or escape. Because the induction time is an important criterion for a successful chemical immobilization, it was chosen to be the main variable in our study.

The iteration procedure used in our study is based on the diagonal Aitken iteration procedure, which is a mathematic method to find the intercept between a straight line and a function. Preferably, when using this method on reindeer, an exact predefined limit for the appearance or disappearance of signs is needed. In the planning stage of the study, 3 minutes (180 seconds) was, therefore, agreed upon to be an optimal induction time. However, in practice it is almost impossible to find the optimal immobilizing dose if the induction time should be exactly 180 seconds in all reindeer. Therefore, an optimal induction time interval had to be defined. According to the mathematic iteration procedure, such an interval is not the best situation, so it had to be defined as narrow as possible. However, from a clinical point of view, the interval had to be long enough to discriminate among different doses. For this reason, the predefined optimal induction time interval was set to 60 seconds (150 to 210 seconds).

To start the iteration procedure, the initial dose of MED-KET used in our study was at the lower end of the dose range reported in the literature. The combination of MED-KET is reported to have a wide margin of safety. However, the iteration procedure involves a potential risk of overdosing if drugs with a low therapeutic index are used. Although various dose ratios for MED and KET in reindeer have been reported, no specific recommendations are given in the literature. The chosen ratio of 1:5 chosen between MED and KET has been successfully used in free-ranging reindeer.

To use the iteration design in a study to determine drug doses, the drugs must have the fundamental characteristic of an increasing response when the dose is increased. \(\alpha\)-2 Adrenoceptor agonists and KET are known to induce sedation and anesthesia in a dose-dependent manner, although a ceiling effect will be reached at a certain dose amount of \(\alpha\)-2 agonists.

In idealized or in vitro systems, the relation between drug concentration and effect is described by a hyperbolic curve. It was reasonable to assume that the relationship between the dose amount of MED-KET and the induction time also is hyperbolic. Our results support this assumption. In such situations, the diagonal Aitken iteration procedure is the optimal method to estimate the intercept with a straight line, with the minimum number of iterations. In our study, the straight line is represented by the optimal induction time limits. Nevertheless, the diagonal Aitken iteration procedure is a mathematic procedure that assumes that the outcome is a fixed number without any variation. In contrast, in a clinical study, the outcome will be a stochastic variable. This means that the variable, in this instance the induction time, has a probability distribution. The inherent random variation in the variable may therefore cause a larger number of required iterations than what would be expected in the mathematic procedure. The worst possible consequence of such random variation could be a never-ending iteration circle. However, to predict the individual dose-response curves, it is sufficient to restrict the number of iterations to a maximum of 8. In our study, only a few iterations were necessary. This supports the applicability of the method.

The repeated administration of the same drug to the same reindeer during the iteration procedure may imply a potential risk for the reindeer to become adapted to the drug by induction of hepatic enzyme systems and increased drug tolerance. As a consequence, the established doses might be overestimated. Medetomidine has a high extraction ratio in the liver. The clearance of such drugs are perfusion-rate limited, and enzyme induction caused by repeated administration is not likely to influence the elimination of the drug. Repeated administration of KET does not lead to development of tolerance or complications. Induction of hepatic microsomal metabolizing enzymes after repeated injections of KET in rats has been described. Therefore, a similar effect of KET in reindeer cannot be excluded.

The dose and the response variable are the 2 main factors in this kind of study. Usually, the doses are fixed to predefined amounts, and the response is observed in different animals. The disadvantage of using such a design is that the required number of animals to be included will be large. An up-and-down method to determine ED50 of propofol for induction of anesthesia in goats and dogs, has been reported. Typically, the first animal is given a single dose, and the response is observed and evaluated. The next animal is given a higher or lower dose, depending on the response to the previous dose. In such studies, however, the total variance consists of variation within and among animals. The iteration procedure uses each animal as its own control, and variation in the drug effects among animals will not influence the validity of the result for each animal. This minimizes the required number of animals. In our study, 12 reindeer were included in the iteration procedure, and all together, 11 different dose amounts were tested. If an equal number of dose amounts had been tested using a parallel group design, at least 198 reindeer would have been required with a significance level of 5%, a power of 90%, and a clinical relevant difference of one SD between the dose amounts.

When the optimal hand-administered injection doses were determined using the iteration procedure, the induction time was the constant, and the dose var-
ied. In contrast, for the repeated indoor immobilization procedure with the optimal doses and immobilization with the predicted optimal darting doses, the induction time was an independent variable. Consequently, the induction time ranges had to become larger in both of these situations, compared with the induction time range of optimal doses during the iteration procedure. If both the induction time ranges should be within the predefined interval, the iteration procedure had to be performed on the basis of a narrower interval. The induction time observed during the iteration procedure was repeatable, which indicates that the iteration procedure is a suitable method for determination of optimal hand-administered injection doses of MED-KET. The slightly longer mean induction time obtained for the predicted optimal darting doses and the increased induction time range do not alter the conclusion of optimality.

The suggested prediction method was based on the assumption that the curve describing the relationship between dose and induction time for darted reindeer in paddocks would lie in parallel above the curve for stalled reindeer that received an injection by hand-held syringe. The results obtained supported this assumption. The mean predicted optimal darting dose was about 50% higher than the mean optimal hand-administered injection dose. The higher dose requirement in darted reindeer in paddocks, compared with stalled reindeer that received hand-hand-held injections, may be the result of factors inherent to the darting technique. Such factors may be the stress involved in being hit by a dart, delayed absorption, and reduced efficacy of the drugs. The drugs may be injected into poorly vascularized tissues, the impact of the dart may cause tissue trauma and bleeding, there may be leakage from the injection site, and a portion of the drug solution may not be injected and may remain in the needle or in the dart. To immobilize wapiti (Cervus elaphus canadensis) within 3 minutes or less with A-3080, dart-administered injection doses were approximately 3 to 10 times higher than the doses injected by hand. The dose requirement may also be influenced by the type of remote injection systems used in different studies.

Animals kept in paddocks are thought to be more easily disturbed than those already restrained, and higher doses of immobilizing drugs are thus being required. However, because the same tamed reindeer were used in the experiments indoors and outdoors in our study, it is reasonable to assume that the higher dose requirement to create the same induction time when the reindeer were darted was mainly caused by factors inherent in the dart technique.

The results support the assumption that the relationship between dose and induction time is hyperbolic. However, the suggested prediction method is based on that this relationship is linear and may, therefore, underestimate the optimal darting dose. Using a hyperbolic relation instead of a linear may strengthen this method.

Although 2 different methods of drug administration were used, no clinically relevant difference was found between the induction times caused by the determined optimal doses for hand- and dart-administered injections. This was further supported by the results of the agreement analysis on this variable between the 2 situations. Therefore, according to the definition of an optimal dose, the predicted darting doses could be considered as optimal. The predicted increase in the dose amount from the indoor to the outdoor situation seemed to be relevant.

Free-ranging reindeer are expected to have a higher amount of stress and excitement than captive reindeer when approached and darted. The optimal darting doses of MED-KET for free-ranging reindeer are probably higher than the darting doses found in our study. Furthermore, reindeer in an other physiologic or genetic status may react differently to the these drugs.

In conclusion, the established optimal immobilizing doses of MED-KET for hand- and dart-administered injections in captive reindeer are comparable to the doses given in the literature. The iteration procedure seems to be applicable for the type of study described here. When clinically acceptable, this design may also be useful for dose-response studies in other species, using appropriate predefined limits for the main clinical variable.

The suggested dose-prediction method seems to be applicable for the determination of optimal doses of MED-KET in captive reindeer. It may also be used to find the optimal dose of MED-KET in free-ranging reindeer and reindeer in other physiologic, genetic status, or environmental conditions.

References


