Gastrointestinal Motility Assessment Comparing Two Species (Rat vs. Mouse)

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1 ABSTRACT

The purpose of safety pharmacology is to investigate effects of test substances on vital organ system function. This is accomplished through the conduct of a core battery of studies that entail evaluation of the cardiovascular, respiratory and central nervous systems (ICH S7A, 2001). Following an assessment of the core battery studies, in which concern for human safety may arise, supplemental safety pharmacology studies may be necessary. Supplemental studies are meant to provide greater depth of understanding than that provided by the core battery from other organ systems of importance. One such area of evaluation is the gastrointestinal (GI) system. The GI tract, from anterior to posterior, is composed of the esophagus, stomach, small intestine and large intestine. Each portion of the GI tract performs a vital function in the digestive process, with many layers of muscles contracting and relaxing resulting in the movement of foods and liquids through the system, while also providing an opportunity for interaction with novel test substances. When the muscle contractions of the GI tract become abnormal and uncoordinated, motility disorders may result. Gastrointestinal motility disorders can affect any part of the digestive tract resulting from two general causes: 1) A direct malfunction within the digestive muscles, or 2) A malfunction of the nerves and/or hormones that regulate the muscles' contractions. As a result, supplemental GI motility studies are an opportunity to further evaluate the gastrointestinal system. The objective of this study was to investigate the inherent natural differences between Crl:CD(SD) rats and CD-1 and C57Bl6 mice. WIN 55,212-2, a known potent CB_1 cannabinoid receptor agonist, was utilized to induce differing levels of percent (%) motility reductions when compared to a vehicle control. Analysis of the results from the motility study, including core body temperature, indicated concordance between the species and parameters evaluated with slightly greater animal variability in the rat model when compared to either mouse strain. Both mouse strains displayed similar results to each other. Our research indicated both species are valuable options to examine GI motility in test compounds.

2 MATERIALS AND METHODS

The objective of this study was to evaluate the effects of intraperitoneal (IP) administration of WIN 55,212-2 (WIN 55) on gastrointestinal motility changes in male Sprague Dawley Crl:CD(SD) rats and male CD-1 or C57BL6 mice. WIN 55 in the IP vehicle (5% DMSO prepared in physiological NaCl solution [0.9% NaCl] or DMSO alone (vehicle control) were administered once via IP injection to appropriate Groups (6-8 males/species/group). The table below (Table 1) represents dose levels, study group arrangement, and dose administration order.

Approximately 15 minutes after WIN 55 or vehicle control dosing, all animals were administered a single oral dose of the charcoal suspension (5% activated charcoal, 10% acacia in deionized [DI] water). All animals were euthanized via decapitation and gastrointestinal (GI) motility was measured at 30 minutes (± 3 minutes) following administration of the charcoal meal suspension. This design paradigm is presented in the Results (Figure 1).

The distances traveled by the charcoal suspension and the total length of the small intestine were measured and used to evaluate the effects of IP administration on WIN 55-induced gastrointestinal motility changes. These measurements were used to calculate percent distance traveled and normalized percent inhibition for each group.

Two calculations were performed to determine test article and reference compound effects:

- Percent distance traveled = (distance traveled x 100)/total length of the small intestine.
- Normalized percent inhibition (WIN 55) = ([mean percent distance traveled of each Vehicle Control Group – mean percent distance traveled of each WIN 55 Group] x 100)/ mean percent distance traveled of Vehicle Control Group.

Table 1.

Group	Species/Strain	Compound	WIN Dose Level (mg/kg)	WIN Dose Conc. (mg/mL)	WIN Dose Volume (mL/kg)	Number of Animals
1	Mouse C57BL6	Vehicle (5% DMSO)	0	0	10	8
2	Mouse CD-1	Vehicle (5% DMSO)	0	0	10	6
3	Rat Crl:CD(SD)	Vehicle (5% DMSO)	0	0	10	6
4	Mouse C57BL6	WIN 55	1	0.1	10	8
5	Mouse CD-1	WIN 55	1	0.1	10	6
6	Rat Crl:CD(SD)	WIN 55	1	0.1	10	6
7	Mouse C57BL6	WIN 55	2.5	0.25	10	8
8	Rat Crl:CD(SD)	WIN 55	2.5	0.25	10	6
9	Mouse C57BL6	WIN 55	5	0.5	10	8
10	Mouse CD-1	WIN 55	5	0.5	10	6
11	Rat Crl:CD(SD)	WIN 55	5	0.5	10	6

3 RESULTS

Based on the study design (Figure 1), body temperatures collected at the time of sacrifice for the 2.5 and 5 mg/kg WIN 55 dose groups were lower than the vehicle control group mean, with the differences increasing in a dose-dependent manner. Body temperatures following administration of 1 mg/kg WIN 55 were generally similar to those observed in the vehicle control group.

Following treatment with WIN 55, statistically significant shorter gastrointestinal motility was observed in rats and mice when compared to the respective vehicle control groups. Gastrointestinal motility in rats and mice was similar between control groups, 86.3%, 67.2% and 72.3% for Groups 1, 2 and 3, respectively. Motility decreased in a dose-dependent manner, with shorter distances observed as the dose level of WIN 55 increased. (Table 2)

Figure 1.

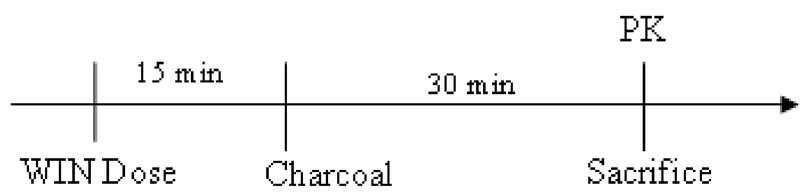

Table 2.

Group	Species/Strain	Compound	Dose Level (mg/kg)	Intestinal Charcoal Transit Distance (%)
1	Mouse C57BL6	Vehicle (5% DMSO)	0	86.3
2	Mouse CD-1	Vehicle (5% DMSO)	0	67.2
3	Rat Crl:CD(SD)	Vehicle (5% DMSO)	0	72.3
4	Mouse C57BL6	WIN 55	1	75.9
5	Mouse CD-1	WIN 55	1	50.4
6	Rat Crl:CD(SD)	WIN 55	1	42.0**
7	Mouse C57BL6	WIN 55	2.5	50.0**
8	Rat Crl:CD(SD)	WIN 55	2.5	38.8**
9	Mouse C57BL6	WIN 55	5	36.0**
10	Mouse CD-1	WIN 55	5	19.3**
11	Rat Crl:CD(SD)	WIN 55	5	35.1**

** = Significantly different from control Group 1 at 0.01 using Dunnett's test.

4 CONCLUSIONS

Intraperitoneal administration of WIN 55 at dose levels of 1, 2.5, or 5 mg/kg male C57B16 mice, CD-1 mice, or Crl:CD(SD) rats resulted in shorter motility as compared to the vehicle control group. Motility was at times significantly different following administration of 1, 2.5, or 5 mg/kg WIN 55. Body temperatures following administration of 1 mg/kg WIN 55 were generally similar to those observed in the vehicle control group; however, body temperatures were lower following administration of 2.5 or 5 mg/kg WIN 55.

Analysis of the results from the motility study, including core body temperature, indicated concordance between the species and parameters evaluated with slightly greater animal variability in the rat model when compared to either mouse strain. Both mouse strains displayed similar results to each other. Our research indicated both species are valuable options to examine GI motility in test compounds.