

## 重篤な神経系副作用（頭痛，末梢神経障害，痙攣・てんかん）の 非臨床試験からの予測性に関する調査

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### Investigation of Nonclinical Safety Assessment Approaches for Predicting Serious Clinical Adverse Reactions of the Nervous System

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#### Summary

Nonclinical safety and toxicology assessments play a critical role in supporting the safe use of new drugs in humans. However, development of new drugs is often terminated due to serious side effects in clinical trials that had not been predicted from non-clinical assessment data. Nervous system adverse reactions, especially, are considered difficult to predict from nonclinical studies. In this article, we retrospectively assessed whether major nervous system adverse reactions (headache, peripheral neuropathy, and convulsion/epilepsy) could have been predicted from a set of standard nonclinical studies for each drug.

Among major marketed drugs reported in the “Manual for Detection and Treatment of Serious Adverse Reactions by Type” created and provided by the Ministry of Health, Labor and Welfare of Japan, we selected drugs for which the new drug application documents and review reports were available on the Pharmaceuticals and Medical Devices Agency (PMDA) website.

Our investigation indicated an association between headache and vascular effects in nonclinical studies, but predictability of headache in humans was not high. Peripheral neuropathy could be predicted from a set of standard nonclinical studies for some drugs, but the detection power was low. However, specific pharmacological studies such as a nerve conduction test were considered to be effective in predicting clinical peripheral neuropathy. Potential risk of convulsion/epilepsy could generally be identified, but it was difficult to assess the degree of the risk.

Our results indicate that safety pharmacology or toxicology studies alone are unlikely to be adequate for predicting the risk of adverse nervous system reactions in humans. Comprehensive examination using both nonclinical safety assessments and information acquired from secondary pharmacology studies and/or application of novel techniques seems to be essential.

#### Key words

Serious nervous system adverse reaction, Nonclinical testing, Prediction, Headache, Peripheral neuropathy, Convulsion/ Epilepsy