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The toxicity of chlorophacinone and warfarin to house mice (*Mus musculus*)

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SUMMARY

Individually caged house mice (*Mus m. musculus*) were fed 0·025 % warfarin (3(2-acetyl-1-phenylethyl)-4-hydroxycoumarin) or 0·025 % chlorophacinone (2-(1-(*p*-chlorophenyl)-1-phenyl) acetyl-1,3-indandione) for periods varying from 1 to 21 days. In all, 320 mice, 160 of each sex, were tested.

A significant difference was found between the mortalities obtained by the two compounds. In feeding periods varying from 1–5 days chlorophacinone produced a mortality of 60–85 % and warfarin only 5–75 %. Five per cent, however, did survive 21 days feeding on each compound.

A great variation in the susceptibility of individual mice was established for chlorophacinone as well as for warfarin.

INTRODUCTION

In Denmark warfarin was the only anticoagulant in use for the control of house mice during the period 1953–68, but after several cases of mice surviving 10–20 days on 0·025–0·050 % warfarin in the laboratory (Annual Report, 1961–2, 1963) it was decided that it was no longer possible to obtain satisfactory results in practice, where other food sources are always present. And since another poison, crimidin, at the same time turned out to be effective against house mice, it was decided to restrict the use of warfarin to the control of rats only.

In the search for other anticoagulants to replace warfarin in mouse control, clorophacinone was investigated a little further, as it was claimed by the manufacturer to be more effective than warfarin against house mice even at lower concentrations (Technical Report, 1965). This was partially confirmed by Rowe & Redfern (1968).

MATERIALS AND METHODS

The animals used were all house mice (*Mus m. musculus*) bred in the laboratory and fed normal laboratory diet during their entire life. In each test an equal number of males and females was used, and as far as possible pregnant females were excluded. The mice were placed individually in metal cages (15 × 10 × 25 cm) containing a glass or plastic food bowl and a small bottle with cotton as a nesting box. Water was supplied from a bottle in the roof of the cage. The method used in all tests was to offer each mouse for a fixed number of days excess amounts of bait

Table 1. *Toxicity of* 0·025 % *warfarin to* Mus musculus

No. of days feeding	No. of mice dead by end of the test (out of 20)	Mortality (%)	Days to death		Weight of mice		Dosage range that killed (mg./kg.)	Dosage range that failed to kill (mg./kg.)
			Mean	Range	Mean	Range		
1	1	5	8·0	—	18·4	15·0–20·5	30	12–45
2	4	20	4·5	4–7	17·3	15·0–22·0	71–126	48–119
3	7	35	5·4	2–12	15·0	14·0–16·5	76–165	113–191
4	10	50	6·6	3–9	14·9	10·5–22·0	61–180	60–121
5	15	75	6·9	4–10	18·1	13·0–23·0	86–219	97–145
6	16	80	7·9	4–15	12·5	9·5–15·0	163–478	146–213
10	18	90	9·2	6–15	13·7	10·0–20·5	107–690	362–527
21	19	95	9·4	4–18	12·7	9·5–22·5	69–704	832

Table 2. *Toxicity of* 0·025 % *chlorophacinone to* Mus musculus

No. of days feeding	No. of mice dead by end of the test (out of 20)	Mortality (%)	Days to death		Weight of mice		Dosage range that killed (mg./kg.)	Dosage range that failed to kill (mg./kg.)
			Mean	Range	Mean	Range		
1	12	60	6·8	4–12	13·2	8·5–20·5	23–65	9–50
2	15	76	5·9	3–11	19·5	15·0–23·5	47–101	57–76
3	14	70	7·2	3–13	14·8	11·5–19·0	43–195	104–160
4	17	85	7·8	4–14	16·3	12·0–20·5	109–266	140–250
5	17	85	7·1	2–13	15·4	11·0–22·0	62–340	227–332
6	18	90	6·9	4–12	18·4	13·0–23·5	67–325	251–292
10	19	95	8·4	3–14	16·4	12·0–22·0	58–500	500
21	19	95	12·4	6–25	12·5	8·0–18·0	125–1168	906

containing either 0·025 % warfarin (3(2-acetyl-1-phenylethyl)-4-hydroxycoumarin) or 0·025 % chlorophacinone (2-(1-(*p*-chlorophenyl)-1-phenyl)acetyl-1,3-indandione). The warfarin bait was a prepared bait on whole wheat, whereas the chlorophacinone bait was made by mixing 1 part of a 0·25 % oily concentrate with 9 parts of oat groats. In the majority of tests the amount eaten was recorded daily, but in some tests exceeding 6 days the bait eaten was measured only at the end of the feeding period.

After each poison-period the bottom of the cage was removed and the cotton renewed to avoid further contamination of the food. Mice which died during the test period were examined for internal bleeding, and the survivors were fed plain bait for about 14 days.

RESULTS

The results of the toxicity tests are given in Tables 1 and 2. Twenty mice were used in each test in feeding periods varying from 1 to 21 days. In all, 320 mice were tested.

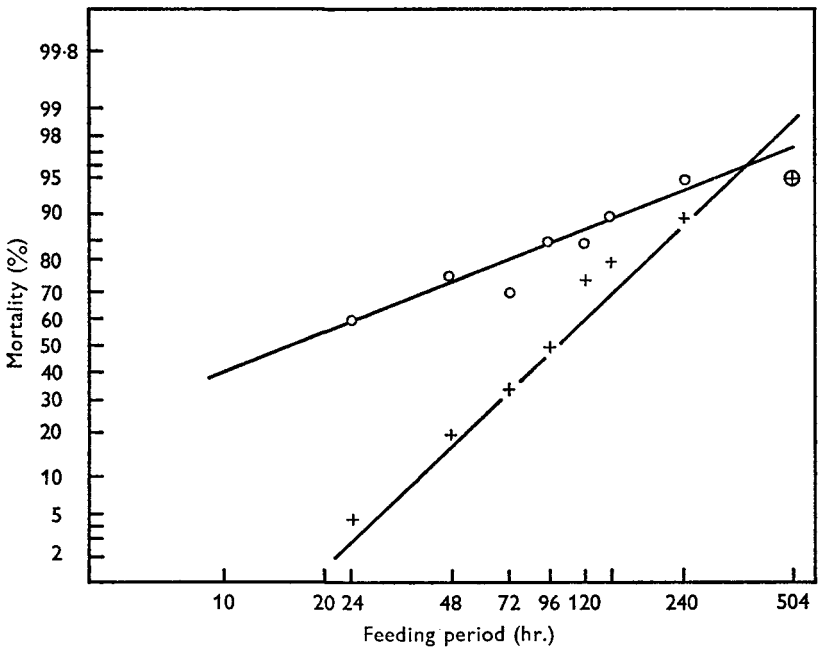

Fig. 1. Effect of two anticoagulants on house mice. ×—×, 0·025 % warfarin; S = 2·04 (1·72 to 2·41). ○—○, 0·025 % chlorophacinone, S = 5·57 (1·92–16·15).

In Fig. 1 the dose/effect lines for the two compounds are given using the method of Litchfield & Wilcoxon (1949). Instead of doses here the feeding periods suggested for anticoagulants by Bentley & Larthe (1959) have been used.

DISCUSSION

Several investigations on the effect of warfarin on house mice have been carried out, especially in England. Bentley & Larthe (1959) in a comparison of five

anticoagulants found a mortality of 90 % (9/10) when feeding house mice for 6 days on 0·025 % warfarin, and a mortality of 100 % when feeding for 7 days. The dosage range that killed varied between 57 and 101 mg./kg., and the highest dose survived was 169 mg./kg. However, rather lower mortalities than these were recorded by Rowe & Redfern (1964). Testing 345 mice from 13 different localities not previously treated with warfarin, they found a considerable individual variation in response, one mouse being killed by a dose of 26·1 mg./kg. and another surviving 1067·2 mg./kg. It was concluded that the lethal feeding period corresponding to a 95 % kill was about 22 days. In a later study (Rowe & Redfern, 1965) it was suggested that probably there are some mice 'resistant' to warfarin in any sizeable population.

In a subsequent comparison of different anticoagulants Rowe & Redfern (1968) repeated these findings with warfarin, whereas chlorophacinone at the same concentration (0·025 %) gave a somewhat better result, e.g. a mortality of 100 % after a 14 days' feeding period. After 3 days' feeding a mortality of 37 % was obtained and it was concluded that chlorophacinone at 0·025 % or 0·0050 % 'is rather more toxic than warfarin at 0·025 %'.

Although the results of the present tests showed a higher mortality to chlorophacinone, no complete kill was obtained with this compound, as with warfarin, even after 21 days' feeding. It seems dubious therefore whether the higher initial kill produced by chlorophacinone can have any practical significance for the control of house mice.

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