Methods of analgesia and euthanasia in backyard poultry

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Summary

The keeping of chickens in the backyard is growing in popularity in urban and suburban areas, numbers of animals are increasing and as a result small animal practitioners are more and more frequently faced with chickens as patient. Clinical conditions in backyard poultry often require the treatment of pain. The challenges regarding the adequate use of analgesics include: 1. Recognition and assessment of pain, which necessitates good knowledge of chicken behaviour, 2. Selection of the adequate drug and dosage based on evidence that is often not available for chickens, but spread over different species of birds, and 3. Implementation of food safety regulations, which result from the dual use of backyard poultry as «food producing pets».

Analgesics used in chickens include opiates, nonsteroidal anti-inflammatory drugs and local analgesics. The opiate butorphanol has been shown to have an analgesic effect of approximately two hours in chickens. Tramadol and methadone show some promise as analgesics, but more evidence is needed especially regarding bioavailability. The nonsteroidal anti-inflammatory drugs meloxicam and carprofen appear to have an analgesic effect. Variable metabolism between breeds of chickens and the risk of accumulation, especially when used for periods exceeding five consecutive days, need to be taken into account regarding dosage. Lidocaine and bupivacaine have successfully been used in chickens for nerve blocks and spinal anaesthesia and should be included as part of multimodal analgesia especially during surgery. In cases, where termination of life is necessary the preferred method consists of an injectable anaesthesia followed by intravenous application of a barbiturate.

Keywords: barbiturate, chicken, local anaesthesia, NSAID, opioid, pain

Methoden der Analgesie und Euthanasie in der Hobby-Hühnerhaltung


Schlüsselwörter: Barbiturat, Huhn, Lokalanästhesie, NSAID, Opioid, Schmerz
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Introduction

Over the last two decades the number of chickens kept as backyard poultry has increased rapidly worldwide. Backyard poultry are typically kept in groups of less than 20 animals in urban or suburban areas. While the original reason for keeping backyard poultry consisted in self-sufficient supply of eggs, and to a lesser amount meat, the emotional value has recently gained importance, rendering backyard poultry «food producing pets» in the Western world. A survey in the United States of America (USA) identified food for home use (95%), gardening partners - fertilization (63%), pets (57%), or a combination thereof, as that the major motives for keeping chickens. 13

Most backyard poultry are hens. The breeds of chicken vary depending on the regions. In Switzerland, commercial layer hybrids predominate, but species of special breeds such as New Hampshire, Welsummer and Wyandotte, especially the small breeds of the latter two, are also popular. The focus on layer breeds constitutes an increased probability of disease occurrence, especially reproductive tract disorders. 30

The dual use of backyard poultry as source of food for human consumption as well as pets make them a unique challenge for veterinarians especially in regard to the use of therapeutics. Owners of backyard poultry will typically consult small animal veterinarians familiar with the treatment of pets, such as dogs, cats or rabbits, for help, however, the use of medication in birds typically differs significantly in dosages and frequencies from mammals. In addition, small animal practitioners are usually not familiar with the treatment of farm animals and the respective legislation related to the use of medications as well as the issue of food safety including residues and withdrawal periods. In general, small animal practitioners’ expertise with birds is limited to psittacine or passerine birds but the examination and treatment of backyard poultry is a marginal topic in veterinary study curricula. A survey in the USA confirmed the increase of backyard poultry.35

Commercial broilers lameness has been extensively investigated from the poultry industry. An overview of decreased and increased behaviours in relation to pain stimuli in chicken with a focus on commercial management situation and laboratory management has recently been published. 3 Although usually associated with different aetiologies, it is helpful to acknowledge studies from the poultry industry. An overview in chickens may be subtle and require a good knowledge of the physiological behaviour and the reaction to acute and to chronic pain. Due to the high metabolism of avian species requiring a nearly constant food update during daytime, anorexia, a potential manifestation of pain, needs to be considered a more severe clinical sign in a chicken compared to a dog. In reverse, food uptake does not necessarily imply the absence of pain.

The main knowledge about nociception in chicken originates from studies from the poultry industry. An overview on decreased and increased behaviours in relation to pain stimuli in chicken with a focus on commercial management situation and laboratory management has recently been published. 3 Although usually associated with different aetiologies, it is helpful to acknowledge studies from the commercial poultry and deduct information for the pain assessment in backyard poultry.

Assessing pain in chickens

Chickens are often considered as stoic animals. However, it could be argued that this presumed stoicism, may only be a reflection of the observer’s inability to recognise pain. The biology and anatomy of chickens make them a special challenge to recognise pain behaviour and to assess pain. Facial expression in birds in general is minimal in relation to domestic mammalian species. Social constraints of chickens within the hierarchy will result in a suppression of signs of pain to avoid aggressive attention of conspecifics.

These aspects may result in the misconception, that birds feel less pain than mammals. It is well known that mammals and birds share the neuroanatomical and neuropharmacological pathways necessary for pain perception, and therefore there is no reason to assume that birds perceive painful stimuli to a lesser degree than mammals. 5

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Commercial broilers lameness has been extensively investigated and advances have been made to assess objectively degrees of lameness. 28,45 A score from 0 to 5 is given based on the animal’s gait, with 0 revealing no signs of lameness, 4 having a severe defect, including skeletal, muscular or nervous pathologies, but still being able to walk when strongly motivated, and score 5 is given to birds that are incapable of sustained walking.28 This system was adapted for the evaluation of large flocks by measuring what percentage of birds maintained standing position for longer than 15 min. 45 While this method allowed the objective assessment of flocks, the study revealed that chickens with gait scores of 2 and 3 were still able to stand for periods longer than 15 min. This may be due to the fact that standing and walking do not test the same type of pathologies, or it reflects individual ways to cope with pain. In that regard it is also interesting to note the results of a study on a single versus repeated pain stimulus. Progressive removal of...
feathers in chickens elicited marked changes in the bird’s behaviour from an alert agitated response upon initial feather removal to periods of crouching immobility following successive removals. Furthermore, responses to pain will vary between acute and chronic pain. Pain scales as they exist for mammals such as dogs and rabbits, are currently missing for chickens. Behaviours relevant to pain assessment in chickens are summarised in Table 1.

In general, nociception may be indicated by the presence of abnormal behaviour as well as the absence of normal, un-stressed behaviour. Whilst clinical signs such as lameness, anorexia, ruffled feathers (piloerection) and lethargy are often recognised as potential signs of pain, others may easily be overlooked, as such, including aggression, reluctance to interact with conspecifics or care takers, reduced vocalisation. Other signs of pain, such as increased recumbency or inap-petence, may be absent or reduced during the clinical examination and therefore overlooked. In this regard, information provided by owners may be of great support, especially in relation to differing personalities and social hierarchy.

General aspects regarding analgesia and euthanasia

Backyard poultry will often be presented to veterinarians with conditions that are likely to be accompanied by pain and depending on the severity will necessitate treatments that include analgesia or even euthanasia.

An evaluation of the 178 backyard poultry cases submitted to the Clinic for Zoo Animals, Exotic Pets and Wildlife at the Vetsuisse Faculty of the University of Zurich in the years 2005 until 2014 revealed that over 40 % of cases received some form of analgesic treatment, which in most cases was meloxicam. Emergency consultations rate for backyard poultry was higher than for psittacine pet species (40 % versus 30 to 36 %, respectively) and the main emergency diagnosis was trauma (31 %). Backyard poultry in that study had a much higher euthanasia rate compared to psittacine pet bird species (20 % versus 6 to 12 %, respectively).

In general, owners of backyard poultry have a very strong commitment to ethical treatment and seeking relief of disease and pain is an important component. They show an interest in the appropriate diagnosis (64 %) and treatment (66 %) of diseases by veterinarians trained and willing to treat small chicken flocks.

Adequate provision of analgesia constitutes an obligation of professional veterinary treatment, it is relevant to welfare and has a positive effect on the healing process. Reasons for the use of analgesia and or euthanasia are typically acute pathologies, especially trauma from predation or intraspecies aggression or more chronic issues such as degenerative disease or chronic disease especially in relation to the reproductive tract.

Two major challenges must be taken into account when applying analgesic treatment in backyard poultry: food safety regulations and evidence regarding the efficacy of the treatment.

Feed safety regulations vary from country to country. In Switzerland, currently no analgesic drugs are approved for chickens and the use thereof is inevitably always off label, but redesignation on a case by case basis is a feasible option, as this is done for any other medication and for which the software application provided by the Vetsuisse Faculty of the University of Zurich (www.vetpharm.uzh.ch/tak/tools.htm) may provide informations. For example, in the case of the use of the commercial solution of meloxicam and carprofen for dogs and cats, a 28 day withdrawal period for meat will be prescribed for poultry. However, not for eggs, because maximum residue levels (MRL) are missing and it is recommended to contact the Federal Food Safety and Veteri-

Table 1: Selected clinical signs of pain in chicken, their relation to organ systems and degree of severity of pain to elicit the clinical sign.

<table>
<thead>
<tr>
<th>Clinical sign</th>
<th>Relation to organ system</th>
<th>Degree of severity (+ – ++++)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lameness</td>
<td>Musculoskeletal, Neurologic</td>
<td>+</td>
</tr>
<tr>
<td>Recumbence</td>
<td>Musculoskeletal, Visceral / Reproductive, Neurologic</td>
<td>++ – +++</td>
</tr>
<tr>
<td>Piloerection</td>
<td>Visceral / Reproductive</td>
<td>++ – +++</td>
</tr>
<tr>
<td>Somnolence (closing eyes) / Lethargy</td>
<td>Musculoskeletal, Visceral / Reproductive</td>
<td>+++</td>
</tr>
<tr>
<td>Separation from flock</td>
<td>Musculoskeletal, Visceral / Reproductive</td>
<td>+++</td>
</tr>
<tr>
<td>Hyporexia / Anorexia</td>
<td>Visceral / Reproductive</td>
<td>+++</td>
</tr>
<tr>
<td>Aggression (from others or against others)</td>
<td>Musculoskeletal, Visceral / Reproductive</td>
<td>+++</td>
</tr>
<tr>
<td>Reduced vocalisation</td>
<td>Musculoskeletal, Visceral / Reproductive, Neurologic</td>
<td>++ – +++</td>
</tr>
<tr>
<td>Egg production reduced</td>
<td>Musculoskeletal, Visceral / Reproductive</td>
<td>+++ – +++</td>
</tr>
<tr>
<td>Focal preening</td>
<td>Musculoskeletal, Visceral / Reproductive</td>
<td>+ – ++</td>
</tr>
</tbody>
</table>

Degree of severity of pain: -: minor, +: moderate, +++: severe
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Evidences and effects of analgesics: considering the variability of species and breeds

Evidence-based efficacy of the analgesic treatment poses an equally important challenge. There are more than 10'000 species of birds, nearly twice as many as mammals; however, considering all birds as one species is a common misconception when it comes to treatment choices. Pharmacokinetic reactions to analgesics vary not only between different taxa such as birds of prey or psittacines but even between breeds. It has to be kept in mind that simply achieving blood levels considered analgesic in other species, does not necessarily result in an analgesic effect in the species in mind. In addition, some medications, such as opioids, may influence behaviour, which may be confused with an analgesic effect or in the case of sedation as worsening of the condition. Yet, general principles of comprehensive analgesic management are valid for avian species as in any other species, such as pre-emptive analgesia in severely invasive procedures of long durations or multimodal analgesia protocols, e.g. combination of local nerve blocks with systemic analgesics.

In the absence of specific evidence, the practitioner has to make decisions based on the currently available general evidence and has to monitor the effect individually and adjust as necessary. In the absence of species-specific pain scores the value of a generic visual analogue pain score on a scale of 1 to 10 or numeric ratings have been successfully applied in avian medicine in relation to assess pain and response to treatment. This can also be an option for the use of analgesics in backyard poultry.

Analgesics for backyard poultry

The main analgesics used in birds include systemic opioids, nonsteroidal anti-inflammatory drugs (NSAIDs) and local analgesics.

Opioids

The use of opioids is recommended in cases of severe pain including surgery and trauma. In birds, opioids can produce sedation and / or antinociception and they typically have a short terminal half-life. Previously assumed kappa-receptor dominance has not proven consistent for all avian species and in chickens the μ-receptor appears to predominate over delta- and kappa-receptors. However, the distribution of opioid receptors was not only found to be affected by age but also does not appear to offer a predictive values for the analgesic efficacy of the respective opioids, as demonstrated in the detailed discussion below.

Methadone is not frequently used in birds as the literature on its use in birds is still scarce. It is a μ-receptor agonist and an antagonist of N-methyl-d-aspartate receptors. The pharmacokinetics and pharmacodynamics of methadone at a dose of 6 mg / kg administered intravenously and intramuscularly to isoflurane-anesthetized chickens revealed a large volume of distribution, moderate clearance, and a high bioavailability after intramuscular administration. No data are available regarding the analgesic effect, but a dosage of 6 mg / kg intramuscularly resulted in a sparing effect of the minimum anaesthetic concentration (MAC) of isoflurane, an effect which was not observed at a dose of 3 mg / kg.

Morphine is a μ-receptor agonist and appears to sedate chickens at a dose of 2 mg / kg subcutaneously. In another study with chicks of less than 15 days of age, a hyperalgesic effect was noted upon the application of morphine up to 5 mg / kg intramuscularly, potentially due to age-dependent variations in opioid-receptor distribution. The short terminal half-life of approximately one hour presents a further limitation. Until more conclusive results are available, morphine does not appear to be a suitable analgesic for chicken.

Butorphanol is a synthetic kappa-receptor agonist and a μ-receptor antagonist. Experiments in chicken with keel bone fractures revealed that butorphanol 2 mg / kg subcutaneously, increased mobility indices compared with saline treatment. Butorphanol was also found to have an analgesic effect at 2 mg / kg intravenously in lame broiler chickens, which was considered to last approximately two hours.

Buprenorphine is a partial μ-receptor agonist and kappa-receptor antagonist. It was ineffective at providing analgesia in chickens and in grey parrots (Psittacus erithacus) at 0.1 mg / kg intramuscularly and has been disregarded as an analgesic agent in many bird species.

Tramadol is a synthetic opioid derivate and a μ-receptor agonist. It has broad activity with binding at kappa- and delta-receptors, as well as increasing noradrenaline and serotonin levels. Because tramadol can be applied orally it is of interest for backyard poultry medicine. Tramadol has been shown in birds to have some antinociceptive activity, but conclusive studies in chickens are missing and as the following studies in other species reveal, some caveats must be taken into consideration, when attempting to use tramadol in chickens.

In Muscovy ducks (Cairina moschata domestica) with experimentally induced arthritis, both tramadol at 30 mg / kg orally and meloxicam at 1 mg / kg orally improved certain objective variables with regard to pain. This dosage of tramadol is high compared with a study in American kestrels (Falco sparverio) in which 5 mg / kg tramadol orally significantly decreased thermal nociception thresholds. At higher doses of 15 and 30 mg / kg adverse effects such as...
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regurgitation, watery diarrhoea, and polyuria were observed in the kestrels. A possible explanation for these discrepancies may lay in differing oral bioavailability of tramadol between species, possibly due to the difference between carnivore and omnivore digestive physiology. In Hispaniolan Amazon parrots (Amazona ventralis) oral bioavailability following of 11 mg / kg was found to be 24 %, whereas in bald eagles (Haliaeetus leucocephalus) it was almost 98 %. Therefore, in the absence of scientific data, a lower starting dose around 5 mg / kg orally appears advisable in chickens, with increasing dosage titrating to effect.

Fentanyl is a highly potent derivative of morphine and a μ-receptor antagonist. In chicken, a dose dependent positive effect following a single intravenous fentanyl bolus (10 and 30 μg / kg) on MAC of isoflurane was measured. However, this effect was very short, less than 15 min. In another study in different breeds of layer chickens a 25 μg / h transdermal patch maintained plasma concentrations above 0,2–1,2 ng / ml for 72 h. A large interindividual variabil-

ity was observed, which was considered to be a result of variable absorption but could possibly also be a result of the different breeds used in the study. Conclusive studies on the analgesic effect of fentanyl in chickens are missing.

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs act by inhibition of enzymes (predominantly cyclooxygenases), blocking in-

flammatory pathways and reducing both inflammation and pain.

Meloxicam, a cyclooxygenase-2-selective NSAID, is likely the most commonly prescribed analgesic in backyard poul-

try. The metabolism of meloxicam varies not only between bird species but also between breeds of poultry. The elimination half-life of meloxicam following a single intra-

venous bolus of 1 mg / kg is three times as long as that in ducks (Anas platy-

ychnchos), ostriches (Struthio camelus), and turkeys (Meleagris gallopavo). Recently it was found that Leghorn chickens have a shorter terminal half-life of meloxicam compared to Bantam Cochin and Columbian Wyandotte breeds including a shorter residue time in eggs. Hence it has been recom-

mended to reduce the dosing frequency of meloxicam of 1 mg / kg orally to once daily in Bantam Cochin and Co-

lumbian Wyandotte chickens compared to the common twice daily frequency.

Meloxicam appears to be well tolerated at the dose of 1 mg / kg orally or by injection, but analgesia has not been evalu-

ated at this dosage. Higher doses have shown to have an analgesic effect, however in a study with oral meloxicam 5 mg / kg twice daily for 5 days, drug accumulation was apparent and 7 out of 11 chickens developed renal pathol-

ogy and visceral gout, mortality was 36 %. This contrasts a study with American kestrels, that did not develop renal pathologies following oral meloxicam at 20 mg / kg twice daily for 7 days, albeit two out of nine animals developed gastric ulcers and a significant correlation was found be-

tween hepatic lipidosis and meloxicam dose.

Carprofen is another cyclooxygenase-inhibiting NSAID, which has been investigated in chickens and showed prom-

ising results regarding the improvement of mobility in lame chickens. A single dose of carprofen at 1 mg / kg subcuta-

neously improved locomotion for one hour after treatment, the total duration of action was not assessed. Adverse ef-

fects were noted when carprofen was administered at 3 to 4 mg/kg in drinking water, 15 % of birds died on day 10 of treatment and it was concluded that oral short-term (<7 days) therapy for lameness may be safe.

Studies in chickens with newer cyclooxygenase-2-selective NSAIDs such as celecoxib, mavacoxib, and robenacoxib are still missing. Oral bioavailability of mavacoxib was found to be high in cockatiels (Nymphicus hollandicus). These NSAIDs may be promising due to longer action, however this will also affect residue time in meat and eggs and might increase the risk of adverse effects due to accumulation.

Local anaesthesia

The use of local anaesthetics such as lidocaine and bupi-

vacaine for nerve blocks including the brachial plexus, the ischiatic-femoral nerve, or the spinal (intrathecal) anaesthesia is gaining importance as part of multimodal anaesthesia and analgesia in avian surgery. Pharmacokinetic variables for lidocaine when administered at a dose of 2,5 mg ⁄ kg intravenously to chickens anesthetized with isoflurane revealed an elimination half-life of 25 min, which was twice as fast as in humans, pigs and dogs and four times as fast as in cats and rabbits. Local nerve blocks at a much higher dose of 20 mg / kg lidocaine and 5 mg / kg bupivacaine reduced the response to noxious stimuli for approximately 60 min for both drugs. An effect was found only in 66 % of birds tested, which must be seen as a considerably high failure rate. Regarding the success rate, application technique may be a factor, as another study found higher success rates (85 %) for ana-

lgesia of brachial plexus blocks in chicken, apparent by a wing drop for 60 min upon a dose of 10 mg / animal of lidocaine.

Pre-emptive intra-articular bupivacaine at a dose of 3 mg in 0,3 ml saline in chickens with a mean body mass of 1,5 kg was found to be effective for management of experimen-

tally induced arthritis.

With regard to spinal anaesthesia in chickens, the peri-clo-

acal region was successfully anesthetized for 20 min with lidocaine at 2 mg / kg applied into the subarachnoid space at the symsacroccygeal juncture. The use of bupivacaine at a dose of 0,5 mg / kg resulted in an effect of 50 min. Li-
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The main potential adverse effect of lidocaine and bupivacaine are cardiovascular. Bupivacaine at 1,94 mg/kg injected intravenously to chickens anesthetized with isoflurane was associated with a 50% probability of a clinically relevant change in mean arterial pressure and heart rate, whereas a dose of 1,33 mg/kg was associated with only a 1% probability of causing the same effect.12 Lidocaine at 6 mg/kg injected intravenously was not associated with adverse cardiovascular effects.5 It therefore appears that lidocaine at a dose up to 6 mg/kg/h is safe even if applied intravenously, whilst for bupivacaine a lower dose should be used, probably 1 mg/kg if applied intravenously.

An aspect to consider in relation to multimodal analgesia is the use of the injectable anaesthetic agent ketamine. A case report in a prairie falcon (Falco mexicanus) describes the successful use of low-dose intramuscular ketamine at 0,5 mg/kg every 12 h as part of control of self-mutilation during fracture healing.38 In that case ketamine was used together with gabapentin and low level laser therapy.

Euthanasia of backyard poultry

Compared with other avian species, euthanasia of chickens is a relatively straightforward procedure. Chickens, particularly sick chickens, are generally easy to restrain and have prominent right jugular, ulnar and tibiotarsal veins, that are easily accessible for injection of euthanasia solution when indicated.

The methods that can be used in Switzerland in chickens for the termination of life are listed in the Technical Information Animal Welfare No. 16.1.17 and euthanasia must be in accordance with the Swiss welfare legislation. Often inhalational anaesthesia will be used prior to euthanasia to induce unconsciousness. But since direct application of isoflurane is likely to result in agitation, the use of injectable anaesthesia (e.g. with ketamine 10 mg/kg and xylazine 1 mg/kg) is recommended. Subsequently, a barbiturate (e.g. pentobarbital at a dose of 300 to 600 mg/kg) can be safely injected intravenously.

Death must be confirmed by determining final cessation of heartbeat.

It should be expected that euthanized backyard poultry will be frequently taken home for burial by their owners.44 As for all euthanized animals that undergo burial, this has to be performed in accordance to local legal statutes especially as the presence of pentobarbital or other anaesthetics in the carcass could represent a risk to other animals. Furthermore, propagation of infectious diseases such as avian influenza have to be taken into account. Owners taking home their chicken following euthanasia should be advised of the risks and cremation is the recommended alternative.

Concluding remarks

Backyard poultry are increasingly presented as patients in small animal practices and medical conditions frequently necessitate the use of analgesics. The decision, which medication is used, is generally equivalent to other pet animals, but in addition withdrawal times must be taken into account, unless their meat and especially eggs are not used as source of food for human consumption.

Evidence regarding the nociceptive effect of analgesic drugs in chickens is still fragmentary and more research is needed to produce objective assessment of pain and pain relief in chickens, as in birds in general. In the absence of evidence, it is especially important to adapt treatments in relation to clinical observation including changing dosage or interval as needed. In addition, adjunct therapy such as physical therapy but also adaptation in the husbandry (human and other animal presence, noise, decreasing light, accommodating cage setup) are important aspects in pain management in chickens (Figure 1). Among the opioids, butorphanol appears to have the best analgesic effect, taking into consideration that the duration is short and that there is a sedative effect. Methadone and tramadol show some potential but more data is needed. With tramadol a lower starting dose is recommended, which can be increased to effect. Meloxicam is the most frequently used NSAID, apparently safe at a dose of 1 mg/kg, but the analgesic effect at this dosage is questionable. At higher doses, accumulation and the risk for renal pathology must be considered when dosage exceeds five consecutive days. The same applies to carprofen, which has been shown to have an analgesic effect. Local anaesthesia is a valuable additional to multimodal analgesia during surgery. Lidocaine and bupivacaine have successfully been applied and appear to result in regional anaesthesia for 30 to 60 min. Cardiovascular adverse effects should be observed when using bupivacaine, especially intravenously.
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Figure 1: Besides the use of analgesics, husbandry management is important in pain management. This backyard chicken has undergone femoral fracture surgery. Attention is given to provide a well-padded resting area, with food and water being easily accessible. The box can be partitioned and is spacious enough to add a second animal as partner when advisable.
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et Carprofen semblent avoir un effet analgésique. En ce qui concerne la posologie, il convient de tenir compte du métabolisme variable selon les races de poules et du risque d’accumulation, en particulier en cas d’utilisation pendant des périodes supérieures à cinq jours consécutifs. La lidocaïne et la bupivacaine ont été utilisées avec succès chez les poules pour les blocs nerveux ainsi que pour l’anesthésie spinale et devraient être incluses dans l’analogésie multimodale, en particulier pendant la chirurgie. Dans les cas où il est nécessaire de mettre fin à la vie de l’animal, la méthode de choix consiste en une anesthésie injectable suivie d’une application intraveineuse d’un barbiturique.

Mots clés: barbiturique, poulet, anesthésie locale, AINS, opioïde, douleur

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