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A retrospective evaluation of species-specific sensitivity for neurological signs in toxicological studies: Is the dog more sensitive than the non-human primate?

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HIGHLIGHTS

- Comprehensive retrospective analysis of toxicology studies for neurological signs.
- Neurological signs of dogs and NHPs were correlated to exposure.
- Comparing C_{max} total and C_{max} free for correlation between species.
- Addresses challenges in collecting data set for direct species comparison.

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ABSTRACT

Selection of the appropriate non-rodent species in preclinical programs is crucial for good translatability and human safety. There is no data available in the literature which provides exact comparison of dog and non-human primate (NHP) sensitivity regarding neurological signs in toxicological studies. We performed a retrospective analysis of 174 toxicity studies with 15 neuroscience substances. Neurological signs in dogs and NHPs were evaluated in correlation to exposure data. Overall incidence of substance induced convulsions was similar in both species and no gender differences were observed. The reported liability of beagles to spontaneous convulsions was not confirmed in our studies. The symptom tremor showed the best inter-species translatability. The current toxicological study design does not include exposure assessment at the time-point of neurological signs, therefore, we propose to include additional toxicokinetic samples. Our analysis revealed factors including housing, handling, and behavior, which prevents direct species comparison. In addition only one non-rodent species is routinely tested in development programs, therefore data for both species is rare. We however, had sufficient data which enabled comparison for one compound. In the spirit of 3Rs further examples should be evaluated.

1. Introduction and background

In the field of neuroscience, diseases such as Alzheimer's, Parkinson's or Multiple Sclerosis present a high burden for the patients and their families (Emsley, 2009) (Heemskerk et al., 2012) (Coleman and Barrow, 2012) (Rubin, 2013). Such neurodegenerative diseases lead to extensive limitations for the patient and ultimately to death. In addition, economic aspects, such as expenses for caregivers, are important factors. Due to the ageing population, there is a high medical need (Kanwar et al., 2012) (Coleman and Barrow, 2012) (Jiang et al., 2015) however, many pharmaceutical companies have reduced their investments in neuroscience drug discovery (Coleman and Barrow, 2012) because of the lengthy drug development. There is a lack of translatable animal models for efficacy testing (LaFerla and Green, 2012) and in order to de-risk clinical programs and to allow clinical testing within a wide therapeutic window, it is important to implement a preclinical program with high translatability for human safety.

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Table 1
Tested species and appearance of neurological symptoms: Neurological symptoms were observed in 12 compounds in the mouse, in 14 compounds in the rat, in 9 compounds in the dog and in 7 compounds in the NHP.

	Mouse		Rat		Dog		NHP	
Compound	Tested	Neurol. symptoms	Tested	Neurol. symptoms	Tested	Neurol. symptoms	Tested	Neurol. symptoms
A	Yes	Yes	Yes	Yes	No	–	Yes	Yes
B	Yes	Yes	Yes	Yes	No	–	Yes	Yes
C	Yes	Yes	Yes	Yes	No	–	Yes	Yes
D	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
E	No	–	Yes	Yes	Yes	Yes	No	–
F	Yes	Yes	Yes	No	Yes	Yes	No	–
G	No	–	Yes	Yes	Yes	Yes	No	–
H	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
I	Yes	Yes	Yes	Yes	Yes	Yes	No	–
J	Yes	Yes	Yes	Yes	Yes	Yes	No	–
K	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
L	Yes	Yes	Yes	Yes	Yes	Yes	No	–
M	Yes	Yes	Yes	Yes	No	–	Yes	Yes
N	Yes	Yes	Yes	Yes	Yes	Yes	No	–
O	No	–	Yes	Yes	Yes	No	Yes	No

neurol. = neurological

Small molecules are tested pre-clinically in a rodent as well as a non-rodent species according to regulatory requirements (ICH Guideline M3(R2), 2009). The predictive value of animal studies for human safety has been controversially discussed for a number of decades (Owens, 1962) (Schein, 1970) (Zbinden, 1991) (Broadhead et al., 2000) (Greaves et al., 2004) (Jolivette and Ward, 2005) (Matthews, 2008) (Van Meer et al., 2012) (Bailey et al., 2013).

The high importance of neurological symptoms for safety assessments was demonstrated by Horner et al. (2013). In the analysis of Horner et al., target organ toxicity in the central nervous system was one of the most common reasons to discontinue development. Within the neuroscience therapeutic area, 7 out of 26 substances were stopped in their analysis before clinical trials due to occurrence of neurological symptoms in preclinical species (Horner et al., 2013). There is very little known about translatability of neurological symptoms between species and to man. In the literature a general non-specific (Igarashi et al., 1995), moderate (Owens, 1962) (Fletcher, 1978) up to reasonable (Schein, 1970) correlation between animal and human data has been reported. In this context, non-rodent data has a higher predictive value than rodent data according to Olson et al., 2000. Dogs (beagle dog), NHPs (Cynomolgus) and minipigs are the most commonly used non-rodent species in toxicology studies (Smith and Trennery, 2002) (Jacobs, 2006) (Table 2. 1 "*number of animals used in experiments for selected purposes*" of the European Commission, 2011). There is however, a lack of published data which could permit direct comparison of species sensitivity of neurological signs. A tendency to spontaneously occurring seizures has been reported in beagle dogs (Redman and Weir, 1969a,b) (Bielfelt et al., 1971) (Edmonds et al., 1979) (Easter et al., 2009) (Hasiwa and Bailey, 2011) and a genetic predisposition in a beagle colony (11.9% of the males and 2.6% of the females) has also been described (Bielfelt et al., 1971). One goal of the retrospective analysis was to compare occurrence of convulsions between dogs and NHPs and to analyze for gender differences. Given the paucity of reported data which allowed reasonable comparison of neurotoxicological findings in relation to exposure data, we created a data base to support species selection without conducting additional experiments, consistent with the spirit of 3Rs.

2. Materials and methods

2.1. Literature research

Literature research was conducted using PubMed®, Pharmapendium®, ZEBET®, PrimateLit®, go3R®, Google Scholar®, HireWire Press® and ProQuestDialog®.

Table 2
Number of animals with neurological symptoms for compounds where dogs and NHPs were tested. Enough data for comparison were only available for compound D.

Compound (Indication)	# of dogs with neurological symptoms/n	# of NHPs with neurological symptoms/n	Comments
Compound D (cognitive disorders)	22/66	64/114	Neurological signs in both species (dogs 33.3%) (NHPs 56.14%)
Compound H (cognitive disorders)	1/40	9/120	Only minor neurological signs in both species, NHPs: repetitive movements, head movements; Dog: shivering, increased activity and high dose effects confounded by strong emesis
Compound K (schizophrenia, Alzheimer`s disease)	0/8	107/118	No dogs with neurological symptoms (NHP: C_{max} total 4.18 μg/ml; C_{max} free 1.81 μg/ml Dog: C_{max} total 0.51 μg/ml; C_{max} free 0.23 μg/ml)
Compound O (multiple sclerosis)	0/16	0/96	No neurological symptoms in both non-rodent species (only rat) (NHP: C_{max} total 19.7 μg/ml; C_{max} free 0.035 μg/ml Dog: C_{max} total 4.52 μg/ml; C_{max} free 0.0034 μg/ml Rat: C_{max} total 42.7 μg/ml; C_{max} free 0.068 μg/ml)

= number; *n* = total number of dogs/NHPs