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Behavioral effects of haloperidol and cocaine in rhesus macaques using operant responding and Irwin-like observation procedures

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The Irwin-like behavioral observation test in non-human primates (NHPs) is a sensitive method for evaluating the central nervous system (CNS) safety profile of new chemical entities (NCEs) to support therapeutic index predictions. We suggest that the substance profile can be refined and supplemented by adding an operant lever-pressing procedure to the preliminary behavioral observation test.

Acute intra-muscular (i.m.) doses of haloperidol (0.003-0.1 mg/kg) and intra-venous doses (i.v.) of cocaine (0.03-3 mg/kg) were assessed first for behavioral signs using an Irwin-like test procedure where four rhesus macaques were observed in their home cage at 5, 15, 30, 60, 120, 240 minutes and 24 hours post-dose. Then, haloperidol (0.003-0.03 mg/kg i.m.) and cocaine (0.1-1.0 mg/kg i.v.) were evaluated in an operant lever-pressing procedure in two rhesus monkeys trained to respond under a fixed ratio (FR30) schedule of food reward. The sessions lasted 2 hours (8 cycles of 15 minutes) during which the rate of responding was automatically recorded in responses per second.

Whereas clear and identifiable behavioral effects were detected in the Irwin-like procedure with haloperidol from 0.03 mg/kg i.m., a dose-dependent and long-lasting impairment was observed in the operant responding tests from 0.01 mg/kg i.m. Similarly, whereas clear and identifiable behavioral effects were detected in the Irwin-like procedure with cocaine from 1 mg/kg i.v. a dose- and time-dependent impairment was observed in operant responding at doses from 0.1 mg/kg i.v.

These results show that analyzing the qualitative data from behavioral observations together with quantitative data from an operant responding procedure provides a more rigorous assessment of drug effects and their duration of action, relevant to safety assessment.