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ABSTRACT: Second-generation anticoagulant rodenticides were introduced to control Norway rats that had become resistant to first-generation compounds. Unfortunately, some rats have become resistant to these as well. The lack of alternative rodenticides with the same attributes of ease of use and relative safety is potentially a serious problem should resistance become so widespread that anticoagulants are no longer effective. However, the second-generation anticoagulants difenacoum and bromadiolone can still be effective provided most rats in a population possess only a low degree of resistance to them. Measures that maximize the uptake of bait, such as using the most palatable formulation, baiting burrows and saturation baiting have to be implemented. The low levels of resistance discovered so far mean that the most potent anticoagulants, such as brodifacoum and flocoumafen, should also control most populations if baits containing either of them are properly applied. These two rodenticides are restricted to indoor use in the United Kingdom and are thus not available to control those rats living outdoors that are highly resistant to all other anticoagulants. Those rats can, however, be controlled with either zinc phosphide or calciferol, preferably after prebaiting. Strategies to manage resistance in the long-term should be implemented before high-degree resistance spreads. One potential tactic is to stop using anticoagulants altogether and allow deleterious pleiotropic effects to reduce the prevalence of resistance in a population. Any attempts to manager resistance are only relevant if the intention is to retain anticoagulant rodenticides, with their undoubted advantages, as the main method of controlling rodent pests.

KEY WORDS: anticoagulants, brodifacoum, bromadiolone, commensal rodents, control, difenacoum, flocoumafen, Norway rats, rats, *Rattus norvegicus*, resistance, rodenticides, UK

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INTRODUCTION

Soon after the introduction in the United Kingdom (UK) in 1975 of difenacoum, the first of the so-called second-generation anticoagulant rodenticides introduced to overcome warfarin resistance (Hadler and Buckle 1992), reports were received from the county of Hampshire in central southern England that it was failing to control some Norway rat (*Rattus norvegicus*) populations (Redfern and Gill 1978). However, these difenacoum-resistant rats still appeared to be relatively susceptible to difenacoum (resistance factor $\approx$ 4), and therefore resistance was not thought to be a serious practical problem (Greaves and Cullen-Ayres 1988). It was suggested that behavioral or ecological factors were operating in this particular area that tended to reduce the uptake of rodenticide bait and allowed these "slightly" resistant animals to survive. Support for this idea came in later studies (Quy, Shepherd and Inglis 1992; Quy et al. 1992) in which the relatively greater abundance of alternative food, particularly stored cereal, in the Hampshire area was a relevant factor. Indeed, Quy, Shepherd and Inglis (1992) suggested that earlier reports (Greaves, Shepherd and Quy 1982) that resistance to two other second-generation compounds, brodifacoum and bromadiolone, was a main cause of treatment failure in the Hampshire area, were premature. It might have been that rats survived treatments largely because they ate little or no bait, as demonstrated in later trials in the same area (Cowan et al. 1995). Furthermore, because resistant rats from Hampshire required more vitamin K than susceptibles (Greaves and Cullen-Ayres 1988), resistant individuals had a selective disadvantage. Withdrawal of anticoagulants should result in resistant rats being replaced, in due course, with susceptible ones, as reported in earlier studies on warfarin resistance (Partridge 1979). This could only occur, of course, if susceptible alleles were present in the existing population or in nearby reservoir populations.

Norway rats that are resistant to second-generation anticoagulants have also been reported in other European countries. A survey in 1992 reported difenacoum and bromadiolone resistance in Denmark, France and Germany with an additional report of bromadiolone resistance in Holland (Myllymaki 1995). At the time of the survey, no European country, other than the UK, had reported resistance to brodifacoum or to two other relatively new second-generation anticoagulants, flocoumafen or difethialone (the latter not registered for use in the UK). However, the author of the report doubts that the full extent of anticoagulant resistance across Europe was discovered, due to the limited facilities available in most countries. In Germany, the area infested by resistant rats appeared limited to about 8,000 sq. km in the northwest of the country with, apparently, anticoagulant susceptible rats elsewhere (Pelz, Hanisch and Lauenstein 1995). The authors suggested that continued use of difenacoum and bromadiolone in the resistance area might lead to further selection of genes that conferred resistance to the most potent compounds. Consequently, it was suggested that the resistant rats should be controlled using the most potent anticoagulants, brodifacoum, flocoumafen or difethialone.

In this paper, the practical aspects of dealing with widespread resistance to second-generation anticoagulants will be considered, including measures to counter the problem in the short- and long-term, although at present

long-term solutions are mostly speculative, because no one has attempted to implement a rodenticide resistance management strategy.

DEGREES OF RESISTANCE TO SECOND-GENERATION ANTICOAGULANTS

The development of blood clotting response (BCR) tests for detecting resistance to second-generation coagulants (Gill et al. 1993, 1994) has enabled relatively quick determination of resistance as well as sequential testing of individual rats to identify how many different anticoagulants they are resistant to. Buckle, Prescott and Ward (1994) argued that because BCR tests are sensitive enough to detect small shifts in susceptibility, they do not necessarily predict a practical control problem. They provide, however, the technology not only to distinguish susceptible rats from resistant ones, but also to differentiate between low- and high-degrees of resistance. They have now become part of the resistance detection methodology in many European countries (e.g., Pelz, Hanisch and Lauenstein 1995). The distinction between low- and high-degree resistance is not clear cut. Cowan et al. (1995) divided rats into groups on the basis of their response to difenacoum in BCR tests. Rats with log10 PCA (percentage clotting activity) <1 were susceptible, 1-1.5 had low-degree resistance, and >1.5 had high-degree resistance. Animals in the latter group would probably survive feeding on field strength baits for several days. With those definitions, the Hampshire rat populations in 1989 to 1992 contained, overall, 51% of animals resistant to difenacoum (log10 PCA >1), but only 22% with high-degree resistance (log10 PCA >1.5). The mean difenacoum PCA for 253 rats was 23.15 ± 1.53. There were insufficient animals tested to estimate the prevalence and degree of bromadiolone resistance among those populations, but from a sample of 19 rats, the mean corrected PCA was 38.1 (log10 1.58) $\pm$ 5.92. The prevalence of warfarin resistance was 84%.

In contrast, most rats in a population discovered in Berkshire, UK (Quy et al. 1995) were highly resistant to both difenacoum (mean PCA 67.5 ± 4.3) and bromadiolone (mean corrected PCA 107.9 ± 5.5). Although some rats died on a 5- or 6-day no-choice feeding test using 0.005% (w/w) bromadiolone, no rat was classified as susceptible on any BCR test. From a total of 50 rats given a bromadiolone BCR test over a two-year period, only one was classified as having a low degree of resistance; of 60 rats given a difenacoum BCR test over the same period, two were found with low-degree resistance. It was assumed that all rats were warfarin-resistant.

In the UK up to 1995, populations containing rats with some degree of resistance to difenacoum have been found in central southern England and also the southeast and east Midlands; bromadiolone-resistant rats have been found in the central area of England between the south coast and the Humber estuary (MacNicoll et al. 1996). The authors also reported low-degree resistance (determined by a feeding test) to brodifacoum in rats from four farms in central southern England and a degree of resistance to flocoumafen (by BCR test) in rats from one farm. All the rats were tested after reports were received of control problems on farms, so it is unclear whether these were isolated incidents or that they reflected the widespread nature of anticoagulant resistance in the UK. Since 1995, rat populations have been sampled in new areas without prior knowledge of control problems. Of the 22 populations tested, 75% contained individuals resistant to warfarin, 30% resistant to bromadiolone, and 5% resistant to difenacoum. The wide distribution of populations containing resistant rats effectively rules out any kind of containment operation, such as the one instigated in the 1960s in an attempt (which failed) to eliminate warfarin-resistant rats from an area along the Anglo-Welsh border (Drummond 1966).

IDENTIFYING RESISTANCE AS A CAUSE OF CONTROL FAILURE

The use of chemical markers to measure how much bait individual rats consume in the field, together with BCR tests to determine their resistance status, has enabled detailed analysis of the reasons for poor control to be carried out (Quy et al. 1992; Cowan et al. 1995; Quy et al. 1995). It is now possible to establish the primary cause of each treatment failure. Such techniques are not immediately available to the occupier or pest control operator who has to control an infestation, and they would probably be seen as prohibitively expensive and a cause of further delay in eradicating a problem. In those situations, the only observations of treatment progress will be bait take and the number of dead rats found. Essentially, two problems are encountered whenever the treatment appears to be failing—either little or no bait is eaten, or bait is eaten but no dead rats are found. A poor uptake of bait does not immediately signal resistance, but it may be important if low-degree resistance is present and the small amount eaten would otherwise kill fully susceptible rats (Quy et al. 1996). In contrast to first-generation anticoagulants, the increased potency of second-generation compounds has meant that as rats may acquire a lethal dose after one feeding, a continuous supply of bait may not be necessary provided the rats are not resistant, a concept know as "pulsed baiting" (Dubock 1984). The practical consequence is that bait points need not be checked as frequently to maintain efficacy, resulting in lower costs to the operator. Nevertheless, where rats are resistant and the most palatable formulation is being used, yet bait take is insufficient to kill, then failure to control could be due to the combined effects of poor bait take and resistance. If pulsed baiting is being used, increasing the amount of bait to maintain a surplus may give better results.

Where bait is readily consumed and there are adequate numbers of bait points but no signs that rat activity is decreasing, then resistance must be considered. The warning dyes added to commercial rodenticide formulations that color droppings are useful indicators that rats are eating the bait. Bait eaten continuously from particular points for longer than seven days should arouse suspicion, whereas bait points reactivated after the same time interval suggest probable reinvasion (Quy et al. 1994). It follows that bait points should be inspected two to three times a week and records kept to avoid drawing the wrong conclusions. In many cases, dead rats are found and, if a sufficient number are killed to reduce the infestation to below nuisance levels, the reason why some

individuals have survived is likely to be seen as immaterial.

Prior knowledge that the area contains warfarin-resistant rats is important when second-generation anticoagulants appear to be failing. It appears that a prerequisite for the selection of resistance against the more potent anticoagulants is the presence of warfarin-resistant animals, which probably form a large proportion of the population. Greaves, Shepherd and Gill (1982) recorded a prevalence of 85% warfarin resistance in the first field investigation of difenacoum resistance in 1979-80. Samples of rats in which all members survived a warfarin feeding test were found in the USA in 1971 (Jackson and Kaukeinen 1972), but the resistant populations were successfully controlled with zinc phosphide, as second-generation anticoagulants were not then available. Pelz, Hanisch and Lauenstein (1995) reported a prevalence of 95.7% warfarin resistance on two farms where bromadiolone and difenacoum resistance was also present.

MANAGEMENT OF LOW-DEGREE RESISTANCE

The lack of alternative rodenticides with the same attributes of practicability and relative safety as anticoagulants means that, contrary to what one might normally recommend for resistance management, anticoagulants may still be the active ingredients of choice provided the degree of resistance is low. The option to use a non-anticoagulant, if one is available, is still there and it has the advantage in that it would kill both resistant and susceptible rats. Rather than withdraw all anticoagulants, in some areas of the UK bromadiolone-resistant rats can be controlled with difenacoum (MacNicoll et al. 1996). If rats also become resistant to that, then brodifacoum or flocoumafen are, subject to restrictions, available. Only a small number of populations have been identified that are bromadiolone-resistant but difenacoum-susceptible. Although bromadiolone baits appeared to be more successful than difenacoum baits against resistant rats in Hampshire (Greaves, Shepherd and Quy 1982), the difference between the resistance factors towards the two compounds (approximately two and four, respectively) was thought to be of no practical consequence (Cowan et al. 1995). A contributory factor to the apparently greater success of bromadiolone baits might have been that baits containing bromadiolone tend to be more palatable than those containing difenacoum (Quy et al. 1996). Thus, rats with a low-degree of resistance might have accumulated a lethal does more quickly during the bromadiolone trials than during the difenacoum trials. The aim in treating a population with low-degree resistance would be to maximize bait take by, for example, placing baits in burrow entrances rather than containers—this technique appears to be beneficial on sites with alternative food sources (Quy et al. 1996). Unfortunately, this option is not available if circumstances demand the use of tamper-resistant bait stations. Moreover, a bait base acceptable to the target population should be used. The advantage of using potent compounds in less acceptable formulations, such as wax blocks (Buckle 1994), to reduce non-target risks, would be compromised. When three different loose-grain baits, all containing bromadiolone, were tested against warfarin-susceptible rats and rats with a low-degree of resistance to difenacoum and bromadiolone, the least palatable formulation was relatively unsuccessful at controlling the resistant populations, although it did eliminate the susceptible ones (CSL, unpubl.). The availability of rodenticide concentrates would allow local mixing of baits that maximize palatability and consumption. Another detrimental aspect of controlling rats with a low degree of resistance is a return to surplus baiting, where previously minimal quantities of bait were sufficient. Pulsed baiting (Dubock 1984) relies on the high potency of anticoagulants such as brodifacoum and flocoumafen to produce the same degree of control with less bait and less labor input. The benefits in terms of non-target risks are that there is a reduced amount of bait available at any one time during a treatment. In taking steps to maximize bait take to overcome low-degree resistance, it must be recognized that risks to wildlife are likely to increase.

Some rat populations in the Hampshire resistance area contained individuals that had ingested doses of difenacoum or bromadiolone in excess of 100 mg/kg body weight and survived (Cowan et al. 1995) and might, therefore, have been considered to be highly resistant. Although these animals represented less than 1% of the survivors examined, the implication is that populations containing predominately low-degree resistant animals, may, nevertheless, contain a few highly resistant individuals. This reinforces the need to carry out a thorough treatment and kill all rats. However, eliminating the last few survivors of a treatment could be disproportionately costly and, on a busy farm, small numbers of animals would probably be overlooked. Further applications of these rodenticides against highly resistant survivors and their descendants may eventually produce a population that is completely refractory to treatment. The fact that, to date, there have been no reports of serious control failures, unequivocally due to resistance, from the Hampshire area suggests either that the selection pressure has not been sufficient, or that highly resistant populations exist there, which are small and not particularly troublesome, or are being controlled by illegitimate means. When populations do become troublesome and seem to be uncontrollable because of high-degree resistance, the additional cost of alleviating the problem may be substantial. It now appears that a high-degree of resistance can be sustained within some populations (Quy et al. 1995).

MANAGEMENT OF HIGH-DEGREE RESISTANCE

The success of anticoagulants, particularly second-generation compounds, no doubt hastened the end of some potentially useful non-anticoagulant toxicants. It seems unlikely that more potent anticoagulants can be produced to overcome the new forms of resistance that are now appearing (Hadler and Buckle 1992). While it appears that the most potent anticoagulants are still effective, for all practical purposes, against all rat populations, both brodifacoum and flocoumafen are registered for indoor use only and for use by professional pest controllers only. They are currently not available to control infestations of rats resistant to difenacoum or bromadiolone, except in those situations where indoor application of these

rodenticides can control a population of rats that may live mostly outdoors. Stopping the use of anticoagulants would, in theory, reverse the selection pressure in favor of susceptible rats. It might take some time for this to happen, particularly if any deleterious effect did not prevent individuals from breeding. In one example (Quy et al. 1995), the descendants of survivors of a population with a high-degree of resistance to bromadiolone and difenacoum were tested after 17 months with apparently no intervening exposure to anticoagulants. The degree of resistance had reduced, but was still too high to be confident of any success with difenacoum or bromadiolone. It was likely that neighboring rat populations, as potential sources of immigrants, were also highly resistant to anticoagulant rodenticides, raising the prospect that the occupier of the site may be unable to achieve any satisfactory control for the foreseeable future with those rodenticides. A further problem, foreseen by Greaves (1994), is where a beneficial pleiotropic effect of the resistance gene occurs which is maintained without artificial selection. If that occurred, resistance would be difficult to eliminate. The longer that resistant populations are allowed to persist, the more likely it is that mechanisms will evolve that dilute the pleiotropic costs of resistance (Cowan et al. 1995).

Faced with a population of rats that could not be controlled with second-generation anticoagulants for reasons of resistance or legal restraints, Quy et al. (1995) used calciferol, even though previous use of this rodenticide had failed to alleviate the problem. The only other option was zinc phosphide, which had also been tried without success. Previous experience with both compounds suggested that, to avoid inducing bait aversions, a period of prebaiting would be needed to maximize the effectiveness of the treatment, given the possibility that a population of highly resistant rats, made bait-shy by sublethal poisoning, could produce an "unpoisonable" infestation.

The likelihood of persuading the majority of rats to eat the prebait, wholly and continuously, hence improving the chance of success with a relatively fast-acting poison, may depend on the type of farm. The continual disturbance that takes place in some farm habitats, particularly those rearing livestock, appears to reduce neophobic responses to bait and bait containers (Quy et al. 1994). In these situations, the prospects for substantial reductions in rat numbers should be good, provided an appropriate toxicant is available. The disadvantage, however, is that when anticoagulants are used on livestock farms, susceptible and partially resistant rats would be quickly eliminated and a highly resistant population selected, as Quy et al. (1995) observed on a pig farm. In place of an unpoisoned prebait, a treatment could start with an anticoagulant bait, which would kill any susceptibles and could also become a prebait for an acute poison such as zinc phosphide. It would be advisable to ensure that the bait base of the anticoagulant formulation was available to mix with the acute poison, as local pesticide regulations might not allow two poisons to be added together. As with any treatment with a fast-acting toxicant, errors in bait placement could undermine effectiveness and complete eradication would be unlikely. The advantage of this approach for the occupier is that, depending on the proportion of susceptible rats in the population, the death of some rats might provide some respite. The disadvantage is that, where there are very few susceptible rats, anticoagulant formulations make very costly prebaits.

Using a non-anticoagulant with prebaiting would probably not require much more labor input than a surplus-baiting anticoagulant treatment. However, such treatments rarely kill all the rats, and a high percentage reduction of a large population may still leave an unacceptable number of survivors. This occurred following the calciferol treatment reported by Quy et al. (1995), and it required extensive trapping to remove the residual infestation. It is noteworthy that the calciferol formulation used in that trial, which was different to the formulation first used on the farm, is not generally available in the UK and is expensive. A relatively new, non-anticoagulant rodenticide in the market place is bromethalin, which is not registered for use in the UK. Bromethalin requires no prebaiting as it does not apparently cause bait-shyness (Jackson et al. 1982). The development of alternative rodenticides is essential to help slow down, at least, the evolution of widespread resistant rat populations.

The use of non-anticoagulant rodenticides in "fire-brigade" actions must be seen as a short-term measure, alleviating urgent control problems. If there is a will to retain anticoagulants for future use in rodent population management, then strategies to control resistant rats in the long-term must be put into practice. So far, this has not occurred. Smith and Greaves (1987) considered resistance management strategies and discussed the theoretical and practical problems with their implementation. One suggestion was the use of a sterilizing agent to treat survivors of an anticoagulant treatment, although a suitable chemical or immunocontraceptive is currently not available. Earlier, Lazarus and Rowe (1982) suggested incorporating a similar agent into the prebait prior to an acute poison treatment, after they had prevented an island rat population from breeding for 10 months by using a synthetic oestrogen. Methods that reduce rat populations gradually over many months are not likely to be well received by occupiers, but small numbers of animals might be tolerated on farms, although probably not in urban or industrial premises. Smith and Greaves (1987) saw a potential advantage in allowing a small population to remain, even if all members were resistant, because it might repel immigrants for a time, thereby slowing down reinfestation.

Should brodifacoum and other highly potent anticoagulants be part of a long-term strategy to control rats resistant to all other anticoagulants? For that to happen, restrictions, where they apply, would have to be relaxed and the potential consequences of non-target hazards considered. Wider availability may result in the evolution of populations of rats also resistant, for all practical purposes, to those compounds. Rats with a low degree of resistance to brodifacoum have already been discovered (Gill and MacNicoll 1991). However, the use of brodifacoum against rats resistant to warfarin, but not to any other second-generation compound, might prevent resistance to difenacoum or bromadiolone evolving almost

indefinitely. Thus, in these circumstances, the advantages of pulsed-baiting with brodifacoum, particularly the reduced non-target risk, would remain.

In contrast to pesticide-dominated strategies to control resistant rats, more environmentally-friendly methods may become prominent if chemical control fails. Whatever the resistance status of populations, techniques that reduce the carrying capacity of a habitat, such as a farm, can potentially reduce the scale of a control problem. Around farm buildings and particularly in urban areas, reducing harborage and denying access to food sources should be possible without affecting populations of other animals. Among field margins this is more problematic, and it has been argued that selective destruction of a pest with a pesticide is preferable (Howard 1967). Unfortunately, this depends on a suitable pesticide being available. Control without the use of anticoagulants would, of course, remove the selection pressure towards increased anticoagulant resistance.

CONCLUSIONS—IS RESISTANCE A PROBLEM?

The unusually large rat population reported by Quy et al. (1995) was a consequence of a favorable habitat combined with a failure to control with anticoagulant rodenticides. The number of rats present reflected the carrying capacity of a typical livestock farm in central, southern England. Populations rarely increase to the limits of the habitat, because control measures are usually instigated long before such a limit is reached. With the controversy surrounding the significance of resistance to second-generation anticoagulants, it is difficult to present any view that is not seen as biased by one party or another. Manufacturers of rodenticides clearly do not like their products to be criticized. Professional pest controllers do not like to be accused of failing to provide a satisfactory service. Legislators feel bound to respond to public concerns about environmental safety and humaneness. The public, presumably, still wants rats to be controlled. Given the high costs of developing and marketing a new rodenticide, it could be argued that industry will take action when it is seen to be profitable. By that time, the highly resistant populations, currently limited to a small area in central, southern England, may be distributed across the country. Smith and Greaves (1987) emphasized the importance of resistance monitoring and early action to eradicate resistant rats. They also stressed the need to stop using anticoagulants when resistance is detected. Although there is no routine monitoring program in the UK, the development of laboratory-based tests and extensive testing of rats from field populations over the last 20 years has been an invaluable and unique tool in understanding the nature of rodent control problems.

The lack of alternative rodenticides is potentially serious; a catalog for a well-known supplier of pest control products in the UK lists 41 rodenticide formulations for the control of rats, of which only two are non-anticoagulants (both zinc phosphide). The danger would be that, faced with an urgent need to control an infestation, occupiers or their agents might resort to unsafe or illegal methods to eradicate the rats if all legitimate means failed. Jackson and Kaukeinen (1972) reported that the farmers and pest control operators depended on the use of anticoagulants to save tidying up the farms to make them less attractive to rats. That view appears to still be widely held. The effect of resistance is probably insidious, only coming to people's attention when other factors unrelated to resistance allow rat population density to increase above what is regarded as normal. Unfortunately, preventive action is hard to justify to those who may be inconvenienced or put to extra expense, when there is uncertainty about when or if future control problems will arise.

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