Adverse Drug Reactions After Administration of Emodeside/Praziquantel (Profender®) in an MDR1-Mutant Australian Shepherd Dog: Case Report

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A 3-year-old male Australian Shepherd was presented with signs of neurological toxicity following the administration of Profender® at the recommended dosage. Unfortunately, the owner had received the product from a veterinarian without any further instructions on fasting as recommended by the manufacturer, so the dog was fed prior to Profender® administration. Neurological toxicity included generalized tremor, agitation and panting, and required hospitalization of the dog. All neurological signs resolved after symptomatic treatment within 24 h and the dog was discharged without the need for further medication. MDR1 genotyping revealed a homozygous mutation of the MDR1 gene, which is normally important to prevent brain penetration of emodepside by an efflux-based transport mechanism at the blood brain barrier. This case indicates that Profender® can lead to serious, but transient neurological toxicity in dogs with homozygous MDR1 mutation even at therapeutic dosage, in particular when fasting recommendations are disregarded. Therefore, the case report highlights both the importance of MDR1 genotyping in predisposed dog breeds as well as strict compliance with fasting recommendations around the time of Profender® administration.

Keywords: Profender, MDR1 (ABCB1) gene, emodepside, MDR1 mutation, dog, adverse drug reaction, drug intolerance, neurological toxicity

INTRODUCTION

The cyclic octadepsipeptide emodepside (EMO), a metabolite of the fungus Mycellia sterilia, is used clinically to treat different kinds of gastrointestinal nematodes in cats and dogs (1–3). In dogs, it is administered orally as a modified-release tablet (Profender®) in combination with praziquantel (PZQ) at a minimal therapeutic dosage of 1 mg/kg EMO and 5 mg/kg PZQ (4). Dogs should be fasted prior to drug application, since serum concentrations of EMO increase when dogs are fed at the time of treatment (5).

In parasitic nematodes, EMO interferes with latrophilin receptors (6, 7) and SLO-1 calcium-activated potassium channels (8), leading to paralysis of the pharynx and body-wall muscles, and finally resulting in inhibition of locomotion, feeding, and...
egg-laying (7, 9, 10). In contrast, EMO has a low acute toxicity in target animals (5, 11) and normally does not enter the brain of vertebrate species due to drug efflux at the blood-brain barrier via the multidrug resistance (MDR1, syn. ABCB1) efflux transporter (12). However, dogs with a homozygous mutation of the MDR1 gene [referred to as nt230(del4) MDR1 mutation (13)] are presumed to show increased drug brain penetration and often suffer from neurological toxicity after application of Profender®, in particular when they are not strictly fasted prior to drug application (14). Dogs predisposed for the MDR1 mutation mostly come from the Collie, Australian Shepherd, Shetland Sheepdog, Longhaired Whippet, and White Shepherd breeds (15).

The current case report describes an MDR1 mutant Australian Shepherd with serious adverse reactions shortly after the administration of Profender®.

**CASE PRESENTATION**

A 3-year-old male Australian Shepherd (weight: 17 kg) was presented at the Veterinary Clinic Norderstedt with generalized tremor, agitation, and panting, which occurred after oral treatment with two Profender® tablets for medium dogs (10 mg EMO plus 50 mg PZQ). The owner had received the product from a veterinarian without any further instructions on fasting, so the dog received a handful (30 g) of dry dog food (Bosch Active) about half an hour before the Profender® administration. Two and a half hours after drug application, the dog showed progressive tremor and severe panting. Furthermore, he developed excessive drooling and salivation and became ataxic.

Therefore, the dog was presented at a veterinary clinic immediately. Initial physical examination revealed a rectal temperature of 40.2°C (104.4°F), heart rate of 136/min, red mucous membranes and a normal capillary refill time of 1 s. The dog showed agitated general condition, panting, and generalized tremor, but was able to stand and walk on his own. Results of further neurological examination were unremarkable. As the patient’s condition was stable, the treating veterinarian decided to perform no further clinical examinations (e.g., blood or urine analysis) and symptomatic treatment was initiated.

The dog was admitted to the intensive care unit and possible seizure activity, body temperature, and intravenous fluid therapy were monitored closely. An IV catheter (Vasofix® Braunüle®, Braun Melsungen) was placed in the right cephalic vein. The patient obtained an intravenous lipid emulsion (Lipofundin® Braunüle, Braun Melsungen) was placed in the right cephalic vein. The patient obtained an intravenous lipid emulsion (Lipofundin® Braun Melsungen) as an IV bolus of 2.0 mL/kg. The respiratory rate was 24/min, the rectal temperature was 38.6°C (101.5°F), the abdomen was slightly tensed and rectal examination was unremarkable. No defecation was observed during the hospitalization, but appetite and urination were normal. Neurological examination was also unremarkable and the dog was discharged to his owner without further medication. The owner reported that the dog vomited multiple times the week after discharge. Apart from that, the dog’s behavior had recovered completely.

Since Australian Shepherds are predisposed to carry the nt230(del4) MDR1 mutation, which is associated with increased susceptibility against several MDR1 reactive drugs, including EMO, MDR1-genotyping was performed (TransMIT GmbH, Giessen, Germany). The dog showed the homozygous mutant MDR1/−/− genotype, resulting in a complete loss of MDR1-mediated drug efflux at the blood-brain barrier.

**DISCUSSION**

Profender® tablets, containing EMO and PZQ, are used for the treatment of nematode and cestode infestations and infections in dogs and are generally well-tolerated. EMO is a broad-spectrum anti-parasitic drug and is effective even against multiresistant parasite strains, which suggests a novel mode of action (2, 3, 16–19). Potential targets for EMO in invertebrates are SLO-1 calcium-activated potassium channels (8, 20, 21), G-protein-coupled latrophilin-like (LAT-1) receptors (6, 7), and gamma-aminobutyric acid (GABA) receptors (1) while the latter seem to be of minor importance (18, 22). In contrast, pharmacodynamic interactions of EMO with vertebrate central nervous system (CNS) receptors are scarcely understood. Nevertheless, it is well-established that EMO has a low toxicity in mammals (11, 23–27). In the present case, however, there is a suspected adverse reaction related to the administration of Profender®. As PZQ has a wide margin of safety and low acute toxicity (28, 29), it is likely that neurological toxicity is provoked by EMO and not by PZQ in this case.

There are two factors known that limit the therapeutic safety of Profender® in dogs: (I) feeding around the time of drug administration and (II) mutation of the MDR1 drug efflux carrier at the blood-brain barrier. Both are related to the pharmacokinetics and brain penetration of EMO. Profender® modified-release tablets have an intended prolonged release period of the active substance in fasted animals. However, feeding around the time of drug administration accelerates the release of the active substance and thus leads to increased plasma drug levels. Studies analyzing the pharmacokinetics of EMO and PZQ after Profender® administration revealed significantly higher Cmax values in dogs fed around the time of treatment.

**Abbreviations:** CNS, central nervous system; EMO, emodepside; PZQ, praziquantel; MDR1, multidrug resistance gene 1; SPC, Summary of Product Characteristics.
compared to fasted dogs (5). Therefore, overnight fasting of a
dog is recommended when Profender® treatment is intended for
the next morning and food should not be made available until
4 h after treatment (4). As in the current case, in practice this
recommendation is often disregarded, either due to ignorance or
because drug application together with food is better accepted by
dogs. However, whereas the increase in plasma concentration at
a non-fasted condition seems to be covered by the therapeutic
index in MDR1 intact dogs, this does not apply for MDR1
mutant dogs (14). In these dogs, drug efflux by the MDR1
efflux transporter is abolished due to a 4-bp deletion in exon
4 of the MDR1 gene, commonly referred to as nt230(del4)
MDR1 mutation (13). Consequently, dogs homozygous for this
mutation (MDR1<sup>−/−</sup> dogs) are completely deficient for MDR1-
mediated drug efflux. Dogs from several breeds are predisposed
for this mutation including Collie, Australian Shepherd, Shetland
Sheepdog, Longhaired Whippet, White Shepherd, and some
others (15). In an mdr1-mutant mouse model, we recently
showed significantly increased brain penetration of EMO in the
absence of MDR1 in the blood-brain barrier. The brain
concentrations of EMO in the mdr1-deficient mice were almost
twice as high as the corresponding plasma concentration,
whereas in mdr1-intact animals, no relevant EMO concentrations
were detectable in the brain (12). In the mdr1-mutant mice,
neurological toxicity indicated by ataxia, hyperkinesia, and
behavioral changes was detected already at 1 mg/kg oral dosage,
whereas mdr1-intact mice did not show any adverse drug
reactions. This indicates that the MDR1 drug efflux at the blood-
brain barrier normally prevents neurological toxicity after EMO
application. A retrospective study on 55 dogs with adverse drug
reactions after Profender® treatment revealed the MDR1<sup>−/−</sup>
mutant genotype in most of the cases. Ataxia, salivation, tremor,
panting, and agitation were the most prominent symptoms in
these dogs (14). The Australian Shepherd dog in the current
case had the MDR1<sup>−/−</sup> deficient genotype as well. Therefore,
it is very likely that neurological toxicity, including tremor,
panting, salivation, ataxia, hyperthermia, and agitation, were
provoked by increased drug penetration into the brain due to
MDR1 deficiency.

Altogether, there is increasing evidence that dogs with
homozygous MDR1 mutation and non-fasted administration of
Profender® tablets are particularly prone to adverse drug
reactions involving the nervous system. In this case, two factors
are combined that have been shown to limit the therapeutic
safety of Profender®. Unfortunately, this scenario was not
evaluated during drug approval. The only pre-clinical studies
that have been performed showed either accelerated drug
release and absorption in non-fasted dogs, or lower margin of
safety in MDR1 mutant Collie dogs that were fasted as
recommended (4, 5). Therefore, occurrence of neurological
toxicity in the current case explicitly does not conflict with these
pre-clinical target animal studies. According to the Guidelines
on Pharmacovigilance for Medical Products for Veterinary Use
[volume 9B of The Rules Governing Medicinal Products in
the European Union (30)], a probable causal relationship exists
between the administration of Profender® and the adverse
reactions in the case presented here. The description of the
clinical phenomena in this case is consistent with the known
pharmacology and toxicology of Profender®. Additionally, there
is a reasonable association in time and there are almost no other
equally plausible explanations. Furthermore, previous knowledge
of similar reports exist in literature (14) and the adverse events
are described in the Summary of Product Characteristics (SPC)
(4) as well. Additionally, in accordance with the Directive
2001/82/EC (31), adverse reactions are serious in this case. Both
mentioned factors known to limit the therapeutic safety of Profender® were disregarded in this case, despite strict
recommendation and information in the SPC. Therefore, this
case report indicates that in practice, the use of Profender®
still leads to adverse drug reactions in MDR1 mutant dogs,
mainly due to ignorance or poor information of dog owners
about the strict fasting regime required around the time of
drug administration.

In general, MDR1-genotyping in dogs from predisposed
breeds is recommended prior to administration of MDR1
reactive drugs, including EMO. Additionally, fasting
recommendations of Profender® should be strictly followed and
dog owners should always be informed, in particular in dogs
with homozygous MDR1-mutation.

As specified in the SPC, signs of neurological disorders may
be more severe in MDR1 mutant dogs, but symptoms are
transient and self-resolving without any treatment (4). However,
adverse reactions of the Australian Shepherd in the current
case were serious and very distressing to both animal and
owner, in a way that was not expected from the SPC statement.
This is particularly significant, since there is no antidote or
treatment option established so far (4, 5, 32). Diazepam and
further benzodiazepines, as well as barbiturates, are often used
to treat generalized tremor, but showed limited improvement in
the present case as well as in former cases (14). The use of
acepromazine appears to have improved the dog’s condition in
the present case. A study investigating the effect of the canine
MDR1-mutation on sedation after IV administration of 0.04
mg/kg acepromazine, suggests that dogs with the homozygous
MDR1-mutation are likely to show increased and prolonged
sedation compared to normal dogs (33). These results indicate
that CNS levels of acepromazine are expected to be increased
in MDR1-mutant dogs and may explain the better effect of
acepromazine compared to diazepam in the present case.
However, the effect giving acepromazine IM and at higher doses,
as described in the present case, has not yet been determined (33).
Therefore, supportive care with fluid or even lipid infusion is
the only treatment option so far. Consequently, further research
analyzing the interaction of EMO with vertebrate CNS receptors
would be essential to reach more specific treatment options in
cases of neurological toxicity after EMO treatment.

CONCLUSION

Despite strict recommendations and information in the SPC,
the use of Profender® still leads to serious adverse drug
reactions. Based on the current knowledge, two factors restrict
the therapeutic safety of Profender®: drug application to
non-fasted dogs and homozygous nt230(del4) MDR1 mutation (MDR1−/−). The combination of both factors probably explains the occurrence of neurological toxicity in the present case. Therefore, MDR1 genotyping in dogs from predisposed breeds as well as a strict fasting regime is recommended prior to Profender® administration. Additionally, it is essential to inform dog owners about these recommendations, in order to ensure appropriate drug application. Although the dog in the present case showed serious adverse reactions, these were transient and resolved without any specific treatment. To the best of our knowledge, there have not been any reports of cases with lethal outcome after the administration of Profender®. Nevertheless, studies elucidating the molecular target of EMO in the vertebrate brain are necessary to reach more specific treatment recommendations that would be needed in even more severe cases of adverse drug reactions after Profender® treatment.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the owner for the publication of this case report and any potentially-identifying information.

AUTHOR CONTRIBUTIONS

CL clinically examined the dog and described the case. DG, MH, and JG discussed the case and drafted the manuscript. All authors reviewed, edited the manuscript, have read, and approved the final manuscript.

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AUTHOR CONTRIBUTIONS

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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