PRUDENT USE OF MEDICINES IN CROCODILIANS WITH SPECIAL REFERENCE TO ANTIMICROBIAL AGENTS

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INRODUCTION

Good treatment practices imply the latest evidence-based treatment and the effective, safe and responsible use of veterinary medicines or medicinal substances in animals based on risk-benefit assessment. The responsible use of veterinary medicines includes implementing practical measures and recommendations intended to improve crocodilian health and welfare. In addition with the use of antimicrobial agents the importance of preventing or reducing the selection, emergence and spread of antimicrobial-resistant bacteria in crocodilians and humans. The prudent or responsible use of antimicrobial agents in veterinary medicine is the scientific and technically directed use of these compounds, which forms an integral part of good treatment practices (OIE 2018; WHO 2017; WVA 2011)

The availability and use of veterinary medicines in animals are controlled in most countries and are based on the authorization of the medicine, for one or more indication, in one or more animal species, based on confirmation of efficacy for each indication and safety in the particular animal species, and on the quality of the medicine (OIE 2018). Veterinary medicines authorized for use in a country are either freely available over-the-counter, from a pharmacy, or on prescription from a veterinarian, depending on the category or schedule of the medicinal compound/substance and the control measures instituted in each country. Some medicinal substances such as narcotics (eg opioids) and psychotropic substances (eg sedatives) are also controlled by international conventions.

Very few, if any, veterinary medicines have specifically been developed and/or authorized for use in crocodilians. Medicines in crocodilians are veterinary medicines or drugs used extra-label or off-label, based on the clinical experience of the veterinarian or on published information of drugs used in crocodilians (Helmick *et al*. 2002, 2004a,b; Martelli *et al*. 2009; Rivera *et al*. 2012) or reptilians. There is limited knowledge on the pharmacology and safety of drugs or medicinal substances used in crocodilians. Known physiological differences in renal blood flow, liver metabolism and body compartments (eg in reptiles compared to mammalians) may result in significant differences in the absorption, distribution and metabolism of drugs in crocodilians (Coulson *et al*. 1987; Moore *et al*. 2009). This has implications on the effective and safe use of drugs in crocodilians and in prescribing a withdrawal period following treatment.

Most drugs administered to animals bring about residues in animal-derived products, such as in meat and skin in crocodilians. Such residues of the medicinal substance and/or its metabolites may have adverse toxic or harmful effects on consumers' health. Maximum residue limits (MRL) in animal edible products are thus established by the relevant national regulatory authority or by Codex Alimentarius under the joint Food and Agriculture of

United Nations (FAO) and World Health Organisation Food Standard Programme (JECFA 2018), which signifies the level at which the residue would be safe for human consumption. Maximum residue limits are not routinely established for skin, other than in fish and poultry.

Antimicrobial and anti-parasitic agents are the primary group of veterinary medicines or medicinal substances of importance used for treatment in production animals, including crocodilians (Tisdall *et al*. 2017). Resistance and resistance development of these agents are inevitable risks of their use that need to be considered and minimized. Antimicrobial resistance poses a very serious threat to both human and animal health. Without effective antimicrobials, many of the benefits of modern medicine will be lost, with potentially catastrophic consequences for human and animal health and well-being. The use of antimicrobial and anti-parasitic drugs in aquaculture has particular differences from their use in terrestrial animals (Romero *et al*. 2012). In crocodilians, such as in aquaculture, they are added to feed, but may also be added directly to the water. This may result in selective pressure in the exposed environments (usually water) and may affect a wide variety of bacteria.

There is also a growing body of evidence suggesting that the extensive use of antimicrobials in animals (and especially in food animals) may play a role in the emergence and dissemination of antimicrobial-resistant bacteria. Commensal bacteria (ie bacteria that occur naturally in the gastrointestinal tract) can constitute a reservoir of resistance genes for (potentially) pathogenic bacteria (Burch 2016; O'Neill 2016; Orand *et al*. 2016; Scandell and Bruce 2015; Tang *et al*. 2017). Resistant commensal bacteria of animals might contaminate meat (products), water and the environment and so reach the intestinal tract of humans. Workers and farmers may be directly exposed to resistant organisms.

GOOD TREATMENT PRACTICES

The development and implementation of a health management plan developed in conjunction with a veterinarian or person experienced in crocodilian health is essential and fundamental to applying good treatment practices. Epidemiological factors that affect the occurrence and spread of the disease, such as means of transmission and life cycle of disease organisms, need to be considered in the design of any disease treatment regimen and control program. Effective biosecurity and hygiene programs are the basis of preventing the introduction and spread of disease or infection.

All treatments need to be based on a working or definitive diagnosis, animal welfare considerations and no indiscriminate use of veterinary medicines or medicinal substances. Good treatment and control practices of disease or any other ailment are evidence-based and require rational (clinical and pharmacological considered) choice of and responsible use of medication. Drugs for the modification of body function (eg gastrointestinal motility, cardiovascular effects and urinary tract function), anesthesia, analgesia, sedation, tranquilization and immobilization are mostly administered and used by veterinarians or under the control of a veterinarian.

The principles for selecting and applying medication in crocodilians should include:

- Benefits of treatment and use of a veterinary medicine or medicinal substance needs to outweigh the risks of use.
- Selecting and using drugs that are effective and safe for the indication intended and where available only veterinary medicines that are authorized for use in crocodilians.
- Adhering to dosage instructions (ie dose, method of administration, interval of treatment and duration of treatment) for those veterinary medicines authorized for use in crocodilians or as prescribed by a veterinarian.
- Taking special caution on extra-label or off-label use of veterinary medicines or medicinal substances in crocodilians. The efficacy, safety, dosage instructions and withdrawal periods established in other species cannot simply be applied or extrapolated for use in crocodilians. Extra-label or off-label use and compounding of a medicine require supervision and instruction of a veterinarian.
- Applying withdrawal periods as indicated for those veterinary medicines authorized for use in crocodilians where meat is used for human consumption or as prescribed by a veterinarian. Withdrawal periods prescribed for a particular medicine are not applicable unless they have been specified for crocodilians. For any veterinary medicine or human medicine used extra-label or off-label in crocodilians or any other medicinal substance prescribed or compounded by a veterinarian for which a withdrawal period is not known, a prolonged withdrawal period should be applied in accordance with local guidelines, if these exist. Using at least 5 terminal half-lives of the particular drug-plasma or blood profile in a crocodilian, if known, is a useful guideline.
- Animal caretakers involved in the treatment of crocodilians need to be sufficiently trained in the proper handling of drugs, administration of medication, and the observation of treatment response and recognition of adverse events.
- Maintaining records of the use of veterinary medicines or medicinal substances, including information such as: date of administration; identification of animal or group of animals to which the medication was administered; Indication or clinical condition treated; dosage; adverse events experienced; withdrawal period; and effectiveness of the therapy.

PRUDENT OR RESPONSIBLE USE OF ANTIMICROBIALS

The use of antimicrobials in food animals and aquaculture can be categorized as therapeutic, prophylactic or metaphylactic (Romero *et al*. 2012). Therapeutic use corresponds to the treatment of established infections. Metaphylaxis is a term used for group-medication procedures that aim to treat sick animals while also medicating others in the group to prevent disease. Prophylaxis means the preventative use of antimicrobials in either individuals or groups to prevent the development of infections.

The prudent use of antimicrobial drugs is of paramount importance to maintain the efficacy of antimicrobial drugs used in crocodilian and humans. Measures need to be taken to mitigate for the development of resistance and to prevent or reduce the transfer of resistant

micro-organisms or resistance determinants within crocodilian populations, the environment and between crocodilians and humans, either directly or as the result of product contamination.

Guidelines for the prudent use of antimicrobials have been developed and published by the World Organisation for Animal Health (OIE 2018), World Health Organisation (WHO 2017) and World Veterinary Association (WVA 2011), as well as by several national organizations and national regulatory organizations (FDA 2012), and livestock organizations (RUMA 2014, 2015).

Principles for prudent or responsible use of antimicrobial in crocodilians include:

- Applying good treatment practices, including the principles and guidelines for selecting and using medication in crocodilians, as described above.
- Reducing the use of antimicrobials by disease prevention through improved biosecurity, vaccination programs and management.
- Using antimicrobial drugs only when it is known or suspected that an infectious agent, which is present, will be susceptible to therapy (Helmick *et al*. 2002). Do not apply antimicrobial treatment routinely.
- The prophylactic use of antimicrobial agents in crocodilians should be discouraged;
- Bacteriological diagnosis with antimicrobial sensitivity testing should, whenever possible, be part of the informed professional clinical judgment.
- Prompt, targeted and appropriate treatment to prevent unnecessary pain and suffering to ensure the welfare of animals.
- It is the responsibility of the veterinarian to choose the antimicrobial product, based on his/her informed professional judgment, balancing the risks and benefits for humans and animals (eg the adverse effect of antimicrobials on the intestinal microbiota in crocodilians), which may be involved in important processes such as epithelial proliferation, the promotion of nutrient metabolism and innate immune responses (Romero *et al*. 2012).
- Not using critically important antimicrobials used in humans as first line treatment in crocodilians, unless there is clear scientific evidence. Critically important antimicrobials are defined as classes of antimicrobials that provide sole therapy, or one of limited available therapies to treat serious infections in humans as well as used to treat infections in humans caused by either bacteria that may be transmitted to humans from nonhuman sources, or bacteria that may acquire resistance genes from nonhuman sources (WHO 2017). Antimicrobials further classified as highest priority critically important should be avoided. These include: cephalosporins; glycopeptides; macrolides and ketolides; polymixins; and, quinolones. (See WHO list at https://www.who.int/foodsafety/areas_work/antimicrobial-resistance/cia/en/).
- Administering the antimicrobial drug for as long as needed, preferably based on pharmacodynamic, pharmacokinetic and bacteriological evidence. Always use the dose prescribed and complete the course of treatment.
- Protecting consumer health by ensuring the safety of food derived from crocodilians with respect to residues of antimicrobial drugs.

- Monitoring and recording the response to antimicrobial treatment and usage. Report any suspicion of an adverse reaction to the medicine in either the treated crocodilians or animal caretakers or other staff having contact with the medicine.
- Reduction in therapeutic response through clinical observation and scrutiny of treatment records needs to be noted and reported to management and/or the veterinarian.
- The need for efficacious, scientifically proven alternatives to antimicrobials, is an important part of good husbandry practices.

METHOD OF ADMINISTRATION

Administration of medication to individual, sick animals is the gold standard for treatment of disease and prevention of antimicrobial resistance. Medication can be administered by intramuscular injection to individual crocodilians. Deep intramuscular injection into a suitable site such as the tail immediately caudal to the hind legs is suggested. Appropriate sterile procedures need to be applied with intramuscular injection. It is, however, recognised that in farmed crocodilians, isolation and handling of individual sick animals for antimicrobial treatment may be sufficiently stressful as to exacerbate disease.

When applying treatment to a group of crocodilians, as example per enclosure, medication is mostly administered in feed. The inclusion rate of the medicine in the feed is based on the dose per kg bodyweight, average estimated body weight of the crocodilians treated and the total amount of feed given per day. Thorough and uniform mixing of the medication in the feed is required. This may require formulating a premix by mixing medication into a smaller batch of feed or suitable carrier before mixing it into the final batch of feed.

The administration of any medication by water to a group of crocodilians in an enclosure is strongly discouraged as the dose intake per crocodilian is less certain, as well as due to environmental concerns related to the disposal of the medicated water.

STORAGE AND DISPOSAL OF MEDICINES

Veterinary drugs and medicinal substances should be kept in a secure cabinet or room and access to medicines limited to only persons/employees authorised in accordance with the veterinary prescription or by management.

It is important to adhere to the storage instructions of the veterinary medicine or that prescribed for the medicinal substance to retain the full activity of the drug. The stability of most drugs is adversely affected by high temperatures and humidity.

No medicine should be used that has exceeded its shelf-life and expiry date, unless it has been established that its strength and other properties stated on the label are still within specification.

Medicines suspected to have been improperly stored should be discarded.

All unused, discarded and/or expired veterinary medicines or medicinal substances must be disposed of in accordance with national and local medicinal or drug regulations and not be released into drains, with the liquid effluent or dumped on municipal sites.

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