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A Comparison of the Emetic Toxicity of Deoxynivalenol and Acetyl Deoxynivalenol in House Musk Shrews (*Suncus murinus*)

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Abstract: The emetic toxicities of deoxynivalenol and its acetyl derivatives were examined using house musk shrews (*Suncus murinus*). Emesis was observed after the oral administration of these toxins at doses ranging from 0-40 mg kg^{-1} B.W. The Effective Dose (ED) causing emesis was calculated using the Probit Method. The ED 50 of deoxynivalenol, 3-acetylnivalenol and 15-acetylnivalenol was 3.85, 0.87 and 8.85 mg kg^{-1} B.W., respectively. The results show that the emetic toxicity of 3-acetylnivalenol is 10 times higher than that of deoxynivalenol or 15-acetyl deoxynivalenol. Even though, acetyl deoxynivalenol has been determined to exhibit equivalent toxicity to deoxynivalenol by the FAO/WHO Joint Food Additives Committee, the different responses of acute emetic toxicity should, therefore be taken into account.

Key words: Emesis, deoxynivalenol, 3-acecylnivalenol, 15-acecylnivalenol, Probit Method

INTRODUCTION

Deoxynivalenol (DON), produced by the Fusarium species of fungi is one of the major mycotoxins contaminated in food and feed. DON contamination is prevalent worldwide in grain and causes adverse health effects in both humans and animals. Low-dose exposure to DON for long periods induces immunotoxic effects such as decreased efficacy of vaccination (Pinton *et al*., 2008), reduction of immune resistance to infectious disease (Sugita-Konishi *et al*., 1998) and refuse feed resulting in weight loss. High doses of DON induce emesis in humans and animals and sometimes cause economic losses for the animal industry.

In 2010, the FAO/WHO Joint Export Committee of Food Additives (JECFA) evaluated DON toxicity. They recognized that 3-acetyl DON (3-ADON) and 15-acetyl DON (15 ADON (Fig. 1a-c) which are DON acetyl derivatives are detected in food and feed with toxicities equivalent to DON (WHO, 2001). The JECFA also evaluated the acute emesis toxicity of DON and determined that the Acute Reference Dose (ARfD) for DON and its acetyl derivatives is 8 ug kg^{-1}. However, regarding emesis toxicity, there are no data comparing DON and its derivatives.

In this study, in order to determine the emesis toxicity of DON and its acetyl derivatives, researchers compared

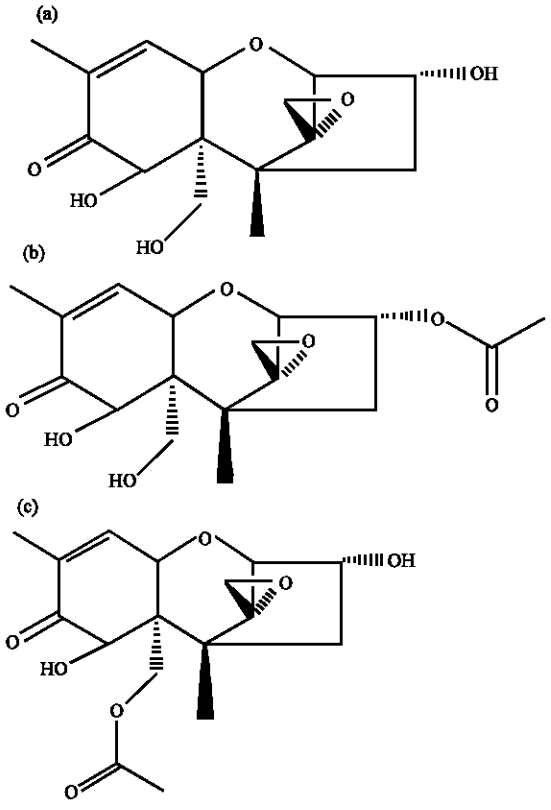

Fig. 1: a) The structures of deoxynivalenol; b) 3-acetyl DON and c) 15-acetyl DON

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emesis toxicities using house musk shrews. Although, dogs (Andrews *et al*., 2001), ferrets (Lau *et al*., 2005) and pigeons (Tanihata *et al*., 2004) have been used for emesis toxicity tests, house musk shrews (Yamamoto *et al*., 2004) are reported to be useful for examining emesis responses to chemical compounds such as enterotoxins (Hu *et al*., 2007) and chemotherapeutics.

The results demonstrate that 3-ADON exhibits the highest emesis toxicity, therefore the risk of emesis with 3-ADON should be recognized.

MATERIALS AND METHODS

Chemicals: DON, 3-ADON and 15-ADON were purchased from Wako Chemical Ltd. (Tokyo, Japan). Skim milk was purchased from Snow Brand Corporation (Japan).

Animals: House musk shrews purchased from Clea Japan were bred and maintained in the animal facilities of the National Institute of Health Sciences. The animals were housed in a temperature-controlled room at 23±1°C under article lighting on 12 h cycles. The animals were freely fed with pellet cat chow and water. The animal experiments were conducted in accordance with the Animal Research Ethics Committee, National Institute of Health Sciences.

Behavioral studies: Female animals (50-60 g, 7-10 weeks old) were used in this study. Various concentrations of DON, 3 and 15-ADON were dissolved with acetonitoril in centrifuge tubes and dried under N_2 gas. The solutions containing DON or 3 and 15-ADON were dissolved and diluted with 10% skim milk. To avoid excess absorption of toxins and hyper-reactions, the toxins were mixed with skim milk and used as a substitute for feed. About 200 μm, of four series of dilution of DON or its derivatives were orally administered (n = 5/each group). The behavioral responses of the animals were observed following oral administration. More than three occurrences of continuous vomiting was defined as emesis in this study.

Statistics: The effective dose was calculated based on the numbers of animals who exhibited emesis using the Probit Method (EcoTox-Statics, JustSystems Corporation, Japan).

RESULTS AND DISCUSSION

Fusarium toxins such as trichothecen mycotoxin are known to cause feed refusal responses and emesis in swine (Trenholm *et al*., 1984). Similar symptoms with the addition of diarrhea were observed in an outbreak of trichothecens in humans (Yoshizawa and Morooka, 1974).

Among trichothecens, DON is the most frequent contaminant in food and feed produced from grains and is a causative agent of food poisoning in both humans and animals. Analytical methods have revealed the presence of DON and its acetylated products in grain. In the JECFA evaluation, acetylated DON was considered to have equivalent toxicity to DON. However, since acute lethal toxicity testing via the oral route in mice showed that acetylated DONs are stronger than DON (Pestka, 2010), it is possible that the acute emesis toxicities of DON and acetylated DONs are different.

When house musk shrews were given oral doses of each diluted toxin, they vomited several times within 2 h (average: 5 times). At a dose of 0.625 mg kg^{-1} B.W., 2 of 5 animals vomited in the 3-ADON group, however emesis was not observed in the other groups. At a dose of 2.5 mg kg^{-1} B.W., 2 of 5 and 4 of 5 animals vomited in the DON and 3-ADON groups, respectively while in the 15-ADON group, no animals vomited. At a dose of 10 mg kg^{-1} B.W., 4 of 5, 5 of 5 and 3 of 5 animals vomited in the DON, 3 and 15-ADON groups, respectively. The maximum dose of these toxins (40 mg kg^{-1} B.W.) induced vomiting in all animals. The analytical results determined using the Probit Method are shown in Table 1. The strength of emetic toxicity was: 3-ADON>DON >15-ADON. The toxicity of 3-ADON was 4.4 and 10 times stronger than that of DON and 15-ADON, respectively at an ED value of 50%. These results demonstrated that the emesis toxicities of the acetylated derivatives are not equivalent, suggesting that 3-ADON induces emesis at lower amounts than DON.

Regarding emesis toxicity, several investigators have described the mode of action of DON. The serotoninergic system plays an important role in the emesis response (Pestka, 2010; Hesketh and Gandara, 1991). Fitzpatrick *et al*. (1988), Smith and MacDonald (1991) and Andrews *et al*. (1998) demonstrated that oral administration of DON induces dramatic increases in the brain concentrations of serotonin in rats. Another study using intragastric administration in pigs indicated that the level of the 5 Hydroxy Tryptophan metabolite (5HT) 5-Hydroxyindoleacetic Acid (5 HIAA) increases significantly in cerebral spinal fluid (Smith and MacDonald, 1991). Meanwhile, oral administration of DON does not enhance the plasma concentrations of 5HT and 5HIAA. Therefore, it is believed that the emesis

Table 1: The emetic toxicities of deoxynivalenol and its acetylated derivatives

Effective dose (mg kg^{-1} B.W.)	DON	3-acetyl DON	15-acetyl DON
10	1.07	0.19	4.17
20	1.66	0.33	5.40
50	3.85	0.87	8.85
80	8.94	2.30	14.50
90	13.87	3.82	18.78

induced by DON is an effect of the Central Nervous System (CNS). However, it is still unknown whether acetylated DONs exhibit the same actions as DON.

Prelusky (1996) reported the results of a comparison study of the emetic toxicities of DON and 15-ADON in pigs. They found that the minimum effective oral doses of 15-ADON and DON were 75 and 50 mg kg^{-1} B.W., respectively. In the current study, the 50% ED doses for 15-ADON and DON were 8.85 and 3.85 mg kg^{-1} B.W., respectively. Although, the experimental animals used in these studies were different, the same tendency was observed that is, 15-ADON exhibited weaker emetic toxicity than DON. Regarding 3-ADON, there are no reports including comparison studies, of the compound's emetic toxicity.

CONCLUSION

Researchers conducted a comparison study of the emetic toxicity of DON and its acetylated derivatives. Researchers found out that 3-ADON exhibits the greatest emetic toxicity. This study is the first report to evaluate the emetic toxicity of 3-ADON. Since, 3-ADON has been reported to be a frequent contaminant in food and feed made from wheat, the risks of 3-ADON must be considered.

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