INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com
ISSN 2230 – 8407

Research Article

EVALUATION OF "YAK001" FOR SAFETY PROFILE: ACUTE ORAL TOXICITY STUDY

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Article Received on: 22/06/15 Revised on: 21/07/15 Approved for publication: 06/08/15

DOI: 10.7897/2230-8407.068110

ABSTRACT

This study determines acute toxicity of a coded drug "YAK001" an oral formulation prepared with suspension of test drug using gum acacia in rats. It was assessed for single dose acute toxicity by employing OECD guidelines 425 using AOT software. The dosed (up down as per requirement) rats were observed for 14 days, for general appearance, cage side behavior including increased or decreasing motor activity, convulsions, straub's reaction, catatonia, muscle spasm, spasticity, ophisthotonus, hyperesthesia, muscle relaxation, anaesthesia, arching and rolling, lacrimation, salivation, diarrhea, writhing movement, mode of respiration and changes in skin color etc., with mortality and autopsy finding in case of dead animal. The test drug did not produce any mortality up to the dose of 2000 mg/kg per oral which is equivalent to 22.4g total dose for a human being weighing 70 kg man.

KEY WORDS: YAK001, Mortality, Acute oral toxicity.

INTRODUCTION

Acute toxicity is that produced after administration of a single dose (or multiple doses) in a period not exceeding 24 hours, up to a limit of 2000 mg/kg. Objective of the study is to identify a dose causing major adverse effects and an estimation of the minimum dose causing lethality, according to regulatory guidelines[1].

Plants or drugs must be ensured to be safe before they could be used as medicines. A key stage in ensuring the safety of drugs is to conduct toxicity tests in appropriate animal models, and acute toxicity studies are just one of a battery of toxicity tests that are used[2]. Toxicity is indication of adverse effects led by the interaction between toxicants and cells. This interaction may vary depending on the chemical properties of the toxicants and the cell membrane, as it may occur on the cell surface, within the cell body, or in the tissues beneath as well as at the extracellular matrix. The toxic effects may take place prior to the binding of the toxicants to the vital organs such as liver and kidneys. Hence, evaluation of toxic properties of a substance is crucial when considering for public health protection because exposure to chemicals can be hazardous and may result in adverse effects on human being [3].

The main aim of our study was to evaluate the trust developed coded drug for assessing its toxic effects before it can be used for applications that are of importance to the public. Hence the coded drug YAK001 was evaluated for its acute toxicity profile with reference to behavioral aspects, in wistar albino rats.

MATERIALS AND METHODS

Collection of sample

Sample of coded drug "YAK001", a polyherbal formulation was collected from sponsor Sri Sri Ayurveda Trust, 21st km, Kanakapura road, Udayapura, Bangalore-560082

Animals and Exposure conditions

Wistar albino rats of either sex weighing about 150–200g were taken for conducting acute oral toxicity study. The animals were procured from Animal house, SDM Centre for Research in "Ayurveda and Allied Sciences, Udyavara. They were randomly distributed according to age, weight, sex and were housed in clean polypropylene cages with stainless steel top grill. The dry paddy husk was used as bedding material and was changed every morning. Before initiation of experiment, the rats were acclimatized for a period of 7 days and were exposed to 12 hours light and 12 hours dark cycle with the relative humidity of 50 to 70 % and the ambient temperature was 22 ± 03ºC. All the animals were fed with Amruth brand rat pellet feed supplied by Pranav Agro Ltd; food was provided throughout the study period except on previous night of dosing i.e. (overnight) fasting before dosing. Drinking water was given *ad libitum* in polypropylene bottles with stainless steel sipper tube under strict hygienic conditions. The animals were marked with saturated picric acid solution in water for proper identification. All procedures were performed in accordance to OECD test guidelines[4] No. 425 after approval from the Institutional Animal and Ethics Committee [No. IAEC-13/12-SDMCAU-YAK001]

Acute Oral Toxicity study

Test drug YAK001 was screened for acute oral toxicity study. The study was performed according to OECD 425 guidelines. The test formulation was made in to fine suspension with vehicle (gum acacia) into suitable concentrations. All the animals were subjected to overnight fasting before the day of dosing. The rats were weighed and the dose was calculated in reference to the body weight. Animals were dosed constant dose volume (1 ml/ 100g body weight) and administered in a single dose orally at one of the three dose level as generated by AOT software. The doses used were 175, 550, 2000, 2000, 2000 mg/kg body weight by using oral feeding needle sleeved on to disposable syringe. The group number, animal number and dose were identified with the help of cage cards, as presented in table 1.

OBSERVATION

Examination of Physical and Behavioral changes

The animal was observed continuously for 4 hours after the dosing. The careful cage side observation was done without disturbing the animal attention and at the end of every hour the animal was individually exposed to open arena for recording the behavioral changes like increased or decreased motor activity, convulsions, straub's reaction, muscle spasm, catatonia, spasticity, ophisthotonus, hyperesthesia, muscle relaxation, anaesthesia, arching and rolling, lacrimation, salivation, diarrhoea, writhing, mode of respiration, changes in skin color etc. exitus, CNS depression – hypo activity, passivity, relaxation, ataxia, narcosis, etc.

Mortality

All the animals were observed at ½, 1, 2, 3, 4, 24 h, 48 h after dosing and there after daily once for mortality during the entire period of the study (i.e.14 days).

Table 1: Dosage of extracts administered to test animals

Sl.no	Identification of animals	Desired dose (mg/kg) (according to AOT)	Body weight (grams)	Calculated dose (ml)
1	Head	175	158	1.58
2	Neck	550	162	1.62
3	Back	2000	156	1.56
4	Base of the tail	2000	160	1.60
5	No mark	2000	154	1.54

Table 2: Sign and symptoms during gross behavioral study

Signs & symptoms		Head (175mg/kg)		Neck (550mg/kg)		Back (2000mg/kg)		Base of tail (2000mg/kg)		No mark (2000mg/kg)	
		Before	After	Before	After	Before	After	Before	After	Before	After
General impression		N	N	N	N	N	N	N	N	N	N
Increased motor activity		A	A	A	A	A	A	A	A	A	A
Convulsion	Tonic	A	A	A	A	A	A	A	A	A	A
	Clonic	A	A	A	A	A	A	A	A	A	A
Straubs reaction		A	A	A	A	A	A	A	A	A	A
Muscle spasm		A	A	A	A	A	A	A	A	A	A
Catatonia		A	A	A	A	A	A	A	A	A	A
Opisthotonus		A	A	A	A	A	A	A	A	A	A
Hyperaesthesia		A	A	A	A	A	A	A	A	A	A
Decreased motor activity		A	A	A	A	A	A	A	A	A	A
Muscle relaxation		A	A	A	A	A	A	A	A	A	A
Anaesthesia		A	A	A	A	A	A	A	A	A	A
Arching and rolling		A	A	A	A	A	A	A	A	A	A
Lacrimation		A	A	A	A	A	A	A	A	A	A
Diarrhoea		A	A	A	A	A	A	A	A	A	A
Writhing		A	A	A	A	A	A	A	A	A	A
Salivation	Viscid	A	A	A	A	A	A	A	A	A	A
	watery	A	A	A	A	A	A	A	A	A	A
Respiration	Stimulation	A	A	A	A	A	A	A	A	A	A
	Depression	A	A	A	A	A	A	A	A	A	A
	Failure	A	A	A	A	A	A	A	A	A	A
Skin colour	Blanching	A	A	A	A	A	A	A	A	A	A
	Cyanosis	A	A	A	A	A	A	A	A	A	A
	Vasodilatation	A	A	A	A	A	A	A	A	A	A
Grip strength		N	N	N	N	N	N	N	N	N	N
Visual placing response		N	N	N	N	N	N	N	N	N	N
Tail pinch response		N	N	N	N	N	N	N	N	N	N
Auditory response		N	N	N	N	N	N	N	N	N	N
mucus membrane		N	N	N	N	N	N	N	N	N	N
Piloerection		N	N	N	N	N	N	N	N	N	N

n=normal, a=absent

RESULT

Physical and behavioral examination

There were no physical and behavioral changes-except mild increase in motor activity, irritability during drug administration, Piloerection was seen in 1 rat in the group 2000 mg/kg and rearing activity seen in 1rat in each group of 550 mg/kg and 2000 mg/kg dose out of all the treated animals on day one at 1, 2, 3, 4 hours intervals after dosing. Thus the data obtained from the study on single dose administration of coded drug YAK001. Oral administration up to 14 days of observation period does not result in any physical and behavioral changes. Parameters observed before and after the administration of the test substance were shown in table 2.

Mortality

All the animals belonging to the treated group survived throughout the 14 days observation period after dosing.

CONCLUSION

The non toxic nature of the coded drug YAK001 is evident from the acute oral toxicity conducted as per OECD guidelines. The normal behaviour and mortality of the test animals during a period of 14 days suggests the non-toxic nature of the drug. Thus it could be concluded that the test drug is without any toxic potential even at the dose of 2000 mg/kg in animals which is equivalent to 22.4 g for human being. This dose in human being is 7.4 fold higher in comparison to normal human dose of 3 g per day.

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Cite this article as:

Hari Venkatesh. K. R., Ankur Patel, Ravi Mundugaru, B. Ravishankar. Evaluation of "YAK001" for safety profile: Acute oral toxicity study. Int. Res. J. Pharm. 2015; 6(8):559-561 http://dx.doi.org/10.7897/2230-8407.068110

Source of support: Nil, Conflict of interest: None Declared