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Review Articles

Non-Steroidal Anti-Inflammatory Drugs in Food Producing Animals

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Abstract: Providing adequate food supply to meet the demands of a growing population is a challenge for this century. The food producing animals bred in optimized conditions supply a large amount of food derivatives. At the same time, society has become progressively more concerned about animal suffering and aware of the need of pain prevention and treatments. One of the measures aimed at improving animals welfare is pain management a rational and controlled use of the anti-inflammatory drugs such as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). However, NSAIDs residues in biological matrices are still an issue. In addition veterinary pharmacology still has a reduced drug armamentarium if compared with human medicine. In order to address these shortfalls investigations on new NSAIDs (off label drug) in food producing animals are needed.

Keywords: Pain Management, Food Producing Animals, Non-Steroidal Anti-Inflammatory Drugs, Off Label Drugs, Residues

Introduction

Over the last decades, animal production science supported the modernization of food animal husbandry in order to provide adequate food supply to meet the demands of a growing population. The food producing animals bred in optimized conditions supply a large amount of food derivatives (milk, eggs, meat, honey and fish) and produce foodstuffs that are safe for the human consumption.

Furthermore, in the recent years, society has become progressively more concerned about food producing animals suffering and aware of the need of pain prevention and treatments due to the routine husbandry procedures such as castration and dehorning (Bomzon, 2011).

'Freedom from pain, injury and disease' for breeding animals was early recognised by the Farm Animal Welfare Advisory Committee in 1967 as one of the five minimal requirements to guarantee animal welfare, known as the 'Five Freedoms' (Brambell, 1965).

Animal welfare has recently made the headlines of the popular media: mishandling of cows, new laws that ban the use of sow gestation crates and chicken battery cages and hidden cameras at intensive breeding farm are only few examples (Fajt *et al*., 2011).

Pain is a sensory process that results from tissue damage and is intended to prevent further tissue damage following injury. Pain activates numerous physiological reactions that often induce negative effects on well-being and behaviour, as well as on growth and reproduction of the animals. However, the main obstacle for the pain management in farm animals is to recognise, quantify and evaluate the pain status of each individual in a farm or to treat pain in a single individual without disturbing the whole group of animals (Guatteo *et al*., 2012).

In veterinary medicine, recently, pain has been shown to affect animal welfare and production and the interest in the field of analgesia has been drastically increasing (Lee *et al*., 2014). Therefore, the desirable medication associated with the pain status of each individual will be important to treat pain in farm animals.

A similar specific approach designed to minimize pain in laboratory animals is also required in farm animals. Nowadays, the concepts of "Replacement, Reduction and Refinement", called the '3Rs' (Russell and Burch, 1959), used in the design of animals experiments to minimise unnecessary pain, is the basis of a new approach the '3S' 'Suppress, Substitute and Soothe pain. This approach is used to review existing practical solutions and find new solutions to eliminate or alleviate pain in farm animals. It is based on the possibility to "suppress" the procedures or environments that are a source of pain, to "substitute" such procedures by others causing less pain and to "soothe" pain when it cannot be avoided (Guatteo *et al*., 2012).

Table 1. Maximum Residue Limits (MRLs) for the most used veterinary NSAIDs and COX-2 inhibitor

Pharmacologically active substance	Animal species	MRLs (μg/kg)	Target tissue
Carprofen	Bovine	500	Muscle
	Equine	500	Muscle
	Bovine	1000	Liver
	Equine	1000	Liver
Flunixin	Bovine	300	Liver
	Porcine	100	Liver
	Equine	200	Liver
	Bovine	100	Kidney
	Bovine	30	Fat
	Bovine	20	Muscle
	Porcine	50	Muscle
	Equine	10	Muscle
5-Hydroxyflunixin	Bovine	40	Milk
Flunixin	Porcine	200	Liver
	Porcine	50	Muscle
	Porcine	30	Kidney
	Porcine	10	Skin+Fat
Meloxicam	Bovine	65	Liver
	Porcine	65	Liver
	Equine	65	Liver
	Bovine	65	Kidney
	Bovine	20	Muscle
	Porcine	20	Muscle
	Equine	20	Muscle
	Bovine	15	Milk
	Porcine	20	Muscle
	Equine	20	Muscle
Tolfenamic acid	Bovine	400	Liver
	Bovine	50	Muscle
	Porcine	400	Liver
	Porcine	50	Muscle
Diclofenac	Bovine	5	Muscle
	Porcine	5	Muscle
Ketoprofen		No MRL required	
Mefenamic acid	Bovine	10	Muscle
	Porcine	10	Muscle
	Equine	10	Muscle
	Chicken	10	Muscle
Naproxen	Bovine	10	Muscle
	Porcine	10	Muscle
	Equine	10	Muscle
	Chicken	10	Muscle
Oxyphenbutazone	Bovine	5	Muscle
	Porcine	5	Muscle
	Equine	5	Muscle
	Chicken	5	Muscle
Phenylbutazone	Bovine	5	Muscle
	Porcine	5	Muscle
	Equine	5	Muscle
	Chicken	5	Muscle
Firocoxib	Equine	60	Liver
	Equine	10	Kidney
	Equine	15	Fat
	Equine	10	Muscle

Table 2. Analytical methods for the determination of NSAIDs and residues in biological matrices

Methods	Matrices	References
LC-MS/MS	Milk	Daeseleire *et al*., (2003); Gallo *et al*., (2008); Penney *et al*., (2005); Boner *et al*., (2003a)
	Liver	Boner *et al*., (2003b); Croubels *et al*., (2004)
	Fat	Boner *et al*., (2003b)
	Muscle	Boner *et al*., (2003b); Chrusch *et al*.,(2008); Penney *et al*., (2005); Van Hoof *et al*., (2004)
	Kidney	Boner *et al*., (2003b); Chrusch *et al*, (2008); Clark *et al*., (2002); Croubels *et al*., (2004)
	Plasma	Croubels *et al*., (2004); Vinci *et al*., (2006)
	Excreta	Croubels *et al*., (2004)
LC/ESI-MS/MS	Milk	Gallo *et al*., (2008)
	Plasma	Vinci *et al*., (2006)
	Liver	Igualada *et al*., (2007)
	Muscle	Igualada *et al*., (2007)
UPLC-ToF-MS	Milk	Stolker *et al*., (2008)
RRLC-MS/MS	Milk	Dowling *et al*.,(2009)
GC-MS	Liver	Hines *et al*., (2004); Takeda *et al*., (2001)
	Milk	Stolker *et al*., (2008); Dowling *et al*., (2008)
HPLC-UV	Plasma	Cartula and Cusido, (1992); De Veau *et al*., (1998); Ian De Veau, (1999); Jedziniak *et al*., (2007); Fiori *et al*., (2004)
	Milk	De Veau, (1996); De Veau *et al*., (1998)
	Liver	Hines *et al*., (2004)
HPLC-FL	Liver	Hines *et al*., (2004)

Animal welfare issues in food production are now being driven by animal activists, food companies and consumers. Consequently, animal welfare assurance programs have been developed and are encoded in non-mandatory codes or guidelines, government regulations, inter-governmental agreements and corporate programs (Fraser, 2006).

One of the measures aimed at improving animals welfare is pain management by using anti-inflammatory drugs. These substances can be effective in suppressing or preventing inflammation, treating allergy, lowering fever and reducing pain.

The classes of anti-inflammatory drugs differ on the basis of their actions towards the biochemical mediators that are released during inflammation and that propagate the inflammatory response. One of the main classes of anti-inflammatory drugs most used in veterinary medicine for food producing animals is the Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) (Gentili, 2007; Malone *et al*., 2009).

The NSAIDs are widely used because of their ability to reduce inflammatory process. NSAIDs can be classified into several groups according to their chemical structure: The propionic acid derivatives (Ketoprofen, Carprofen, Vedaprofen , Naproxen); the anthranilic acid derivatives (Tolfenamic acid, Mefenamic acid); the nicotinic acid derivatives (Flunixin); the pyrazolones (Phenylbutazone]) and the acetic acid derivatives (Diclofenac); the class of oxicams (Meloxicam) (Dubreil-Chéneau *et al*., 2011).

In veterinary practice NSAIDs are used in the treatment of musculoskeletal disorders, coliform mastitis, pulmonary diseases and enteritis in several animal species. NSAIDs, however, because of their toxicity, can affect the gastro-intestinal, hematopoietic and renal systems. Gastro-intestinal ulcerations are the most common and serious side effect of NSAIDs, especially in cases of overdose or chronic abuse. In the last decade a new sub class of NSAID named Cyclooxygenase-2 selective inhibitor (COX-2), has been developed and introduced in veterinary medicine. A benefit of this class is that it seems to lower the adverse effects triggered by the classical NSAID drugs. On the other side the COX-2 inhibitor drug pharmacokinetic and pharmacodynamic profiles can change from species to species (Kim *et al*., 2014a; 2014b) and very few data in food producing animal species are available so far. Another concern is their cost that so far is much higher than that of classical NSAID.

A wide number of classical NSAIDs are authorized for food producing animals. The widespread use of these drugs presents the potential risk for the consumers if food containing residues enters the food chain. For this reason there is a need for the control of residues and development of methods to monitor their compliance with legislation (Jedziniak *et al*., 2010). In order to protect consumer health, the European Union has set Maximum Residue Limits (MRLs) for these substances. The MRLs range from 10 to 1000 μg kg^{-1}, depending on the compound and matrix (Igualada *et al*., 2007). Table 1 show the MRLs for NSAIDs in food producing animals in different matrices (Jedziniak *et al*., 2010; Gentili, 2007; Dubreil-Chéneau *et al*., 2011; Igualada *et al*., 2007). Differently, only firocoxib in the COX-2 selective inhibitor class is authorized in the European Union in a single farm animal species (horse) with a MRLs range from 10 to 60 μg kg^{-1}, depending on the matrix (Woodward, 2012; EMEA, 2006).

Different methods for the determination of NSAIDs in biological matrices and concerning residues of these drugs in food of animal origins are widely described in the literature (Table 2). Multitude of analyses and low limits of NSAIDs residues in biological matrices make LC-MS/MS the preferable technique for both screening and confirmatory purposes. Moreover, the development of multi-residue procedure for drugs differing in chemical properties is the main challenge in determination of NSAIDs residues (Jedziniak *et al*., 2010).

The steadily emerging concept of pain management in veterinary medicine has resulted in increased interest in the development of new techniques for pain management (De Vito *et al*., 2014). However, veterinary pharmacology still has a limited drug armamentarium. It is pivotal that new human drugs and therapies be tested also in veterinary species (Lee *et al*., 2014).

Furthermore in farm animals, veterinarians are commonly faced with the need to administer drugs to a species that is not in accordance with label directions. When using pharmaceuticals in an extralabel fashions, the veterinarian assumes the legal responsibility of assuring that the product is safe, efficacious and will not leave harmful residues in animal products intended for human consumption. The Animal Medicinal Drug and Cosmetics Act allows veterinarians to prescribe approved animal drugs in an extralabel fashion but also defined several conditions and stipulations including:

- Extralabel use of an approved human drug is not permitted in food producing animals if an approved animal drug can be use in extralabel fashion
- Extralabel drug use is permitted only by the order of a licensed veterinarian within the context of a valid veterinarian-client-patient relationship
- No other approved animal drug is labelled and contains the same active ingredient in the required dosage and concentration, except when the veterinarian finds the approved drug to be clinically ineffective
- The health of the animals is threatened, or suffering or death may result from failure to treat
- Extralabel drug use is not permitted to enhance production or feed additives
- Assure that the identity of the treated animal is recorded and records are maintained
- Appropriate labelling information including withdrawal times for meat, milk and eggs as specified by the veterinarian must be provided
- Extralabel use that may result in residues above an established safe level or tolerance or present a risk to public health is not permitted (Lin and Walz., 2014; Bates *et al*., 2014)

Conclusion

In conclusion, classical NSAIDs are considered drugs of high regulatory concern in food producing animals because of the potential for harm to humans consuming food and food by-products containing residues. It is important hence for veterinarians dealing with food producing animal to be familiar with drugs useful to reduce pain. At the same time they have to be aware of the regulations governing the use of approved and extralabel drugs in practice, respecting the right and different MRLs and withdrawal time to produce foodstuffs that are safe for the human consumption (Smith *et al*., 2008).

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