

IX. PRE-CLINICAL TOXICOLOGY

SAFETY/TOXICITY STUDIES ON AYURVEDIC FORMULATIONS (A,B,C,D,E) (WHO BIENNIUM PROGRAMME)

The traditional use of Ayurvedic formulations is one of the widely accepted therapies especially in chronic diseases viz. arthritis, asthma, and inducing fertility, rejuvenation etc. The data on safety of the Ayurvedic formulations has become important for wider global acceptance. The coded Ayurvedic formulations developed by CCRAS, MoH & FW are reported to have potential therapeutic activity in chronic diseases and are considered essential for pre-clinical toxicity screening as per WHO guidelines. The present investigations are therefore undertaken to evaluate the safety of five Ayurvedic formulations 'a, b, c, d & e' by acute/ sub-acute toxicity tests in mice/rats as desired by sponsor.

Objectives

To conduct acute and sub-acute toxicity of Ayurvedic Formulation-[a, b, c, d & e] in male and female Swiss Albino Mice and Wistar-NIN Rats respectively as per the guidelines of sponsorer .

Methodology

The animals were selected, conditioned, and exposed to the test compounds (Ayurvedic Formulation-[a, b, c, d & e]) through oral route at various dose levels (Table 26). The animals were observed for lethality for 14 days in acute toxicity study after single exposure at 10x of therapeutic dose (table 27). In sub-acute toxicity study (28 days) the following observations were recorded before and after exposure to test compound (Table 27).

Table 26. Dosage details

S.No	Sample code	Human* /day	Mice* (per kg)	Rat* (per kg)
1	a	3000 mg	390 mg	270 mg
2	b	1500 mg	195 mg	135 mg
3	c	1400 mg	182 mg	126 mg
4	d	3000 mg	390 mg	270 mg
5	e	15000 mg	1950 mg	1350 mg

Route of administration Oral

Table 27. Test Details (species/doses/duration)

Test details	Test species	Dosage	Duration	Study duration
Acute	Swiss Albino Mice 5 M +5F	10x	Once	14 days*
Sub acute	Rats (Wistar rat) 20 M+20F@	1x Therapeutic 5x Average Dose 10x High Dose VC Vehicle control	Daily 28 days	30 days*

@ 10 (5M+5F) in each group (1x, 5x, 10x & VC) 1x = (therapeutic dose), 5x = (5 times of the therapeutic dose), 10x = (10 times of the therapeutic dose), Additional 5 days for conditioning animals.

Observations: Food intake, body weight, routine physical, physiological examinations have been recorded at frequent intervals. Hematology, clinical chemistry in blood samples and gross necropsy, histopathology of liver, kidney, lungs and brain has been investigated at the end of experiment.

Data is compiled and analyzed for significant difference between treatment groups and vehicle control group by appropriate tests.

Results

The experimental work was initiated in August 2004 with formulation 'a' and the work was completed by October 2004. The results of formulation 'a' are provided here with. However, studies are in progress with formulation 'b' 'c' 'd' & 'e'.

1) Acute:

No mortality, morbidity, weight loss and abnormal behaviour was recorded after a single exposure of a test compound with ten times of the recommended therapeutic dose after 14 days in Swiss albino mice.

2) Sub Acute

There were pre-terminal deaths in animals receiving therapeutic dose(10%), average dose(30%), high dose(70%) for formulation-(a).

No significant treatment related effect on food intake, body weight, clinical signs and behavioral activity etc were observed in the animals found alive during the experiment.

No significant changes were observed in hematological parameters in the surviving animals. There were no significant changes in clinical chemistry parameters in the surviving animals.

No specific test compound induced pathological changes were observed in various organs collected during euthanization of the animals.

Conclusion

1. No abnormal findings were recorded after administering single dose of 10x dose.
2. Pre-terminal deaths ranging between 30-70% in animals receiving 5 and 10 times of the recommended therapeutic dose were observed for formulation-(a).

Current status: Data compilation and report writing is in progress for formulations b,c,d & e.