BLONANSERIN PRE-CLINICAL TOXICOLOGICAL ASSESSMENT IN ALBINO WISTAR RATS

[1]P.LOHITHA, [2]SRIKANTH VARMA J, [3]KONTHAMREDDY SADHANA, [4]B.KIRAN
[1]Professor, [2,3]Assistant Professor, [4]UG Student, [1,2,3,4]Department of Pharmacy, Brilliant Grammer School Educational Society Group of Institutions-Integrated Campus, Hyderabad, India.

ABSTRACT
The most prevalent severe neurological condition is psychosis. Several methods through which blonanserin exert its antipsychotic activity have been identified. It is very useful for treating schizophrenia. Blonanserin works by blocking adrenergic, histaminergic, 5-HT2A, 5-HT (1-4-6-7), and serotonergic receptors. The preclinical safety of "Blonanserin" was assessed in the current investigation using Wistar rats. Ten animals—five males and five females—in a research on acute toxicity were each given five times the planned therapeutic dose. Each dosage level has six male and six female participants in four groups. Tare is found in research on subacute toxicity. The low dose, middle dose and high dose groupsreceives test item at various dose levelsThe vehicle control group received sterile water,. The test item has been administered through oral route for 28 days. The histopathological studies of liver and kidneys were carried out by using Eosin and Hematoxylin and there was no change observed in gross histopathological changes in liver and kidneys in high dose when compared to control group.This shows that Blonanserin is relatively in-toxic in doses given to rat. The rat's heart, spleen, lungs, and testes had no abnormalities, according to histopathological investigations. The liver and kidneys are important in many metabolic processes. Blonanserin is in fact predominantly metabolised by the liver through N-glucuronidation and acetylation, and the kidneys are responsible for excreting almost all of its metabolites (84 percent). Thus, attention was made on Blonanserin's impact on these organs' functionality. Hepatocellular and nephrotic function were unaffected despite a minor variation in the biochemical markers following oral administration of Blonanserin.

INTRODUCTION

An interdisciplinary branch of research called toxicology examines how detrimental (or poisonous) chemicals or physical agents may be to living things under certain exposure situations. (1) It does this by compiling a list of all potential hazards (i.e., organ toxicities) related to a medicine as well as specifying the exposure circumstances under which those hazards/toxicities are generated. This is done by carrying out experimental studies into the occurrence of these effects. Many interactions between these two restrictions are possible. (2)A few examples of toxicity testing are acute, subacute, developmental, and cutaneous toxicity.

Drug information

Blonanserin was used obtained from sai chemicals visakhapatnamThe volume administered was 2ml/kg for all groups of animals.The concentration of TI for Low Dose-1.1 mg/ml,Middle Dose-3.3 mg/ml,High Dose-11 mg/ml.Wistar rats of both sexes, 6–8 weeks old, and weighing 180–200gm have been used.The animals used in this study were obtained from sai chemicals Hyderbad. (Reg.No.93/1999/CPCSEA).One of the suggested species for use as test animals in toxicity investigations is the wistar rat. They are frequently employed in the industry for the assessment of product safety.

RANDOMIZATION

The allocation of treatments to animals or groups is guaranteed by randomization to be independent of their characteristics and consistent across all groups.

NUMBERING OF ANIMALS

GROUP	NUMBER OF ANIMALS	ANIMAL NUMBER	
		MALE	FEMALE
VEHICLE CONTROL	12(6males6Females)	101-106	151-156
THERAPEUTIC DOSE	126males6Females)	201-206	251-256
AVERAGE DOSE	126males6Females)	301-306	351-356
HIGH DOSE	126males6Females)	401-406	451-456

The animals were fed on pelleted feed containing standard composition of all macro and micronutrients, purified water collected through aqua guard was provided to animals ad libitium.
Animals were identified by ear punching. Each cage was identified with individual cage tags by study number, animal numbers, dose, group, route, species, sex and date of initiation.
The TI was administered by oral route.

STUDY DESIGN

The study consists of total 48 mice (24 males+24 females) divided into four groups. The test item(BLONANSERIN) was administered through oral route at a concentration of 1.1 mg/ml for low dose,3.3 mg/ml for middle dose,11 mg/ml for high dose group animals& the volume administered was 2ml/kg.On day 29, all of the animals were sacrificed. All of the animals were checked twice a day for morbidity and mortality.[3] At regular intervals, home cage observations, hand held observations, open field activity, stimulus response, nervous and muscle measurements were performed. Biochemistry, haematology, necropsy, and histopathological examination of all vital organs were performed on all animals (viz.,brain,spleen,kidney,heart,lungs,liver,stomach and testes).DOSAGE REGIMEN : CLINICAL
DRUG DOSE : 24mg/day
DOSAGE REGIMEN : EXPERIMENTAL
ROUTE OF ADMINISTRATION : Oral route

Rat dose (calculated) =Human dose recommendedXconversionfactor(f*)(Man torat)
=(24mg) xf*(0.018)
=0.44mg(200gm)
=2.2mg/kg

S.N0	GROUP	DOSE (INMG/KG)	ROUTE OF ADMINISTRATION	NO.OF ANIMALS
1.	VC	Sterile water		12(6males6Females)
2.	LD(Therapeuticdose)	2.2mg		126males6Females)
3.	MD(3XTD)	6.6mg	ORAL	126males6Females)
4.	HD(10XTD)	22mg		126males6Females

STATISTICAL ANALYSIS

The data on body weight, food intake, haematology, biochemistry, and various organ weights were analysed using graph pad prism version 5.0 and post hoc testa (Bonferroni).

ACUTE TOXICITY STUDIES

Each group had five animals of either sexes. Animals were given a single bolus of the test substance (BLONANSERIN) orally within 24 hours and monitored for 14 days.[4] Intoxication symptoms, effects on body weight, and severe histopathological changes were all reported.

SUB ACUTE (28 DAYS) TOXICITY STUDIES

Cage-side observations, bodyweight changes, food/water intake, blood biochemistry, Hematology, and gross and microscopic examinations of all viscera and tissues were among the observation parameters.

OBSERVATIONS

The animals were observed twice daily for 28 days after the first exposure to the test item to record any toxicity symptoms and mortality. In the event of death, an autopsy was performed, and vital organs were collected for histipathological examination.

PRE TERMINAL DEATHS

FUNCTIONAL OBSERVATION BATTERY

HOME CAGE BBSERVATIONS

1. body posture2. respiration character3. tremors 4. convulsions 5. vocalization 6. palpebral closure.**hand held observations**the following physiological activities were monitored once weekly1. response to handling2. mucous membrane3. skin4. fur5. lacrimation 6. salivation7. piloerection**open field activity**the following physical observations were recorded periodically1. noof rearings2. gait3. tail elevation4. head position 5. occurrence of sterotype6. feces color7. urine color8. stimulusresponsethe following activities were monitored once weekly.pinnareflexrightingreflex**nervous and muscle measurements**the following nervous and muscle measurements were monitored once weekly1. abnormal tone2. limb tone3. grip strength

CLINICAL LABORATORY INVESTIGATIONS

BIOCHEMISTRY

Blood samples were collected from the orbital plexus and centrifuged at 3000rpm for about 10 minutes to separate the serum for biochemistry analysis using a fully automated random access biochemical analyzer (ERBA XL 300)

The principles used to investigate various parameters are as follows.1. ALBUMIN2. ALP3.BILIRUBIN4. CREATININE5. GLUCOSE6. AST7. ALT8. TOTAL PROTEIN 9. UREA

1. ORGAN WEIGHTS
2. GROSS OBSERVATIONS
3. HISTOPATHOLOGY

RESULT ANALYSIS

ACUTE TOXICITY RESULTS There were no pre-terminal deaths in the vehicle, therapeutic, middle, or high dose groups of animals.[(5)]

Table No.1 EFFECT 0F BLONANSERIN ON FOOD INTAKE EXAMINED IN WISTAR RATS(gms)

Days	Vehicle	Low dose	Middle dose	High dose
0^{TH} DAY	7.85+0.08	8.05+0.09	7.72+0.10	7.89+0.10
7^{TH} DAY	8.00+0.08	8.12+0.09	7.82+0.10	7.97+0.11
14^{TH} DAY	8.05+0.09	8.20+0.09	7.62+0.10	8.15+0.11

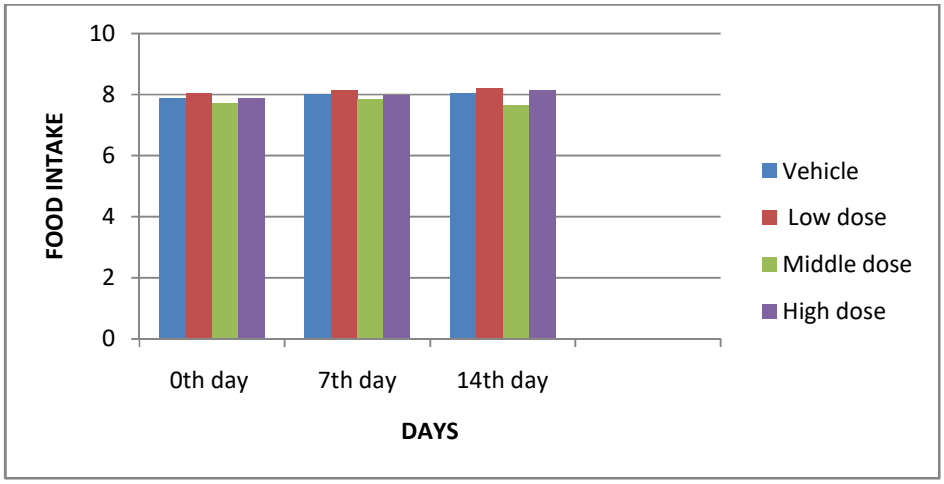

Fig 1 **Shows the Effect of Blonanserin on Food Intake Examined in Wistar Rats in (gms**

Table No.**2 EFFECT OF BLONANSERIN ON BODY WEIGHTS EXAMINED IN WISTAR RATS**

DAYS	VEHICLE	LOW DOSE	MIDDLE DOSE	HIGH DOSE
OTH DAY	157.42+_4.35	160.74+3.74	154.74+4.66	157.42+4.06
7^{TH} DAY	167.91+5.96	162.65+5.63	158.94+5.43	159.67+4.67
14^{TH} DAY	174.96+6.04	173.36+5.76	160.50+5.17	169.98+6.90

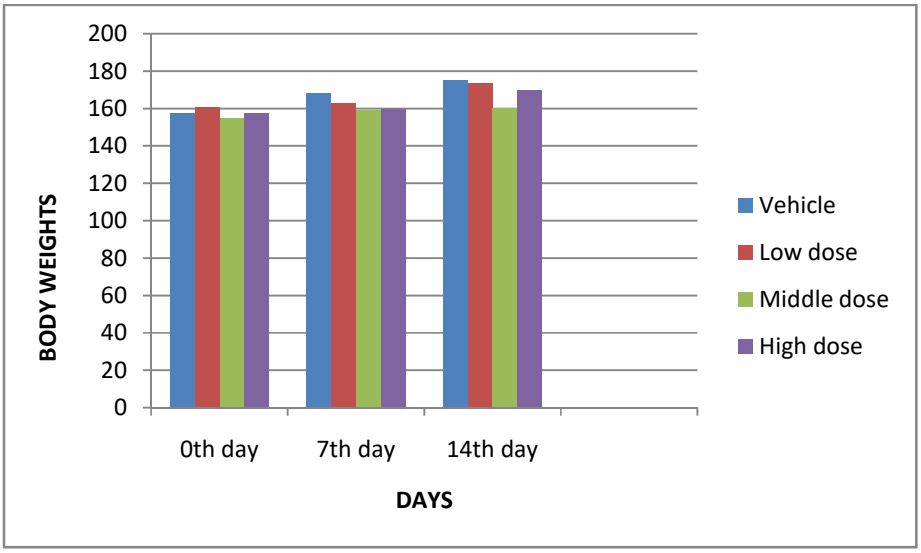

Fig.2 Shows the Effect of Blonanserin on Body Weights Examined in Wistar Rats in (grams)

SUB ACUTE TOXICITY RESULTS

FUNCTIONAL OBSERVATIONS

HOME CAGE OBSERVATIONS

1. BODY POSTURE:

HAND HELD OBSERVATIONSDuring the experimental phase, there were no significant abnormalities in body posture in any of the animal groups. 2. RESPIRATION CHARACTER:There were no significant differences in respiration character or rate in any of the animal groups during the experimental phase.[6]

3. TREMORS: The animals had no tremors before or after being exposed to the test item.

4. CONVULSIONS: No convulsions were observed in any group of animals immediately following the administration of the test item or during the post-exposure period.

5. VOCALIZATION: No spontaneous vocalisation was observed.

6. PALPEBRAL CLOSURE: There was no abnormal closing of the animal's eyes in the cage**.**

The following physiological activities were monitored once weekly.

1. RESPONSE TO HANDLINGThere was no abnormal behavior observed while removing from the cage.

2. MUCOUS MEMBRANEThere was no abnormal eye mucous membrane observed during the experimental period.3. SKINThere was no abnormal condition of skin observed during the experimental period.4. FURThe clean groomed fur was observed in all the animals exposed to teat item.5. LACRIMATION During the experimental period, no excessive lacrimation was observed in any of the groups. 6. SALIVATION During the experimental period, no excessive salivation was observed in any of the groups. PILOERECTION 7 There was no piloerection in any of the groups.

OPEN FIELD ACTIVITY

The following physical observations were recorded periodically

1. NO.OF REARINGS

There was no abnormal number of rearing observed in 3 minutes timeduring the experimental period.2. GAITThere was no abnormal gait in all groups of animals3. TAIL ELEVATION

All the animals in all groups lifted tail while walking during the experimental period.4. HEADPOSITIONHead position was normal without

OCCURRENCEOF STEROTYPE

There was no abnormal (Bizarre behavior) observed in all groups

1. FECES COLORThere were no abnormalities in the fecal color& amount during the experimental period in all the groups of animals.2. URINE COLORThere was no abnormal urine color observed in all groups3. STIMULUS RESPONSEThe following activities were monitored once weekly4. PINNA RESPONSEThere were no abnormal pinna touch responses in all groups of animals5. RIGHTING REFLEXThere was no abnormal righting reflex observed in all groups[7].

NERVOUS AND MUSCLE MEASURE MEASUREMENTS

The following nervous and muscle measurements were monitored once weekly

1. ABNORMAL TONEThere was no abnormal muscle tone observed in all groups

2. LIMB TONEThere was no abnormal limb tone observed in all groups.

3. GRIP STRENGTHThere were no abnormal changes in grip strength observed in all groups of animals4. LOCOMOTOR ACTIVITYThe loco motor activity has found to be normal in all groups of animal[8]

FOOD INTAKE

The food intake in Grams was calculated for all the groups of rats for every seven days of study. They were comparable with vehicle control group animals. They were comparable with vehicle controlanimals in groups

Throughout the study period, all groups receiving vehicle and test item at various doses consumed normal amounts of food..

Table 3:Effect of BLONANSETRIN on Food intake Examined in Wistar Rats In (grams)

Days	Vehicle	Low dose	Middle dose	High dose
0th day	7.85+0.08	8.05+0.09	7.72+0.10	7.87+0.10
7th day	8.00+0.08	8.15+0.09	7.82+0.10	7.92+0.11
14thday	8.05+0.09	8.20+0.09	7.82+0.10	8.12+0.11
21st day	8.25+0.06	8.35+0.09	7.95+0.10	8.17+0.10
28th day	8.37+0.08	8.45+0.09	8.05+0.10	8.22+0.11

MEAN+SEM of 48 animals are used to calculate the values.
Symbols represent significant differences from controls at P <0.05, P< 0.01, and P< 0.001.
Two-way ANOVA was used to compare statistical significance, followed by the BonferroniPost test.

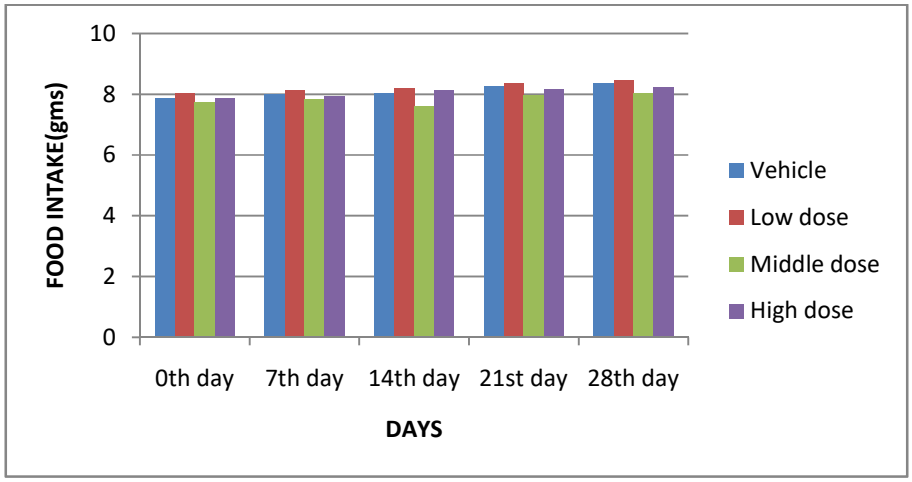

Fig no.3 Graph Shows the Effect of Blonanserin on Food intake Examined in Wistar rat

BODY WEIGHTS

Every seven days during the study period, the body weight in grammes of each rat group was calculated. Body weight increased gradually in both male and female animals, and was comparable to the vehicle control group of animals.

BODY WEIGHTS

Table :4Effect of BLONANSERIN on body weights examined in Wistar rats

Days	Vehicle control	Low dose	Middle dose	High dose
0th day	157.52+4.39	160.74+3.74	154.74+4.66	157.42+4.07
7th day	167.91+5.96	162.65+5.64	156.95+5.50	158.67+4.97
14th day	174.93+6.04	173.35+5.76	160.50+5.17	168.84+6.91
21st day	184.94+7.62	182.73+5.77	165.96+6.19	177.44+8.14

28th day	197.28+8.68	185.05+7.87	171.74+6.51	178.44+8.99

MEAN+SEM of 48 animals are used to calculate the values.
Symbols represent significant differences from controls at P <0.05, P< 0.01, and P< 0.001.
Two-way ANOVA was used to compare statistical significance, followed by the BonferroniPost test.

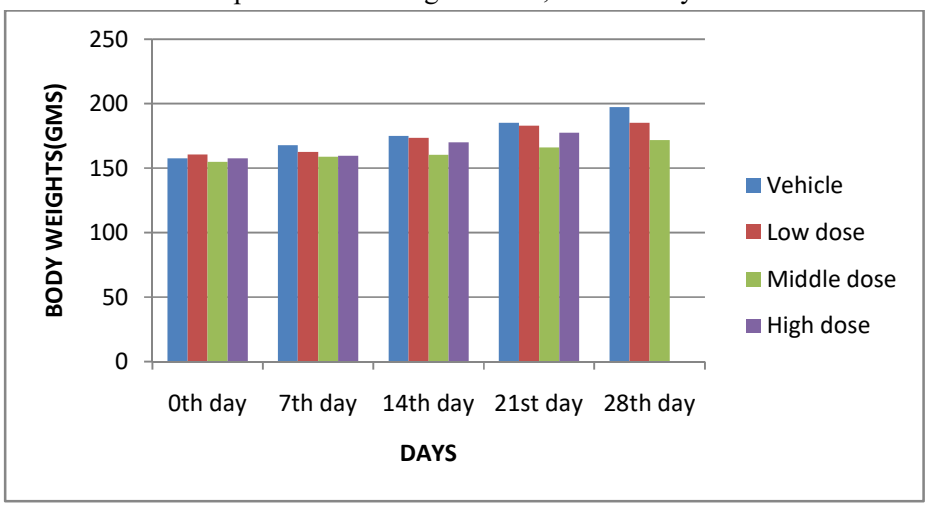

Fig:4 Shows the Effect of Blonanserin on Body Weights Examined in Wistar Rats in (grams)

CLINICAL LABORATORY INVESTIGATIONS:

Hematology:

The haematological parameters in all of the rat groups were found to be within normal limits and comparable to the vehicle control group animals.[9]

Table 5:Effect of BLONANSERIN on Hematological Parameters examined in Wistar Rat

HAEMATOLOGIAL PARAMETERS	VEHICLE	LOW DOSE	MIDDLE DOSE	HIGH DOSE
WBC (10^3 cells/m3) cells/m3)	11.30+1.43	13.18+0.88	14.29+0.92	14.24+1.21
RBC (10^6 cells/mm3)	7.92+0.21	7.67+0.18	7.70+0.13	7.70+0.14
HAEMAGLOBIN (gm/dl)	14.45+0.26	13.98+0.28	13.91+0.16	13.93+0.21
HCT (%)	44.86+0.96	43.39+0.98	43.30+0.70	43.37+0.72
MCV(µ3)	56.75+0.51	56.59+0.40	56.26+0.39	56.30+0.35
PLTX10^3	78.75+34.96	667.50+41.15	747.00+33.21	768.91+26.12

Comparing Vehicle control group with treated groups
MEAN+SEM of 48 animals are used to calculate the values.
Symbols represent significant differences from controls at P <0.05, P< 0.01, and P< 0.001.
Two-way ANOVA was used to compare statistical significance, followed by the BonferroniPost test.
The biochemical parameters tested for rats in various doses did not change. All of the parameters were comparable to the animals in the vehicle control group.

Table 6Effect of BLONANSERIN on Biochemical Parameters examined in Wistar Rats.

BIOCHEMICAL PARAMETERS	VEHICLE	LOW DOSE	MIDDLE DOSE	HIGH DOSE
Glucose (mg/dl)	80.41+5.56	96.08+2.25	98.66+2.29	92.56+8.15
Albumin(g/dl)	3.58+0.08	3.61+0.04	3.64+0.05	3.60+0.66
Total protein(g/dl)	7.17+0.06	7.21+0.08	7.56+0.11	7.38+0.08
ALP(µ/L)	175.75+12.34	220.66+8.88	228.75+10.14	229.66+11.12
ALT(µ/L)	45.16+1.58	53.91+1.65	50.33+2.15	57.00+1.38
AST(µ/L)	154.75+5.32	158.83+6.23	180.58+6.95	168.83+6.22
Biluribin	0.17+0.00	0.15+0.00	0.16+0.00	0.14+0.00
Creatinine	0.43+0.01	0.39+0.01	0.41+0.01	0.39+0.00
BUN	15.91+0.49	15.08+0.22	15.08+0.54	16.41+0.72

Comparing vehicle control group with treated groups.
MEAN+SEM of 48 animals are used to calculate the values.
Symbols represent significant differences from controls at P <0.05, P< 0.01, and P< 0.001.
Two-way ANOVA was used to compare statistical significance, followed by the BonferroniPost test.
After exposure to the test item at all dose levels, there were no significant test item related abnormalities in urine samples tested qualitatively for the presence of albumin,sugarurobilinogen,bilirubin, etc. [(10)]At the end of the experiment, proteinurea was found in both the control and treated groups. Rest of the parameters did not show any dose related changes**.**

Table 7**:URINE ANALYSIS RANGE VALUES**

TESTS	NIL	+	+	++	+++	++++
Blood(RBC/µL)			10	50	250	
Bilirubin (mg/100ml)			0.5	1.0	3.0	
Urobilinogen(mg/100ml)	0.1+..Normal	0.1+…… Normal	1	4	8	12
Ketones(mg/100ml)		5	10	50	100	
Protein(mg/100ml)		10	30	100	300	1000
Nitrate	-	-	-	-	-	-
Glucose(mg/100ml)		100	250	500	1000	2000
pH	5	6	7	8	9	
Specific Gravity	1.000	1.005	1.010	1.020	1.025	1.030

ORGAN WEIGHTS

There were no significant changes in the animals organ weights of liver, kidneys,lungs,heart,spleen,brain,testes etc., and the weights of all organs were observed to be in normal range in treated groups of animals and comparable to vehicle control group animals.

Table 8 **Effect of BLONANSERIN on Organ Weights examined in Male Rats (Grams/100gm body weight)**

WEIGHTS	VEHICLE	LOW DOSE	MIDDLE DOSE	HIGH DOSE
Body weights	217.55+9.00	206.43+3.55	180.26+9.39	200.48+9.50
liver	3.50+0.15	4.68+0.16	4.5+0.19	4.55+0.11
kidneys	0.78+0.02	0.86+0.02	0.93+0.03	0.82+0.03
Lungs	0.57+0.03	0.77+0.66	0.77+0.77	0.65+0.03
Heart	0.33+0.00	0.37+0.01	0.38+0.22	0.34+0.01
Testis	1.19+0.44	1.13+0.05	1.02+0.08	1.28+0.06
Spleen	0.59+0.05	0.67+0.05	0.65+0.04	0.63+0.03
Brain	0.79+0.02	0.80+0.02	0.92+0.04	0.87+0.05

Comparing vehicle control group with treated groups.
MEAN+SEM of 48 animals are used to calculate the values.
Symbols represent significant differences from controls at P <0.05, P< 0.01, and P< 0.001.
Two-way ANOVA was used to compare statistical significance, followed by the BonferroniPost test.

Table 9:Effect of BLONANSERIN on Organ Weights Examined in Female Rats(Grams/100gm body weight)

WEIGHTS	VEHICLE	LOW DOSE	MIDDLE DOSE	HIGH DOSE
Body Weights	173.95+3.60	180.18+3.35	180.66+4.22	178.31+4.60
liver	3.47+0.14	3.46+0.06	3.21+0.11	3.30+0.08
kidneys	0.67+0.04	0.70+0.04	0.69+0.03	0.69+0.03
Lungs	0.66+0.05	0.66+0.22	0.65+0.22	0.74+0.07
	0.35+0.01	0.39+0.22	0.39+0.01	0.38+0.22

Heart				
Spleen	0.46+0.01	0.51+0.66	0.51+0.05	0.59+0.06
Brain	0.85+0.07	1.03+0.03	0.97+0.02	1.035+0.04

S.No	Findings	VC	LD	MD	HD
1.	No abnormalities detected	6/6	6/6	6/6	6/6
		6/6	6/6	6/6	6/6

Comparing vehicle control with treated groups
MEAN+SEM of 48 animals are used to calculate the values.
Symbols represent significant differences from controls at P <0.05, P< 0.01, and P< 0.001.
Two-way ANOVA was used to compare statistical significance, followed by the BonferroniPost test.

GROSS OBSERVATIONS
No Significant gross changes in the organs of animals in any of the groups (VC, LD, MD, and HD) were present.
Table 10gross changes in the organs of animals in any of the groups

Histopathology:
Histopathological observations of all the vital organs indicates that there were no test item (BLONANSERIN) induced morphological changes in the organs studied

Table11 Histopathological observations of all the vital organsof animals

S.No	Organs	Diagnosis	VC	HD
1.	Liver	Normal	100(12)	100(12
2.	Lungs	Normal	100(12)	100(12)
3.	Brain	Normal	100(12)	100(12)
4.	Pancreas	Normal	100(12)	100(12)
5.	Testes/Ovaries	Normal	100(12)	100(12)
6.	Stomach	Normal	100(12)	100(12)
7.	Adrenals	Normal	100(12)	100(12)

8.	Spleen	Normal	100(12)	100(12)
9.	Kidney	Normal	100(12)	100(12)
10.	Heart	Normal	100(12)	100(12)

Summary and conclusion

Toxicology studies in animals are conducted to help assess the safety and characterise the risks of proposed new substances before they are administered to humans. Short-term toxicity studies, typically lasting up to one month, are used to support the first clinical trials in humans, while longer-term studies, typically lasting up to six months, are used to support phase II and III clinical trials.

Animal toxicity data is used to (i)identify target organ toxicity, (ii)characterize the relationship between substance exposure and response, (iii)determine whether an observed effect will recover when treatment is discontinued, and (iv)provide data to allow a risk assessment for humans.

Blonanserin is a novel antipsychotic medication that is primarily used to treat schizophrenia. Blonanserin primarily functions as a Dopamine (D2), histaminic, and muscarinic receptor antagonist.Toxicology research findings are becoming increasingly important to society as a whole (Ettlin and Hodel 2000)At an acute dose of 22mg/kg, the test drug showed no signs of toxicity or mortality. In general, a decrease in body weight gain and internal organ weights after exposure to a toxic substance is a simple and sensitive indicator of toxicity (Raza et al., 2002; Teo et al., 2002).Blonanserin did not produce a statistically significant difference in either parameter in the current study.Toxicological data is required for a drug to be marketed in India, according to DCGI guidelines, and thus toxicological evaluation is performed.

Furthermore, all of the animals were evaluated on a daily basis for:

DURING THE STUDY PERIOD, FUNCTIONAL OBSERVATIONS were made of body posture, respiratory character, tremors, vocalisation, and palpebral closure, and no abnormalities were found in these parameters in any of the groups.

HAND HELD OBSERVATIONS were performed twice daily and included response to handling, mucous membrane, fur, skin, larimation, salivation, and piloerection. No abnormalities in these parameters were found in any of the four groups.

The animals were also observed for open field activity, stimulus response, nervous and muscle movements, and no abnormal changes were observed in any of the four groups throughout the study period. Among biochemical parameters such as plasma glucose, total proteins, albumin, blood urea nitrogen, AST, ALT,ALP; glucose and ALT levels in the male satellite group were significantly normal with LD and HD as compared to the control group.

REFERENCES

1. Zbinden G, Flury-Roversi M. Significance of the LD50-test for the toxicological evaluation of chemical substances. Archives of toxicology. 1981 Apr;47(2):77-99.
2. Hunter WJ, Lingk W, Recht P. Intercomparison study on the determination of single administration toxicity in rats. Journal of the Association of Official Analytical Chemists. 1979 Jul 1;62(4):864-73.Bliss, C.I., *Quart. J. Pharm. Pharmacol*, *11*, 192-216, 1938.
3. Raj J, Chandra M, Dogra TD, Pahuja M, Raina A. Determination of median lethal dose of combination of endosulfan and cypermethrin in wistar rat. Toxicology international. 2013 Jan;20(1):1.
4. Weil CS. Tables for convenient calculation of median-effective dose (LD 50 or ED 50) and instructions in their use. Biometrics. 1952 Sep 1;8(3):249-63.Thompson, W., *Bact. Rev.*, *11*: 115-141, 1947.

5. Lipnick RL, Cotruvo JA, Hill RN, Bruce RD, Stitzel KA, Walker AP, Chu I, Goddard M, Segal L, Springer JA, Myers RC. Comparison of the up-and-down, conventional LD50, and fixed-dose acute toxicity procedures. Food and chemical toxicology. 1995 Mar 1;33(3):223-31.
6. vanNoordwijk AJ, van Noordwijk J. An accurate method for estimating an approximate lethal dose with few animals, tested with a Monte Carlo procedure. Archives of toxicology. 1988 Apr;61(5):333-43.
7. Tupper DE, Wallace RB. Utility of the neurological examination in rats. ActaNeurobiolExp (Wars). 1980 Jan 1;40(6):999-1003.Gad, S.C. (1982).
8. Edginton AN, Ritter L. Predicting plasma concentrations of bisphenol A in children younger than 2 years of age after typical feeding schedules, using a physiologically based toxicokinetic model. Environmental health perspectives. 2009 Apr;117(4):645-52.
9. Moser VC, McDaniel KL, Phillips PM. Rat strain and stock comparisons using a functional observational battery: baseline values and effects of amitraz. Toxicology and applied pharmacology. 1991 Apr 1;108(2):267-83.
10. Donald JM, Golub MS, Gershwin ME, Keen CL. Neurobehavioral effects in offspring of mice given excess aluminum in diet during gestation and lactation. Neurotoxicology and teratology. 1989 Jul 1;11(4):345-51.