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The Importance of Refining Anesthetic Regimes to Mitigate Adverse Effects in Very Young and Very Old Wild Animals: the European Badger (*Meles Meles*)

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ABSTRACT

Safe and effective anesthesia is vital to the welfare of animals used in laboratory and field research, yet very young and very old animals may benefit from refinements to standard protocols and the therapeutic mitigation of adverse effects. Here we report rare but important instances of adverse effects across a sample of 11,645 anesthesia procedures, involving 1806 individual European badgers (1987-2018). Small cubs (<2.3 kg) benefitted from being administered just 50% of adult anaesthetic dose rates, else a proportion were at risk of exhibiting protracted recovery from sedation. These individuals responded well to treatment with a glucocorticoid (0.1 mg/kg Dexadreson® / dexamethasone). Females older than 8 yrs were susceptible to seizures, treatable with benzodiazepines (0.2 mg/ kg midazolam). We advise that practioners working with less familiar wild species are alert to these kinds of welfare risk factors and have appropriate treatment on hand to alleviate adverse effects.

Keywords: *Anesthesia, Adverse effects, European badger, Geriatric, Cubs, Seizures*

INTRODUCTION

Safe and effective anesthesia is fundamental to the welfare of a substantial proportion of animals used in various laboratory or wildlife research projects. Indeed, advising on the design and refinement of appropriate anesthetic protocols is central to the remit of the Animal Welfare and Ethical Review boards of academic institutions and biomedical laboratories. In the UK, such careful consideration is mandated under the Animals (Scientific Procedures) Act (1986), ASPA and under similar legislation in other jurisdictions [1].

A major challenge when developing appropriate anesthetic regimens is, however, that a protocol that best suits the majority of subject animals may bring about adverse effects at the tail ends of the normal distribution of typical population responses, such as in very young or very old animals. In some circumstances these less-suitable research subjects may be excluded from experiments, but in ecological field research and conservation programs it is often necessary to try to capture, sedate and sample the complete population. Even if these individuals are rare in a natural population (as is usually the case with only a few elderly individuals surviving in the wild), if large numbers of animals are caught and processed by assiduous long-term studies, then ultimately a substantial number of procedures may benefit from specific anesthetic refinements. In order to ensure high standards of animal welfare for the entire population being studied it is thus crucial to report such adverse effects, as mandated under the ASPA, and to develop appropriate treatment regimes with the advice of veterinarians.

Here we describe the treatment of occasional adverse sedation effects observed for a small proportion of very young and very old European badgers (*Meles meles*; hereafter 'badger'). We do so in the spirit of good practice and in accord with the recommendations of Animal Care and Ethical Review guidelines, and Home Office guidelines under the ASPA. Aside from the general point this illustrates on the need to give special care to very young and very old age classes, refining badger anesthesia is singularly relevant because of the large numbers of individuals caught and sedated as part of studies and management interventions investigating

their role in the epizootiology of bovine tuberculosis in the UK [2] and Ireland [3]. Badgers are also among the wild animal species anaesthetized most often by veterinarians in general practice, to treat wounds or injuries arising from road traffic accidents [4]. Our research group has reported previously on anesthetic options suiting badgers [5, 6, 7, 8]. This has led us to favour the use of ketamine hydrochloride [5]. When used solely in badgers it produces rapid and consistent induction, complete unconsciousness, good muscle relaxation, well maintained cardiopulmonary function and gingival mucous membrane coloring, as well as having a wide safety margin [9].

This anesthesia protocol is well-suited to the majority of the population; nevertheless, side effects may occur, especially if ketamine is not stored well, or if doses are insufficient to induce full sedation in animals that are initially agitated [10]. Side effects may include sneezing, light and sound sensitivity, skeletal muscle hypertonicity, excessive salivation, retention of swallow reflex, and, in rare instances, spasms, and convulsions [5,6,7].

Our specific objective here was to report that a proportion of very small cubs tended not to recover from anaesthesia at a rate typical of the adult population, but instead would have entered into a protracted torpor without treatment. At the other end of the age distribution, we also note a pattern where a proportion of elderly individuals can experience seizures under sedation. These were ad hoc observations, and not part of a clinical anesthetic trial, where our ASPA project license and ethical remit requires that we treat all adverse effects appropriately in consultation with our Named Veterinary Surgeon (NVS), and we cannot withhold treatment to see what untreated outcomes would be. Similarly, we did not treat animals unnecessarily that exhibited no adverse effects.

Despite the need to adapt and refine anesthetic protocols, it was vital to trap these age classes to achieve our research objectives, where our general focus involves behavioral ecology, population ecology, and genetics – including a portfolio on juvenile diseases and senescence (reviewed in 11). Cubs must be caught as early as it is safe to do so in order to make an accurate assessment of initial cohort size from which juvenile mortality rate can be estimated [12], and to assign parentage and fecundity functions [11]. Care was taken not to trap cubs until weaned, and this restricted our earliest trapping window to late May / early June (badgers are typically born in mid-Feb; [13]); however, these young/small cubs present the need for precise anesthesia.

Older animals must be trapped in order to estimate maximum lifespan [12] and to study reproductive and somatic senescence [14]. However, as with other species (e.g., [15]), as badgers become elderly their general health and condition tends to deteriorate [16] making them more susceptible to anesthetic risks. A further complication being that it is not possible to estimate the age of a badger reliably from observation alone.

We describe the incidence of these adverse effects and effective treatments with a view to raising awareness that responses to very young and very old age classes may be atypical, especially if anaesthetizing less-familiar wild animal species.

MATERIALS AND METHODS

Badger Trapping and Sedation Protocols

These data arise from lab-book records and observations of 11,645 sedations involving 1806 individual badgers processed between 1987 and 2018. These were trapped as part of a long-term mark-recapture ecological study conducted on the high-density (40 individuals/km$^{2)}$) badger population resident in Wytham Woods, Oxford shire, UK (reviewed in [12]). Badgers in this population were trapped routinely and anaesthetized three to four times annually, and each received an individual identifying inguinal tattoo upon first capture for subsequent re-identification and accurate age assignment [11]. All protocols and procedures employed were approved by the the University of Oxford's Zoology Department Animal Welfare and Ethical Review board and followed the expert advice from our Veterinary Service Department (Named Veterinary Surgeons, NVS, under the Animals (Scientific Procedures) Act, 1986, currently PPL: 30/3379).

Traps, baited with peanuts, were checked between 6.30-8.00 am and captured animals were transferred to holding cages and transported to a central field station before being anaesthetized (typically starting no later than 8 am) via intramuscular injection with ketamine HCl (various brands used over the study: Vetalar® Pfizer Ltd, UK; Narketan® Vetoquinol UK Ltd; Ketaset® Zoetis UK;

Ketamindor® Chenelle Animal Health UK), 100 mg/ml USP into the quadriceps [5,6]. Adults received a dosage of 20 mg/kg, estimating badger weights visually, typically to an accuracy of 0.5kg. Very small cubs were weighed in their holding cages, and then the weight of the cage was deducted, to estimate body-weight more accurately.

Induction time averaged 3-4 minutes for all ages. Sedation resulted in complete immobilization and unconsciousness, adequate for us to make morphometric measurements, as well as perform minor invasive procedures: e.g., blood collection, sub caudal gland secretion collection, enema administration and applying an identifying tattoo on first capture, enabling us assign age accurately and to track individual life-histories. To assess quality of anesthesia we monitored, heart rate (femoral pulse; bpm), quality of respiration (regular deep, irregular deep, irregular shallow, shallow panting), mucous membrane color (normal/pink, pale, grey/blue, white), relaxation (complete, stiff, hunched, semiconscious); for details see [10]). A typical procedure (from initial sedation to return to holding cage, see details in [17,12]) required 5-15 minutes per badger, depending on the range of procedures involved; for example, occasional radio-collaring involved longer handling periods [10].

After processing, each badger was returned to its holding cage, and placed in a dark quiet place recovery room. Thereafter, blinking, paddling and re-gaining motor reflex sequentially indicated the onset and progression of recovery. Badgers were typically assessed as fit for release (in accord with conditions defined in our PPL: i.e., the resumption of full motor skills and lucidity with health status equivalent to when trapped initially) after 3 hours of recovery and returned to their site of capture.

Given our > 80% annual recapture rate ([12]; and thereafter from further analysis), badgers in this study have become somewhat accustomed to these capture and restraint protocols (see [10]). Nevertheless, in instances where animals were agitated, or would benefit from analgesia (i.e., those with naturally occurring bite wounds/ injuries), we used ketamine / butorphanol (Torbugesic®; Zoetis inc., UK) combinations (20 mg/kg ketamine + 0.4 mg/kg butorphanol, intramuscular injection into the quadriceps), where this opioid potentiates sedation [18,19] – although none of the elderly badgers reacting adversely, and only 5 cubs, were given this regimen initially.

Adverse Effects

Very young / small cubs: During spring 2001 a number of unusually small cubs were caught. One of these (Female 837; 1.9 kg) failed to exhibit a normal rate of recovery, and after 30 minutes remained sedated but with deep and regular respiration, good gum perfusion and a strong heart rate; as though in a state of physiological torpor, of which badgers are capable (see Newman et al. 2011). We urgently consulted our NVS who prescribed an intra-muscular dose of Solumedrone® (Pfizer, UK; 1 ml / 40mg ampoule methylprednisolone: for reasoning behind this choice of treatment see Discussion). Subsequently, we reduced the dose rate of ketamine (see Results) and have treated other very small / immature cubs not exhibiting typical rates of recovery prophylactically with an alternative glucocorticoid, 0.1mg / kg dexamethasone (Dexadreson®; MSD Animal Health, NZ). Note; our objective was to redress this adverse effect immediately, not to undertake any clinical trial of treatment by either withholding Dexadreson to see what would ultimately happen to the cub, or to unnecessarily treat cubs responding normally, for comparison.

Geriatric badgers: On the 11th Sept 2010 we observed a badger (female 859F; Table 1) present with seizures under sedation, i.e. initial muscle rigidity, followed by rapid rhythmic convulsions. Convulsions lasted ca. 30 seconds then stopped, and recovery was normal thereafter with the individual fit for release after 3 hrs. In consultation with our NVS we decided upon a treatment involving intramuscular administration of 0.2 mg/ kg midazolam (a benzodiazepine, Versed®), supplemented with 0.4 mg/ kg butorphanol (administered only to badgers sedated with ketamine alone). Thereafter, when other badgers have presented seizures, this midazolam treatment was administered. See results for responses to treatment and patterns among the proportion of badgers presenting seizures.

Anesthetic Data Extraction

All data collected and anaesthetic monitoring throughout our long-term study, from 1987-2018, was recorded on data sheets which was then transfered to a Microsoft Access database. To assess how well mitigation worked for cubs

suffering protracted sedation we extracted all records mentioning the administration of dexamethasone, along with the individual's weight, sex, body condition, and any other notes on treatment.

To assess how effective this mitigation was in alleviating symptoms among that small proportion of adults exhibiting seizures under sedation we extracted records of instances of seizures / convulsions, along with the individual's sex, age, pathophysiological response, and any other notes on presentation and treatment. All statistical analyses were performed using RStudio (0.99.896) and R (R-3.2.4).

RESULTS

Cubs

To alleviate protracted sedation we have treated 19 cubs (of 984 procedures conducted on cubs in spring trapping sessions 2000-2018; i.e., 1.9%) with an intra-muscular dose of 0.1mg / kg dexamethasone (Dexadreson® or equivalent glucocorticoid synthetic predisolone analogue; [20, 21]), in combination with warmed subcutaneous fluid (saline or lactated ringer) therapy (not more than 35-40 ml per site and not more than 50 ml/kg in total. Note, intra-venous (iv) fluid administration was impractical in a recovering wild animal. All of these treatments were made when cubs were young during our May/June trapping session.

Furthermore, we identified a pattern where all of this sub-sample of cubs requiring dexamethasone were less than 2.3 kg (a condition only noted during their early development in May/June trapping sessions); however, this does not imply that all cubs under 2.3 kg require dexamethasone, with just 1.9% of total cub procedures requiring treatment. Indeed, from 2010 we introduced a second mitigation step, establishing that a normal level and duration of sedation could be induced in cubs <2.3kg using half the adult dose rate of ketamine (i.e., 10 mg/kg). This regimen reduced the incidence of prolonged recovery requiring dexamethasone treatment to just 6 (of 475; 1.2%) cubs processed thereafter in May/June.

After treatment, cubs recovered lucidity and full motor control over a period of 20-25 minutes. Prior to implementing this treatment regimen the longest duration of torpid-like sedation we observed lasted 90 minutes, until a glucocorticoid was administered. Throughout protracted sedation cubs exhibited hearts rate of 180-120 bpm (consistent with ketamine anaesthesia, decreasing over time) a normal breathing rate (regular, c. 6 deep breaths / min), normal rectal temperature (38.6C) and no other pathophysiology of concern (zero mortality).

Combinations involving butorphanol (n=5) were found to worsen this effect through respiratory depression (and medetomidine would be counter-productive, reducing peripheral circulation). After dexamethasone administration onset of recovery was stimulated within 2-5 minutes, and all cubs have been fit for release with no latent malaise after the normal 3 hrs post-anaesthetic recovery period in a dark, quiet room, as per our established protocol [10].

Geriatric Badgers

Seizure/convulsions under anaesthesia occurred in four individuals (12 procedures), all at least 8 years old, and all female (1.74% of females > 8; Table 1). This adverse effect was not observed in any other age group. All of these individuals were processed under our standard anaesthetic protocol (20 mg/kg ketamine). Notably, these elderly females also took longer for anaesthetic induction, requiring, on average 8.4 ± 4.2 mins (n=12), compared to 3-4 mins in typical procedures [10]; providing some pre-warning that adverse effects might be anticipated, to consider treatment.

Seizures presented with initial muscle rigidity, followed by rapid, rhythmic convulsions. Mucous membranes became pale, but not cyanotic. Other symptoms included incontinence, hypersalivation and prolific nasal mucous secretion, causing sternuation (sneezing).

Our best treatment results involved the intramuscular administration of 0.2 mg/ kg midazolam (a benzodiazepine, Versed®; Roche, Switzerland), supplemented with 0.4 mg/ kg butorphanol, which caused the rapid cessation of seizures (< 1 min; consistent with [22]). Fluorescent laboratory lights were also switched off during these compromised procedures to alleviate any contributory risks of visually-induced occipital seizures [23]. This midazolam treatment was repeated, as necessary during anesthetic recovery, after a 30 min interval. These elderly badgers were also administered subcutaneous fluids by syringe (as per cubs, above), to remediate any potential dehydration arising. Affected badgers treated with this regimen were fit for release after 3 hrs, as per

our normal protocol; all except one instance (badger 1115F, case 08/09/17) where convalescence was extended through 24hrs prior to release, during which time this badger was provided (and consumed) peanut butter mixed with honey and water, *ad libitum*.

Table1. *Cases of tonic-clonic seizures in four individual badgers sedated with ketamine.*

Badger ID	Year of birth	Number of captures since birth	Occurence of seizures/ convulsions and pathophysiological response noted during anaesthesia	Age at seizure	Anaesthetic protocol, initial and top up (+) with timing
911F	2003	32	15/11/10 ; padding, irregular deep respiration, epileptic seizure	7 years 9 months	2ml ketamine
			08/09/ 11 ; epileptic seizure, body hunched	8 years 7 months	2ml ketamine + 1.5ml ketamine (+6min) + 1ml ketamine (+5min)
			11/11/11 ; seizre	8 years 9 months	2ml ketamine
			05/06/12 ; continuous twiching	10 years 4 months	2ml ketamine
			24/08/13 ; seizure	11 years 6 months	2ml ketamine + 0.4ml ketamine (+5min)
859F	2001	27	11/09/10 ; irregular pulse, seizure	9 years 7 months	2ml ketamine + 0.5ml butorphanol (+5min)
			26/05/11 ; irregular deep respiration, seizure	10 years 3 months	2ml ketamine + 1ml ketamine (+7min) + 0.5ml butorphanol (+3min)
			09/09/11; epilepsy	10 years 7 months	2ml ketamine
1115F	2006	24	31/ 05/ 14 ; epileptic seizure	8 years 3 months	2ml ketamine + 1ml ketamine (+6min) + 1ml ketamine (+5min)
			13/11/15 ; twicthing, high HR, seizures	9 years 9 months	2ml ketamine + 1ml ketamine (+3min) + 1ml ketamine (+8min)
			08/09/17 ; repeated fits, growling, epilepsy	10 years 7 months	2ml ketamine
912F	2003	27	21/08/13 ; hard to sedate, seizures stoped after lights turned off.	10 years 6 months	2ml ketamine + 1ml ketamine (+4min)

Note: *all badgers experiencing seizure were treated with midazolam 0.2 mg/ kg (Versed®)*

DISCUSSION

Only 5% of badgers lived to be > 8 years old in our Wythan study population, with just 1% reaching 12, with a maximum verified lifespan of 14 years [11]. Nevertheless, we average 30 procedures per year on badgers older than 8 years.

Notably, none of these individuals exhibited any convulsive symptoms while conscious during the trapping, pre-sedation or release phases of our protocol. Furthermore, this Wytham wild badger population has been subject to extensive video surveillance over many years (following [24]), and no seizures have been noted among subjects observed. Ketamine hydrochloride is used widely as a dissociative anesthetic agent in many domestic and wild mammals, particularly for carnivore species [25,26,27]. Ketamine is a short acting (dose dependent) drug with a wide safety margin that produces a loss of sensation and consciousness with moderate analgesia [28]. As an anesthetic it can be used solely or in combination with other drugs[6] and our previous work has shown that it provides good muscle relaxation, complete unconsciousness and a wide safety range in badgers [5,6, see also 7]. Nevertheless, we recommend that dose rates in young animals < 2.3 kg should be reduced significantly (50% adult dose) to prevent prolonged recovery times, although in small cubs a minor risk is still present even with

reduced dosage. We found that treatment with dexamethasone (where we initially treated with Solumedrone®; a similar glucocorticoid), stimulated the onset of recovery effectively in these cases. This novel treatment application was arrived at through the innovation of our NVS, but has proven very effective at alleviating adverse effects.

We infer that the mechanism through which torpor-like states were alleviated in cubs was due to glucocorticoids increasing cardiac output while simultanously decreasing peripheral vascular resistance, and stabilising the cellular and lysosomal membranes against endotoxic damage (Zoetis Ltd drug sheet), thus also aiding the metabolism of any residual ketamine. Having first treated this condition with Solumedrone® we swapped to Dexadreson® (dexamethasone – a potent glucocorticoid with minimal mineralocorticoid activity and 10-20x the anti-inflammatory activity of prednisolone) which had comparable effectiveness in alleviating symptoms but was more cost effective than Solumedrone.

In geriatric badgers > 8 yrs old, ketamine appeared to induce tonic-clonic seizures in some individuals, as noted in susceptible humans [29] and dogs [30,31,32]. Furthermore, all four (repeatedly) affected individuals were females, where Monteiro *et al.* [33] report that female dogs are prone to more frequent cluster seizures than males, possibly due to pro-convulsan effects of oestrogen which enhances neuronal excitability [34]. Through genetic pedigree [35], we also ascertained that two of these four elderly individuals were siblings, suggesting a possible degree of heritability of this geriatric condition, although more data would be needed to fully support an epilepsy diagnosis.

The effect is consistent with the proconvulsant properties reported for ketamine [31,32] during anaesthesia involving both humans [29] and animals (mostly dogs: [31, 32]). Ketamine increases the release of endogenous excitatory amino acids such as glutamate and aspartate [36] and is generically contraindicated for animals with pre-existing seizure disorders. Seizures generally result from insufficient Gamma Aminobutyric Acid (GABA) that inhibits the activity of over-exited neurons arising from the stimulatory effect of neurotransmitters such as glutamate and aspartate [22].

Paradoxically, ketamine can also cause a N-methyl-D-aspartate (NMDA, glutamate-gated cation channels with high calcium permeability) receptor blockade, hence it has also been used to treat status epilepticus in dogs and humans [37, 38, 31]. Nevertheless, when used at higher dosages, without combination (especially GABA-agonists), or pre-medication (i.e benzodiazepines), it will typically increase spontaneous muscular activity [31].

Seizures among elderly badgers responded well to treatment with midazolam; which henceforth we will include in initial combination anaesthetic regimens if/when high-risk individuals are recognized. Benzodiazepines, such as midozolam, are strong anticonvulsants used as the primary treatment for drug-induced seizures, which act mainly on the $\alpha GABA_A$ subunit [22]. Benzodiazepines enhance GABA activity by increasing chloride channel opening frequency which hyperpolarizes the neuron [39], inhibiting neurone messaging, thus terminating convulsive activity.

CONCLUSIONS

We advise that veterinarians and research practitioners are alert to the particular risks of sedating very small/young wild-animal subjects requiring much smaller dose rates of anaesthetic, and are prepared to use steroid / fluid therapy. Similarly, special care should be given when sedating very elderly wild animals (evident in badgers from toothwear under examination; [40]) and especially older female individuals, with benzodiazepine treatment on hand, or including midazolam as part of an anesthetic combination for higher-risk individuals, along with facilities for post-procedural care. Because these effects are comparatively rare, and because most wild-animal studies comprise far smaller sample sizes of captured and sedated individuals than our study, with less reliable re-capture rates to elucidate patterns, these effects can easily be over-looked and/ or attributed to inter-individual effects rather than age-dependency. We thus speculate that similar sedation-associated risks might also be prevalent in other wild mammals, but have hitherto remained unreported. We therefore commend Ethical Review and ASPA regulations processes for encouraging the reporting and treatment of adverse effects in research.

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