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TERATOGENIC EFFECTS OF AN ANTIEMETIC AGENT ROLAPITANT ON BRAIN OF DEVELOPING CHICK EMBRYOS: A MORPHOLOGICAL AND HISTOPATHOLOGICAL STUDY

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ABSTRACT: The chick was chosen as a model because it is more readily available than rats or mice and its organogenesis is analogous to that of humans. Rolapitant is a highly potent, powerful antagonist of the neurokinin-1 receptor, featuring a high degree of infiltration to the brain. The study aimed to assess the morphological and histopathological analysis of the brain (cerebral cortex) of growing chick embryos in response to the rolapitant's effect. Three hundred fertilised white leghorn chicken eggs were utilised, separated into five control groups (C1 to C5) and five experimental groups (E1 to E5), each with thirty eggs. On the fifth day of incubation, eggs from five experimental groups were exposed to different concentrations of rolapitant at 0.00039 mg, 0.0005 mg, 0.00075 mg, 0.001 mg, and 0.00125 mg respectively, whilst five control groups received the same concentration of normal saline. Chick brains were obtained and weighed. The cerebral cortex (brain) was sectioned and stained to examine the histopathological abnormalities. A significant growth retardation and decreased weight of the brain of experimental groups were noted. The number of chick embryos with abnormal "Histopathological findings such as" neuronophagia and perineural vacuolation in the cerebral cortex was also significant in experimental groups E4 and E5 (p-value < 0.05). Mild to moderate degenerative changes in the cerebral cortex of experimental groups E3, E4 and E5 and some haemorrhagic spots in experimental groups E4 and E5 were also noted. When taken in large doses, the rolapitant demonstrated its toxic effects on the brain of chick embryos.

INTRODUCTION: Experimental research on chick embryos always has an advantage over pregnancy registries in identifying graded abnormalities, dose-related effects, and elucidating malformation manifestations.

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However, experimental research on chick embryos always has an advantage over pregnancy registries in terms of identifying graded abnormalities, dose-related effects, and elucidating malformation manifestations.

The chick was chosen as a model because it is more readily available than rats or mice and because chick embryo organogenesis is analogous to that of humans [1]. The chick embryo test is reliable and provides quantitative endpoints for evaluation using teratology's fundamental concepts [2]. Numerous novel procedures, such as the chick

embryotoxicity screening test (CHEST) [3], the chick embryo blastoderm model, and others, have been created recently. Chick embryos meet all criteria for tests to be classified as bottom tier in teratological investigations [4].

The US-FDA, or Food and Drug Administration of US (2015), validated rolapitant, an unusual NK1RA blocker, for treating nausea and vomiting associated with chemotherapy [5, 6]. It is quickly absorbed by the body systems and serves as a highly potent, powerful antagonist of the neurokinin-1 receptor [7] (NK1RA) and featuring a high degree of infiltration to the brain and spinal column [8]. It has been approved for use in combination with other antiemetic agents [9]. It is also detectable in blood plasma after 30 minutes of its administration. It was previously revealed that its half-life remains greater than 180 hours, producing long-lasting effects on the central nervous system [10] and making it considerably more than that of an oral aprepitant (9–13 hours) [11]. The optimum concentration in the blood (Cmax) is attained following four hours. The mechanism of absorption of rolapitant from the fatty meal is not affected when given in large and increased doses. Still, it produces high exposure to various body systems like the brain, liver and kidney for a long time [12].

Against this background, this study aimed to assess the morphological analysis of the brain and histopathological examination of the cerebral cortex of growing chick embryos in response to the rolapitant's effect. The information produced by this experiment will help comprehend the harmful consequences that rolapitant causes in developing chick embryos, which may have implications for human health.

MATERIAL AND METHODS:

Experimental Animals: This was a prospective cross-sectional study conducted in the Department of Anatomy, Government Medical College, Barmer, in collaboration with the Department of Zoology, Government Dungar College, Bikaner, Rajasthan, from year 2018 to 2022. The Institutional Ethical Committee approved the study with reference number SU/2017/1226(19) and by the Animal Ethical Committee, registered under 1066/GO/Re/S/CPCSEA-New Delhi, dated 21/07/2017. The eggs of the fertilized white leghorn chicken (Gallus Domesticus) were obtained from G.S. Hatchery Farm Company at Jaipur Road, Ajmer, Rajasthan.

Inclusion and Exclusion Criteria: A total of three hundred out of three hundred and fifty fertilized white leghorn chicken (Gallus Domesticus) eggs were utilized. However, fifty eggs were excluded from the study due to extremely light-weighted, improperly calcified or shattered eggshells, hematoma in the air cell and deformed or absent air cell.

Experimental Design: Before incubation, the eggs were marked by lightening up their insides to inject the solution into the air cell. Prior to injection, the eggs were sterilized with 70% isolated ethanol. They were separated into five control groups, namely C1, C2, C3, C4 and C5 and five experimental groups, namely E1, E2, E3, E4 and E5, each with thirty eggs. The incubator was set at 38±1 °C with relative 85-90% humidity from day one of incubation. The drug solutions and sterile water were employed to treat all experimental and control groups respectively. Sterile water was utilized to make the drug's solution. The recommended dose of rolapitant (180 mg) was estimated per gram per body weight (3 grams per kilogram). The concentrated drug volumes were set according to the weight of the chick embryo (0.13 gram) on the fifth day of incubation [13]. These were 0.00039 mg for group E1, 0.0005 mg (1.2 times the recommended dose), 0.00075 mg (1.9 times the recommended dose), 0.001 mg (2.5 times the recommended dose) and 0.00125 mg (3.2 times the recommended dose) for groups E2, E3, E4 and E5 respectively. The eggs of all control groups were treated with the respective volumes of sterile water as represented in **Table 1.**

TABLE 1: DOSES PLAN FOR EXPERIMENTAL AND CONTROL GROUPS

Experimental groups			Control groups		
Name of Groups	**Doses (mg) (Rolapitant)**	**Sample Size**	**Name of Groups**	**Doses (ml) (Normal Saline)**	**Sample size**
E1	0.00039	30	C1	0.039	30

E2	0.0005	30	C2	0.05	30
E3	0.00075	30	C3	0.075	30
E4	0.001	30	C4	0.1	30
E5	0.00125	30	C5	0.125	30

Injection Techniques: The eggs were shaken with a wrist twist just before the injections. The movement allowed the germinal disc to float free in the eggs since it periodically stuck to the air cell and may be damaged with the needle's point. The drug and sterile water solutions were filled in the insulin injector and the needle was put into the air cell horizontally. The needle was cleansed with a sterilized gauze pad between two subsequent injections. As soon as the eggs were injected with solutions within the air cell, the hole at the eggshell was immediately sealed with candle wax to prevent the injected solution from leaking out [14, 15].

Dissection Technique and Histological Process: The viable embryos were sacrificed using the drawing technique on the twentieth day of incubation [16]. The chick embryos were dissected to obtain the whole brain. During the dissection, we meticulously removed the scalp, detached the meningeal coverings and cranial connections of the brain, dismantled the embryos by cutting through the level of the junction between the medulla oblongata and spinal cord corresponding to the level of first cervical vertebra. The brain's components like the cerebrum, cerebellum and medulla oblongata were examined morphologically for gross anatomical malformations. The weight of the brains of both groups (control & experimental) was measured through a digital weighing machine. After morphological analysis, each group's brain was preserved separately in different jars containing 10% formaldehyde solution. Under running water, the cerebrums were completely cleaned. All tissue samples were processed through an automated tissue processor (Thermo Scientific, Germany) for twenty-four hours, adhering to strict aseptic procedures to prevent cross-contamination and to perform critical histological procedures such as dehydration, cleaning, and embedding. Cerebral tissue blocks were created, sectioned by a rotating microtome at a thickness of 4 to 6 micrometers and placed on tissue slides. Haematoxylin and eosin were used for tissue staining using the standard method. Light and compound microscopes were used to view the stained sections for histopathology.

Statistical Analyses: SPSS (Statistics Package for Social Sciences) Version 21.0 was used for statistical analysis. Number (percentage), mean and standard deviation (SD) were used to represent the values. Continuous variables were compared using the paired/unpaired t-test, if appropriate. The chi-squared test was used to assess statistical significance as a probability value (p-value) < 0.05.

RESULTS:

Morphological Analyses: A significant growth retardation and decreased weight of the brain of experimental groups were noted in comparison to control groups of chick embryos. The brain's mean weight was lower in the experimental groups than in the control groups. It was statistically significant (p-value < 0.05) in groups E4 (p = 0.0213) and E5 (p = 0.0265), except in the weight of chick embryos of experimental groups E1, E2 and E3 as compared to control groups C1, C2 and C3 respectively as shown in **Table 2.**

TABLE 2: MEAN WEIGHT OF BRAIN OF CHICK EMBRYOS OF EXPERIMENTAL AND CONTROL GROUPS

Groups (N = 300)	Mean Weight of Brain of Chick Embryos ± SD (gm.)	T value	P value
C1	1.007 ± 0.04641	0.5228	0.6031[n]
E1	0.9997 ± 0.5678		
C2	1.009 ± 0.04571	1.025	0.3094[n]
E2	0.9957 ± 0.05691		
C3	0.9927 ± 0.05206	1.903	0.062[n]
E3	0.9617 ± 0.07245		
C4	1.019 ± 0.04927	2.368	0.0213*
E4	0.981± 0.07374		
C5	0.98967 ± 0.04881	2.277	0.0265*
E5	0.9557 ± 0.06564		

[n]- Not Significant, * - Significant value, SD - Standard Deviation, N (Sample Size) - 300 (30 in each group), gm. – Grams.

No obvious morphological or gross abnormalities were found except for reduced brain weight. In an attempt to analyse brain architecture for gross abnormalities, we found that the cerebrum, cerebellum, midbrain, and medulla oblongata were the three fundamental regions of the brain. The cerebrum, which optimally has two cerebral hemispheres with a triangle form, was discovered in the brain's frontal and rostral areas. The cerebrum's surface was smooth since there was an absence of sulci and gyri. A longitudinal fissure separated the cerebrum into right and left cerebral hemispheres and a transverse fissure separated two cerebral hemispheres and two cerebellar hemispheres from each other. The cerebellum was just behind the transverse fissure. The vermis was placed in the centre of the cerebellum. The medulla oblongata was a short and narrow section of the brain that linked the brain to the spinal cord. Two optic lobes and tectum were discovered in the front of the cerebrum. There was an optical chiasma at the lower part in the centre of both hemispheres. The above features were similar in both the control and experimental groups as illustrated in **Fig. 1.**

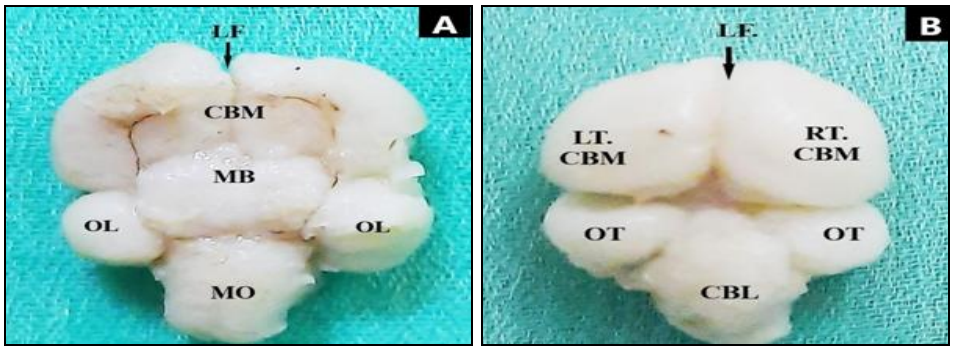

FIG. 1: BRAIN OF CHICK EMBRYO AT TWENTIETH DAY (A) VENTRAL VIEW, (B) DORSAL VIEW.LF- Longitudinal Fissure, LT. AND RT. CBM- Left and Right Cerebrum, MB- Mid Brain, MO- Medulla Oblongata, OL- Optic lobe, OT- Optic Tectum and CBL- Cerebellum.

Histopathological Analyses: In histological analyses of the cerebral cortex of both groups, the cerebrum's interior was composed of grey matter (cortex) and white matter (medulla). The cortex spanned the apex of the brain and a portion of the surface beneath the pia mater, while the medulla was discovered deep within the cortex. The cerebrum was made up of six cellular layers. From superficial to deep, there was a molecular layer, an external granular layer, a pyramidal layer, an internal granular layer, an internal pyramidal layer and a multiform layer. The nuclei of the huge and large-sized pyramidal cells were massive and pale, with Nissil's granules in the cytoplasm. A considerable number of satellite cells with small bodies and large nuclei were discovered. Satellite cells contain a variety of cytoplasmic processes.

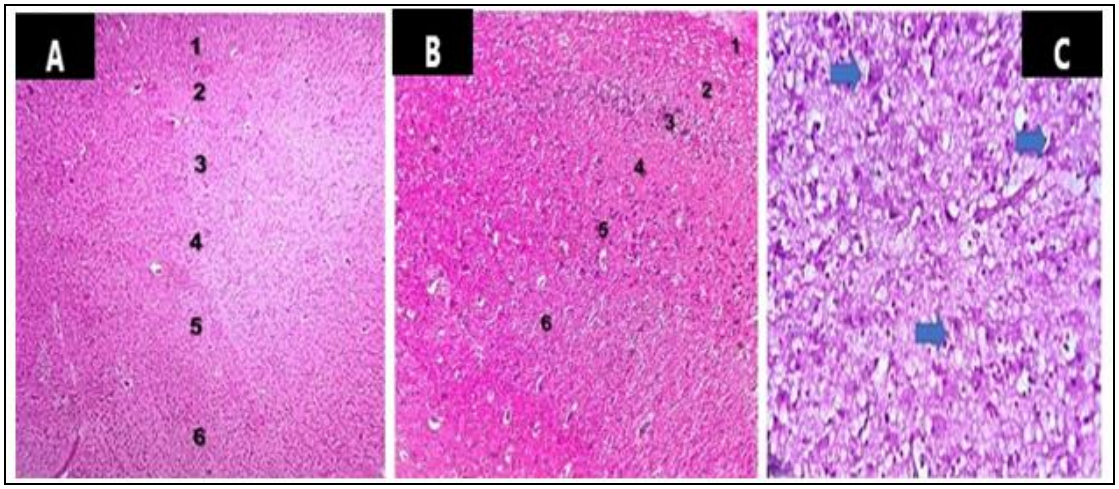

FIG. 2: T.S. OF CEREBRUM(A) 1x4X, (B) 1x10X and (C) 1x40X SHOWING PYRAMIDAL CELLS (BLUE ARROW). 1-Molecular layer, 2-External Granular layer, 3-External Pyramidal cells layer, 4-Internal Granular layer, 5-Internal pyramidal cells layer and 6-Multiform layer.

The medulla was a thick bundle of nerve fibres and glial cells were located deep within the cortex. The bodies of glial cells are tiny ovals with a little dark nucleus. These have a unipolar character. Compared to satellite cells, the number of glial cells was much higher than in the cerebral cortex. All the histological cellular arrangements in the cerebral cortex were organized normally in chick embryos of all experimental and control groups as shown in **Fig. 2.**

However, as shown in **Fig. 3 and 4**, mild to moderate degenerative alterations were identified in the cerebral cortex of groups E3, E4, and E5 but not in E1 and E2. The number of chick embryos with aberrant histopathological alterations was found to be substantial in groups E4 and E5 compared to groups C4 and C5 respectively. Some neurons inside the cerebral cortex's exterior granular layer in groups E3, E4, and E5 were discovered to be surrounded by microglial cells, indicating neuronophagia.

Mild degenerative changes with perineural vacuolation were observed in the internal pyramidal cells layer in the cerebral cortex in groups E4 and E5 only. Some small hemorrhagic patches were occasionally detected in the cortical grey matter of the brain of experimental groups E4 and E5. No necrosis, malignancy, atrophy, hypertrophy, dystrophy, or granulomas were observed in the cerebral cortex in any experimental group.

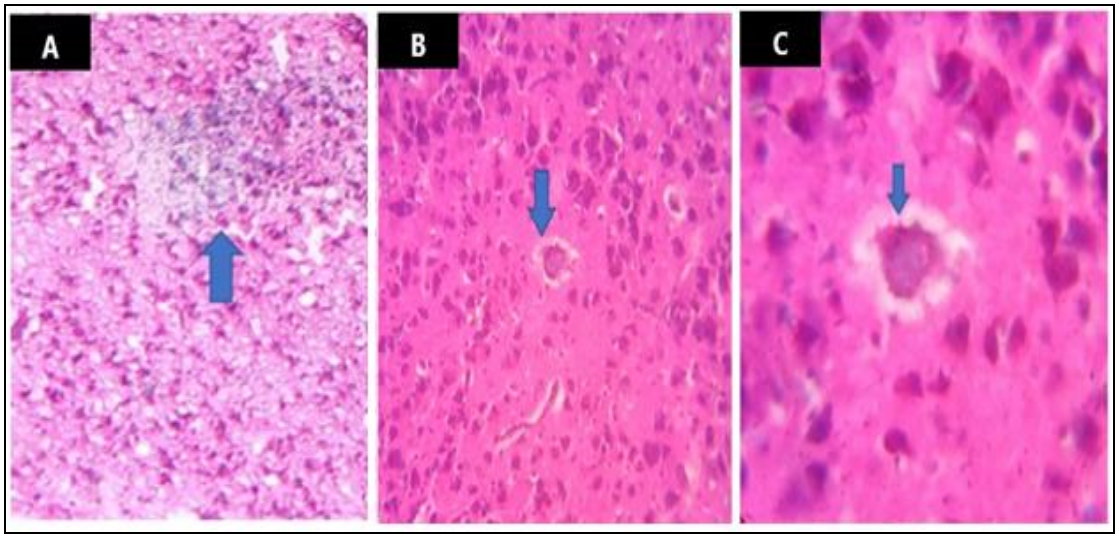

FIG. 3: T.S. OF CEREBRAL CORTEX(A) 1x10X, (B) 1x40X AND(C) 1x100XSHOWING NEURONOPHAGIA OF GRANULAR CELL IN EXTERNAL GRANULAR LAYER (BLUE ARROW)

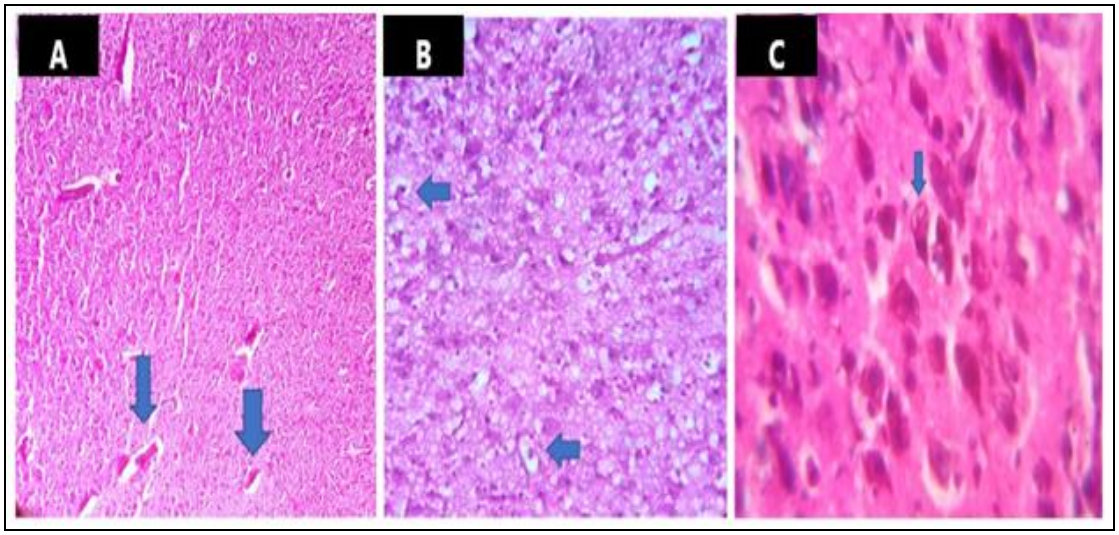

FIG. 4: T.S. OF CEREBRAL CORTEX (A) 1x10X, (B) 1x40X AND (C) 1x100X SHOWING PERINEURAL VACUOLATION IN PYRAMIDAL CELL (BLUE ARROW)

When the total number of chick embryos with or without histopathological alterations in the cortex (cerebrum) of experimental and control groups were compared, the experimental groups had greater histopathological changes than the control groups. Most of the histopathological changes found in the embryos belong to experimental group E5 followed by E4. Statistical analyses of the number of chick embryos with histopathological changes in each respective experimental and control groups are tabulated in **Table 3.** The level of significance (p-value) less than 0.05 was observed in groups E4 (p = 0.0444) and E5 (p = 0.0114).

TABLE 3: NUMBERS OF CHICK EMBRYOS WITH HISTOPATHOLOGICAL ABNORMALITIES IN CEREBRAL CORTEX WITH P-VALUES AS COMPARED EXPERIMENTAL VERSUS CONTROL GROUPS

Groups	Numbers of chick embryos with Histopathological changes in cerebral cortex	Numbers of chick embryos without histopathological changes in cerebral cortex	Total numbers of chick embryos	Chi square	Degree of freedom	P value
C1	0	30	30	N/A	N/A	N/A
E1	0	30	30			
C2	0	30	30	N/A	N/A	N/A
E2	0	30	30			
C3	1	29	30	1.964	1	0.1611[n]
E3	4	26	30			
C4	1	29	30	4.043	1	0.0444*
E4	6	24	30			
C5	1	29	30	6.405	1	0.0114*
E5	8	22	30			

[n] - Not Significant, * - Significant Values, N/A- Not Applicable.

DISCUSSION: The phrase "Teratogenic Mechanism" refers to the series of events that take place when a teratogen affects the tissues of developing chick embryos, resulting in morphological or functional abnormalities. A teratogen and its byproducts can be produced by the organism through several fundamental processes. Exposure to certain chemicals or pesticides during organogenesis which act as teratogens, produce deformities in the primordial organ after its formation, malformations in the primordium of the embryo [17] in advance during its formation, tissues from the mother that pass through the placenta and give rise to defects in the developing embryo [18].

The present study observed that the mean brain's weight was higher in the control group in all doses than the experimental group and was statistically significant, except in the initial dose. Reduction in the weight of the brain is relevant to the mal-development of neuronal cells. Neuronophagia and perineural vacuolation in the study are strong evidence of such neuronal destructions and neurotoxicity [19] which resulted in weight loss of the brain. Probably, some mild histopathological changes detected at initial doses of rolapitant might be reversible in the later stage of life but maybe fatal at higher doses of the drug. There was high mortality among the chick that received the highest doses [20]. Severe toxic effects of drugs or chemicals on tissue may lead cell membranes to be severely damaged and disrupted, which might result in cell vacuolation. The cytoplasmic vacuolation may also develop as a result of nuclear material breakdown [21]. It was observed that the intrinsic cell difference is the most important factor in determining the level of destruction of cells. Cytotoxic substances act differently on individual cell-mediated reactions which might cause neuronophagia. The cell's fate (living or death) might be determined by such factors [22].

The cells that are farthest from their nutritional supply suffer the most. There is plenty of evidence that acetylcholinesterase inhibition is the mechanism by which how these chemical compounds produce their acute toxic activities. Exposure to reduced drug concentration destroys the cell more slowly but might not cause deformity. The nutritional condition of a cell, determined by diffusion, also affects the cell's sensitivity to teratogens. The ectodermal cells exhibit severe anomalies which was evident in the study [23]. Rolapitant toxicity was also observed in a study in which the mean CR length of chick embryos was

lower in experimental groups than the control groups and higher percentages of death were also recorded in experimental groups of chick embryos. The lethality was higher in proportion to increased doses of rolapitant. Most morphological deformities were observed in experimental groups than in the control groups such as scanty feather, yolk sac retraction, short beak, and hematoma or subcutaneous haemorrhage. The intensity of skeletal anomalies (disorientation, poor ossification, fusion, bent or displacement, thinning, undeveloped, or absence of the bones) in axial and appendicular skeletons of chick embryos was detected when rolapitant was administered in large doses [24, 25].

The possible negative effects of rolapitant on embryos and foetuses during organ development were studied in pregnant mice. Mice administered rolapitant showed maternal toxic effects within the first week of life, such as reduced body weight increase or loss and concomitant decreased food consumption. Data on the toxicity of juvenile animals revealed the lower mean implantation sites, viable embryos and corpora lutea were noted at 1.3 and 2.6 times the recommended intravenous dosage for humans in comparison to the control group. The study's findings suggested that the larger rolapitant dosages produced unfavourable effects. When tablet varubi (Rolapitant 180mg) was administered in the first cycle of controlled randomized trials conducted by the US Food and Drug Administration, the incidence of side events was higher than when a placebo was provided. The general population of the United States was studied to determine the estimated prevalence of miscarriages and serious congenital defects in pregnancies with medical diagnoses [26]. Even when a substance is beneficial for development, its high dose is proportional to its toxicity. A study found that in-vivo administration of high doses of omega-3 fatty acid resulted in detrimental histological alterations in the liver of chick embryos. In contrast, its low doses were beneficial for normal development [27].

Meanwhile, Ruth A. Duffy *et al.* examined the effects of rolapitant in ferrets. After oral administration, they found that the rolapitant was a highly active antiemetic substance. NK1 agonist-induced gerbil foot tapping was reversed after administration of selective brain NK1RA. The study suggested that the rolapitant successively blocked NK1RA by allowing it to effectively penetrate the brain regions in charge of inducing nausea and vomiting. The effects were also reported to be long-lasting. This investigation showed evidence of the rolapitant's extremely effective action on the brain and neurological system [28]. In a Camilio Rojas, *et al.* investigation, when rolapitant's effectiveness in treating chemotherapy-induced nausea and vomiting (CINV) was evaluated, it was found that patients tolerated the drug well and the side effects such as headaches, lethargy, constipation, and weight loss were reported [29]. Schwartzberg LS et al. reported a significantly large number of patients receiving the recommended dose (180mg) of rolapitant had a full response in delaying CINV and incidence of adverse events like fatigue, constipation, and headache were recorded in both rolapitant and control active groups. The most common adverse event in the rolapitant versus control groups was neutropenia (32 [5%] v/s 23 [3%] patients) for cycle-1 [30].

CONCLUSION: The current study established morphological changes in the brain and histological abnormalities in the cerebral cortex of chick embryos due to the rolapitant's impacts. When taken in large doses, the rolapitant demonstrated its toxic effects on the brains of chick embryos. A significant loss in the brain's weight and histopathological abnormalities in the cerebral cortex were observed especially at the higher dose. As a result, rolapitant should be used only when a valid diagnosis has been confirmed and only at the recommended dose and duration.

Limitations of the Study: The availability of data on the toxic effects of rolapitant needs to be increased. The author has remanded a comprehensive research and comparative analysis with large sample size and in multi-directional ways so that findings in the current investigation could be reliably and substantially applied.

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