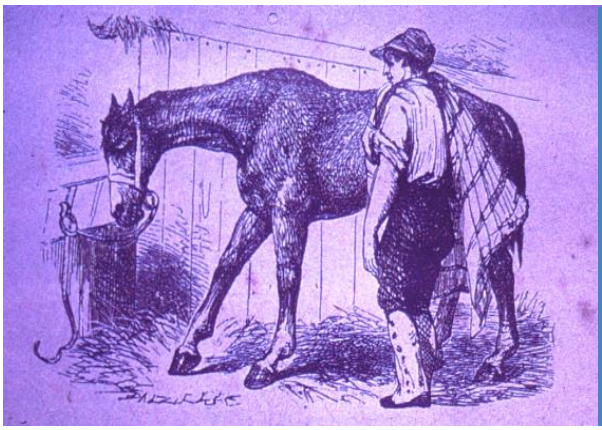
EFTBA Veterinary Newsletter 35



Bisphosphonates - What are they? What are the precautions?

The posture of a horse with navicular disease

August 2020

. *Bisphosphonates are drugs commonly prescribed to prevent bone loss in elderly humans.*

. *The effects of these drugs on the skeleton of horses have not been studied yet.*

. *Bisphosphonates seem to have an effect on the treatment of navicular disease. However, diseases with a genetic predisposition are normally better looked after by genetic studies and specific selection.*

"Many thanks to Mrs. Eva-Maria Bucher-Haefner, Moyglare Stud Farm, for her valued sponsorship of this newsletter."

Welcome to EFTBA's veterinary newsletter

Dear EFTBA members,

Enclosed you will find the 35th edition of the EFTBA Veterinary Newsletter, which is so professionally researched and produced by Hanspeter Meier and kindly sponsored by Moyglare Stud's Eva-Marie Bucher-Haefner.

The edition is dedicated to the topic of Bisphosphonates, which are new drug products available for veterinary use. Hanspeter Meier's looks at what they are and what are the precautions.

As we know Bisphosphonates are a group of medicines used to treat bone problems, called osteopenia or osteoporosis, which are conditions associated with thin or fragile bones that are at increased risk for fracture.

The matter of Bisphosphonates has been widely discussed, debated and well documented over the last year or so by breeders, owners, representative bodies, trainers as well as veterinarians. The administration of Bisphosphonates and the view taken by individual racing authorities differs greatly in terms protocols, procedures and subsequent penalties. While some EU racing authorities' protocols include retrospective disqualification, other racing authorities are yet to publish their stance on the matter.

Like this and so many other issues facing the European bloodstock industry, be that breeding or racing and in particular the areas of veterinary and welfare; the need for harmonisation across the principle EU bloodstock countries cannot be over stressed. Constant dialogue and engagement between breeding bodies and racing bodies is essential as it can strengthen the entire industry and allow breeders and trainers dovetail together for the betterment of all.

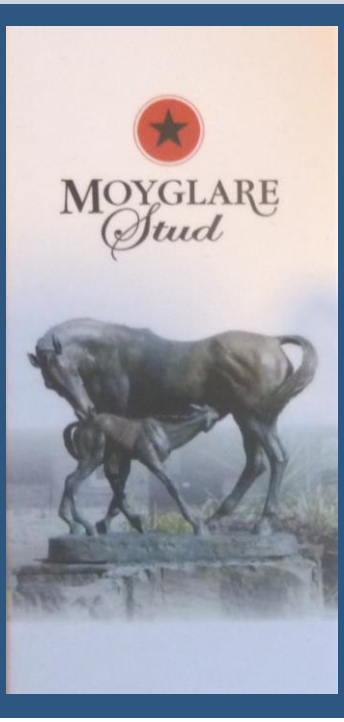
As we all know Hanspeter is very giving of his time and expertise. I would like to encourage you or a member of your breeding association to submit any equine disease or welfare concerns for Hanspeter to review and produce a newsletter on.

Simply email Kerry Ryan, EFTBA secretariat on kryan@itba.ie

Best regards

Joe Hernon

Chairman, EFTBA



Editorial

For the first time in the history of the EFTBA, our annual general meeting had to be cancelled, due to Covid-19. Of course, health is the most important subject to be looked after and we all did understand this decision. However, the soundness of our horses is also of primary importance for us breeders, wherefore the veterinary committee meeting was nevertheless held - via zoom - on the 15th of June. The subjects were an update on the High Health Horse status in the EU animal health law, vaccinations, African Horse Sickness in Thailand and drugs (corticosteroids, regumate and bisphosphonates). Bisphosphonates are new products in veterinary medicine – informations on them therefore are the subjects of this newsletter.

Dr Hanspeter Meier

EFTBA veterinary advisor & Newsletter editor

Introduction

The reasons for discussing bisphosphonates are quite obvious as these drugs are mentioned in the Agreement of the International Federation of Horseracing Authorities (Article 6 D Racing – **Code of Medication Practice for Horses in Training**, p. 26-27, see annex).

In this code we find diverse specific requirements for the use of bisphosphonates, as for instance that they are not to be administered to a racehorse under the age of three years and six months. A quite unusual requirement, isn't it? - There really must be something pretty special about bisphosphonates.

Bisphosphonates – what are they?

According to the U.S. Food and Drug Administration (2020), **bisphosphonates** are a class of drugs commonly prescribed to **prevent bone loss in people**. Here they already have been used for many years and some experience is available. Knowing how bisphosphonates work in people should help to better understand this drug class, both overall and especially also **adverse reactions seen in horses**.

Bones undergo constant turnover, with osteoblasts forming bone and osteoclasts resorbing it. In normal bone tissue, there is a balance between bone formation and bone resorption. But in diseased bone tissue, this balance is disrupted.

Such a disruption is well known in **human medicine**, the so-called **osteoporosis** where the loss of bone outpaces the growth of new bone. The bones become porous, brittle and prone to fracture. Osteoporosis is the most common reason for a broken bone among the **elderly humans**. Until a fracture occurs, there are typically no symptoms. Bones may weaken to such a degree that a fracture may occur with minor stress or spontaneously. Bisphosphonates are useful in decreasing the risk of future fractures in persons who have already sustained such a problem due to osteoporosis. This benefit is present when taken for three to four years (Wikipedia).

Bisphosphonates inhibit bone resorption by causing osteoclasts to undergo cell death, leading to a decrease in the breakdown of bone. They preferentially "stick" to calcium and bind to it. Because most of the body's calcium is stored in bones, these drugs accumulate to high concentrations in bones. Bisphosphonates are incorporated into the bone matrix and are gradually released over months to years.

What are the precautions for bisphosphonates in horses?

The informations for Equine Veterinarians from the U.S. Food and Drug Administration (2020) also point out that **bisphosphonates can cause gastrointestinal and renal toxicity**.

Bisphosphonates can cause **signs of colic** in horses, including abdominal pain, discomfort, and agitation. These colic signs usually occur shortly after the drug is given and may be associated with altered intestinal motility.

Because bisphosphonates are excreted by the kidneys, conditions that impair **renal function** may increase the blood plasma level and lead to more adverse reactions. It is not recommended to use bisphosphonates in horses with impaired renal function. Use caution if you give bisphosphonates along with other potentially nephrotoxic drugs, and be sure to monitor renal function.

Bisphosphonates affect also the blood plasma **levels of some minerals and electrolytes**, such as calcium, magnesium and potassium. The effects are immediate and can last up to several hours. Use caution when you give bisphosphonates to horses with conditions affecting mineral or electrolyte homeostasis (for example, hyperkalemic periodic paralysis or hypocalcemia) or conditions which may

be worsened by hypocalcemia (for example cardiac disease).

In regard to the use of bisphosphonates for racehorses, the U.S. Food and Drug Administration (2020) informs also that the safe use of ***Tildren*** and ***Osphos*** has not been evaluated in horses less than 4 years of age.

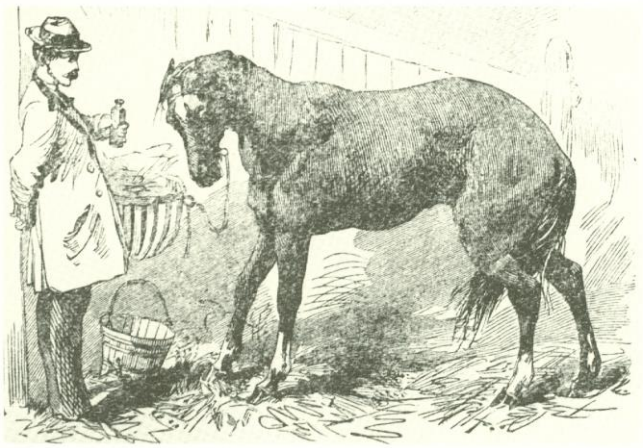
The effect of bisphosphonates on the skeleton of growing horses has not been studied yet, though bisphosphonates may negatively affect bone growth and bone health.

Moreover, the safe use of either *Tildren* or *Osphos* has also not been evaluated in breeding horses or pregnant and lactating mares - but bisphosphonates have been shown to cause **abnormal fetal development in laboratory animals**. The uptake of bisphosphonates into fetal bone may be greater than into maternal bone, which can increase the risk of skeletal or other abnormalities in the fetus. Bisphosphonates may also be excreted in milk and absorbed by nursing animals.

Therefore, bisphosphonates have been declared as extra-label use in racehorses under the age of 4 years (US-coalition of 29 Mid-Atlantic Thoroughbred organizations). The Maryland Racing Commission went even further, ruling horses of any age treated with bisphosphonates to be ineligible to run in any race, and a veterinarian found to have given bisphosphonates to a horse will be suspended for one year (U.S. Food and Drug Administration 2020).

Beside these fundamental and binding informations from the USA, further clear notices were also published by the **Associations of British Thoroughbred Breeding** and **British Horseracing** (TBA & BHA) last year. These organizations did also update in regard to **particular considerations during the sales period**. Here, they mention correctly that the use of bisphosphonates in young horses carries an unknown risk, due to the limited scientific research that has been completed to date. Evidence suggests, in both humans and animals, **that bisphosphonates should not be administered to juvenile athletes**. The actions of bisphosphonates include effects on bone remodeling plus anti-inflammatory and pain-relieving effects; these may predispose racehorses to potentially catastrophic skeletal injuries.

Moreover, they mention that there has been a significant lag between the implementation of the BHA Rule and the implementation of the Rule in some international jurisdictions. Therefore is a risk that non-GB bred horses - which are purchased for racing in Great Britain - may test positive to bisphosphonates. As due to the action of the drug, horses under the age of three and a half years may test positive for over a year post-treatment, there is no screening limit in place for this age group. Should such horses be found to have been administered bisphosphonates under the age of three years and six months, they will also be **permanently ineligible to race in Great Britain** (TBA and BHA, 2019).



Some early remedies were worse than the disease (Smithcors 1975)

The global racing industry, the International Federation of Horseracing Authorities (IFHA), also showed concerns about the negative effects of bisphosphonates on the bone health of horses - at least almost all members. It therefore is really unintelligible that one country did not sign this code of practice (Article 6 D of the IFHA International Agreement, s. annex).

Why are bisphosphonates used in equine medicine?

Getting to know all the problems in regard to the use of these drugs and the risk for injuries and fatalities of sport-horses, one certainly wonders why a drug, which normally is used for ailments of elderly humans, did find its way into equine medicine?

We do get an answer for these questions by taking notice of the fact, that the two equine drugs - *Tildren* and *Osphos* - are FDA-approved to control the clinical signs of **navicular syndrome**, a common cause of forelimb lameness in horses - though the exact mechanism of action in horses with navicular syndrome still is unknown.

To my knowledge, the first study about *Tiludronate* as a new therapeutic agent in the treatment of na-

vicular disease was published by French vets almost 20 years ago (Denoix et al. 2003). They performed a double-blind placebo-controlled clinical trial to compare 2 doses of Tiludronate with 73 horses, split into 2 subpopulations of recent and chronic cases. Their objectives were to determine if bone remodeling changes in navicular disease might be corrected with therapies regulating bone metabolism. Horses treated with the higher dose showed optimal improvement of lameness and return to normal level of activity 2-6 months post treatment. The more recent the onset of clinical signs at the time of treatment, the greater the efficacy. The lower dose failed to significantly improve the condition. They did conclude that their results support the clinical relevance of bone remodeling changes in the outcome of navicular disease (at the dose of 1mg/kg bwt).

Navicular syndrome

(also called navicular disease, podotrochlosis, podotrochlitis, palmar foot pain, etc.)

The results of the study of Denoix et al. (2013) certainly did find great interest, as the navicular syndrome has been one the most important reasons of front leg lameness in horses for centuries.

We therefore better have a look at a short description of it in Wikipedia: "*Navicular syndrome, often called navicular disease, is a syndrome of lameness problems in horses. It most commonly describes an inflammation or degeneration of the navicular bone and its surrounding tissues, usually on the front feet. It can lead to significant and even disabling lameness. There is no single known cause of navicular syndrome, although there are many theories, and several primary factors.*"

In my opinion, Wikipedia tells us with the last sentence *(no single known cause, many theories, several factors)* exactly the great problems with the navicular syndrome. Let's have a look at its' nature (Figures 1-5).

Fig. 1 Sliding surface of a sound navicular bone

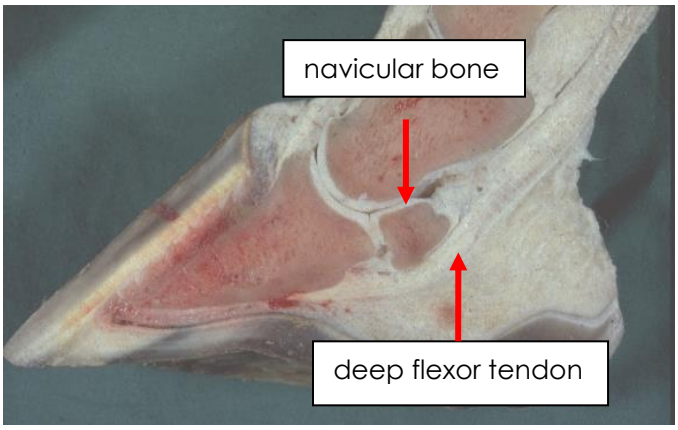


Fig. 2 The navicular bone acts as a guide pulley for the deep flexor tendon and causes pain in the palmar part of the foot in the case of disease

Fig. 3 Already in 1753, Eisenberg showed the typical posture of horses with navicular disease. In France, this posture was called "montrer le chemin de St. Jacques" (the way to the abattoir).

Fig. 4 The sliding surface of a diseased navicular bone with severe alterations.

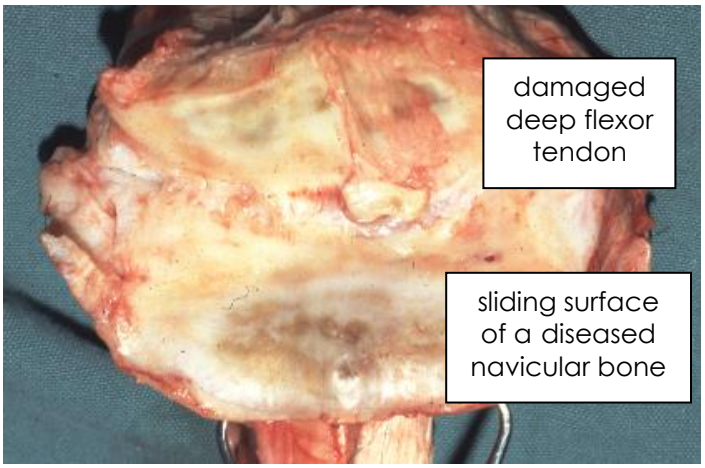


Fig. 5 The altered sliding surface of the navicular bone leads also to severe damages of the deep flexor tendon (e.g. adhesions) and further structures in this part of the hoof.

The prognosis for a horse with navicular syndrome is guarded - easy to understand with the figures as above. Many times the horses do not return to their former level of work and/or are retired. As example may serve the examination of 8'340 horses of the Swiss army (1952-1963) (Löhrer 1981). Here, the proportion of early retired horses due to navicular disease was 31.2 %.

These very unfavorable facts led to quite some research at the University of Berne in the last century, and in 1983, Margrith Diehl (also a TB-breeder) and J. Cordey undertook a study by means **of densitometry of healthy and diseased navicular bones** (Fig. 6 - 9).

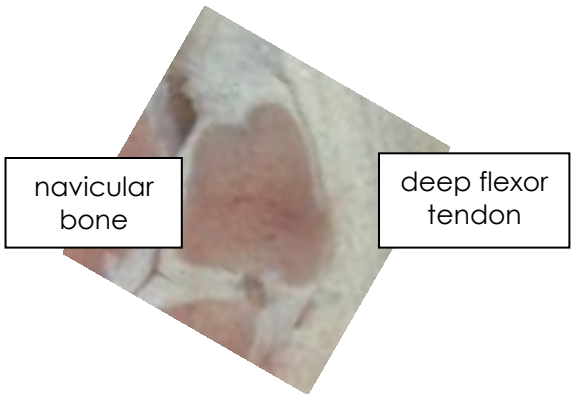


Fig. 6 Axial view of a navicular bone.

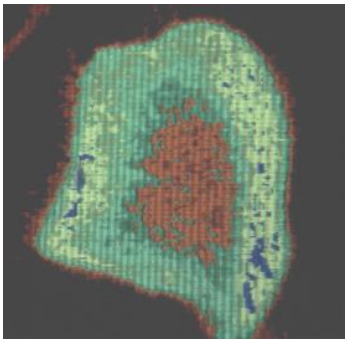


Fig. 7 View of a healthy navicular bone by axial densitometry with a less dense spongiosa (red) in the center.

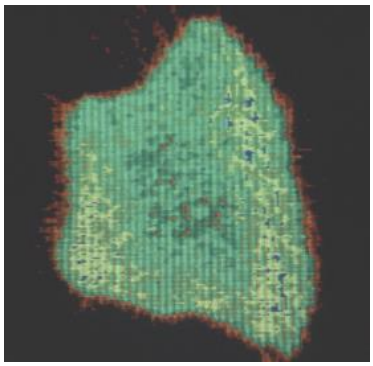


Fig. 8 Lightly diseased navicular bone: The center of the bone begins to be calcified.

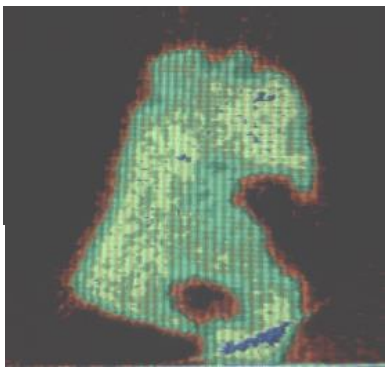


Fig. 9 Severely diseased navicular bone: sclerosis of the bone without a pattern of the density and a greatly damaged sliding surface (right side)

This research showed for the first time the disturbed metabolism in the diseased navicular bone and proved that the condensation starts in its centrum and not along the sliding surface.

In my opinion, this finding also explains the experience of Denoix and co-workers (2013) that the efficacy of the treatment with bisphosphonates only can be greater in earlier stages.

Beside this investigation, Diehl and Ueltschi (1987) also wanted to know, whether the navicular syndrome may be due to the workload or the age of the afflicted horses. For answering this question, they examined the 454 navicular-patients in the clinic in the years 1978-1980 (Fig. 10). Almost half of the diseased horses (42%) were in the age-group from 6 to 8 years – at the time when riding-horses normally are expected to show some performance. The patients obviously didn't suffer from lifelong work, the distribution much more showed the pattern of a hereditary disease.

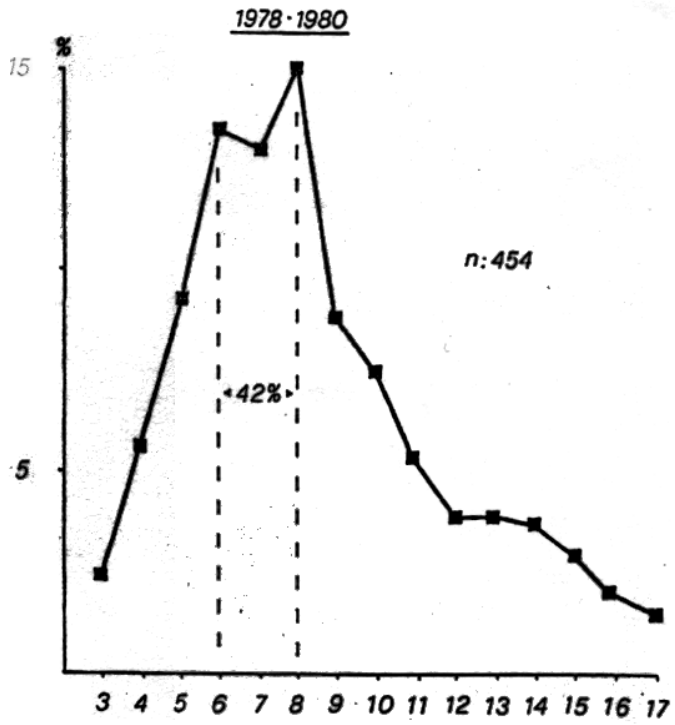


Fig. 10 The age-distribution of the horses with navicular disease showed that it most often (> 50%) became evident in young horses (3-8 years of age) (Diehl and Ueltschi 1987).

The results of the research at the University of Berne led to the decision to also examine the hypothesis of a **possible heritability of the navicular syndrome** - probably the first thesis we breeders would like to be answered. However, this question didn't arise for the first time as, for instance, the Royal Dublin Society already had instructed in 1892 that the registration of stallions and mares and the distribution of premiums only was possible for horses free of genetic diseases; navicular disease was included (Lewis 1980). At the same time, Smith (1893) even considered the hereditary predisposition already as uncontested and accepted (please note, these are just two references of many more). In 1988, Stornetta devoted his doctoral thesis to the heredity of the navicular disease by examining (by means of radiography) two Franches-Montagnes stallions and their progeny. His investigations allowed also to conclude that "*the genetic predisposition of the navicular syndrome couldn't be called in question*".

But in spite all the presumptions and findings of more than 150 years in regard to the genetic aspects and the developments in genetics, we still (!) haven't got more precise information about the mode of inheritance (s. Online Mendelian Inheritance in Animals: https://omia.org).

Conclusions

Despite the well-characterized health benefits of bisphosphonate (BP) use in humans, in the horse there exists currently a dearth of information regarding the effects of single and repeated doses. In the equine setting. BPs are FDA-approved primarily for the treatment of navicular syndrome. Here, they may provide beneficial effects in early cases. They might help prevent bone remodeling and also cause an analgesic effect (Rosenthal 2020).

Following the development of a better understanding of BP effects in the horse, appropriately designed and powered placebo-controlled studies will determine to what extent beneficial BP effects are due to the inhibition of bone resorption and ascertain the details of repeat dosing in the equine setting. Such a strategy is required to ensure safer clinical use and produce a sufficient level of evidence to ensure safety. Well-designed research by non-biased researchers with germane bone parameters as outcome measures must be completed (Mitchell et al. 2019).

At this stage, the specific requirements regarding bisphosphonates of the IFHA and other stakeholders certainly are more than justified and reasonable.

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Diehl M. and Cordey J.(1983): Knochendensitometrie: Mittels axialem Tomograph "Isotom" am gesunden und kranken Strahlbein beim Pferd "in vitro". Berl. Münch. Tierärztl. Wschr. 96, 305-307. Translation: Bone Densitometry: By Means of Axial Tomograph „Isotom" on Healthy and Diseased Navicular Bone in Horses "in vitro".
Please pay attention: If you consult this publication, please note that the English translation of the following sentence in the summary is wrong(!): *"Defects occurring on the sliding surface always precede the metaplasia process in the body of the navicular bone"*. It must read: *"The metaplasia process in the body of the navicular bone always precedes defects occurring on the sliding surface"*.

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Löhrer A. (1981): Statistische Untersuchungen über die Strahlbeinlahmheit im schweizerischen Kavalleriepferdebestand von 1952 bis 1972. Diss. med. vet. Bern

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TBA Veterinary Notice – BHA Notice on Bisphosphonates (2019, 24.09.)

U.S. Food and Drug Administration (2020): *Tildren* and *Osphos* for Navicular Syndrome in Horses – Information for Equine Veterinarians, 21.04.

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If there is any aera you would like covered in these very informative newsletters you should contact Kerry on kryan@itba.ie and she will forward your request on.

Joe Hernon, Chairman EFTBA

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Annex

International Agreement IFHA

Article 6 D (RACING) – MEDICATION IN TRAINING

CODE OF MEDICATION PRACTICE FOR HORSES IN TRAINING

Definition of treatment

For the purpose of this Article, the term treatment includes:

1. The administration on any substance (including any medication) to a horse and;
2. The administration of application of any physical procedure to a horse intended to have an effect.

Guiding Principles

The following guiding principles apply to the treatment of horses in training:

1. All treatments are the responsibility of the trainer and must be administered under veterinary supervision.
2. Every treatment must be administered in the best health and welfare interests of the horse.

Accordingly:

1. The trainer must obtain veterinary advice from the attending veterinarian on the management, treatment and appropriate level of training for a sick or injured horse.
2. Treatment of a horse by the administration of a substance or a medication containing a prohibited substance may only be performed on the advice of a veterinarian with appropriate knowledge of the condition, health status and management of the individual horse. In the case of substances controlled by government regulation, these may only be administered by, or on the prescription of, a veterinarian.
3. The trainer is responsible for creating and maintaining full and accurate records of all treatments given to a horse, including all veterinary procedures performed and all medications administered. These records must be kept for a minimum of 12 months and be readily available for inspection by regulatory officials when requested.
4. With the exception of normal feed and water by mouth, no substance shall be administered to any horse on race day before the race in which it is entered, unless such treatment is authorized by the Horseracing Authority. This includes any substance administered by injection, into the mouth, by inhalation, topically or by any other method of administration.
5. The trainer must comply with mandatory horse rest periods for specific drugs or treatments, as enforced by the Horseracing Authority.
6. Horses that are unable to be trained due to injury or illness must be taken out of training and given appropriate veterinary treatment and/or rest. All treatments must be administered in the best interests of the horse and not to facilitate the continuation of training.

Specific requirements regarding bisphosphonates:

Any bisphosphonate is not to be administered to a racehorse:
. under the age of three years and six months as determined by its recorded date of birth; and
. on the day of the race or on any of the 30 days before the day of the race in which the horse is declared to run.

The bisphosphonate product administered must be licensed for use in horses in the country in which it is being used, and be administered in accordance with the label instructions.

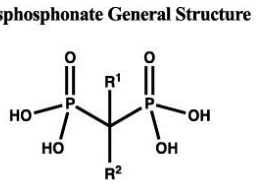
There must be a diagnosis determined by a veterinary surgeon that supports the use of a bisphosphonate as an appropriate treatment, and such treatment must be administered by a veterinary surgeon.

Updated February 2019

Fully signatory - agreed by:			
AUSTRALIA	AUSTRIA	BRAZIL	CHILE
CYPRUS	GERMANY	HONG KONG	IRAN
IRELAND	KOREA	LEBANON	MACAU
MALAYSIA	MAURITIUS	MOROCCO	NORWAY
OMAN	QATAR	ROUMANIA	SAUDI ARABIA
SERBIA	SINGAPORE	SLOVAKIA	SOUTH AFRICA
SPAIN	TURKEY		
Partial signatory - by:			
CZECH REPUBLIC *we are preparing an implementation to the Racing Rules*	GREAT BRITAIN *(because of requirement for all veterinary procedures to be recorded)*	JAPAN *Currently there is no provision for Bisphosphonates, but now Japan is under consideration for the future revision of the regulations.*	PANAMA *the use of anabolics and testosterone is permitted*
PERU	PHILIPPINES *Not currently in compliance but will adapt into the racing rules and regulations towards implementation*	UNITED STATES OF AMERICA *'Accordingly' §3: veterinary treatment records are kept for 6 months. §4: Furosemide is permitted on race day Bisphosphonate §: As Bisphosphonates are currently not listed in the ARCI Model Rules they are considered a prohibited substance*	URUGUAY *use of drugs in the country is not limited to vets*
Not a signatory - by:			
SWITZERLAND			

Glossary

Bisphosphonates



Bisphosphonates (BPs) are a family of molecules characterized by two key properties:

- their ability to bind strongly to bone mineral
- and their inhibitory effects on mature osteoclasts and thus bone resorption.

Densitometry

A bone density test is used to measure bone mineral content and density. It may be done using X-rays, dual-energy X-ray absorptiometry (DEXA or DXA), or a special CT scan that uses computer software to determine bone density.

Osteo

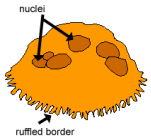
Osteo is the Greek word for bone.
There are three special types of cells that are found only in the bone.
These cell names all start with "osteo".

Osteoblast

Osteoblasts are the cells that form new bone.
They come from the bone marrow and are related to structural cells. They have only one nucleus. Osteoblasts work in teams to build bone. They produce new bone called "osteoid" which is made of bone collagen and other protein. Then they control calcium and mineral deposition. They are found on the surface of the new bone.

When the team of osteoblasts has finished filling in a cavity, the cells become flat and look like pancakes. They line the surface of the bone. These old osteoblasts are also called Lining Cells. They regulate passage of calcium into and out of the bone, and they respond to hormones by making special proteins that activate the osteoclasts.

Osteoclast

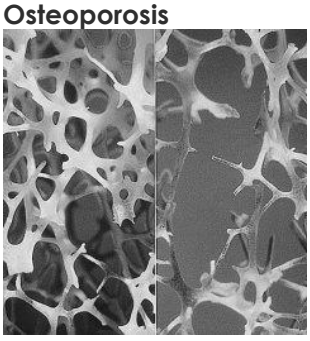


Osteoclasts are large cells that dissolve the bone.
They come from the bone marrow and are related to white blood cells. They are formed from two or more cells that fuse together, so the osteoclasts usually have more than one nucleus.
They are found on the surface of the bone mineral next to the dissolving bone.

Osteocyte

Osteocytes are cells inside the bone.
They also come from osteoblasts. Some of the osteoblasts turn into osteocytes while the new bone is being formed, and the osteocytes then get surrounded by new bone. They are not isolated, however, because they send out long branches that connect to the other osteocytes. These cells can sense pressures or cracks in the bone and help to direct where osteoclasts will dissolve the bone.

Osteoporosis



Left: normal bone
right: osteoporotic bone

Osteoporosis, which literally means porous bone, is a disease in which the density and quality of bone are reduced. As bones become more porous and fragile, the risk of fracture is greatly increased. The loss of bone occurs silently and progressively. Often there are no symptoms until the first fracture occurs.

Our bones are living tissue and constantly changing. From the moment of birth until young adulthood, bones are developing and strengthening. Our bones are at their most dense in our early 20s – called peak bone mass.

As we age, some of our bone cells begin to dissolve bone matrix (resorption), while new bone cells deposit osteoid (formation). This process is known as remodeling.

For people with osteoporosis, bone loss outpaces the growth of new bone. Bones become porous, brittle and prone to fracture.