Ivermectin use and resulting milk residues on 4 Canadian dairy herds

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Abstract — The Canadian gFARAD was contacted for milk withdrawal recommendations after multiple cases of topical ivermectin use in lactating dairy cows. The following 4 cases included pertinent milk residue information and illustrate the challenges faced by producers, veterinarians, and regulatory authorities when ivermectin use occurs in dairy cows.

Résumé — Résidus médicamenteux retrouvés dans le lait après utilisation d'ivermectine dans 4 troupeaux laitiers du Canada. Le site canadien gFARAD a été consulté au sujet du retrait du lait de vaches laitières en lactation à la suite de plusieurs cas d'utilisation topique d'ivermectine. Les 4 cas suivants comprennent des renseignements pertinents sur les résidus dans le lait et illustrent les défis auxquels font face les producteurs, les vétérinaires et les autorités réglementaires lors d'utilisation d'ivermectine chez les vaches laitières.

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Ivermectin is a member of the macrocyclic lactone class of endectocides, commonly referred to as avermectins. It is labeled for the treatment of internal and external parasites in dogs, cats, horses, pigs, sheep, and cattle. Subcutaneous (SC) and topical (TOP) formulations are available for use in nonlactating dairy cattle, at a dose of 0.2 and 0.5 mg/kg bodyweight (BW), respectively. In Canada, no maximum residue limit (MRL) has been established for ivermectin in milk; therefore, any amount detected in milk constitutes a residue violation.

Case description

The CgFARAD was first contacted about ivermectin milk residue depletion in October 2003 after a dairy farmer in Ontario applied topical ivermectin (1 mL/10 kg, Ivomec Pour-On, Merial; Baie d'Urfé, Quebec) to all cattle in his herd, including 36 lactating cows, 2 recently dry-treated cows, 3 dry cows near parturition, and 7 heifers under 1 y of age. The farmer had previously used eprinomectin (Eprinex Pour-On; Merial) but had mistakenly purchased ivermectin from his local veterinary clinic. The ivermectin was applied, as per label instructions (1 mL/10kg BW), topically over the midline. The following evening the farmer noticed the label warning against use in lactating cows and phoned his veterinarian. Milk from the treated animals was still in the bulk tank and had not yet been shipped to the processing plant. The veterinarian and producer agreed to contact the Dairy Farmers of Ontario (DFO) for advice. The CgFARAD was contacted the following day (2 d after ivermectin application) for withdrawal advice. Information on ivermectin residue depletion in milk was limited, so no immediate recommendation was provided. However, the CgFARAD personnel warned that ivermectin residues would persist for a long time and milk would need to be tested before being shipped for processing. At the time, no commercial laboratories in Canada were capable of measuring ivermectin concentrations in milk. The producer was advised to brush and wash all treated animals to remove any remaining product from the skin and to dispose of the contaminated milk. Two milk samples from the commingled bulk tank and 2 samples from cows at 6 d post-treatment were sent to the University of Guelph, and were then forwarded to the Pennsylvania Animal Diagnostic Laboratory (Kennett Square, Pennsylvania, USA). All 4 milk samples tested negative for ivermectin, using liquid chromatography/mass spectrometry (LC/MS) with a limit of detection (LOD) of 50 ppb (μg/kg). At this point, the DFO informed the producer that the milk was acceptable and shipments could resume. In the 9 d between the applications of ivermectin and the negative residue confirmation, 9426 L of milk, with an approximate value of $4700, were discarded. During this process, the CgFARAD learned that the Canadian Food Inspection Agency (CFIA) was validating its own ivermectin assay for milk, with a limit of detection of 0.3 ppb. A milk sample was delivered to the CFIA's Calgary Laboratory and tested by liquid chromatography/tandem mass spectrometry (LC/MS/MS). The ivermectin concentration was 1.8 ppb, technically a residue violation but below the LOD of the laboratory in Pennsylvania.

The 2nd CgFARAD withdrawal request occurred in November 2004 after a single prepartum heifer was treated with an unknown dose of topical ivermectin (Ivomec Pour-On; Merial). The heifer calved approximately 25 d later. In early January (approximately 6 wk after treatment and 2.5 wk after

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parturition), a milk sample was submitted for ivermectin residue analysis, using the CFIA's LC/MS/MS methodology. The sample contained 0.8 ppb ivermectin. Milk from this heifer was discarded until another sample taken approximately 11 wk after treatment was below the LOD.

Two months later, 4 cows (3 lactating, 1 dry) on a different farm were accidentally treated with an unknown dose of topical ivermectin (Ivomec Pour-On; Merial). Milk samples were collected from the lactating cows approximately 36 h after treatment and shipped to the CFIA for analysis by LC/MS/MS. All 3 samples contained detectable ivermectin residues (7.1 ppb, 0.9 ppb, and 7.5 ppb). Further milk samples were collected 17 d after treatment from all 4 treated animals, as the dry cow had recently freshened. Two of the 4 samples contained detectable levels of ivermectin (1.6 ppb and 1.1 ppb), while the other 2 samples were below the LOD. The producer was instructed to wait for another 30 d before shipping milk from the 2 positive cows.

In July 2005, a dairy farmer in Ontario accidentally treated 20 lactating cows with topical ivermectin (1 mL/10 kg BW, Ivomec Pour-On; Merial). The error was noted immediately after treatment and the cows were washed and housed outdoors in the rain to remove as much of the product as possible. The following day, the DFO, the CgFARAD, and the CFIA were consulted. Milk samples were collected approximately 48 h after the ivermectin application and shipped to the CFIA for analysis. The average ivermectin concentration in the milk was 5.2 ppb (range 4.3 to 6.3 ppb). The producer was advised to discard milk from the treated animals until ivermectin concentrations depleted below the LOD. At 14 d, the average concentration was 0.6 ppb, but the samples submitted at 21 and 28 d after exposure were below the LOD. The producer was informed that milk shipments could begin after 21 d.

Discussion

Ivermectin is a commonly used endectocide on beef cattle across Canada. The lack of label milk withdrawal time and an MRL in milk indicate that ivermectin should not be used in lactating dairy cows. A related compound, eprinomectin, is licensed for use in dairy cows with no milk discard required. The percentage of the total dose secreted into the milk is much lower for TOP eprinomectin (0.1%) than for SC ivermectin (5%) (1,2). This is reflected by eprinomectin's lower milk:plasma ratio than ivermectin's (0.102 vs. 0.766, respectively) (1,2). As well, eprinomectin has an administrative MRL of 20 ppb in Canada (3), which allows for minimal residues in milk without constituting a violation.

There is little incentive for ivermectin milk residue depletion studies when it is clearly not labeled for use in lactating dairy cows and the manufacturer carries a similar product (eprinomectin) that does have label approval for these animals. The only information from the manufacturer resembling an ivermectin milk withdrawal time is a label warning "not to be used within 2 mo of calving"; however, this statement is not an actual withdrawal time, as it is not based on any residue depletion kinetics. Residue depletion data in milk is sparse and incomplete. One study found that an SC injection of 0.2 mg/kg BW ivermectin produced milk residues above 5 ppb for 16 d, with a milk elimination half-life of 4.7 d (1). Data from a clinical case of ivermectin use in dairy cows demonstrated a similar milk elimination half-life of approximately 4.2 d (4). In a study using a 5 mg/mL topical solution with a 0.58 mg/kg BW dose on 8 cows, milk samples contained detectable ivermectin residues for 10 d, with maximum residues occurring 3–4 d post-treatment (5). Similar data were found from earlier trials in which the same dose was used with milk samples from 6 Holstein and 6 Jersey cows, all of which contained residues 9 d post-treatment (6), with the milk from the Jersey cows containing significantly more ivermectin than that of their Holstein counterparts. Milk samples were not analyzed beyond 9 d post-treatment, so a complete residue depletion profile cannot be determined from these studies. Based upon these limited data, ivermectin application at the label dose for beef cattle will cause detectable milk residues that may persist for an extended period.

Small amounts of ivermectin in milk are not a human health risk. A provisional acceptable residue (PAR) of 20 ppb ivermectin in milk has been proposed in the United States (7). This would result in a daily ingestion of 30 μg ivermectin from milk, given a food consumption factor of 1.5 L/d. The Joint Expert Committee of Food Additives and Contaminants (JECFA) recommended a temporary MRL of 10 ppb for ivermectin in milk (5). Ivermectin is approved for use in humans in some countries. In Canada, as ivermectin is not approved for dairy cattle, there is no legal MRL, and any detectable amount is considered a violation. Currently, the CFIA methodology is sensitive down to 0.3 ppb in milk (8), while US laboratories use less sensitive methodology (sensitive to 5 ppb).

In keeping with the mandate of the Dairy Farmers of Canada's Quality Assurance program, milk containing detectable ivermectin residues is unacceptable. Because there is no rapid screening test for avermectins in milk, the testing methodologies (Charm II and Charm Cowside; Charm Sciences, Lawrence, Massachusetts, USA; IDEXX SNAP; IDEXX Laboratories,Westbrook, Maine, USA; and Delvotest SP; DSM Food Specialties, Delft, The Netherlands) used by milk processing plants will not detect ivermectin residues. In each of the 4 cases reported, the producer informed the Dairy Farmers of Ontario of the ivermectin use. Had the producers not volunteered this information, the ivermectin residues would only have been detected if screened by the CFIA. In 2005/2006, violative endectocide residues were found in only 2.5% of random raw milk samples (n = 400) tested by the CFIA (9). Of the 10 cases, 4 samples contained moxidectin (range 2 ppb to 22 ppb) and 5 samples contained ivermectin (range 0.2 to 6 ppb). Eprinomectin was detected in 1 sample at 4 ppb, considered violative as the sampling occurred before the Veterinary Drugs Directorate had proposed a regulatory amendment for eprinomectin, resulting in a milk MRL of 20 ppb. Ivermectin residues in milk are known to occur elsewhere. In a recent Brazilian study, ivermectin residues of between 2 and 10 ppb were found in 17.8% of milk samples purchased from retail markets (10). The authors concluded that while no milk samples contained ivermectin residues above the Brazilian MRL (10 ppb), the widespread occurrence of residues demonstrated that producers were not following label recommendations to not use ivermectin in lactating dairy cows.

Care should be taken when using ivermectin for treatment of nonlactating animals on a dairy farm. Treating dry cows can result in ivermectin residues in milk if insufficient time elapses between treatment and parturition, as happened in 2 cases described here. Treated animals must also be kept separate from nontreated cows, as grooming can lead to oral exposure of nontreated animals. In 1 study evaluating dermal absorption of ivermectin, doramectin, and moxidectin, the untreated "control" cows, which were housed freely with treated animals, contained detectable plasma concentrations of all 3 compounds (11). The authors estimated that oral ingestion accounts for two-thirds of systemic bioavailability after topical avermectin application, with the remaining bioavailability due to dermal absorption (11). If dairy cattle are accidentally treated with topical ivermectin, they should be washed with soap and water as soon as possible to remove any remaining product, as this will likely reduce the systemic absorption and subsequent elimination into milk.

Veterinarians need to remind staff and producers to read all medication labels carefully. One point of confusion may have been that until late 2006, Eprinex (Merial), eprinomectin, also carried the word "ivomec" on the package, possibly leading to clients asking for "Ivomec" (Merial), ivermectin, mistakenly. As well, the graphics on these products are similar, except for the color of the box. Because the spectrum of activity of ivermectin and eprinomectin are similar, there is no medical reason for dairy producers to use off-label ivermectin. We suspect the recent ivermectin price reduction following the arrival of generic products may be a reason why dairy producers might risk using ivermectin on lactating cows.

These cases and other anecdotal information from the CgFARAD case files alerted the authors to problems associated with topical endectocide use in lactating dairy cows. In all cases, the DFO took the necessary precautions to ensure that unsafe milk was not shipped for consumption. The key summary of these cases is that ivermectin use on dairy farms can result in detectable residues in milk, at great cost to the producer. As veterinary clinics are often the point of sale for endectocides, it is imperative that clinic staff be informed of the difference between various products and remind producers to carefully read the labels on all medications.

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