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Behavioural Teratogenic Effect of Cimetidine on the Offspring's of Albino Rats

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ABSTRACT

The aim of this research was to determine the Behovioural teratogenic effects of cimetidine on the offspring's of Albino Rats. It was designed to test if cimetidine will have effect on offspring born to mothers who took cimetidine during gestation period. Sample of this study comprises of 3 pregnant albino rats which were randomly assigned into three (3) groups, grove A B and C. group A is the control group that did not receive any treatment while group B and C were the experimental group that received the experimental treatment. The experimental group B was given 2ml of cimetidine injection with cannula two times daily i.e.in the morning and in the evening. The experimental group C was given 2ml of cimetidine injection with a cannula daily i.e. 2ml of cimetidine injection in the morning and in the evening throughout their gestation period. 19 pups littered by the 3 female albino rats of both the control group and experimental groups were also used as the subject in the study. Three hypothesis were formulated and tested in this study, Hypothesis one was there will be a significant difference between the offspring's of albino rats who were injected with cimetidine to those born to mothers who were not injected with cimetidine on a T-maze test. This was confirmed [DF (2,9)=33.96,P<.01]. Hypothesis two, was that offspring's of albino rats who were injected with cimetidine during gestation will significantly perform low on the performance ability test (classical maze test) than those born to mother who were not injected was also tasted and confirmed [DF (2,9)=14/15, P<. 01]. The third hypothesis was that offspring's born to albino rats who were injected with cimetidine during gestation will have a significant low birth weight than those offspring's of mother who were not injected with cimetidine during gestation [DF (2,9) = 13.02, P< .01]. Data was analyzed using one way analysis of variance (ANOVA). We conclude that cimetidine intake during pregnancy will have effects on the memory, performance ability and birth weight of children. We therefore recommend that women who used cimetidine should stay away from it's uses during pregnancy, because it is a teratogenic agent and could cause harm or impairment to their offspring's.

KEYWORDS: Behavioural, Teratogenic, Cimetidine, Offspring, Albino rats

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INTRODUCTION

Teratogen is any agent or factor such as drug, virus or radiation that induces or increase the incidence of abnormal development. Cimetidine is a medication that belongs to a class of drugs known as H2 blockers. It reduces the amount of acid produced by the stomach and it is used to treat ulcers gastro esophageal reflux disease (GERD) and other conditions. Cimetidine is a drug with the indication of peptic ulcer disease, gastroesophageal reflux disease, and for dermatological condition (Schubert, 2017). In adults, cimetidine therapy appears to be beneficial with low toxicity in the treatment of recalcitrant warts (Martínez, 2014). There are also reports that cimetidine can inhibit heme biosynthesis and results in symptomatic improvement in children with acute intermittent porphyria, and porphyria cutanea tarda (Matok, 2010). Cimetidine is a gastric acid reducer used in the short-term treatment of duodenal and gastric ulcers (Sharma, 2011). The drug is effective in managing gastric hypersecretion, and therefore, used for the management of reflux esophagitis disease and in the prevention of stress ulcers. Cimetidine has shown beneficial effects on cell-mediated immunity following burn injury, (Lam, 2014) and alleviated damages induced by long-term low-dose neutron and gamma combined irradiation in animals via antioxidation

and immunomodulation (Dasgupta, 2015). Other studies support cimetidine as a treatment for bladder pain resulting from interstitial cystitis. The H2-receptor antagonist cimetidine competitively blocks histamine from stimulating the H2-receptors located on the gastric parietal cells (these cells are responsible for hydrochloric acid secretion and secretion of the intrinsic factor). The effect results in reducing the volume of gastric acid secretion from stimuli, including histamine, food, caffeine, and insulin (Sheu, 2011). High doses of cimetidine (over 5 g/day) can cause reversible impotence or gynecomastia (Matsumoto, 2017). This effect appears to be the result of the antiandrogenic potential of cimetidine, which depends on an increase in prolactin levels secondary to histamine H2 receptor blockade. Also, cimetidine has nonspecific actions that stimulate prolactin secretion, causing galactorrhea in men in a dose-related pattern (Langendonk, 2017; Teng, 2017). The effects could also be related to a blockade of the 2-hydroxylation of estradiol.

Cimetidine raises the pH of the gastric contents. This increased pH may lead to decreased absorption of drugs that require a lower pH to dissolve or increased absorption of drugs with absorption reduced by acid inactivation in the stomach (Gaggiano, 2019, & Kokhaei, 2014). Impairment of vitamin B12 absorption raises the possibility that long-term, full-dose therapy with cimetidine may produce B12 deficiency similar to that observed in other hypochlorhydric states (Wang, 2017).

MATERIALS AND METHODS

Study Area

The study was conducted in Adamawa State University, Mubi in Mubi North Local Government Area of Adamawa State, Nigeria. Mubi North has land area of 924.32km^2 with annual average temperature of 32.1^{0}C Maximum and 18.5^{0}C minimum. Average annual rainfall is about 1,000mm. The major settlements is Fali, Mayo- Bani and Mubi with a population of 214,580. Mubi North borders Michika to the North, Borno State to the northwest, Hong to the west, Maiha and Mubi South to the South and Cameroon republic to the East.(Adebayo *et al*., 2020)

Research Design and Sampling Collection:

It involves the use of multi-group experimental design with three independent groups i.e. the control group, the experimental group 1 and the experimental group 2.The subject for this study include three pregnant females' albino rats whose pregnancy ranges between one to two months old at the time of purchase, they were purchased from a breeders at Research garden of Zoology Department, Adamawa State University, Mubi. Pups littered by the 3 pregnant albino rats of both the control group and experimental groups were also used as the subject in the study.

Instrument

4 packs of 10 ampoules of 2ml cimetidine injection gotten from AA Michika Pharmaceutical store Mubi (Sishui Xierkang Pharmaceutical Company Ltd) were administered to the two experimental group female albino rats in the cause of the experiment . The experimental rats were kept in a cage at the animal house throughout the period of the research.

T-Maze: This was used to test for the spatial working memory test of the albino rats (pups).

Classical maze was used to measure the performance ability of the offspring's of the albino rats.

Electronic scale was used to measure the weight of the offspring at birth. Other instruments includes; water, thick hand gloves, plastic plates, feeding tray, stop watch and cannula.

Test Performance

Memory test and performance test was also carried out on albino rats offspring's (pup) five (5) weeks after delivery. In testing for memory, the pups were placed in a maze to trace food that was placed at one end. Each pups were given two trials and the number of times they could locate the food was recorded. In the other hand, in testing for performance, the pups were placed in the classical maze to locate food placed at the end of the classical maze, the time it took the pups to locate the food was recorded using stop watch. The test was done twice and the time taken for each trial was recorded.

Statistical Analysis

Data gotten from the experimentation was analyzed using a one way analysis of variance (ANOVA).

RESULTS

Hypothesis Testing

Earlier on, three hypotheses were stated and tested scientifically and statistically during the cause of this study.

Hypothesis 1: There was a significant difference between the offsprings of albino rats who were injected with cimetidine to those who were not injected with cimetidine on a T-maze test i.e. offspring's of albino rats who were injected with cimetidine during gestation period had a significant low memory than those offspring of mothers who were not injected with cimetidine during gestation period. In regard to this, the hypothesis was tested with a one-way analysis of variance (ANOVA) presented below:

Table 1. T-Maze Test

Source	SS	DF	MS	F^O	P
Total	154.92	11	-		
Between	136.793	2	68.397	33.96	**P< .01**
Within	**18.127**	**9**	**2.014**		

Keys: *SS-Sum of squares: DF-Degree of Freedom: MS-Mean Square: F^O- Variation between/within sample. P-Probability*

Since the calculated result of the one-way ANOVA of the effect of cimetidine during gestation on the test for spatial working memory shows that cimetidine significantly affected memory of their offspring's (DF (2.9) = 33.96, P< .01). Hypothesis 1 was confirmed and accepted.

Hypothesis 2: Offspring of albino rats who were injected with cimetidine during gestation performed low on the classical maze than those born to mothers who were not injected with cimetidine during gestation.

Table 2. C-Maze

Source	SS	DF	MS	F^0	P
Total	192.25	11	-	-	
Between	145.5	2	72.75	14.15	**P> .01**
Within	**46.75**	**9**	**5.14**	**-**	

Keys: *SS-Sum of squares: DF-Degree of Freedom: MS-Mean Square: F^O- Variation between/within sample. P-Probability*

Since the calculated result of the one way analysis of variance of the effect of cimetidine during pregnancy on performance ability shows that cimetidine statistically and significantly affected performance ability of their offspring's (F(2,9) = 14.15, P> .01). It therefore means that the hypothesis which state that cimetidine will have a significant effect on the performance ability test (classical maze test) was conformed and accepted.

***Hypothesis 3*:** Offspring's born to albino rats who were injected with cimetidine during gestation have a significantly low birth weight than those offspring's of mother who were not injected with cimetidine during gestation; This was also carried out with the use of one-way analysis of variance (ANOVA) and the result presented below.

Table 3. Birth Weight

SOURCE	SS	DF	MS	F^0	P
Total	7.357	11	-		
Between	5.4695	2	2.735	13.02	**P< .01**
Within	**1.887**	**9**	**0.21**		

Keys: *SS-Sum of squares: DF-Degree of Freedom: MS-Mean Square: F^O- Variation between/within sample. P-Probability*

The result of one-way ANOVA on the effects of cimetidine intake during gestation on the birth weight of offspring's of albino rats shows that cimetidine significantly affects the birth weight of their offspring's. (DF (2, 9) = 13.02, P< .01). Hence, hypothesis 3 was confirmed to be significant.

DISCUSSION

The result of this study extends previous research on the "behavioral teratogenic effects of cimetidine on the offspring of albino rats". The variables in the study include "cimetidine" which is the independent variable and the variable of interest, as well as "the offspring's born to albino rats" which is the dependent variable.

During the cause of this study, three hypotheses were advanced and tested. The following studies supports the first hypothesis which stated that there will be a significant difference between the offspring of albino rats who were injected with cimetidine to those born of mother's who were not injected with cimetidine on a T-maze test. This was confirmed (Df (2,9) = 33.96, P< .01) indicating that offspring of albino rats who were injected with cimetidine during gestation will have a significant low memory than those born of mother who were not injected with cimetidine during gestation. This finding is in consonance with the works of Charles *et al.,* (2019) who established the fact that cimetidine can impair and cause headache, anxiety, somnolence, depression and confusion. This also correspond to the work of Goldschmidt *et al; 2008;* who observed that memory difficulties including problem solving, memory planning, impulsive, and attention.The second hypothesis which stated that offspring of albino rats who were injected with cimetidine during gestation period significantly perform low on the performance ability test (classical maze) than those born to mothers who were not injected with cimetidine during gestation was also tested and confirmed (Df (2,9) = 14.15, P> .05). This finding is in consonance with the findings of Herrmann, King, and Weitzman, (2008) who established that cimetidine is linked to a lower IQ throughout childhood.

The third hypothesis which stated that offspring's born to albino rats who were injected with cimetidine during gestation have a significant low birth weight than those offspring's of mother who were not injected with cimetidine during gestation: This finding was in consonance with the findings of Qamar *et al;* (2010) who established that cimetidine had been linked to low birth weight and pregnancy complications etc.

CONCLUSION

From the findings of this research work we conclude that cimetidine intake during pregnancy will have effects on the memory and performance ability of child. It was also discovered that cimetidine intake will significantly affects the birth weight of children born of mothers who were exposed to cimetidine during pregnancy.

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