

Toxicity of fipronil in rabbits as a therapeutic drug for "*Psoroptes cuniculi*": A preliminary observation

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ABSTRACT

In the current report, a preliminary observation to study the adverse effects of the broad use acaricides fipronil (FPN) in rabbits infested with *Psoroptes cuniculi*. Two separate groups (5 rabbits/each) treated topically (poured on at the base of the neck) with fipronil 5%, 1 vial/ 10 kilogram body weight (kg bw) and 1 vial/ 5 kg bw. After FPN spot on application, rabbits in both groups examined microscopically on the 7th, 14th, and 28th day post treatment and the number of live mites (larvae, nymphs, and adults) on each rabbit counted at the end of the experiment (28th day). The results showed that the number of mites in rabbits topically treated with FPN did not show significant decrease, moreover a decrease in both treated rabbits body weight (bw) and in performance observed clearly, with some attendant mortality. In conclusion, this work showed that FPN was with limited efficacy on *P. cuniculi* and had some undesirable side effects. Further and in-depth studies on FPN toxicity in rabbits and other animals are necessary.

KEYWORDS: Fibronil, Rabbits, *Psoroptes cuniculi*, Acaricide.

INTRODUCTION

Fipronil (FPN) is a phenylpyrazole broad-spectrum insecticide with acaricidal activity. It is originally used in agricultural purposes, but recently FPN is widely used in fighting tick and flea infestations in dogs, cats and cattle (Chanton et al. 2001; Aajoud et al. 2003; Cid et al. 2016). Its mechanism of action involves the neurotransmitter aminobutyric acid (GABA) block (Raugh et al. 1990; Postal et al. 1995). FPN binds GABA receptors in insects more strongly to the same receptors in vertebrates, resulting eventually in insect death (Hainzl and Casida 1996; Matsuda et al. 2001; Payne et al. 2001; Hovda and Hoser 2002).

The choice of an effective acaricidal drug is a critical point to combat mite infestation in various livestock. Several criteria are considered to choose one, includes its cost, efficacy, application method, and nevertheless its toxicity or adverse reactions. Multiple drugs and therapeutics are already available to treat mange "mite infection" in animals such as ivermectin (Bowman et al. 1992; Kurade et al. 1996), doramectin (Narayanan et al. 2004; Kanbur et al. 2008), selamectin (McTier et al. 2003; Kurtdede et al. 2007; Farmaki et al. 2009) and moxidectin (Wagner and Wendlberger 2000), all these drugs by different doses and several ways of deliveries are effective against *P. cuniculi* in rabbits.

The aim of the present study is to report some toxic or adverse reactions observed during use of FPN spot-on as a therapeutic agent of ear mange in rabbits.

MATERIALS AND METHODS

During an experimental trial to test different therapeutic agents to treat ear mange in rabbits (see Elhawary et al., 2017). Two separate groups (5 rabbits/each) treated topically

(acaricide drug poured on at the base of the neck) with Fipronil 5% (BARS®, AVZ animal health, Russia) 1 vial/ 10 kg live body weight and 1 vial/ 5 kg live body weight, respectively. After therapy, all rabbits examined microscopically on the 7th, 14th, and 28th day post treatment. To calculate the efficacy of the experiment, the number of live mites (larvae, nymphs, and adults) on each rabbit counted at the end of the experiment (28th day). The sampling procedures adhered to institutional ethical and animal care guidelines, and all methods conducted in accordance with the Guide for the Care and Use of Laboratory Animals.

RESULTS AND DISCUSSION

The number of mites (Figure 1) was not significantly decreased in rabbits topically treated with FPN spot-on at a dose of 1 vial/10 kg live bw (Table 1). One rabbit died and all rabbits in this group experienced a decrease in body weight and performance. Administering FPN in a double dose (1 vial/ 5 kg live bw) resulted in a significant decrease in the number of mites. But this accompanied with a decrease in the rabbits' performance and in their body weight, and 3 rabbits died.

When FPN initially debuted, published, extralabel dosing recommendations for it were used successfully in rabbits (Cutler 1999; Webster 1999) but later, extralabel administration in rabbits have become contraindicated due to toxicity concerns (Webster 1999, Gupta 2012). Now, the concept of usage of FPN is contraindicated in rabbits due to its adverse effects is well-known, although some studies used it in combinations with Ivermectin (Cutler, 1999). In Egypt, FPN is considered as a new veterinary drug used mainly for combating fleas and ticks infestations in dogs and cats. Due to the Egyptian regulations, veterinary drugs that were approved and registered in the European

Union, USA, and New Zeland are approved directly to use in Egypt (Aidaros, 2005); this means that FPN-containing veterinary products can used by Egyptian veterinarians. Due to misuse or little knowledge of FPN adverse reactions and contradictions, it may used by veterinarians and/or rabbit holders to treat cases of rabbit mange. In our trial, after commencing treatment with FPN, one rabbit died from the group and 3 died from the second group. All rabbits in both groups received FPN spot-on manifested general weakness and poor body condition. FPN is originally used as agricultural insecticide that is extremely used to control insects in different grain crops; it is more efficient than organophosphate, carbamate and pyrethroids insecticides against several species of insects (Hainzl and Casida 1996). Currently, exposure to phenylpyrazole pesticides is a

global public health issue and concerns are increasing about the relative safety of these pesticide groups because of widespread use, their toxicity, and releases into the environment (Mossa et al., 2015). FPN is neurotoxic to insects and the primary mechanism of action refers to blocks ion tropic gamma-amino butyric acid receptor (GABAR) of the central nervous system that causes hyper-excitation at low doses and convulsions leading to insect death at high doses (Cole et al., 1993). FPN is more toxic to insects than mammals (Zhao et al., 2003) and has moderate acute oral toxicity LD₅₀'s ranging from 40 to 100 mg/kg body weight in rats and mice (US Environmental Protection Agency 2002). Therefore, complete selectivity of pesticides is difficult and most of the pesticides are toxic to non-target organisms, including humans (Ernest and Patricia, 1997).

Table 1. Number of live mites per gram / ear scraping in control and treated rabbit groups.

Rabbit	*Group			
	G1	G2	G3	G4
R1	0	100	4	1
R2	0	67	6	1
R3	0	60	11	D
R4	0	90	5	D
R5	0	80	D	D
Mean **	0^d	79.4^a	6.5^c	1^{cd}
D= dead R= Rabbit **= p < 0.01				

Means designated by the same letter are not significantly different at 5% level using Duncan's multiple range test.

*G1= non-infected control, G2= infected and non-treated control, G3= infected and treated by fibronil pour-on at a dose 1 vial/10 kg b wt, and G4= infected and treated by fibronil pour-on at a dose 1 vial/5 kg b wt.



Figure 1. Male *Psoroptes cuniculii* detected in ear swabs of infected rabbits.

Previous studies showed that topically applied FPN had a low percutaneous passage in dogs (Cochet et al. 1997); in cats, FPN also had low percutaneous penetration, primarily in the stratum corneum and sebaceous glands (Birckel et al. 1996). Application of Frontline® spray for dogs and cats at a dose five times higher than recommended for 6 months did not cause any clinical, biochemical, hematological or cutaneous abnormalities. In rabbits, dermal absorption of topically applied FPN is low at 0.07%, oral absorption is higher at 30% to 50% of the ingested dose and is possible if the rabbit licks the product off after topical application (Gupta 2012). However, in rabbits FPN exhibited a significant toxicity, penetrating the skin at a rate up to 10 orders of magnitude higher than it penetrates the skin of rats. This would seem to be a predisposing factor to the higher toxicity of this medication found in rabbits than

in other animal species (Walters and Brain, 1990) and indeed it seems that rabbit neurotoxicity does result from dermal exposure to the FPN (Hainzl and Casida 1996). In one study (Gupta 2012), 10 mg/kg/day of FPN applied topically to rabbits for 21 days caused decreases in mean body weight, weight gain and food consumption. Other studies have shown that dermal dosing in rabbits causes hypersalivation, tremors, hyperactivity, diarrhea, emaciation and death (FAO 1997). Adding all these observations, reports and studies on FPN toxicity in rabbits (e.g. Walters and Brain 1990; Birckel et al. 1996; Hainzland Casida 1996; Cochet et al. 1997, Webster 1999, Gupta 2012) to our preliminary observations in the current work, it seems clearly that FPN has low efficacy when used to fight *P. cuniculi*, moreover showed its undesirable side-effects.

Unfortunately, we did not have further in-depth investigations about the dynamics or ways of toxicity of FPN in rabbits, but this will be a great point of interest, as well as antagonism of FPN toxicity, further studies may deal with these points. So in conclusion, the use of FPN as an acaricidal therapeutic agent in rabbits is strongly contraindicated, until further evidences appear that makes its efficacy and toxicity more clear.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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