

Tiamulin and narasin toxicosis in nursery pigs

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Summary

This case report describes a clinical case of tiamulin and narasin toxicosis in a group of nursery pigs, caused by the inadvertent introduction of narasin at 83.1 g per tonne into a ration containing tiamulin at 31.4 g per tonne. The affected pigs were anorexic and showed signs of weakness, depression, ataxia, and incoordination to the point of recumbency, without paddling or other neurological signs. Pathologically, a diffuse, extensive degenerative myopathy was

present. The feed-mixing error was caused by a mechanical problem with the micro-ingredient discharge equipment at the feed mill. Steps were taken by the feed manufacturer to correct and prevent the occurrence of another incident.

Keywords: swine, nursery pigs, toxicity, narasin, tiamulin

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Resumen - Toxicosis de narasina y tiamulina en cerdos de destete

Este reporte describe un caso clínico de toxicosis con narasina y tiamulina en un grupo de cerdos de destete, causada por la introducción inadvertida de narasina a 83.1 g por tonelada en una ración que contenía 31.4 g de tiamulin por tonelada. Los cerdos afectados estaban anoréxicos y mostraban signos de debilidad, depresión, ataxia e incoordinación al grado de echarse

sin mover las extremidades ni presentar otros signos neurológicos. Patológicamente, se presentó una miopatía degenerativa extensiva y difusa. El error en la mezcla del alimento fue causado por un problema mecánico con el equipo de descarga de los micro ingredientes en el molino de alimento. El fabricante de alimento tomó las medidas para corregir y prevenir la presencia de otro incidente.

Résumé - Toxicosis du narasine et du tiamuline dans les cochons à la pouponnière

Ce rapport décrit un cas clinique de toxicosis du narasine et du tiamulin dans un groupe de porcelets dans la pouponnière, causé par l'introduction inattentive de narasin à 83.1 g par tonne dans une ration qui contient 31.4 g de tiamuline par tonne. Les porcelets affectés étaient anorexiques et ont montré des signes de débilité, dépression,

ataxie et incoordination au point de position de décubitus, sans pédalage ou présenter autres signes neurologiques. Pathologiquement, une myopathie dégénérative diffus, étendu était présent. L'erreur de la mélange a été causée par un problème mécanique avec l'équipement de la décharge des micro ingrédients. Le fabricant de moule a pris des mesures pour corriger et prévenir l'événement d'un autre incident.

Although acute toxicoses in swine are not extremely common, the occurrence is frequent enough to warrant their inclusion as a differential diagnosis in swine health problems.¹ They may occur with contamination of the environment or feed or in association with management practices, potentially affecting large numbers of animals.¹⁻³

Overdosing with narasin (Monteban 70; Elanco, Division of Eli Lilly Canada, Guelph, Ontario, Canada), an ionophore licensed in Canada for use in swine as a growth promotant, causes a toxic syndrome similar to that described for monensin and other ionophores.⁴⁻⁸ Toxicosis is characterized by partial or complete anorexia, diarrhea, dyspnea, ataxia, depression, recumbency, and death.⁹⁻¹¹ Lesions include focal degenerative cardiomyopathy, necrosis of skeletal muscle, and congestive heart failure.⁹ As these clinical signs are not pathognomonic, ionophore toxicosis has been confused with other intoxications, acute infectious diseases, and nutritional deficiencies.⁹ Differential diagnoses to be considered when ionophore toxicosis is suspected in young pigs include selenium toxicosis and an unusual manifestation of *Streptococcus suis* septicemia.

Unusually severe toxicosis may be observed when pigs are fed one of the monovalent ionophores (monensin, salinomycin, or narasin) and are concurrently treated with tiamulin, an antibiotic commonly used in swine and poultry for treatment or prevention of bacterial infections.¹⁰⁻¹³ This report describes a case of ionophore toxicosis in nursery pigs, associated with inadvertent introduction of narasin into a ration containing tiamulin.

Herd description

The affected herd was a 500-sow farrow-to-finish operation housed, except for one finishing barn, on a single site. All barns on the main site were interconnected, and animals were moved all-in, all-out by room in the farrowing and nursery areas. Pigs were weaned two to three times a week as farrowing-crate demand dictated, at an average

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age of 15 days and an average weight of 5 kg. The nursery contained eight mechanically ventilated rooms, each accommodating a total of 280 pigs (the target number of pigs to be weaned each week), with eight pens and 35 pigs per pen. Wet-dry feeders provided in each pen were not connected to the water supply, and water was provided in separate drinkers.

Feed was purchased from an independent feed mill. The Phase One nursery ration, which was medicated with 220 g per tonne of chlortetracycline and 31.2 g per tonne of tiamulin, was provided in 25-kg bags that were regularly stocked (floor stocked) at the feed mill. The Phase Two nursery ration, medicated with 220 g per tonne of chlortetracycline and 31.2 g per tonne of tiamulin, and the Phase Three ration, medicated with 440 g per tonne of chlortetracycline and 132.4 g per tonne of penicillin, were provided in bulk. Nursery feed was delivered once a month.

Creep feeding, using the Phase Two ration, was started when pigs were 3 days of age. The Phase One ration was fed for 2 days at weaning, and then blended with the Phase Two ration. Beginning on day 3 post weaning and continuing for 7 to 10 days, only the Phase Two ration was fed. The Phase Three ration was introduced approximately 2 weeks post weaning.

Case description

The producer reported that on June 6, 2003, approximately nine pigs in Room One, weaned 3 to 7 days earlier, were showing signs of anorexia and weight loss. All pigs in this room (on the Phase Two ration) were eating less than expected. The nipple drinkers were checked and flow rate was appropriate. On June 7, the condition continued to worsen in these pigs and the number affected increased to 27. By June 8, morbidity had risen to 41 pigs. On June 8, it was noticed that some pigs in Room Two also appeared to be affected, and one pig was weak and was dog-sitting.

On June 9, a total of 166 of 433 pigs in Rooms One and Two, that had been weaned for 1 to 2 weeks and were on the Phase Two and Phase Three rations, were anorexic and appeared wasted. The producer contacted his feed supplier to report the problem. Ten 25-kg bags of floor-stock Phase Two ration was provided by the feed supplier to replace the old feed in the feeders

in Rooms One and Two, and the pigs ate the new feed readily. Feed records were reviewed. The Phase Two feed bin had been emptied before the last load of the Phase Two ration had been delivered on May 31. On June 2, the pigs in Room One had started eating the Phase Two ration from this delivery. Between June 1 and June 5, the pigs in Room Two, currently on the Phase Three ration, had been fed from the same batch of Phase Two ration as the pigs in Room One. The computer-generated batch sheets from the feed mill showed that the proper ingredients had gone into this batch. Two dedicated feed carts in the nursery barn were used for the Phase Two ration, and no unusual chemicals that might have contaminated the feed had been stored in the feed room.

As the first clinical signs were observed 4 days after the pigs in Room One had started eating the Phase Two ration delivered on May 31, it appeared that there was a problem with the Phase Two ration rather than the Phase Three ration. Therefore, starting on June 9, the floor-stock Phase Two ration was fed instead of the Phase Two ration from the feed bin. The feed bin was emptied and refilled with a new batch of Phase Two ration on June 10, and a sample of the suspect feed was retained for testing. The herd veterinarian was called to investigate the problem.

On June 10, the feed supplier contacted the herd veterinarian to report that there might have been a mechanical problem with the micro-ingredient discharge equipment resulting in inadvertent introduction of narasin (Monteban 70) into the Phase Two ration. The feed mill's feed retainer sample of the Phase Two ration was submitted to Agri-Food Laboratories, Guelph, Ontario, and was tested for moisture, protein, calcium, phosphorus, and sodium. Feed retainer samples were also submitted to Elanco (Division Eli Lilly Canada Inc) for assay for Monteban 70 and to Bio Agri Mix Ltd (Mitchell, Ontario) for assay for tiamulin.

Clinical signs

When the herd veterinarian visited the farm on June 9, pigs were showing increased signs of weakness, ataxia, and incoordination to the point of recumbency, without paddling or other neurological signs. In Room One, 103 of the 270 pigs were in poor condition. One pig was able

to stand only with assistance, but appeared alert and was not blind. In Room Two, 63 of 163 pigs were losing condition and many were weak and ataxic, with four pigs unable to stand. Approximately 75% of the pigs in each pen were anorexic, while the others appeared normal.

Laboratory findings

Five live representative pigs were submitted to the Animal Health Laboratory (AHL; Guelph, Ontario) on June 9 for necropsy and diagnostic testing. Differential diagnoses included selenium toxicosis, an unusual manifestation of *S suis* septicemia, and ionophore toxicosis.

Significant lesions were not noted on the carcasses of the submitted pigs. No gross lesions were noted in any body tissues, except for a slight increase in peritoneal fluid in three pigs. Stomachs contained a small amount of bile-stained mucus. Microscopic lesions were confined to the skeletal muscles. Myodegeneration was marked, involving up to 100% of myofibers in some sections of muscle. In the most severely affected areas, cross-striations were not visible, and some fibers appeared amorphous, hypereosinophilic, and swollen. However, most fibers were undergoing regenerative repair, with invasion by macrophages. Mineralization of muscle fibers was not apparent. Final diagnosis was diffuse, extensive degenerative myopathy consistent with ionophore (eg, narasin) toxicity.

Feed analysis indicated that the retained feed sample was within acceptable limits for moisture, protein, calcium, phosphorus, and sodium, and contained 83.1 mg per kg of narasin and 31.4 mg per kg of tiamulin. The combination of narasin and tiamulin at these levels would be likely to result in the clinical signs observed.

Treatment and outcome

The pigs were treated with a water-soluble form of penicillin on June 9 because of the possibility that the problem might be due to *S suis* infection. The citric acid that was being used for postweaning scour control was discontinued in case it was exacerbating the situation. Beneficial effects were not identified.

On June 12, approximately 50% of the 433 pigs in Rooms 1 and 2 were markedly unthrifty, 25% were less severely affected,

and only 25% could be considered “normal.” The decision was made to euthanize 194 of the most severely affected pigs. A number of less severely affected pigs were left to see how they would progress following the removal of the problem feed. By June 17, the growth rate in this group of pigs was considerably less than expected, and they were still not performing well 2 weeks after the contaminated feed had been removed. To limit damages due to poor performance throughout the grow-finish period, and because of the uncertainty concerning the proper withdrawal time for the combination of narasin and tiamulin, it was decided to euthanize the remaining pigs. This was carried out on June 20, and the carcasses were buried on site in order to avoid the risk of their introduction to the rendering system.

Discussion

The carboxylic ionophores (maduramicin, monensin, lasalocid, narasin, salinomycin, and semduramicin), a group of antibiotics produced by the fermentation of fungal *Streptomyces* species, have activity against some Gram-positive bacteria, coccidia, *Neospora* species, and *Toxoplasma gondii*.¹⁴ These compounds can be classified according to their complexation affinities for monovalent or divalent cations.⁹ The monovalent carboxylic ionophores include monensin, salinomycin, and narasin.⁹ Narasin (Monteban 70), used primarily in chickens as a coccidiostat or to prevent necrotic enteritis, is licensed in Canada for use in swine as a growth promotant at the level of 15 g per tonne of finished feed (M.A. Paradis, Eli Lilly Canada, written communication, 2005).

Ionophore toxicoses are seen only when these products are administered at the wrong dose, to the wrong species, or concurrently with other products that interact with ionophores.¹⁴ Assays for ionophores in the feed provided to the affected animals are needed to confirm and quantify exposure to a particular product.⁹ A confirmatory diagnosis of ionophore toxicity is based on finding significantly higher than recommended use levels of ionophores in the feed.⁹

A target-animal safety study has shown that narasin at 25 g per tonne of complete feed does not cause adverse effects in medicated pigs (M.A. Paradis, Eli Lilly Canada, written communication, 2005). However, an-

orexia, dyspnea, depression, leg weakness, ataxia, and recumbency were observed in pigs fed narasin at 75 and 125 g per tonne for 8 to 14 days (M.A. Paradis, Eli Lilly Canada, written communication, 2005). In a second Elanco safety study (Trial T2NCA8514), forty-eight 9-week-old cross-bred pigs received a single oral dose ranging from 2.5 to 80 mg narasin activity per kg of body weight, and were observed for 14 days. The median lethal dose was 8.9 mg per kg body weight (95% confidence limits, 6.0-12.2 mg per kg).¹⁵ In this case, it is estimated that the pigs ingested a dose of 3.75 mg per kg body weight of narasin. No pigs died directly as a result of ingesting the narasin and tiamulin. However, all affected and exposed pigs were euthanized due to continuing poor performance and residue concerns at market.

In this case, differential diagnoses included selenium toxicosis and an unusual manifestation of *S suis* septicemia, although the clinical signs were not fully supportive of these possibilities. In selenium toxicosis, pigs with either quadriplegic or posterior paralysis remain mentally alert and continue to eat and drink,¹ while the pigs in this case were anorexic. Clinical signs of *S suis* infection include sudden death, fever, lameness, neurological signs, cyanosis, wasting, dyspnea, and inappetence.¹⁶ Early nervous signs include incoordination and adoption of unusual stances, which soon progress to inability to stand, paddling, opisthotonus, convulsions, and nystagmus.¹⁷ In this case, pigs showed increased signs of weakness, ataxia, incoordination, and recumbency, but no paddling or other neurological signs, and there was no response to penicillin. In addition, pigs with *S suis* infection would not have eagerly accepted the new batch of Phase Two ration as in this case.

Tiamulin, a semisynthetic derivative of the diterpene antibiotic pleuromutulin,¹⁸ has a very wide range of safety when used alone (E. Sanford, Boehringer Ingelheim, written communication, 2005). No adverse effects were observed in pigs receiving tiamulin in the feed at a concentration of 220 g per tonne for 99 days, and there were no deaths in pigs that received a dose of 100 mg per kg of body weight (E. Sanford, Boehringer Ingelheim, written communication, 2005). However, tiamulin may cause severe interactions with certain ionophores.¹⁹

Tiamulin administered concurrently with lasalocid, maduramicin, or semduramicin does not cause the severe adverse interactions seen when it is administered concurrently with monensin, salinomycin, or narasin, even when treatment levels of tiamulin (31.2 g per tonne) are used.¹⁹ The interaction between tiamulin and the monovalent carboxylic ionophores is dose-related. Low levels of tiamulin in feed (eg, 40 g per tonne) do not cause signs of toxic interaction when administered concurrently with salinomycin at 60 g per tonne or monensin at 100 g per tonne.¹⁹ Signs of interaction are seen with tiamulin at 40 g per tonne and narasin at 70 g per tonne, but this level of narasin approaches its early toxic threshold in pigs.¹⁹ It has been suggested that the interaction between the monovalent ionophores and tiamulin is caused by accumulation of the ionophore, resulting from inhibition of its oxidative biotransformation by tiamulin.¹⁸ Tiamulin selectively inhibits oxidative drug metabolism via the formation of a cytochrome P450 metabolic intermediate complex.¹⁸ When tiamulin is administered concurrently with a compound that is predominantly metabolized by cytochrome P4503A, changes in residue concentrations of the compound may occur.¹² In experiments using isolated perfused rat liver, elimination of monensin was reduced by 60% in the presence of tiamulin.²⁰ Evidence suggests that the damage seen with the toxic effects of narasin and tiamulin is ultimately due to calcium overloading.⁹ The microscopic lesion is toxic myopathy characterized by degeneration and necrosis of cardiac and skeletal muscles with a variable inflammatory component.⁹

Following an extensive investigation in this case, the feed manufacturer determined that one ingredient had caused a major problem in the micro-ingredient batching system. The affected portion of the micro system was dismantled, inspected, and cleaned. The problem ingredient, an inorganic acidifier, had caused a gumming of the mechanical parts of the system, building up and plugging the airlocks. The micro system held back ingredients from the batch made just before the contaminated Phase Two ration, and then released those ingredients into it.

As soon as the ingredient responsible for the equipment malfunction was identified,

the feed manufacturer removed the product from the system and ultimately from the feed mill. A daily inspection of the equipment was implemented to ensure that there would be no recurrence of this problem. Sensors were installed to detect any non-flow of product, and all ingredients used in the system were tested for flowability and humidity. New procedures were set up for regular inspection and cleaning of the micro systems, and a new ingredient-processing procedure was introduced to better evaluate products brought into the feed mill.

Implications

- Acute toxicosis should be included in the differential diagnosis of swine health problems.
- As tiamulin induces signs of ionophore toxicity by blocking the metabolism of narasin, tiamulin and narasin should not be administered concurrently to swine.
- When swine feeds containing tiamulin are mixed at a feed mill where ionophores are also used, all possible care should be taken to ensure that there is no carry-over of ionophores into these rations.

References

1. Carson TL. Toxic minerals, chemicals, plants, and gases. In: Straw BE, D'Allaire S, Mengeling WL, Taylor DJ, eds. *Diseases of Swine*. 8th ed. Ames, Iowa: Iowa State University Press; 1999:783–796.
- *2. Hooser SB. Swine toxicoses. *J Swine Health Prod*. 1996;4:247–250.
3. Buck WB. Clinical toxicosis induced by pesticides in livestock. *Veterinary Medicine / Small Animal Clinician*. 1978;73:810,812–819.
4. Novilla MN, Folkerts TM. Ionophores: Monensin, lasalocid, salinomycin, narasin. In: Howard JL, ed. *Current Veterinary Therapy Food Animal Practice 2*. Academic Press, New York, New York; 1986:359–363.
5. Van Vleet JF, Amstutz HE, Weirich WE, Rebar AH, Ferrans VJ. Clinical, clinicopathologic, and pathologic alterations of monensin toxicosis in swine. *Am J Vet Res*. 1983;44:1469–1475.
6. Van Vleet JF, Amstutz HE, Weirich WE, Rebar AH, Ferrans VJ. Acute monensin toxicosis in swine: effect of graded doses of monensin and protection of swine by pre-treatment with selenium-vitamin E. *Am J Vet Res*. 1983;44:1460–1468.
7. Van Vleet JF, Runnels LJ, Cook JR, Scheidt AB. Monensin toxicosis in swine: potentiation by tiamulin administration and ameliorative effect of treatment with selenium and/or vitamin E. *Am J Vet Res*. 1987;48:1520–1524.
8. Miskimins DW, Neiger RD. Monensin toxicosis in swine. *J Vet Diagn Invest*. 1996;8:396–397.
9. Novilla MN. The veterinary importance of the toxic syndrome induced by ionophores. *Vet Hum Toxicol*. 1992;34:66–70.
10. Romváry A, Fisi I. Poisoning caused by the interaction of tiamulin and narasin in pigs. *Magyar Állatorvosok Lapja*. 1988;43:487–488.
11. Sakar D, Belcic Z, Blagovic S, Pompe-Gotal J. Narasin toxicity in pigs and its incompatibility with tiamulin. *Veterinarski Arhiv*. 1991;61:269–282.
- *12. Witkamp FR, Nijmeijer MS, Van Miert ASJPAM. Tiamulin selectively induces and inhibits oxidative drug metabolism in pigs and rats via the formation of a stable-inactive-cytochrome P-450 metabolite complex. *Proc 6th Cong Eur Assoc Vet Pharmacol Toxicol*. Edinburgh, Scotland. 1994:27.
13. Sályi, G, Glávitis R, Molnár T, Csepló A. Ionophor antibiotics caused poisoning in swine herds [in Hungary]. *Magyar Állatorvosok Lapja*. 1994;49:140–146.
- *14. McKellar Q, Lawrence K. Ionophores. *In Practice*. 1996;18:385–386.
- *15. Elanco Animal Health. *Naracin for swine. Safety in Pigs*. D-1, version 0.03, April 1974.
16. MacInnes JI, Desrosiers R. Agents of the “suicide diseases” of swine: *Actinobacillus suis*, *Haemophilus parasuis*, and *Streptococcus suis*. *Can J Vet Res*. 1999;63:83–89.
17. Higgins R, Gottschalk M. Streptococcal diseases. In: Straw BE, D'Allaire S, Mengeling WL, Taylor DJ, eds. *Diseases of Swine*. 8th ed. Ames, Iowa: Iowa State University Press; 1999:563–578.
18. Witkamp RE, Nijmeijer SM, Monshouwer M, Van Miert AS. The antibiotic tiamulin is a potent inducer and inhibitor of cytochrome P4503A via the formation of a stable metabolic intermediate complex. Studies in primary hepatocyte cultures and liver microsomes of the pig. *Am Soc Pharmacol Exp Ther*. 1995;23:542–547.
- *19. McKellar QA, Burch DGS. Ionophores – potential toxicities. *In Practice*. 1997;19:32.
20. Meingassner JG, Schmook FP, Czok R, Mieth H. Enhancement of the anticoccidial activity of polyether antibiotics in chickens by tiamulin. *Poult Sci*. 1979;58:308–313.

*Non-refereed references.

