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Some rodenticidal properties of coumatetralyl

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INTRODUCTION

Coumatetralyl (3-(α-tetralyl)-4-hydroxycoumarin), an anti-coagulant rodenticide developed by Farbenfabriken Bayer A.G., has been used extensively against rats in Germany (Schultze, 1965). Comparatively little information is available, however, concerning its rodenticidal properties. The present laboratory study was therefore undertaken to investigate the toxicity of the anti-coagulant to warfarin-resistant and warfarin-susceptible rats (*Rattus norvegicus* Berk.) and to compare its palatability with that of warfarin (3-(α-acetonylbenzyl)-4-hydroxycoumarin).

METHODS

Wild rats, presumed not to be resistant to warfarin (NR rats) were caught in a Midlands refuse destructor and on a Surrey farm. Warfarin-resistant (WR) rats were trapped on farms in three different areas of Britain: Nottinghamshire (WR Notts), Gloucestershire (WR Glos) and the Salop–Montgomeryshire area (WR Welsh). Field investigations had shown that the rats on the Nottinghamshire and Gloucestershire farms could not be controlled with warfarin. All ten WR Glos rats used in tests with coumatetralyl had first been given, and had survived, unrestricted feeding for 6 days on 0·005 % warfarin in the laboratory and similarly all but six of the 23 WR Notts rats had first been given periods of from 3 to 6 days on warfarin. The 53 WR Welsh animals had survived either 6 days feeding on 0·005 % warfarin or a single subcutaneous injection of 200 mg./kg. of warfarin, or had shown a minimal increase in prothrombin time 24 hr. after subcutaneous injection of 1 mg./kg. of warfarin (Greaves & Ayres, 1967).

Animals allegedly resistant to coumatetralyl were obtained from two sources. The first (CR Welsh), a farm where a coumatetralyl treatment had failed, was in the Salop–Montgomeryshire area where warfarin-resistance is prevalent. Three of the rats from this source were first given 0·005 % warfarin in medium oatmeal for 6 days, their survival indicating them to be resistant to warfarin. The second source (CR Notts) was a Nottinghamshire farm where it had been found impossible to eradicate the rats with warfarin or subsequently with coumatetralyl. Allegedly coumatetralyl-resistant animals from both sources were thus most probably resistant also to warfarin.

Finally, 15 laboratory-bred WR rats were tested. These animals were also shown by preliminary laboratory tests to be resistant to warfarin. All animals to which warfarin was administered in preliminary tests were permitted a recovery period

of at least 3 weeks, except for five WR Welsh rats which were allowed only 12–19 days before being given coumatetralyl.

Rats were caged singly for all experiments. In toxicity tests approximately equal numbers of males and females were given unrestricted access to medium oatmeal containing coumatetralyl, without alternative food, for specified numbers of days or until death. Consumption of the toxic food was normally measured daily and mortality was recorded for at least 14 days after the start of each test. In palatability tests wild NR rats were given a choice for 2 days between plain medium oatmeal and the same food containing poison; after the first day fresh food containers were provided and the positions in the cage of the two foods were interchanged.

Pure compounds were used in the majority of experiments, but in others either of two proprietary pre-mixes containing 60 % or 0·75 % coumatetralyl and a balance of inert ingredients was employed. There was no indication that toxicity was affected by the method of formulation.

RESULTS

The results of toxicity tests are given in Table 1. The median lethal feeding periods (LFP_{50}) for groups 1–4 were calculated by the probit analysis method given by Finney (1952), employing a logarithmic transformation of feeding period. Analyses of relative potency for the same groups were carried out, taking an individual potency ratio to be statistically significant if its 95 % fiducial limits did not span the value of unity. Not unexpectedly, coumatetralyl was significantly less toxic at 0·005 % than at 0·05 % to NR rats. At 0·05 % it was significantly less toxic to WR Welsh than to NR rats and again at 0·05 %, the compound was significantly less toxic to CR Welsh than to WR Welsh rats.

A further analysis of relative potency involving groups 1–4 of Table 1 was performed in which coumatetralyl was compared with warfarin, an anticoagulant which, on account of its widespread use as a rodenticide, provides a useful reference standard. For this purpose data from Drummond & Wilson (1968) were used. These authors, who used methods essentially the same as ours, offered NR rats bait containing 0·005 % warfarin for 1, 2 and 3 days and obtained corresponding mortalities of 3/12, 19/29 and 30/30, leading to an LFP_{50} estimate of 1·2 days. Our results (groups 1–3) were not found to differ significantly from theirs. Coumatetralyl at 0·05 % was found, however, to be significantly less toxic to CR Welsh (group 4) rats than was 0·005 % warfarin to NR rats.

Though the results for groups 5–12 are not suitable for statistical analysis the feeding behaviour of the four WR rats (in groups 7, 8 and 12) that survived 6 days' feeding on 0·05 % coumatetralyl and also of the longest-surviving CR animal in each of groups 10 and 11 calls for comment. The daily consumption of the toxic food by these six rats fell almost to zero after 3–5 days and then rose again in three animals; doubtless the remaining rats would have shown a similar increase had the experiments continued. This oscillation in food consumption, which is attributable to a period of illness induced by the anti-coagulant alternating with a period of more or less complete recovery, occurred four times before the longest-surviving CR Welsh rat finally succumbed.

Table 1. *Mortality in rats after unrestricted feeding on medium oatmeal containing coumatetralyl*

Group	Type of rat	Conc. of coumatetralyl (%)	Feeding period (days)	Mean body weight (g.)	Mortality	Range of lethal doses (mg./kg.)	Highest dose survived (mg./kg.)	Range of days to death	Median lethal feeding period (days)
1	NR	0·005	1	250	3/10	3–5	5	4–7	1·6
			2	262	6/10	6–8	8	4–7	
			3	304	8/10	7–15	13	4–9	
2	NR	0·05	1	239	7/10	22–35	42	4–14	0·7
			2	239	10/10	44–77	—	4–9	
			3	190	9/10	25–118	101	3–6	
3	WR Wales	0·05	1	222	4/15	31–51	54	3–8	1·6
			2	224	9/15	53–98	118	2–8	
			3	167	13/16	58–160	160	4–7	
4	CR Wales	0·05	3	313	1/6	136	207	5	5·1
			4	286	2/6	87–93	229	4	
			6	190	4/6	112–187	260	5–7	
5	WR Wales	0·05	6	238	7/7	67–165	—	5–9	—
6	WR Notts	0·05	3	279	8/10	53–96	115	5–7	—
7	WR Notts*	0·05	6	281	14/15	49–176	128	5–8	—
8	WR Glos	0·05	6	245	9/10	72–205	200	4–9	—
9	CR Notts	0·05	3	231	0/2	—	115	—	—
10	CR Notts*	0·05	until death	252	2/2	120–123	—	6–13	—
11	CR Wales*	0·05	until death	188	17/17	54–401	—	4–26	—
12	WR Lab. bred	0·05	6	342	13/15	58–183	79	5–9	—

*Includes survivors of shorter feeding periods.

Table 2. *Palatability of coumatetralyl and warfarin to rats*

Poison and Concentration		Amounts eaten (g.) Plain food	Amounts eaten (g.) Poisoned food	No. of rats preferring plain food and total no. in test	Significance of difference
Coumatetralyl	0·05 %	155·3	160·6	7/10	n.s.
Coumatetralyl	0·1 %	195·2	155·2	9/12	n.s.
Warfarin	0·005 %	170·2	221·7	4/12	n.s.
Warfarin	0·025 %	208·8	202·9	6/11	n.s.
Warfarin	0·05 %	301·8	104·3	9/10	0·01

The results of palatability tests of coumatetralyl, together with some comparative data for warfarin, are presented in Table 2. The significance of each mean difference between the amounts of the two foods eaten was assessed by means of Student's *t*. There was no evidence that pure coumatetralyl was unpalatable at concentrations of up to 0·1 %. Pure warfarin, in contrast, was markedly unpalatable at half this concentration.

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DISCUSSION

It has been shown that coumatetralyl at 0·005 % or 0·05 % is about as toxic to NR rats as is warfarin at 0·005 %. Further, at concentrations of 0·05 %–0·1 % coumatetralyl is clearly more acceptable than warfarin to rats. Coumatetralyl is therefore to be regarded, concentration for concentration, as a good alternative to warfarin for use against *R. norvegicus* and will probably give better results than warfarin at concentrations of the order of 0·05 %.

Over a 6-day feeding period coumatetralyl at 0·05 % was lethal to all but two of the WR rats obtained from Nottinghamshire and Gloucestershire. The survival of one animal from each of these sources was evidently a result of the toxic effects of the poison preventing the ingestion of a lethal dose. In field conditions where many rats may often feed only partly on poison bait, animals of this type might well therefore survive treatments with coumatetralyl indefinitely—as perhaps happened with the CR rats, all of which, though eventually succumbing to coumatetralyl in the laboratory (groups 10 and 11, Table 1), had survived expertly conducted treatments with coumatetralyl in the field.

The finding that 0·05 % coumatetralyl is about as toxic to WR Welsh rats as 0·005 % warfarin is to NR rats suggests that coumatetralyl would be effective against WR Welsh rats in the field. The high toxicity of coumatetralyl to WR Welsh rats is also of considerable interest in the light of the report (Drummond & Wilson, 1968) that these animals can survive after feeding for 6 days or more on oatmeal containing concentrations of up to 1·0 % warfarin. An insight into this difference in toxicity between the two very similar compounds will probably depend upon elucidation of the mechanism of resistance to warfarin.

In assessing the possible value of coumatetralyl for destroying warfarin-resistant rats, the evidence that these animals were also somewhat resistant to coumatetralyl must be considered. Where resistance to warfarin occurs only sporadically, as it has in Nottinghamshire and Gloucestershire, such cross-resistance to coumatetralyl, if present, may be of relatively minor importance since by special efforts the few affected infestations can normally be eradicated by other means. In the Salop–Montgomeryshire area, however, where resistance to warfarin, apparently due to a major gene, occurs in rat populations extending over hundreds of square miles, cross-resistance is of greater potential significance. The discovery in the area of an infestation which could not be controlled by treatment with coumatetralyl taken together with the finding that coumatetralyl was, on average, less toxic to WR Welsh than to NR rats suggests that there may be reserves of variability in the warfarin-resistant population sufficient to allow an increase in resistance to evolve in response to the general use of coumatetralyl. Furthermore, to the extent that warfarin-resistant rats are more likely to survive treatments with coumatetralyl than are non-resistant animals, the use of coumatetralyl would be likely to increase the incidence of resistance to warfarin. Thus while coumatetralyl would be expected to give good results against warfarin-resistant rats initially, this use might eventually result in an increase in the incidence of resistance to both anti-coagulants.

SUMMARY

The toxicity and palatability of coumatetralyl (3-(α-tetralyl)-4-hydroxycoumarin) to rats (*Rattus norvegicus* Berk.) were investigated in the laboratory by means of feeding tests. Animals resistant to warfarin (3-(α-acetonylbenzyl)-4-hydroxycoumarin) and warfarin-resistant rats from infestations refractory to coumatetralyl, as well as non-resistant animals, were employed in the tests.

Medium oatmeal containing a concentration of 0·1 % coumatetralyl was not markedly less palatable than the same food unpoisoned. In comparison warfarin at 0·05 % but not at 0·025 % was significantly less readily eaten than the plain food. Coumatetralyl at 0·05 % and 0·005 % was about as toxic as 0·005 % warfarin is reported to be to non-resistant rats. Warfarin-resistant rats were significantly less susceptible to coumatetralyl than were non-resistant rats. Warfarin-resistant rats from an infestation refractory to coumatetralyl were significantly less susceptible to coumatetralyl than were animals from other sources.

It is considered that coumatetralyl at concentrations of the order of 0·05 % in bait would be a good alternative to warfarin against non-resistant rats. While it would be expected that, at this concentration, coumatetralyl would often give good results against warfarin-resistant infestations, this use might eventually produce an increase in the incidence of resistance to both anticoagulants.

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