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Case Report - Chronic oak toxicity (*Quercus suber*) in beef cattle in the south of Portugal: 17 cases (2014-2018)

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Abstract

Oak toxicity in cattle results from ingestion of acorns, buds, leaves, sprouts, and saplings from several species of trees in the genus *Quercus,* all of which contain high concentrations of tannins. Consumption of acorns by ruminants, principally between late summer and early winter, is common in the south of Portugal, where there is a high prevalence of *Quercus suber.* Oak poisoning can lead to progressive damage to the kidneys and may result in renal failure and death. This study involved 17 beef cows that died of chronic oak poisoning related to ingestion of *Quercus suber*. The most relevant findings from necropsy examinations were abdominal fluid accumulation, atrophic/fibrotic kidneys, mesenteric and sub-mandibular edema, absence of body fat reserves and muscle atrophy, and weight loss. The most significant histopathologic finding was chronic interstitial nephritis. Elevated blood urea nitrogen, creatinine, and K^+ values and reduced albumin values were found in 4 cows examined ante-mortem. Straight-bred Mertolengo cows appeared to be highly resistant to oak toxicity.

Key words: beef cattle, *Quercus suber*, chronic oak toxicity, chronic interstitial nephritis

Résumé

La toxicité du chêne chez les bovins résulte de l'ingestion de glands, de bourgeons, de feuilles, de germes et de gaules de plusieurs espèces d'arbres du genre Quercus, qui contiennent tous de fortes concentrations de tanins. La consommation de glands par les ruminants, principalement entre la fin de l'été et le début de l'hiver, est courante dans le sud du Portugal, où la prévalence du Quercus suber est élevée. L'empoisonnement au chêne peut entraîner des lésions progressives des reins et entraîner une insuffisance rénale et la mort. Cette étude a porté sur 17 vaches de boucherie mortes d'un empoisonnement chronique au chêne lié à l'ingestion de Quercus suber. Les résultats les plus pertinents des examens d'autopsie étaient l'accumulation de liquide abdominal, les reins atrophiques / fibrotiques, l'œdème mésentérique et sous-mandibulaire, l'absence de réserves de graisse corporelle et d'atrophie musculaire et la perte de poids. La découverte histopathologique la plus importante était une néphrite interstitielle chronique. Des valeurs élevées d'azote uréique sanguin, de créatinine et de K + et des valeurs réduites d'albumine ont été trouvées chez 4 vaches examinées ante mortem. Les vaches de race pure Mertolengo semblaient très résistantes à la toxicité du chêne.

Introduction

Oak toxicity is well documented in several parts of the world, including the UK,[4,11,23] USA,[18,19,22] South Africa,[14] India,[9] Spain,[17] and Portugal.[7] In the south of Portugal oak trees (*Quercus suber* and *Quercus ilex*) are common in most beef cattle pastures. Oak poisoning occurs sporadically in some years, and not in others. In southern Portugal, this toxicity tends to occur whenever there is a large crop of acorns that fall from trees in pastures, namely during late summer and fall, which provides an opportunity for cattle to consume excessive amounts of acorns. Outbreaks of acute acorn poisoning in cattle are well documented in the literature.[4,11,14,19,22] The onset of clinical signs and death can occur from 1 day to 3 to 4 weeks following an acorn drop.[16]

Chronic acorn toxicity has not been characterized as well as acute poisoning. To our knowledge, chronic oak poisoning has only been reported 7 times previously, and the clinical aspects of those cases were not always thoroughly characterized and documented.[1,2,7,15,16,22,23] Chronic oak toxicity is a protracted debilitating illness caused by decompensating renal function over a period of weeks.[16]

The most likely principal toxic agent in *Quercus* spp is tannic acid or other tannins, which become hydrolyzed in

the rumen to gallic acid, pyrogallol, and other compounds.[20] Evidence infers, but does not firmly establish, that tannic acid or its derivatives are the principal toxic agents for oak poisoning in cattle.[16] The level of toxicity of oak tannins appears to be variable, and poisoning can occur regardless of the plant part consumed.[16] It has been suggested that young leaves are more toxic than mature leaves.[9] The kidney is clearly the most susceptible organ to tannic acid effects in domestic ruminants, especially cattle.[16] Tannic acid toxicosis causes renal disease and subsequent kidney failure.[16]

At necropsy examination of acute cases, the kidneys are slightly swollen and pale with petechiae on the surface that extend into the cortex. In the gut, there is congestion and mucosal erosions of varying severity and location, extending from the mouth to the colon, and deep ulcerations and hemorrhages are sometimes evident.[2] In chronic cases, the renal surfaces present a more roughened or pitted appearance.[2] Although renal lesions are always present, lesions in other tissues may or may not be present.[16]

The objective of this case study was to describe multiple cases of chronic oak poisoning in beef cattle on a farm in the south of Portugal. This is the first report in the literature describing chronic oak poisoning in beef cattle due to ingestion of tannins present in *Quercus suber*, the tree referred to as 'The cork oak'. This species of tree is indigenous to the Mediterranean region, and is the source of much of the world's natural cork supply.

Materials and Methods

This case study took place on a 12,500 acre (5,000 ha) farm located in Alcácer do Sal, 50 miles (80 km) south of Lisbon, Portugal. There were approximately 1,000 head of cattle, 600 of which were adult cows, on the farm. The cows were pure Mertolengo (a Portuguese beef breed; 300 cows) and crossbred Mertolengo with Blonde d'Aquitaine and/or with Charolais and/or with Limousin breed influence (300 cows). The other 400 animals were yearling heifers and weaned calves. The cows were divided into 5 groups, with approximately 120 cows per group. There were also 10 Limousin bulls and 2 Mertolengo bulls in the herd.

Each group of cows rotated between different pastures (6 to 7 pastures per group). Each parcel of pasture was approximately 250 acres (100 ha) in size. Some pastures had natural grasses (6,200 acres; 2,500 ha) and forages and others were cultivated grasses and legumes (1,235 acres; 500 ha). The amount of available forage was similar for all 5 groups of cattle, as well as the exposure to oak. During the winters of 2016 and 2017, the cows were supplemented with corn silage (4.4 lb [2 kg]/d) and straw (2.2 lb [1 kg]/d) because of drought. The dominant trees in the pastures were oaks (*Quercus suber*) and pines (*Pinus pinela*).

Cows eat acorns after they drop from the trees (September to January) and can browse young trees, buds, sprouts, and leaves, which are available all year long. The quantity of acorns available and/or consumed varies from year to year, depending on weather and unknown factors. Cattle are not known to consume any parts of pine trees. The cows were vaccinated against bovine viral diarrhea virus[a] and *Clostridium perfringens* type *B*, *C*, and *D*, *chauvoei*, *hemolyticum*, *novyi*, *septicum*, and *tetani*[b] twice a year (May and November). The cows were dewormed with ivermectin[c] in May, and combination ivermectin and closantel[d] in November, beginning at 1 year of age.

This investigation began in November 2014 and extended through November 2018, and involved 17 adult cows. Fourteen of the cows were found dead in the pastures, and the remaining 3 were very sick and were euthanized because of the severity of clinical signs. A blood sample was collected from the caudal vein of the 3 cows that were euthanized, and from 1 cow that had just died (#485); creatinine,[e] albumin,[e] blood urea nitrogen (BUN),[f] and potassium[f] concentrations were measured. Ocular fluid (aqueous or vitreous fluid)[5] was collected from 1 cow (#117), which had been dead for about 1 hour, to determine creatinine,[e] blood urea nitrogen (BUN),[f] and potassium levels.

Field necropsies were performed as soon as possible after the cows were found dead**,** and thin slices of kidney, liver, and large intestine were fixed in 10% formalin and sent to the pathology laboratory of the "Faculdade de Medicina Veterinaria, Lisboa" for histopathologic examination. These tissues were selected because acute oak toxicity in cattle is characterized by renal and gastrointestinal alterations, which can be confirmed by necropsy and histopathologic examination.[2]

The mortality rate, from all causes, among the 600 adult cows on this farm during the study period (2014 – 2018) was 8.8% per year, totaling 264 cows that died of all causes. This death rate is well above the average (<2%) for herds raised under similar conditions in this part of Portugal. The mortality rate in the calves was 3%/year, which was less than most other beef cattle herds in Portugal, as well as in most well managed beef herds in the other western countries of the world.[6]

Statistical Analysis

In order to test the association between the mortality rate and the genetics of the cows in the herd (straightbred Mertolengo vs crossbred Mertolengo), a Fisher exact test was performed.[21]

Results

Cow data, serum chemistry values, gross necropsy findings, and major histopathologic findings are shown in Tables 1 to 4 and Figures 1 and 2.

All 17 cows that died were cross-bred Mertolengo cattle, with up to as much as 50% parentage from the Blonde d'Aquitaine and/or Charolais and/or Limousin breeds. There

Table 1. Cow identification, year of death, age, and breed for cows that died of oak toxicity.

Cow ID (year of death)	Age (years)	Breed
280 (November 2014)	4	Crossbred
F115 (December 2014)	9	Crossbred
F114 (January 2015)	9	Crossbred
265 (January 2015)	5	Crossbred
123 (April 2015; euthanized)	14	Crossbred
485 (June 2015)	4	Crossbred
281 (November 2015)	6	Crossbred
185 (December 2015)	6	Crossbred
6929 (January 2016)	4	Crossbred
239 (April 2016)	7	Crossbred
277 April 2016)	7	Crossbred
206 (January 2017)	12	Crossbred
204 (March 2018)	14	Crossbred
2174 (April 2018; euthanized)	5	Crossbred
050 (June 2018; euthanized)	5	Crossbred
117 (November 2018)	11	Crossbred
191 (November 2018)	10	Crossbred

was a highly significant difference in mortality rates between straight-bred Mertolengo cows (zero) and the crossbred cows (17 or 5.7%); $P<0.0001$.

Discussion

In the south of Portugal, beef cattle often have access to large amounts of acorns that fall from trees like *Quercus suber* or *Quercus ilex* from late summer to early winter. The amount of acorns available can vary from year to year. During the entire year, the cows frequently have the opportunity to graze young oaks and foliage of mature oak trees. Bausch and Carson[1] classified oak poisoning in cattle according to the season. Oak bud and oak leaf poisoning are usually seen in the spring, while acorn poisoning is seen in the autumn after the acorn fall drop.[1,16] At low levels of intake, oak is an important forage, but as tannin levels increase in cattle diets, roughage digestibility may decrease.[18]

As mentioned, the mortality rate on this farm during the period of the study (2014-2018) was much higher than the average for this part of the country. There are 2 major reasons for this. First, cows were underfed, especially during certain years due to drought. In some months of the year, when the pasture is very poor (June until November), there is no grass available, and supplemental feed is not provided. Secondly, these cows have access to acorns, buds, leaves, sprouts, and saplings throughout the year. On this farm, unlike others, the presence of young trees in the fields is scarce, which strongly suggests that the cows use them as a source of feed.

According to Neser et al,[14] the toxicity of acorns has been poorly understood**,** since they may be completely harmless on some occasions**,** but highly toxic at other times. Feed intake restriction, as occurs in situations of overstocking, is one of the most important risk factors for the development of toxicosis.[8,17] Other predisposing factors include sudden large acorn "drops" caused by severe windstorms and heavy rain, which shake tree branches and cause large quantities of acorns to fall over a short period of time.[1] However, there is no available evidence to suggest that any of these particular predisposing circumstances occurred on this farm prior or during the time of this case study.

The initial clinical signs of acute oak poisoning in cattle include gauntness, listlessness, and constipation followed by diarrhea, excessive thirst, frequent urination (urine may be clear and colorless or, in some early cases, red-colored because of polyphenolic metabolites), and feces may be bloody or black and tarry.[2,12] These clinical signs are a consequence of gastrointestinal and kidney lesions which can be confirmed by necropsy and histopathologic examination of tissues. However, because beef cows are on the pasture and not frequently checked or closely examined, the onset of initial clinical signs may not always be observed by herdsmen.[1] Unfortunately, oak toxicosis is very difficult to reproduce experimentally for reasons not well understood.[17] In this case study**,** the clinical signs most consistently observed were weight loss and submandibular edema (Figure 3). Cows were usually noted to be dull, although according to the herdsman an aggressive behavior was sometimes observed.

Elevated blood urea nitrogen and creatinine support a diagnosis of oak toxicity, and they may be extremely elevated.[22] However, 75% loss of glomerular function is necessary to impact BUN and creatinine concentrations.[22] Consequently,

Table 2. Serum chemistry values from cows with oak toxicity that were euthanized (n=3, ID 123, 2174, 050), died just before necropsy (n=1, ID 485), and ocular fluid from cow that died just before necropsy (n=1, ID 117).

Cow ID	BUN (mg / dL)	Creatinine (mg / dL)	Albumin (g / dL)	Potassium (mmol / L)
123	140	6,6	2.1	6.6
485	627	23	2.1	nq
2174	59	1.9	1.8	4.3
050	130	5.4	2.4	8.1
117*	130	4.4	nq	nq
Reference range[22]	10 - 25	0.5 - 2	2.5 - 3.8	3.6 - 4.9

nq = not quantified

* Values from cow #117 were from ocular fluid

it may be difficult to evaluate the significance of renal lesions found in individual dead cows during necropsy examination. In uncomplicated acute tubular injuries, regeneration of epithelial cells generally begins after about 7 to 10 days following renal damage. In mild cases, full recovery of architecture may occur within 2 to 3 weeks, with longer recovery periods being required for more severe renal injury.[10] According to Dixon et al,[4] BUN and creatinine estimations can be of prognostic value. In the current study, BUN from the 4 cows that were sampled was well above the reference ranges (10-25 mg/dL), albumin was slightly below the reference range (2.5-3.8 g/dL), and creatinine was well above the reference range (0.5-2 mg/dL) in 3 cows.[13] Blood potassium was above the reference range in 2 of 3 cows (3.6-4.9 mmol/L)[13] (Table 2). BUN and creatinine levels from the ocular fluid was well above the reference levels (data not shown).

The characteristic postmortem lesions, combined with a history of access to oaks, are usually sufficient to make a tentative clinical diagnosis.[2] Presence of oak leaves, and/or acorns in the rumen, especially when disease occurs within a few days following a storm which causes large numbers of acorns to drop from trees, is also usually sufficient to permit a clinical diagnosis of oak toxicity. However, in the present study, cows could have ingested moderate amounts of acorns and/or browsed throughout the year, resulting in a more prolonged, chronic clinical syndrome, one that was more difficult to recognize and diagnose. Although there are studies[15] that show that compensatory weight gain can occur in steers after an outbreak of oak bud toxicosis, the cows of this study were never weighed, so this phenomenon, if it occurred, was not detected. Five dead cows had acorns in the rumen; 2 of these cows died in November, 1 in December, 1 in January, and 1 in March. Ten of these cows (60% of the cows) died while they had plentiful access to acorns, but little grass. However, the other 7 cows (40%) died when there was an abundance of grass available (March to May).

One of the difficulties facing a clinician during episodes of chronic oak poisoning is trying to predict the outcome in apparently unaffected animals. Cows on this farm had contact with acorns in different stages of maturity (from September to January), and young trees, leaves, buds, and stems during the rest of the year, but most of them never showed clinical signs It is not clear why cows in spring or early summer died from oak poisoning when there was ample grass available. Three cows (#281, #185, #191) died in late autumn/early winter without finding acorns in their rumen. It is possible that these cows had a foraging preference for leaves from young oak trees, which are available all year around. It would

Table 3. Necropsy findings from cows suspected with oak toxicity.

Cow	Fluid accumulation	GI tract lesions	Kidney	Mesenteric edema	Submandibular edema	Acorns in rumen	Weight loss
280	5 L (abdomen)	Small ulcers (abomasum)	Autolysis	No	Yes	Yes	No
F115	No	Hemorrhagic jejunitis, blood	Autolysis	No	No	Yes	No
F114	Yes – nq (pericardium)	Edema of the abomasum folds	Atrophy	No	Yes	Yes	No
265	No	No	Atrophy	No	No	No	Yes
123	No	Edema of the abomasum folds	Atrophy	Yes	Yes	No	Yes
485	Yes - nq (abdomen)	Edema of the abomasum folds	Atrophy	Yes	No	No	Yes
281	No	No	Atrophy	No	No	No	No
185	No	Hemorrhagic jejunitis	Autolysis	No	No	No	No
6929	No	No	Autolysis	No	No	No	No
239	10 L (abdomen)	Edema of the abomasum folds	Autolysis	Yes	Yes	Yes	No
277	No	Hemorrhagic enteritis	Atrophy	No	No	No	No
206	No	No	Atrophy	No	No	No	No
204	No	No	Atrophy	No	No	Yes	No
2174	20 L (abdomen)	Yes	Atrophy	Yes	Yes	No	No
050	2 L (abdomen)	Edema of the abomasum folds	Fibrosis	Yes	Yes	No	Yes
117*	5 L (abdomen)	Edema of the abomasum folds	Fibrosis	Yes	Yes	Yes	Yes
191	No	No	Fibrosis	No	Yes	No	Yes

nq = not quantified

* Values from cow #117 were from ocular fluid

be very costly to prove this theory, as it would require hiring someone to monitor cows every day for the better part of a year.

Three cows (#F115, #185, #277) died suddenly without showing signs of sickness. Necropsy of cow #F115 revealed large intraluminal blood clots in the small intestine; lesions resembled hemorrhagic bowel syndrome which has been associated to *Clostridium perfringens* type A.[3] Cows #185 and #277 showed marked hemorrhagic enteritis lesions which could be associated with overgrowth of *Clostridium* spp.[3] Some of the cows in this study showed rapid autolysis (Table 3), which can also be associated with the proliferation of *Clostridium perfringens* within the small intestine.[3] These cows, however, were vaccinated twice each year for *Clostridium perfringens* type B, C, and D. In spite of these findings, it is significant that the 3 cows that died suddenly had histopathologic evidence of chronic renal lesions, suggestive of acorn poisoning (Table 4).

One cow (#281) had oxalate crystals in the kidney (renal tubules). There were at least 4 plants on the farm that can accumulate potentially toxic amounts of oxalates (*Amaranthus* spp, *Chenopodium* spp, *Rumex* spp, and *Oxalis pes-caprae*).[12] The populations of *Amaranthus* spp and *Chenopodium* spp on the farm were low, and considered to be an insignificant risk. However, at the beginning of the winter after the first fall rains, the cows did have access to significant populations of *Rumex* spp and *Oxalis pes-caprae.* The kidney from this cow, in addition to oxalate crystals, had lesions characteristic of oak poisoning (chronic interstitial nephritis).

Gross lesions at necropsy were not uniformly present in all affected cows (Table 3). Eight cows showed submandibular edema (Figure 3). Twelve cows had kidneys that were gray in color, and were also fibrotic and atrophic (Figure 1). In the other 5 cows the kidneys had some degree of autolysis, making histopathologic evaluation difficult. Six cows had marked edema of the abomasal folds, 6 had mesenteric edema, 6 had variable volumes of excess fluid in the peritoneal cavity, 5 had acorns inside the rumen, 6 had marked weight loss without any fat inside the abdominal cavity, 3 showed lesions of enteritis, 1 had abomasal ulcers, and 1 had excess pericardial fluid. Because necropsies of many of these cows were not performed on the day of death, there was usually some autolysis present in the internal organs.

Visual examination of the internal organs in the majority of the necropsies did not reveal any major gross pathologic changes. Nevertheless, in some cases, liver, lung, or intestinal samples were taken for histopathological examination when these tissues were reasonably free of severe autolysis. In 4 of the cows necropsied, the carcass had a strongly uremic odor (#280, #239, #2174, #117). Whether or not a cow with renal failure survives is dependent on the severity of

Table 4. Major histopathology findings in cows suspected of oak toxicity.

Cow	Kidney	Liver	Other organs
280	Interstitial nephritis; glomerular degeneration.	nd	Moderate abomasitis
F115	Fibrocystic interstitial nephritis	Multifocal necrotic hepatitis caused by bacteria (microabscesses)	nd
F114	Chronic interstitial nephritis	nd	nd
265	Chronic interstitial nephritis	nd	nd
123	Chronic interstitial nephritis; glomerular amyloidosis.	Periportal necrosis	Interstitial pneumonia
485	Chronic glomerulonephritis; interstitial fibrosis.	nd	nd
281	Chronic interstitial nephritis; deposition of oxalate crystals.	nd	nd
185	Chronic interstitial nephritis.	Microabscesses	nd
6929	Interstitial fibrosis.	nd	nd
239	Chronic interstitial nephritis; parenchymal calcification.	nd	nd
277	Chronic interstitial nephritis	Focal necrosis	nd
206	Chronic interstitial glomerulonephritis	nd	nd
204	Interstitial fibrosis; multifocal tubular calcification	Necrosis	nd
2174	Interstitial fibrosis; multifocal tubular necrosis; glomerular atrophy.	Congestion and focal necrosis	nd
050	Chronic interstitial nephritis	Sinusoidal congestion	Necrotic enteritis (cecum)
117	Chronic interstitial nephritis.	nd	nd
191	Chronic interstitial nephritis; tubular necrosis; tubular calcification.	nd	nd

nd = not determined

Figure 1. Severe fibrosis of a kidney from a cow with chronic oak toxicity, presenting granular irregular surface and abnormal greyish coloration.

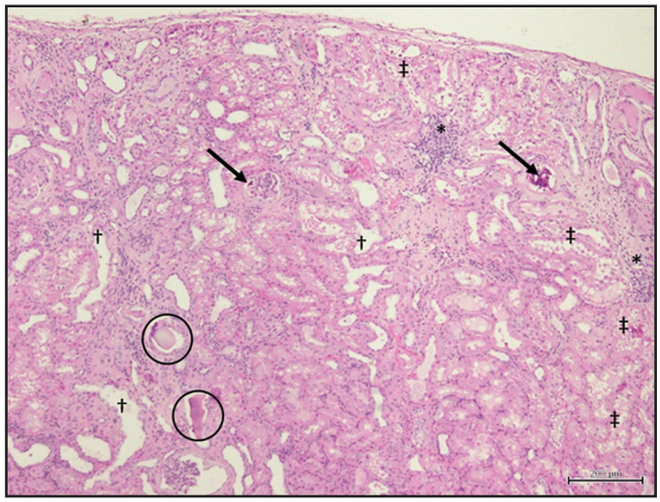

Figure 2. Histological alterations in the kidney (H&E staining; 40x). Exuberant interstitial fibrosis, tubular necrosis (‡), glomerular atrophy (arrow), formation of cylindrical hyaline casts (circle) and renal tubule dilation (†). Multifocal mononuclear inflammatory cells infiltration (*). Aspects associated with interstitial glomerulonephritis with tubular necrosis, compatible with chronic oak toxicity.

the renal lesions, and the ability of the renal tubular cells to regenerate.[19] Interestingly, the histopathological examination of tissues revealed remarkably consistent changes that were confined almost exclusively to the kidneys (Table 4). These changes were compatible with chronic renal tissue injury, in particular the amount of fibrotic interstitial tissue, glomerular damage, mononuclear inflammatory cell infiltration, and in some cases, calcification of renal tubules and parenchyma (Figure 2).

Previous reports described a syndrome that affects calves born from dams that ingested large numbers of acorns under poor forage conditions during the second trimester

Figure 3. Cow with suspected oak toxicity showing weight loss and a marked submandibular edema.

of pregnancy. These calves, referred as "acorn calves", have very short leg bones, may have abnormal hoof development, and may have a short or long, narrow head.[12,20] There are no reports of this problem on the farm in this case study.

An important observation from this study was that only crossbred cows were affected, in spite of the fact that the Mertolengo cows made up approximately 50% of the cows in the herd. In Spain, there are also reports suggesting that some indigenous breeds, including the black Avilena, the Morucha, and the Retinta, do not appear to be susceptible to oak poisoning.[8]

According to Smith,[20] young cattle (under 440 lb [200 kg]) are often more severely affected than adult cattle. This was not confirmed in our study, since the youngest cow dying was 4-years of age. One explanation for this is that young cattle are often moved to good quality pasture when they are weaned, and not grazed on marginal pastures where they are exposed to oak trees and acorns. Portuguese farmers recognize the increased requirements for maintenance and growth in weanling calves, thus they are provided better quality forages.

Removing animals from oak-infested areas or reducing stocking rates to allow greater forage availability during oak budding and early leaf growth is the most reliable method for preventing oak toxicosis.[2] Removal of cattle from pastures when the acorn drop is abundant can be adequate therapy for mildly affected animals.[4] Supplemental feeding may be required during at-risk periods on ranches where oak poisoning is a problem.[18]

Several treatments have been shown to be effective for treating cows with acute acorn poisoning.[2,12] Oral administration of 5 to 10% calcium hydroxide solutions may have beneficial effects by neutralizing the tannins in the rumen. Active charcoal polyvinylpyrrolidone and polyethylene glycol (PEG, 10g/day) have also been reported to be protective against dietary tannins.[2] However, we envision 2 problems

with implementing these therapeutic measures. First, we doubt that the kidney lesions observed in many cows in the present study would be reversible. Second, the long distance between many of the pastures and the corrals where working facilities were located made treatment attempts impractical. An alternative option is to feed pelleted rations containing 10 to 15% calcium hydroxide to the cows as a preventive measure, as long as the pellets are palatable.[2,12] The strategy adopted on this farm was to identify the cows that were losing weight and had early signs of submandibular edema, remove them from the pasture, and feed them a mixed grain/hay ration, and eventually market them for slaughter after they have improved body condition scores.

Chronic oak toxicity has not been reported in Portuguese dairy cattle. There are relatively few dairy cattle on pasture in southern Portugal, and those that are on pasture are fed diets comprised of various grain and hay mixes, therefore little to no exposure to oak buds, leaves or acorns.

Conclusions

Chronic oak poisoning of beef cattle in Portugal occurs primarily in cows that are at least 2 years of age and nursing a calf, and is associated with ingestion of the acorns, buds, leaves and/or stems of oak trees of the species *Quercus suber*, and less commonly *Q. ilex*. On this farm, straightbred Portuguese Mertolengo cattle did not appear to be susceptible to this toxicity, presumably the result of their unique genetics. All 17 cases in this study occurred in crossbred Mertolengo cattle that were less than 50% Mertolengo. The other (>50%) genetic influence was mostly Blonde d'Aquitaine, Charolais, or Limousin.

Clinical diagnosis can be challenging, and requires a combination of indepth knowledge of on-farm feeding and animal management, physical examination of affected cows, as well as biochemical analysis of serum samples from affected animals, and gross and histopathologic examinations of kidney tissues from fatal cases. The main risk factors appear to be inadequate nutrition and poor pasture management that forces lactating cows to eat plants (i.e., *Q. suber* and *Q. ilex*) that they would not ordinarily want to graze or browse, in order to meet their dietary nutritional requirements.

Endnotes

[a] Bovilis® BVD, MSD Animal Health, Lda., 2770-192 Paço de Arcos/Portugal
[b] Covexin 8®, Zoetis Portugal, Lda., 2740-271 Porto Salvo/Portugal
[c] Virbamec®, Virbac Portugal Laboratórios, Lda., 2710-693 Sintra/Portugal
[d] Closamectin®, Norbrook Laboratories, Ltd, BT35 6QQ Newry/Northern Ireland
[e] Rx Daytona, Randox Laboratories Limited, Crumlin, UK
[f] i-Stat, Sensor Devices Incorporated, Waukesha, WI, USA

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CYSTORELIN®

(gonadorelin)

By Merial

For treatment of cystic ovaries in dairy cattle

For use with cloprostenol sodium to synchronize estrous cycles to allow for fixed time artificial insemination (FTAI) in lactating dairy cows and beef cows.

CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION:

CYSTORELIN® is a sterile solution containing 43 mcg/mL of gonadorelin (GnRH) as 50 mcg/mL gonadorelin diacetate tetrahydrate suitable for intramuscular or intravenous administration according to the indication. Gonadorelin is a decapeptide composed of the sequence of amino acids—

5-oxoPro-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH2—

a molecular weight of 1182.32 and empirical formula $C_{55}H_{75}N_{17}O_{13}$. The diacetate tetrahydrate ester has a molecular weight of 1374.48 and empirical formula $C_{59}H_{91}N_{17}O_{21}$.

Each mL of CYSTORELIN contains:

Gonadorelin diacetate tetrahydrate (equivalent to 43 mcg gonadorelin)	50 mcg
Benzyl Alcohol	9 mg
Sodium Chloride	7.47 mg
Water for Injection	q.s.

pH adjusted with potassium phosphate (monobasic and dibasic).

Gonadorelin is the hypothalamic releasing factor responsible for the release of gonadotropins (e.g., luteinizing hormone [LH], follicle stimulating hormone [FSH]) from the anterior pituitary. Synthetic gonadorelin is physiologically and chemically identical to the endogenous bovine hypothalamic releasing factor.

INDICATIONS FOR USE:

Cystic Ovaries

CYSTORELIN is indicated for the treatment of ovarian follicular cysts in dairy cattle. Ovarian cysts are non-ovulated follicles with incomplete luteinization which result in nymphomania or irregular estrus. Historically, cystic ovaries have responded to an exogenous source of LH such as human chorionic gonadotrophin. CYSTORELIN initiates release of endogenous LH to cause ovulation and luteinization.

Reproductive Synchrony

CYSTORELIN is indicated for use with cloprostenol sodium to synchronize estrous cycles to allow for fixed time artificial insemination (FTAI) in lactating dairy cows and beef cows.

DOSAGE AND ADMINISTRATION:

Cystic Ovaries

The intravenous or intramuscular dosage of CYSTORELIN is 100 mcg gonadorelin diacetate tetrahydrate (2 mL) per cow.

Reproductive Synchrony

The intramuscular dosage of CYSTORELIN is 100 mcg gonadorelin diacetate tetrahydrate (2 mL) per cow, used in reproductive synchrony programs similar to the following:

1. Administer the first CYSTORELIN injection (2 mL) at Time 0.
2. Administer 500 mcg cloprostenol (as cloprostenol sodium) by intramuscular injection 6 to 8 days after the first CYSTORELIN injection.
3. Administer the second CYSTORELIN injection (2 mL) 30 to 72 hours after the cloprostenol sodium injection.
4. Perform FTAI 0 to 24 hours after the second CYSTORELIN injection, or inseminate cows on detected estrus using standard herd practices.

WARNINGS AND PRECAUTIONS:

Not for use in humans.

Keep out of reach of children.

WITHDRAWAL PERIODS:

No withdrawal period or milk discard time is required when used according to the labeling.

The Safety Data Sheet (SDS) contains more detailed occupational safety information. To obtain a SDS or for technical assistance, contact Merial at 1-888-637-4251. To report suspected adverse drug experiences, contact Merial at 1-888-637-4251. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS, or http://www.fda.gov/AnimalVeterinary.

PHARMACOLOGY AND TOXICOLOGY:

Endogenous gonadorelin is synthesized and/or released from the hypothalamus during various stages of the bovine estrus cycle following appropriate neurogenic stimuli. It passes via the hypophyseal portal vessels, to the anterior pituitary to effect the release of gonadotropins (e.g., LH, FSH). Synthetic gonadorelin administered intravenously or intramuscularly also causes the release of endogenous LH or FSH from the anterior pituitary.

Gonadorelin diacetate tetrahydrate has been shown to be safe. The LD50 for mice and rats is greater than 60 mg/kg, and for dogs, greater than 600 mcg/kg, respectively. No adverse effects were noted among rats or dogs administered 120 mcg/kg/day or 72 mcg/kg/day intravenously for 15 days.

It had no adverse effects on heart rate, blood pressure, or EKG to unanesthetized dogs at 60 mcg/kg. In anesthetized dogs it did not produce depression of myocardial or system hemodynamics or adversely affect coronary oxygen supply or myocardial oxygen requirements.

The intravenous administration of 60 mcg/kg/day of gonadorelin diacetate tetrahydrate to pregnant rats and rabbits during organogenesis did not cause embryotoxic or teratogenic effects. Further, CYSTORELIN did not cause irritation at the site of intramuscular administration in dogs with a dose of 72 mcg/kg/day administered for seven (7) days.

TARGET ANIMAL SAFETY:

In addition to the animal safety information presented in the PHARMACOLOGY AND TOXICOLOGY section, the safety of CYSTORELIN was established through the review and evaluation of the extensive published literature available for the use of gonadorelin-containing products.

The intramuscular administration of 1000 mcg gonadorelin diacetate tetrahydrate on five (5) consecutive days to normally cycling dairy cattle had no effect on hematology or clinical chemistries.

In field studies evaluating the effectiveness of CYSTORELIN for the treatment of ovarian follicular cysts, the incidence of health abnormalities was not significantly greater in cows administered CYSTORELIN than cows administered a placebo injection.

The target animal safety of, and injection site reactions to, gonadorelin when used with cloprostenol sodium were evaluated during the conduct of effectiveness field studies. The incidence of health abnormalities was not significantly greater in cows administered gonadorelin than cows administered a placebo injection.

EFFECTIVENESS:

The use of CYSTORELIN for treatment of ovarian follicular cysts in dairy cattle was demonstrated to be effective with a treatment dose of 100 mcg gonadorelin diacetate tetrahydrate.

The effectiveness of gonadorelin for use with cloprostenol sodium to synchronize estrous cycles to allow for FTAI in lactating dairy cows was demonstrated in a field study at 10 different locations in the U.S. Four of the locations represented conditions that would typically cause heat stress in lactating cows. A total of 1607 healthy, non-pregnant, primiparous or multiparous lactating dairy cows within 40-150 days postpartum were enrolled in the study. A total of 805 cows were administered gonadorelin (1 mL; 100 mcg gonadorelin as the acetate salt) and 802 cows were administered an equivalent volume of water for injection as an intramuscular injection twice in the following regimen:

Day 0: 100mcg gonadorelin (as the acetate salt) or sterile water for injection
Day 7: 500 mcg cloprostenol (as cloprostenol sodium)
Day 9: 100mcg gonadorelin (as the acetate salt) or sterile water for injection

Fixed time AI was performed on Day 10, approximately 11 - 31 hours after the Day 9 injection. Cows were evaluated for pregnancy on Day 45 ± 5 days by trans-rectal ultrasound or rectal palpation. Pregnancy rate to FTAI was significantly higher ($P < 0.0001$) in cows treated with gonadorelin (33.4%) than the pregnancy rate to FTAI in cows treated with water (13.6%). The environmental condition (heat stress or not heat stress) did not affect the conclusion of effectiveness. The effectiveness of gonadorelin for use with cloprostenol sodium to synchronize estrous cycles to allow for FTAI in beef cows was demonstrated in a field study at 10 different locations in the U.S. A total of 706 healthy, non-pregnant, primiparous or multiparous beef cows within 40-150 days postpartum were enrolled in the study. A total of 364 cows were administered gonadorelin (1 mL; 100 mcg gonadorelin as the acetate salt) and 342 cows were administered an equivalent volume of water for injection as an intramuscular injection twice in the following regimen:

Day 0: 100mcg gonadorelin (as the acetate salt) or sterile water for injection
Day 7: 500 mcg cloprostenol (as cloprostenol sodium)
Day 9: 100mcg gonadorelin (as the acetate salt) or sterile water for injection

Fixed time AI was performed immediately after the Day 9 injection. Cows were evaluated for pregnancy on Day 55 ± 5 days by trans-rectal ultrasound. Pregnancy rate to FTAI was significantly higher ($P = 0.0006$) in cows treated with gonadorelin (21.7%) than the pregnancy rate to FTAI in cows treated with water (7.4%).

The effectiveness of a 2-mL dose of CYSTORELIN delivering 100 mcg gonadorelin diacetate tetrahydrate (86 mcg gonadorelin) for use with cloprostenol sodium to synchronize estrous cycles to allow for FTAI in lactating dairy cows and beef cows was also demonstrated through references to scientific literature.

HOW SUPPLIED:

CYSTORELIN is available in a concentration of 50 mcg/mL gonadorelin diacetate tetrahydrate (43 mcg/mL gonadorelin) pH adjusted with potassium phosphate (monobasic and dibasic).

CYSTORELIN is supplied in multi-dose vials containing 10 mL and 30 mL of sterile solution.

STORAGE, HANDLING, AND DISPOSAL: Store at or below 77°F (25°C). Brief excursions to 86°F (30°C) are permitted. Use within 6 months of first puncture.

NADA 098-379, Approved by FDA

Marketed by:
Merial, Inc.
Duluth, GA 30096-4640 U.S.A.

SYNCHSURE™

(cloprostenol sodium)

By Merial

Prostaglandin Analogue for Cattle
Equivalent to 250 mcg cloprostenol/mL

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION:

SYNCHSURE (cloprostenol sodium) is a synthetic prostaglandin analogue related to prostaglandin $F_{2\alpha}$. SYNCHSURE is indicated for intramuscular use at a two mL dose to induce luteolysis in beef and dairy cattle. The luteolytic action of SYNCHSURE can be used to manipulate the estrous cycle to better fit certain management practices, to terminate pregnancies resulting from mismatings, and to treat certain conditions associated with prolonged luteal function.

USES OF SYNCHSURE:

Unobserved or Nondetected Estrus: If a mature *corpus luteum* is present, SYNCHSURE can be used to induce estrus. Estrus is expected to occur 2 to 5 days following injection. Treated cattle should be inseminated at the usual time following detected estrus or twice at 72 and 96 hours post injection if estrus detection is not possible or desirable.

Pyometra or Chronic Endometritis: Endometritis is inflammation of the uterus and pyometra is characterized by the lack of cyclical estrus behavior and the presence of a persistent *corpus luteum*. SYNCHSURE induces luteolysis which usually results in evacuation of the uterus and a return to normal cycling activity within 14 days after treatment.

Mummified fetus: Induction of luteolysis with SYNCHSURE usually results in the expulsion of the mummified fetus from the uterus. (Manual assistance may be necessary to remove the fetus from the vagina). Normal cyclical activity usually follows.

Luteal Cysts: Luteal cysts may cause abnormal cycling patterns in cows. Treatment with SYNCHSURE can restore normal ovarian activity by causing regression of the luteal cyst.

Pregnancies from mismating: SYNCHSURE can be used to terminate unwanted pregnancies in cattle from 1 week after mating until about 5 months of gestation. The induced abortion is normally uncomplicated and the fetus and placenta are usually expelled 4 to 5 days after the injection. The efficacy of SYNCHSURE in inducing abortion decreases after 5 months of gestation, while the risk of dystocia and additional consequences increases.

Controlled Breeding: SYNCHSURE can be used to schedule estrus and ovulation for individual animals or a group of animals to control breeding times. SYNCHSURE can be used in controlled breeding programs through either single or double injection protocols. Only animals with a mature *corpus luteum* should be treated with the single injection protocol to obtain a maximum response to the single injection. Prior to treatment, cattle should be examined rectally and found to be anatomically normal and nonpregnant. Before a controlled breeding program is planned, the producer and his consulting veterinarian should review the operation's breeding history, herd health and nutritional status and agree that a controlled breeding program is practical in that particular situation.

The use information provided here is not comprehensive. Talk to your veterinarian and consult the full prescribing information available at www.synchsure.com for further details on uses of SYNCHSURE.

SAFETY AND TOXICITY: AT 50 and 100 times the recommended dose, mild side effects may be detected in some cattle including increased uneasiness, slight frothing, and milk let-down. The risk information provided here is not comprehensive. To learn more, talk to your veterinarian about SYNCHSURE or call 1-888-637-4251. The full prescribing information can be found at www.synchsure.com.

CONTRAINDICATIONS: SYNCHSURE should not be given to pregnant animals whose calf is not meant to be aborted.

WARNINGS: For animal use only. Do not use in humans. Keep out of reach of Children. Women of childbearing age, asthmatics and persons with respiratory problems should exercise extreme caution with handling this product. In early stages, women may not be aware of their pregnancies. SYNCHSURE is readily absorbed through the skin and may cause abortion and/or bronchiospasms: direct contact with the skin should be avoided. Accidental spillage on the skin should be washed off immediately with soap and water.

PRECAUTIONS:

Careful aseptic techniques should be employed to decrease the possibility of post-injection bacterial infection. Antibiotic therapy should be employed at the first sign of infection. The Safety Data Sheet (SDS) contains more detailed occupational safety information. For technical assistance, to request an SDS, or to report a suspected adverse event, contact Merial Technical Support at 1-888-637-4251. For additional information about adverse event reporting for animal drugs, contact FDA at 1-888-FDA-VETS, or http://www.fda.gov/AnimalVeterinary.

Rev 10/2016

MERIAL

1050-2907-0A
Rev. 12/2017

CONGRATS, IT'S A CALF! AGAIN!

It's easy to be confident that your cows will get pregnant when you use Cystorelin® (gonadorelin) and Synchsure™ (cloprostenol sodium) together. They're an effective combination for reproductive efficiency. So, after use, this test is more of a formality.

MAXIMIZE REPRODUCTIVE EFFICIENCY ON YOUR OPERATION AT SYNCTHEHERD.COM.

IMPORTANT SAFETY INFORMATION FOR CYSTORELIN: Do not use in humans. Keep this and all drugs out of the reach of children.

IMPORTANT SAFETY INFORMATION FOR SYNCHSURE: FOR ANIMAL USE ONLY, NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN. Women of child-bearing age, asthmatics, and persons with bronchial and other respiratory problems should exercise extreme caution when handling this product. In the early stages women may be unaware of their pregnancies. SYNCHSURE is readily absorbed through the skin and may cause abortion and/or bronchospasms: direct contact with the skin should therefore be avoided. Accidental spillage on the skin should be washed off immediately with soap and water.

Boehringer Ingelheim

Cattle First.

CYSTORELIN®
(gonadorelin)
By Merial

SYNCHSURE™
(cloprostenol sodium)
By Merial