THE DEVELOPMENT OF AN IRWIN-LIKE TEST IN THE NON-HUMAN PRIMATE FOR CNS SAFETY ASSESSMENT

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INTRODUCTION

The Irwin test in rodents is an established CNS safety method for evaluating the behavioral and neurological effects of new chemical entities (NCEs) in development. We suggest that non-human primates (NHPs) provide better translational relevance for prosecuting NCEs with respect to efficacy and safety endpoints. In this way, simple behavioral methods that extend safety observations from rodents to NHPs offer significant value in facilitating decision making. We have developed an NHP Irwin-like test in rhesus monkeys using a range of behaviors and have assessed standard agents to provide relevant benchmarking.

MATERIAL & METHODS

This procedure which aims to detect the maximally tolerated dose, the active dose range, and the principal effects of a test substance on behavior in the rhesus monkey (Macaca mulatta), is based on that described by Jafre et al. (Arch. Int. Pharmacodyn., 259, 194221, 1982). Four rhesus monkeys (2 males and 2 females) were administered a test substance or its vehicle and were assessed for behavioral signs in their home cages at predetermined time points: 5, 15, 30, 60, 120, 240 minutes and 24 hours. Each animal was observed individually for 30 seconds and the presence or absence of each sign was recorded by a nonblinded observer. The observation grid contained the items listed in the tables below. Five commonly used reference substances were assessed: caffeine (1-30 mg/kg s.c.), haloperidol (0.003-0.1 mg/kg i.m.), promethazine (1-10 mg/kg i.m.), cocaine (0.033 mg/kg i.v.) and risperidone (0.1-1 mg/kg i.g.). There was a washout period of at least 48 hours between each dose to avoid residual effects.

RESULTS

Results obtained with caffeine, haloperidol, promethazine, cocaine and risperidone are shown in Figures 1-5 respectively. The numbers within the colored blocks represent the number of monkeys showing the sign (maximum of 4). The key results demonstrate caffeine (10–30 mg/kg s.c.) induced mild hyperactivity and a flushed skin appearance, haloperidol (0.030.1 mg/kg i.m.) sedation and catalepsy, promethazine (10 mg/kg i.m.) loss of balance and sedation, cocaine (1-3 mg/kg i.v.) vocalization and hyperactivity, while risperidone (0.1-1 mg/kg i.g.) induced sedation relative to vehicle control.

CONCLUSION

These results suggest that the Irwin-like test in NHPs is an appropriate method to detect key behavioral signs induced by various classes of pharmacological agents with known stimulant or sedative-like properties. Importantly, a wide range of behaviors can be scored and assessed over an extended time period to provide a behavioral signature with onset and duration of action for an NCE. We suggest that this test in the NHP provides a sensitive method for evaluating the CNS safety profile of NCEs to support therapeutic index predictions.