SAFETY PHARMACOLOGY

Irwin Test (modified) model

The Irwin observation test is used to evaluate the effects of a new substance on behavior and physiological function[1] and it integrates the core battery of safety pharmacology studies. When carried out carefully by trained observers, the Irwin test can be a powerful tool to alert us to potential safety issues, including problems of sedation, motor impairment and convulsive potential. These effects should then be followed up with more specific tests to confirm these findings.

Species: *Rattus norvegicus* (Sprague Dawley or Wistar Hannover)
Number of animals/group: 8 animals
Route of administration: upon request
Treatment mode: acute

Main read-outs: Excitation, sedation, stereotypy, motor, pain and autonomic parameters. More details, upon request.

Validation Data

Behaviors and clinical signals observed in Irwin test (*modified*) after Caffeine and Chlorpromazine administration

Dose and administration route	Vehicle saline, 1 mL/kg, p.o.							Caffeine 24 mg/kg, p.o.							Chlorpromazine 30 mg/kg, p.o.						
Parameters	Evaluation time																				
	0-15 m	15 m	30 m	60m	120 m	180 m	24 h	0-15 m	15 m	30 m	60m	120 m	180 m	24 h	0-15 m	15 m	30 m	60m	120 m	180 m	24 h
Tremor								1-2/8													
Excitation slight (+)									3-4/8	5-6/8	3-4/8	5-6/8	5-6/8								
Excitation moderate (++)									3-4/8	1-2/8	5-6/8	1-2/8	1-2/8								
Excitation marked (+++)										1-2/8											
Increased reactivity touch									5-6/8	5-6/8	3-4/8	3-4/8	3-4/8								
Increased fear		3-4/8	5-6/8	7-8/8	1-2/8	1-2/8				5-6/8	7-8/8	3-4/8	3-4/8					1-2/8			1-2/8
Sedation slight (+)																3-4/8	5-6/8		1-2/8		1-2/8
Sedation moderate (++)																	1-2/8				
Sedation marked (+++)																	1-2/8	7-8/8	7-8/8	7-8/8	1-2/8
Decreased reactivity touch																3-4/8	3-4/8	7-8/8	7-8/8	7-8/8	3-4/8
Decreased fear																			1-2/8	1-2/8	1-2/8
Stereotypy (chewing)															3-4/8						
Motor (loss of traction)																			1-2/8	1-2/8	1-2/8
Autonomic (ptosis)																		5-6/8		7-8/8	3-4/8
Autonomic (defecation)		5-6/8	3-4/8	1-2/8	1-2/8	1-2/8	5-6/8		5-6/8		3-4/8	3-4/8	1-2/8	3-4/8		5-6/8	1-2/8				5-6/8

0/8 1-2/8 3-4/8 5-6/8 7-8/8

Table: Behaviors and clinical signals observed in Irwin test (modified) after Caffeine and Chlorpromazine administration. The evaluation time was 0-15 min, 15, 30, 60, 120, 180 min and 24 h after the treatments acute administration. The data are expressed by the number of rats which expressed the parameter per the total number of evaluated rats (total sample number: 8). Caffeine (CNS stimulant) and Chlorpromazine (antipsychotic) were used as references compounds and saline was used as control.

To avoid bias and to allow reproducibility all in vivo experiments follow the ARRIVE guidances[2]. Rat colony from Charles River Laboratories is breed and maintained in SPF conditions. The project includes study plan and final report. Raw data are inspected by quality assurance unity. The experimental procedures was previously approved by the CIEnP Committee on the Ethical Use of Animals.

References:

[1]Roux S, Sablé E, Porsolt RD. Primary observation (Irwin) test in rodents for assessing acute toxicity of a test agent and its effects on behavior and physiological function. Curr Protoc Pharmacol, Chapter 10:Unit 10.10, 2005.
[2]Kilkenny C, Browne WJ, Cuthill IC, Emerson M, Altman DG. Animal research: reporting in vivo experiments: The ARRIVE guidelines. PLoS Biol. 8 (6): e1000412, 2010.

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