Spontaneous convulsions in Charles River Wistar rats

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Summary
Spontaneous clonic convulsions in the Charles River Wistar rat have been observed at an incidence of 1.5%. Females (2.3%) are more susceptible than males (0.7%). These convulsions are not seen in rats of less than approximately 16 weeks of age. Some animals have exhibited single convulsions whilst others have convulsed on numerous occasions. No histopathological abnormalities of the brain have been recorded for these animals following routine examination.

Keywords  Rat; spontaneous convulsions

Some strains of Wistar rat have been shown to exhibit non-convulsive electroencephalographic (EEG) paroxysms (absence epilepsy) and are used as models of human petit mal epilepsy (Willoughby & Mackenzie 1992). The Centre of Neurochemistry in Strasbourg report that about one-third of 6 to 12 month old Wistar rats from their laboratory breeding colony show this spontaneous phenomenon (Micheletti et al. 1985). This abnormality can be inbred such that by the third generation of crosses between affected rats all offspring present the characteristic EEG pattern, whilst a similar number of crosses between unaffected rats produces no affected offspring (Vergnes et al. 1986). We have found no reports in the literature of spontaneous clonic convulsions in the Wistar rat.

In the Alderley Park Wistar rat (Alpk:APcSD), usually used in this laboratory, the recorded incidence of clonic convulsions is negligible (<0.1%). In March 1991 Wistar rats (Crl:WI)BR) from Charles River UK Ltd, Margate, Kent, England were received at this laboratory between 14 March 1991 and 25 June 1992. The animals were 3½ to 4 weeks old on arrival and approximately 6 weeks of age at the start of studies.

Husbandry
All animals were housed in the Barriered Rodent Studies Unit which has been designed to ensure that studies proceed without interference from infection and environmental variability.

Five rats of the same sex were housed together in stainless steel mesh cages (57 x 35 x 20 cm). The cages were suspended on a metal rack over trays lined with absorbent paper. The tray papers were changed every day and the cages were
Spontaneous convulsions in Wistar rats changed approximately every 2 weeks during the studies.

Artificial light was provided in the room and controlled to give 12 h of darkness and 12 h of light; the period of darkness was between approximately 18:00 and 06:00 h. A range of air-pressure regimens were pre-set throughout the facility in order to maintain suitable air flow. The pre-set range for environmental temperature was 21 ± 2°C and for the relative humidity was 45–70%.

All animals were offered pelleted irradiated R and M No. 1 (modified) diet (made by Special Diets Services Ltd, to ZENECA specification) and drinking water ad libitum.

The animals were acclimatized for up to 2 weeks before the start of any experimental procedures.

Experimental procedures

The animals were used for a variety of studies for the safety evaluation of novel pharmaceutical agents (6 and 12 month toxicity and 2 year oncogenicity studies) and some to provide control data for this strain of rat in this laboratory. The safety evaluation studies generally consisted of a control group and 3 groups given the test compound at low, medium or high doses.

In these studies, all animals were inspected at least twice daily for gross abnormality or mortality and given a detailed physical examination weekly. The animals were also handled when being dosed (not all animals i.e. control data studies and those where test compounds were administered in the diet), when body weights were being recorded (usually weekly up to about 3 months of age and monthly thereafter) and when blood or urine samples were being taken (not all animals).

On completion of the study periods, surviving animals were killed by inhalation of halothane (‘Fluothane’, ICI plc) and given a full necropsy. Animals that died or were killed prematurely were similarly treated. Tissue from all major organs was taken for routine histological examination. For the brain this consisted of the preparation of 3 thin transverse sections (one through the cerebellum and 2 through cerebrum; 2 mm from the cerebellum and 1 mm from the olfactory lobes) from a wax block, staining with haematoxylin and eosin and examination under a light microscope.

Statistical methods

The proportion of animals convulsing was statistically analysed using the GLIM package (GLIM 1978). A binomial distribution was fitted by maximum likelihood using a logit link. The differences between the sexes, between studies, the actual duration of the study or recording period and interactions between these were all assessed. Two analyses were done, one using just control animals and one using all animals but additionally allowing for group differences.

Observations

Following the introduction of the Crl: [WI]BR Wistar into this laboratory, animals were observed to be convulsing spontaneously. These convulsions were predominantly clonic in nature but sometimes contained tonic elements. Total recovery was usually apparent following these convulsions. One animal, however, showed progressively worsening convulsions over a period of months and finally became moribund, following a convulsion, and was humanely killed.

Review of records (see Table 1), up to the end of 1992, from a total of 2460 (1230 male and 1230 female) rats shows the overall incidence of this abnormality to be 1.5%. The incidence of convulsion amongst animals receiving a pharmacological agent (0.9% of males, 1.9% of females) was similar to that seen in control animals (0.6% males, 2.8% of females). Statistical analysis showed no real evidence of an overall effect due to receiving a test compound (P > 0.6). Thus, all subsequent comments on statistical analyses refer to those where all animals were included.

In all studies the incidence of spontaneous convulsions in females (2.3%
<table>
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<tr>
<th>Study</th>
<th>Nominal duration of study (months)</th>
<th>Actual duration end 1992 (months)</th>
<th>Incidence of animals showing spontaneous convulsions</th>
<th>Age of first animal showing convulsions (weeks)</th>
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<td>Males according to dose levela</td>
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<td>Single sex total</td>
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<td>9/1230  = 0.7%</td>
<td>28/1230 = 2.3%</td>
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<td>Overall total</td>
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<td>37/2460 = 1.5%</td>
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*aStudies consisted of a control group(s) and 3 groups receiving the test compound at low, medium and high doses*
Overall) was higher than in males (0.7% overall), except in the one study where no convulsions were observed. Statistical analysis showed that the likelihood of a female rat convulsing was more than 3 times that for a male rat (3.2, 95% confidence interval 1.5–6.8) and there was strong evidence of a difference between the sexes (P<0.005). The incidence of convulsion in specific studies has been much higher than the average for females (up to 10% [10/100] — Study D).

The first observation of these convulsions has been made in animals as young as approximately 16 weeks of age but some animals have not shown this abnormality until they are over a year old. The oldest animals in this review were approximately 67 weeks of age. Statistical analysis showed that the duration of the study or recording period accounted for most of the inter-study variability (P<0.005).

Some animals have been observed to convulse only once, others on numerous occasions. Some animals have been observed to convulse in their home cages, without obvious external stimuli, whilst others seem to be triggered by handling.

In those animals which have completed their study periods or died prematurely, routine histological examination has not revealed any histopathological abnormalities in the brain.

**Discussion**

The observed incidence of spontaneous clonic convulsions in the Charles River Wistar rat, reported here, is probably much lower than the actual incidence as animals are under observation for only a very short period every day.

The almost equal number of control animals and animals receiving a pharmacological agent which showed this abnormality indicates that the administered compounds were not involved in the generation of these seizures.

The age of rats at onset of these convulsions means that they are unlikely to be seen in studies where animals do not attain 4 months of age.

Review of historical data for the Alderley Park Wistar rat (Alpk:APfSD) usually used in this laboratory, between 1984 and 1990, showed only one recorded occurrence of a clonic convulsion in studies of approximately one year duration and longer (i.e. 1/3964 rats). If studies of 6 months duration, from this period, are also included a further 3 female rats showed clonic convulsions on one or 2 occasions (i.e. 3/1580). These latter female animals, however, were from high dose groups and it is, therefore, possible that these observations were related to the administration of a high dose of a pharmacological agent.

The occurrence of these spontaneous convulsions in the Charles River Wistar rat could impact on the successful completion of safety evaluation studies as these animals may die or need to be killed prematurely because of these events. It may not be possible to perform experimental procedures, such as oral or parenteral dosing or withdrawal of blood, on animals which convulse on handling and these would, consequently, need to be removed from studies.

**Acknowledgments**

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**References**


