Reversible chemical restraint of free-range cattle with a concentrated combination of tiletamine–zolazepam, ketamine, and detomidine

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Abstract

The aim of this study was to determine the efficacy of a concentrated combination of tiletamine–zolazepam (TZ, 0.53 mg/kg body weight (BW)), ketamine (Ket, 0.53 mg/kg BW), and detomidine (Det, 0.04 mg/kg BW) in the immobilization of free-range cattle for clinical procedures. The combination was administered intramuscularly to 53 animals. Anesthesia was reversed with the $\alpha_2$-adrenoceptor antagonist atipamezole. Locoregional anesthesia was provided with lidocaine when required. The TZKD combination induced suitable immobilization for minor surgical procedures or medical treatments. Anesthetic onset was rapid, taking a mean of 6.1 min (standard deviation (SD) 2.8 min). The duration of anesthesia depended on the time of administration of the antagonist; the animals recovered in the standing position in 12.9 $\pm$ 8.9 min after the administration of atipamezole. The quality of anesthesia and analgesia were satisfactory. In conclusion, this TZKD combination can be used for both immobilization and minor surgical procedures in free-range cattle.

Introduction

Chemical restraint of free-range ruminants in the field has been obtained with a combination of the opioid etorphine and the tranquilizer acepromazine (Immobilon; Novartis Animal Health UK Limited, Frimley, United Kingdom), which can be used in association with an $\alpha_2$-adrenoceptor agonist (1–3). Immobilon has been used extensively as an immobilization agent in ungulates. In Spain, and in several other countries, Immobilon has been banned for safety reasons or has legal restrictions as a scheduled substance. Pharmacologic alternatives include tiletamine and zolazepam (TZ) plus ketamine (Ket), combined with an $\alpha_2$-adrenoceptor agonist (4–6). However, little information is available regarding the use of these drugs in free-range cattle (7–10). Recently, a combination of TZK with detomidine (Det) was tested in calves, and its efficacy as an immobilization combination agent producing anesthesia and analgesia was confirmed (11). The objective of this study was to determine the clinical efficacy of TZKD used in free-range cattle under field conditions.

Materials and methods

Animals

A prospective observational clinical study from July 2007 until September 2011 was conducted with free-range cattle from 8 ranches. Free-range bovines requiring chemical restraint for diagnostic or therapeutic (surgical or medical) reasons were included in the study independently of breed, gender, and age. No animals were excluded because of administered treatment or health status. However, animals in which restraint was clearly not achieved, most likely owing to a failure in drug administration (such as broken darts), were excluded, and their data were not recorded.
Drug combination and administration

For the drug combination, 500 mg of 10% Ket (Imalgene 1000, 5 mL; Mérieux Laboratorios, Barcelona, Spain) and 40 mg of 1% Det (Domosedan, 4 mL; Pfizer Animal Health, Alcobendas, Spain) were added to a vial containing 250 mg each of lyophilized T and Z (Zolletil 100; Virbac, Esplugues de LLlobregat, Spain). The final solution contained 52.6 mg/mL each of TZ and Ket and 4.2 mg/mL of Det; the total volume was 9.5 mL.

All of the animals were given the same dose, selected on the basis of pilot field studies, in a volume of 1 mL/100 kg of body weight (BW): 0.53 mg/kg BW of TZ, 0.53 mg/kg BW of Ket, and 0.04 mg/kg BW of Det. An additional dose (50% of the initial dose) was given to those animals whose procedures lasted longer than the expected duration of a single dose and was administered when the first spontaneous pinna movement was observed. The additional dose was calculated from clinical criteria and in relation to the estimated time for completion of the clinical procedure. Body weight was estimated visually. Weight tapes were not considered, because the correlation coefficients have not been determined for these breeds (12). When needed, locoregional anesthesia was provided with 2% lidocaine plus epinephrine.

The method of TZKD administration depended on the distance from the animal as well as the material and facilities available. Remote intramuscular injection with a blowpipe 15 mm in diameter and high-performance 5-mL darts (Telinject USA; Agua Dulce, California, USA) or a syringe was used whenever possible. The injection site depended on the field conditions but was chosen in the following order of preference: back of the thigh, rump, loin, and neck.

The effect of the combination was reversed in all of the animals with the α₂-adrenoceptor antagonist atipamezole (Antisedan; Pfizer Animal Health, Alcobendas, Spain), 0.02 to 0.06 mg/kg BW, given intravenously. The time of administration varied according to procedural requirements.

Data collection

The following times were recorded: onset of anesthesia (defined as the time from administration of the drug combination until the animal became recumbent, either sternally or laterally), duration of anesthesia (defined as the time from the onset of recumbence to the administration of atipamezole), recumbence time (defined as the amount of time that the animal remained recumbent, with its head on the ground), and recovery time (defined as the time at which the animal regained a standing position).

Analgesia was evaluated according to the response of the animal to a needle prick in the rump and was rated as excellent (absence of response), fair (mild response, with mild muscle fasciculation), or poor (very responsive, with moderate to severe muscle fasciculation) (4). The quality of the anesthesia was rated as good (good anesthesia and analgesia), fair (good anesthesia and fair analgesia), or poor (fair anesthesia and analgesia).

The volume of the anesthetic combination administered, the dose and route of administration of the antagonist, the estimated weight of the animal, the method of administration, and the site of injection were also recorded.

| Table I. Procedures requiring immobilization and anesthesia with tiletamine-zolazepam, ketamine, and detomidine (TZKD) in 53 free-range bovines |
|--------------------|-----------------|-----------------|
| Category of procedure | Procedure technique | (number of animals) | Locoregional technique |
| (number of animals) | (number of animals) | number of procedures) |
| Ophthalmologic (31) | Subconjunctival infiltration (31) | Topical infiltration of ocular globe (31) |
| Surgical (20) | Orchiectomy (11) | Testicular infiltration (7) |
| Goring repair (3) | Abscess treatment (3) | Local wound infiltration (9) |
| Abdominal herniorrhaphy (2) | | |
| Farm transfer (1) | — | — |
| Lameness (1) | Joint infiltration | — |

Statistical analysis

Means and standard deviations (SD) were calculated for the quantitative variables. Additionally, a decision tree was constructed with the induction and recovery times considered as independent variables. All of the analyses were done with SPSS software, version 15 for Windows (SPSS, Chicago, Illinois, USA).

Results

For the 53 animals (50 males and 3 females) whose data were included in the study, the age ranged from 5 d to 15 y (mean 3.1 ± 3.1 y) and the body weight from 35 to 650 kg (mean 335 ± 156 kg). Of these animals 42 were fighting bulls and 11 of the local red mottled strain. These animals were anesthetized for the reasons presented in Table I. Most of the procedures lasted less than 1 h and were considered to be minimally or moderately painful. The procedure took longer for the repair of 2 abdominal hernias and 1 goring, and additional doses of the combination were administered to prolong the anesthesia.

The mean dose of the anesthetic combination was 1.07 ± 0.13 mL/100 kg BW (Table II). Animals that received an additional dose (half of the initial dose) did so an average of 42 ± 3 min after the initial dose. In 1 of the herniorrhaphy cases, 3 additional doses were required to prolong anesthesia, the total volume being 13.3 mL (2.9 mL/100 kg BW). The combination was administered by blowpipe (n = 39), syringe (n = 11), or pole syringe (n = 3) to the back of the thigh (n = 21), rump (n = 18), loin (n = 6), neck (n = 4) and, accidentally, tail (n = 1), shoulder blade (n = 1), rib cage (n = 1), or head (n = 1). The analgesic response to a needle prick was excellent in all cases. The quality of anesthesia was rated as good in 51 cases and fair in 2 cases (orchietomy without locoregional anesthesia).

Table III presents mean data for the anesthetic variables measured. The duration of anesthesia ranged from 5 to 119 min. The decision-tree analysis showed no relationship between the recumbence time
and the animal’s breed, farm, age, gender, or body weight, the dose/volume of TZKD, or the mode or area of administration. Of the 53 animals, 26 lay in sternal recumbency and 27 in lateral recumbency, 19 of the latter dropping their head to the ground. According to the procedural requirements the animals were maintained in sternal (n = 33), lateral (n = 18), or dorsal (n = 2) recumbency. In all cases the head was positioned to prevent regurgitation.

The mean dose of atipamezole was 0.9 to 3.1 times higher than the dose of detomidine (Table II). The antagonist was administered 6 to 41 min after the TZKD except in the 3 animals that required additional doses; in those cases the antagonist was administered 75 to 124 min after the initial dose of TZKD. The recovery time was independent of the total dose/volume of TZKD or atipamezole and of the atipamezole/detomidine dose ratio.

### Table II. Doses of the TZKD components and of the $\alpha_2$-adrenoceptor antagonist atipamezole, and the ratio of these agents, administered to the 53 animals

<table>
<thead>
<tr>
<th>Units</th>
<th>Tiletamine–zolazepam</th>
<th>Ketamine</th>
<th>Detomidine</th>
<th>Atipamezole</th>
<th>Atipamezole/detomidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/kg</td>
<td>0.56 ± 0.07</td>
<td>0.56 ± 0.07</td>
<td>0.045 ± 0.005</td>
<td>0.03 ± 0.01</td>
<td>0.7 ± 0.2</td>
</tr>
<tr>
<td>mL/100 kg</td>
<td>1.07 ± 0.13</td>
<td>0.5 ± 0.2</td>
<td></td>
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</tr>
</tbody>
</table>

BW — body weight; SD — standard deviation.

### Table III. Times measured after administration of the anesthetic combination and the antagonist

<table>
<thead>
<tr>
<th>Variable</th>
<th>Animal group (number); mean time (± SD), min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (53)</td>
</tr>
<tr>
<td>From TZKD administration until</td>
<td></td>
</tr>
<tr>
<td>Onset of anesthesia</td>
<td>6.1 ± 2.8</td>
</tr>
<tr>
<td>Head drop</td>
<td>7.9 ± 3.4</td>
</tr>
<tr>
<td>Atipamezole administration</td>
<td>23.6 ± 19.4</td>
</tr>
<tr>
<td>Duration of anesthesia</td>
<td>17.5 ± 19.4</td>
</tr>
<tr>
<td>From atipamezole administration until</td>
<td></td>
</tr>
<tr>
<td>Head lift</td>
<td>5.6 ± 5.0</td>
</tr>
<tr>
<td>Standing</td>
<td>12.9 ± 8.9</td>
</tr>
</tbody>
</table>

SD — standard deviation.

In this observational study, the dose used in the free-range cattle, 1 mL/100 kg BW, easily allowed the immobilization of bulls weighing up to 650 kg. The volume of anesthetic drugs has been a major limitation and has conditioned the choice of drugs and dosages and prevented the use of commercial formulations. In the present study, a solution of 10% ketamine and 1% detomidine was used as a solvent to dilute lyophilized tiletamine–zolazepam. This mixture allowed a reduction in the total volume of the combination while maintaining the required dose of each drug.

Rapid induction of anesthesia is a key issue for chemical restraint in wild animals (17) and reduces the likelihood of complications. Most animals receive anesthesia under stressful conditions and in some instances after a period of increased muscular activity before the drugs can be administered by dart. With the TZKD combination the time required for the induction of anesthesia was independent of the mode of administration (method and site), indicating its effectiveness. The mean induction time was 6.1 min, similar to that found in a randomized controlled study of the same drug combination and doses in calves (11). Furthermore, considering that the combination was administered to animals of different ages and breeds and in very different conditions (11), the anesthetic effects appear to be highly consistent. Similar induction times (6 to 9 min) have also been observed in different breeds of cattle (8). The induction time was 7.5 min in banteng (Bos javanicus) restrained with detomidine, tiletamine, and zolazepam (15) and in wood bison restrained with a combination of medetomidine, tiletamine, and zolazepam (16). Although times may exceed 10 min (15), the ideal induction time would be shorter to allow the use of these combinations under field conditions (15) and to prevent capture myopathy (14).

## Discussion

The anesthetic combination TZKD produced adequate immobilization and anesthesia to allow all the procedures to be done in the free-range cattle under field conditions.

The doses of drugs used in the anesthetic combinations administered to free-range cattle and wild ruminants are within a relatively narrow range, but high variability has been observed in their effects (8,13–15), and not all combinations of dissociative anesthetics and $\alpha_2$-adrenoceptor agonists produce adequate anesthesia. Most anesthetic combinations cannot be used in wild ruminants or free-range cattle owing to the volume that would usually be required for administration by dart and several injections may be required to reach the dose necessary to produce immobilization (14–16), which may preclude the use of these agents in field conditions.
Reversal of anesthesia is a requirement under field conditions to limit the possibility of attacks from surrounding animals. In this study, the antagonist was administered within 30 min except in 6 animals, for which administration was 30 to 40 min after the dart was used, suggesting that the TZKD combination induced anesthesia lasting at least this long. Moreover, animals that required a longer anesthesia time received the first additional dose no earlier than 40 min after initial administration of the combination. In fact, the anesthesia time was slightly longer in our study than that observed in young calves (30 ± 8 min) (11).

Analgesia was not tested or measured, although the level was adequate to perform all procedures, including the surgical procedures. Nevertheless, locoregional techniques, including local infiltration in the incision, were used in the cases of hernia repair, orchectomy, and ophthalmologic procedures (altogether in 47 of the 53 cases), and the local anesthesia would have improved the analgesia.

The animals were not fasted, although this factor does not seem to have resulted in side effects such as regurgitation or bloat, which have often been described in ruminants (18). There was increased production of saliva, which is normally observed in ruminants under injectable anesthesia (19). However, the saliva production was not considered to be profuse and did not cause sufficient accumulation in the oral cavity to require aspiration or endotracheal intubation.

The anesthesia was reversed with atipamezole, an α2-adrenoceptor antagonist. Although tiletamine, zolazepam, and ketamine were not antagonized, clinical reversal of the combination is easily obtained and also allows the reversal of respiratory depression (20). Phencyclidines (21,22) are N-methyl-D-aspartate receptor antagonists and cannot be antagonized. The dose of atipamezole used in this study (0.02 to 0.06 mg/kg BW) allowed the reversal of anesthesia without causing excitation. The relatively low atipamezole/detomidine dose ratio of 0.7:1 used in this study was chosen on the basis of the results of pilot studies in which rapid reversal of anesthesia was achieved with the lowest possible dose. Dose ratios between 1.1:1 and 1.6:1 have also been used in nondomestic ruminants (15,23), although higher dose ratios, between 3:1 and 6:1, are commonly administered (10). Although unlikely, a severe reedation effect in the animals in this study was not assessed, and therefore it is possible that higher dose ratios might be necessary to ensure full antagonism.

High variability in recovery time has been observed after administration of the α2-adrenoceptor antagonist. Differences between species and breeds, anesthetic drugs and doses, chosen antagonist and dose, and route of administration may account for the observed differences. The antagonist reverses only the effects of agonists of α2-adrenergic receptors; thus, the recovery time and its quality can be influenced by residual effects of other drugs used concurrently.

The present study excluded animals that failed to respond as expected to the anesthetic combination. Failure of anesthesia delivery was determined when animals were not recumbent within the first 10 min after drug administration. No record was made of the excluded animals, although they could have provided additional information related to the rate of administration failure. Owing to the consistency of the results obtained from the animals included in the study, administration failure, rather than variability of the TZKD combination, is the most likely reason for the lack of sedation in the excluded animals.

An important limitation of the study was that oxygenation was not determined. In a previous study in calves, the most important adverse effect of this anesthetic combination was respiratory depression leading to potentially dangerous hypoxia (11). Although oxygen supplementation could be suggested, it is not a realistic option under field conditions; therefore, it is highly advisable to adequately position the animal in right recumbency with the head lifted to avoid regurgitation and to monitor the mucous membranes.

In conclusion, low volumes of the TZKD combination administered with darts allowed the immobilization and anesthesia of wild cattle. The induction of anesthesia was rapid, and the duration was sufficient to perform all of the procedures. However, additional doses could be administered to prolong the anesthesia time when necessary. In all cases, the effects of the TZKD combination were clinically reversed with the antagonist atipamezole.

References


