TREMORGENIC MYCOTOXINS: COMPARATIVE CLINICAL STUDIES IN PIGS AND SHEEP

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Introduction. Mycotoxins are substances produced by fungi which are toxic to animals and man. They form a diverse array of complex chemical structures having varied and often potent pharmacological effects on animals. Some (eg. aflatoxin, ochratoxin, zearalenone and stachybotryotoxin) are now recognised as the cause of hitherto idiopathic syndromes.

The tremorgenic mycotoxins verruculogen and penitrem A are representative of a group of secondary fungal metabolites with a specific effect on the central nervous system. This characteristic of producing sustained tremor, in the absence of other neurotoxic effects, has led to suggestions that mycotoxins are the cause of rye-grass staggers, and other staggers syndromes, in ruminants, and the situation has recently been reviewed (Mantle and Penny, 1981).

Acute Toxicity Trials. The mycelium of Penicillium simplicissimum and P. crustosum was suspended in water and given to the pig or sheep by stomach tube. Penitrem A or verruculogen were given intravenously and the pigs or sheep were then placed in a large pen and closely observed for the onset of symptoms.

In sheep the symptomatology of the tremor was similar to that already described (Penny and others, 1979). At low doses, or soon after oral administration of higher doses, tremor in sheep was first apparent in facial muscles, head and ears. This was rapidly followed by whole body tremor which included tremor of the fore and hind limbs.

In the pig however, the tremor was first seen in the tail and hind-quarter region, and particularly in the anterior muscles of the thigh. Tremor was seen in the head region only after it had spread from the hind quarters to the whole body. Despite the lack of a fleece in the pig and obvious differences in muscular development, this was considered to be a definite species difference and to date the physiologists consulted have been unable to offer an explanation other than different circuitry.

In both pigs and sheep tremors were exaggerated by forced exercise, and this was most obvious with the low doses, or after the severe tremor with higher doses was subsiding and the animal had been allowed to rest.

Variations in the speed of onset and degree of tremor induced were seen between the species, the preparations used and the route of administration. However, oral dosing was as effective in the pig as in the sheep which indicated that ruminant digestion was not involved. In general pigs were less susceptible than sheep when dosed on a body-weight basis and in this species the clinical picture seen with low doses bore a close resemblance to so-called congenital tremor (Table 1).

Effects of Anaesthesia or Sedation. Animals were anaesthetised with long, medium and short acting barbiturates, or they were sedated, and verruculogen or penitrem A were then given intravenously. In all cases tremor was blocked, even with doses of mycotoxin many times those known to cause severe tremor or even death in conscious animals. It was concluded that the ability of anaesthetised or sedated animals to survive such high doses of tremorgen is an indication that the toxicity of these agents is due to completely reversible processes.

Table 1

Tremorgenic activity of Penicillium simplicissimum and P. crustosum mycelia and their toxins verruculogen and Penitrem A

Tremorgen	No.	Route+	Dose	Tremor	
				Time to onset	*Deg
P.simplicissimum					
mycelium	5 lambs	ST	73 mgKg	30 min	++
	5 sheep	ST	110 mgKg	30 min	++
	2 pigs	ST	150 mgKg	30 min	++
verruculogen	2 sheep	IV	1.5 µgKg	3-5 min	+
	5 sheep	IV	3.0 µgKg	5 min	+
	2 sheep	IV	4.5 µgKg	2-4 min	++
	1 sheep	IV	13.3 µgKg	2 min	++++
	5 pigs	IV	6.0 µgKg	5 min	+
	1 pig	IV	7.0 µgKg	4 min	+
	2 pigs	IV	8.2 µgKg	4 min	++
	1 pig	IV	13.3 µgKg	2 min	+++
P. crustosum					
mycelium	2 pigs	ST	100 mgKg	2 hrs	+
Penitrem A	2 sheep	IV	25 µgKg	5 min	+++
	1 pig	IV	24 µgKg	8 min	+++

+ stomach tube - ST, intravenous - IV

* range 0 to ++++, no tremor to very severe whole body tremor bordering on convulsions.

A film will be shown to illustrate the paper.

References

Mantle, P G and Penny, R H C (1981) Veterinary Annual, 21, 51.

Penny, R H C, O'Sullivan, B M, Mantle, P G and Shaw, B I (1979) Veterinary Record, 105, 392.