Anticoagulant resistance in the UK and a new guideline for the management of resistant infestations of Norway rats (*Rattus norvegicus* Berk.)

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Abstract

Anticoagulant resistance was first discovered in UK Norway rats (*Rattus norvegicus* Berk.) in 1958 and has been present ever since. The possible detrimental impact of resistance on effective rodent control was quickly recognised and, for almost three decades, extensive research was conducted on the geographical distribution and severity of anticoagulant resistance in UK rats. Various schemes for the eradication of resistant rats were also implemented. At first, surveys showed resistance only to the first-generation anticoagulants, such as warfarin, chlorophacinone and coumatetralyl, but later resistance to the more potent second-generation anticoagulants, such as difenacoum and bromadiolone, was also discovered. Unlike some European countries, where only one or two resistance mutations occur, virtually all known rat resistance mutations occur in the UK and five are known to have significant impacts on anticoagulant efficacy. Little is currently known of the geographical extent of anticoagulant resistance among Norway rats in the UK because no comprehensive survey has been conducted recently. At an operational level, anticoagulants generally retain their utility for Norway rat control but it is virtually impossible to control resistant rats in some areas because of restrictions on the use of the more potent resistance-breaking compounds. This paper describes the development of resistance in Norway rats in the UK, outlines the present situation for resistance management and introduces a new resistance management guideline from the UK Rodenticide Resistance Action Group (RRAG, 2010).

Keywords: anticoagulant resistance, resistance management, Norway rat, resistance mutations:Y139C, Y139F, Y139S, L120Q, L128Q

Background

Effective rodent control in the UK relies upon the anticoagulant rodenticides but resistance to them is widespread. Early surveys of resistance in Norway rats (*Rattus norvegicus* Berk.) revealed foci scattered across much of England, as well as parts of Scotland and Wales. One such survey, conducted in the years to 1972, showed resistance in 14 separate locations (Greaves and Rennison, 1974). The largest of these was an area on the Anglo-Welsh border, which became one of the most well-known and extensive UK resistance foci. Another substantial focus was first discovered in 1968 in Kent and East Sussex. It remained at least until 1974, when field trials of difenacoum were conducted there, but then was lost to sight. Among the other locations only one, first discovered in Hampshire in 1969, came to be a practical problem over a significant area (Greaves and Cullen-Ayres, 1988). It was thought that many of the other resistance foci recorded in 1974 had either died out naturally or had been removed by efforts at eradication (Greaves, 1995) but subsequent events have shown that neither was likely the case.

Resistance testing and resistance mutations in the UK

Laymen who hear the term ‘resistant’ often think that it is synonymous with the word ‘impervious’. In other words rats said to be resistant to a particular anticoagulant cannot be killed by it. This is very rarely so and all resistance testing requires a degree of qualitative interpretation. This was certainly the case with the feeding test used to distinguish resistant from susceptible rats in the early work of Greaves and Rennison (1974) and is even more so with the blood-clotting response (BCR) test which came to replace it (Prescott et al., 2007). A degree of certainty was provided, however, when a new genetical test was developed for resistance by workers based in Germany (see Pelz et al., 2005). For the first time it became possible to examine the DNA of individual rats and know for certain if they possessed a genetical resistance mutation. However, detailed biological work is still required to determine the practical impacts on operational rat control of a resistance mutation identified by DNA sequencing. Nevertheless, this test has revolutionised the study of anticoagulant resistance in the UK, and world-wide. A list of DNA mutations found at UK rat resistance foci, and locations of some of their foci, is given in Table 1. Knowledge of resistance in UK continues to increase and a new focus, or more likely an old one that had

remained undetected for many years, was recently identified in Kent with a DNA mutation not previously found in the UK (Prescott et al., 2011).

Tab. 1 Known anticoagulant resistance mutations in Norway rats in UK (from Pelz et al., 2005; Prescott et al., 2011)

Resistance mutation	Abbreviated mutation name	Where present
Leucine128Glutamine	L128Q	Central Southern Scotland, Yorkshire, Lancashire
Tyrosine139Serine	Y139S	Anglo-Welsh border
Leucine120Glutamine	L120Q	Hampshire, Berkshire
Tyrosine139Cysteine	Y139C	Gloucestershire, Norfolk, Lincolnshire, Yorkshire, SW Scotland
Tyrosine139Phenylalanine	Y139F	Kent
Phenylalanin63Cysteine	F63C	Cambridge/Essex
Argenine33Proline	N33P	Nottinghamshire

UK Rodenticide Resistance Action Group (RRAG) Guidelines

Laboratory and field studies conducted previously in the UK, and elsewhere, provide an understanding of the effects of some of these mutations on operational rat control. The practical impacts of two (F63C, N33P) are unknown. Among the remainder, two mutations (L128Q, Y139S) confer resistance to the first-generation anticoagulants but are largely susceptible to compounds of the second-generation, such as difenacoum and bromadiolone. These compounds are recommended for use against them and, more generally, anticoagulants are effective for rat control in the UK. However, three widely-distributed mutations (L120Q, Y139C, Y139F) confer a degree of resistance to bromadiolone and difenacoum. Resistance management is compromised at sites with these mutations because UK regulations, unlike those proposed under the Biocidal Products Directive, restrict potentially effective anticoagulants, brodifacoum, difethialone and flocoumafen, to use 'indoors', making them virtually useless for rat control. The reason for this restriction is concern about secondary poisoning of wildlife (Carter and Burn, 2000). Consequently, rat control practitioners continue to use bromadiolone and difenacoum at sites where they are resisted. This situation, in existence for about 25 years in the UK, has probably exacerbated the severity of anticoagulant resistance and promoted its spread (Greaves, 1995). RRAG Guidelines (RRAG, 2010) state the obvious, namely that anticoagulant compounds should not be used where there is resistance to them. Where bromadiolone and difenacoum resistance occurs, and rats cannot be controlled by other means, a procedure is proposed whereby those wishing to control resistant rats apply to the UK Health and Safety Executive to use brodifacoum, difethialone or flocoumafen 'in and around buildings'. It remains to be seen whether this proposal is acceptable to UK authorities and whether the applications can be administered in a timely and cost-effective manner.

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