EFFECT OF LITHIUM ON THE DEVELOPING TEETH OF RABBITS

[1]SHAKILA NAZIR, BDS, MCPS
[2]MOHAMMAD TARIQ AFTAB, MBBS, PhD
[3]MASOOD AHMED, MBBS, M.Phil, PhD

ABSTRACT

The objective of the present study was to evaluate the changes in the dimensions of the teeth in new born babies of the mothers who receive lithium for a long time during pregnancy. The incidence of congenital defects due to Lithium was studied because, oral and dental structures are frequently the sites of adverse drug reactions. These include salivary glands, oral mucosa, periodontal tissues, teeth, alveolar bone, and other structures[1]. The study was conducted on the female rabbits, which were kept on this specific drug during pregnancy. The off springs of these treated female rabbits were used for research purpose. They were sacrificed and the teeth were examined for the congenital defects developed during Intrauterine life. This study was expected to provide suggestions for the use of this drug during pregnancy.

The results showed large variations by analysing statistically in the different teeth i.e. the size reduced in maxillary incisors, first and second molars only. The nature of the insult is unlikely to be determinable and the results are generally not in accordance with the predicted outcome. However, the drugs should be used by doctor's prescription only, especially during pregnancy, avoiding the teratogenic effect on the dentition of the new borns.

Key words: *Lithium, Bipolar, Female rabbits, Teratogenic, Dentition.*

INTRODUCTION

Lithium Carbonate is often referred to as "antimanic" drug, but in many parts of the world it is considered a "mood-stabilizing" agent because of its primary action of preventing mood swings in patients with bipolar affective (manic-depressive) disorder.[2]

Regarding Lithium, the incidence of congenital defects was studied because oral and dental structures are frequently the sites of adverse drug reactions. These include salivary glands, oral mucosa, periodontal tissues, teeth, alveolar bone, and other structures.[1] The "mood-stabilizing" agents are particularly used in European countries, so it can be hypothesized that the drug could possibly cause teratogenic effect in any of the developing body tissues. It is absorbed completely from gastrointestinal tract within 8 hours. Peak plasma level reaches in 2-4 hour, after oral dose. Li^+ is initially distributed in extra cellular fluid and then gradually accumulates in various tissues. Pharmacologic effects proved to have a wide variety of central nervous system, autonomic, and endocrine effects. (Approximately 95 % of single dose of Li^+ is eliminated in urine).[3]

Lithium is transferred to fetus through placenta and the nursing infant by breast milk. Lithium toxicity in newborns is manifested by lethargy, cyanosis, poor suck and Moro reflexes. However, more recent data suggest that Lithium carries a relatively low risk of teratogenic effects.[2] Serum concentration of Lithium ion is characterized by vomiting, diarrhea, tremor, seizures and cardiac arrhythmias & hypotension.[3]

[1] Associate Professor Oral Biology, Baqai Dental College / Baqai Medical University Karachi. Contact # 03008283345, e-mail address shakila.nazir@gmail.com

[2] Professor of Pharmacology, Karachi Medical & Dental College, Karachi

[3] Professor of Anatomy, Baqai Medical University, Karachi

Cells responsible for the development of dental tissues e.g. ameloblasts and odontoblasts, which form the enamel and dentine respectively are very sensitive to the teratogenic stimuli, febrile diseases and any drug used by the pregnant female.

Generally, gross anatomical malformations result from disturbed morphogenesis, from 18 to 55 days of intra-uterine life, which is the most susceptible period for adverse drug effects. A single dysmorphogenic agent interferes with the simultaneous organization of many systems and may produce a multiplicity of malformation at various sites.[4]

According to a report of (The Merck Manual. 2007), more than 90% of pregnant women take prescription or nonprescription (over-the-counter) drugs during pregnancy. About 2 to 3 % of all birth defects result from the use of drugs other than alcohol. Drugs taken by a pregnant woman reaches the fetus primarily by crossing the placenta, can act directly on the fetus, causing damage, (leading to birth defects), or death. Sometimes drugs are essential for the health of the pregnant woman and the fetus. In such cases, a woman should consult her doctor or other health care practitioner about the risks and benefits of the drugs.[5]

Every drug can produce untoward consequences, even when used according to standard or recommended methods of administration. The mouth and associated structures can also be affected by many drugs or chemicals.

Dentists and specialists of oral diseases should be aware of the adverse drug oral reactions for better diagnosis of oral diseases, administration of drugs, and patient compliance during drug therapy.[6] In developmental defects of the enamel (D.D.E.) of the deciduous dentition, the most affected teeth were the second molars (44.4 %), followed by the first molars (23.5 %). Defects were more in the upper arch (58.2 %). Assessing enamel hypoplasia separately, a prevalence of 15.1 % was observed, with the most affected teeth being the canines (33.6 %) and second molars (33.6 %).[7] The prevalence of enamel defects in the first permanent molars among children has been reported to be high particularly in the European countries.

Demarcated opacities affected 11 per cent upper right; 14 per cent upper left; 10 per cent lower left and 9 per cent lower right molars. Possible risk factors for enamel defects remains to be tested.[8] The risk of major congenital malformation (MCM) in the offspring did not have any significant association to family history.[9]

The major body structures are formed in about the first 12 weeks or so. Interference in this process causes a teratogenic effect. If a drug is given after this period, it will not produce a major anatomical defect.

Being a teratogen does not mean that a drug will always cause harm in the first trimester, for example, anticonvulsants are teratogenic in less than 10 % of fetuses exposed to the drug.[10] A fine balance should be maintained. No harm should be allowed to befall the baby because of the drug, but equally no harm must come to the mother.[11]

Lithium is present in traces throughout earth's crust. It is amazingly versatile and can run laptop computers, treat bipolar disorder, (though scientists don't know exactly how, it prevents mood swings) and even give ceramics a brighter glaze.[12]

METHODOLOGY

The study was conducted on the female rabbits. Normal healthy female rabbits of 1.5 to 2.0 kg were selected for the research purposes. Female rabbits were grouped into two different categories. One group was selected for giving the drug. The second one was considered control.

There were seven rabbits in each group (n=7). The drug used was Lithium Carbonate with the trade name (Neurolith® SR. 400 mg.).[13]

Dose of the drug was determined according to the body weight of the animal.[14] Neurolith® SR. 400 mg. (one tablet) was dissolved in 10 ml. of the distilled water to prepare the drug (0.176 mg/Kg). 3 ml. of this prepared drug was administered orally, twice a week to the female rabbits of the treatment group.

All the drug treated female rabbits were kept with equal number of their male partner, separately. The drugs were administered according to the predetermined dose, until the birth of their offsprings.

Record of the number of doses given to a particular animal was maintained, in a predesigned proforma . Another proforma was designed to keep the record of any toxicity developed by the administered drug. i.e. diarrhoea, ulceration, loss of physical activity, loss of interest in food, hair loss, odema, weight variation in grams.

The offsprings of these treated female rabbits were used for the research purposes. After reaching the age of three months, these offsprings of the rabbits were sacrificed to obtain their upper and lower jaws, taking immense care, not to damage the teeth. These jaws were checked regarding the eruption, status and alignment of the teeth. The upper and lower jaws were properly cleaned using the instruments i.e. (Tweezers, Artery forceps, Scissors, Scalpel, and Scalers). Measurements of the crowns of the teeth were taken with the help of a Vernier calliper, in millimetres.

All the dentition of upper and lower jaws was included in the study, except the maxillary and mandibular third molars because they were not fully erupted at the age of three months.

Crowns of the teeth were measured in three dimensions.

- Cervico-incisal/occlusal
- Mesio-distal
- Labio/Bucco-lingual

Data of the measurement were recorded in the pre designed proforma. Dental formula of the permanent human dentition is documented as;

I–2/2 : C–1/1 : Pm–2/2 : M–3/3 (× 2 = 32 total teeth).[15]

Unlike human dentitions, rabbits have a different number, type, and alignment of the teeth. Rabbits are herbivores. Their teeth are unrooted and grow continually.

The dental formula of the rabbit teeth is;

I–2/1: C–0/0 : Pm–3/2 : M–3/3 (× 2 = 28 total teeth).[16,17.]

Rabbit's teeth, just like the human dentition are also identified with their particular code numbers.[18] They are as follows;

101- Rightmaxillary central Incisor.

102- Right maxillary lateral Incisor.

106- Right maxillary first Premolar.

107- Right maxillary second Premolar.

108- Right maxillary third Premolar.

109- Right maxillary first Molar.

110-Right maxillary second Molar.

111- Right maxillary third Molar.

301- Left mandibular Incisor.

307-Left mandibular first Premolar.

308-Left mandibular second Premolar.

309-Left mandibular first Molar.

310-Left mandibular second Molar.

311-Left mandibular third Molar.

201- Left maxillary central Incisor.

202- Left maxillary lateral Incisor.

206- Left maxillary first Premolar.

207- Left maxillary second Premolar.

208- Left maxillary third Premolar.

209- Left maxillary first Molar.

210-Left maxillary second Molar.

211-Left maxillary third Molar.

401- Right mandibular Incisor.

407-Right mandibular first Premolar.

408-Right mandibular second Premolar.

409- Right mandibular first Molar.

410- Right mandibular second Molar.

411-Right mandibular third Molar.

Measurements were recorded and volumes of all the dentition were calculated individually, expressed in $(mm)^3$ for both the groups, i.e. 168 samples of the treated and 168 of the control group. Thus the total number of 336 samples were then analyzed.

The collected data were analyzed using SPSS version 13. Continuous response variables like, volumes of all the dentition except maxillary and mandibular third molars, were included. Numerical data were expressed as Mean and standard deviation (SD), between the study groups based on dichotomous (normal vs. treatment group) using student's t-test. The data summary was presented in the table-1 and graphs

Fig 1 & Fig 2. Statistical significance was presented in terms of P-values and a P-value ≥ 0.05 was considered statistically significant result.

RESULTS

The dentitions of the treated and control group were examined. By carefully measuring the dimensions, it was not possible to identify, except in few areas, any gross morphological effects of the drug on the dental development.

Maxillary central incisors, second and third premolars and maxillary first molars appeared comparatively smaller in treated groups as compared to the control group (Fig 1). While in the mandibular teeth, only the incisors were reduced in size and the rest of the teeth did not show any change in the volumes compared with the control group (Fig 2). It was pragmatic that dental asymmetries in size were more apparent in the posterior teeth as compared to the anterior ones. According to the statistical analysis, a large variation in the sample population of both the groups was observed, which were evident in the results, i.e. the P-values being ≤ 0.05.

These insignificant results were supported by the large standard deviations found in the study groups. (Table 1).

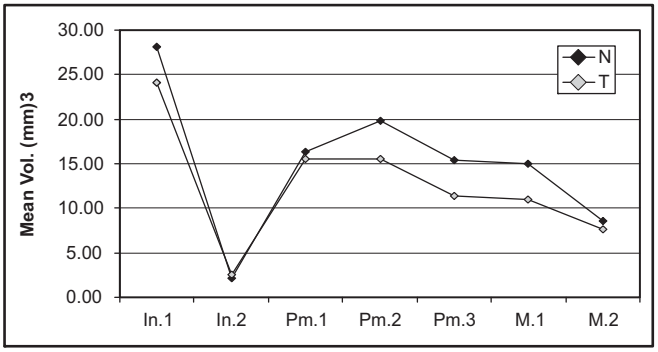

Fig 1: Showing the variation in the size of maxillary teeth of experimental & control group.

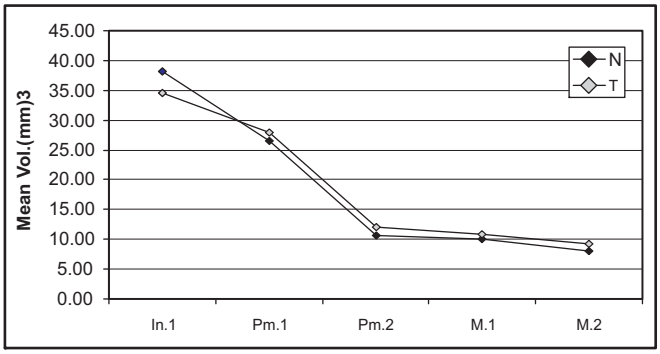

Fig 2: Showing the variation in the size of mandibular teeth of experimental & control group.

Thus the statistically significant effects for treatment groups were not observed.

TABLE 1: REPRESENTING THE MEAN VOLUME IN MILIMETERS AND STANDARD DEVIATIONS OF ALL THE EXPERIMENTAL AND CONTROL GROUPS

[T-Test. Group Statistics] [Vol-(mm)^3]

TEETH	N	MEAN ± SD		Sig.
		CONTROL GROUP	TREATED GROUP	
Max. incisor. 1	7	28.14 ± 11.908	24.00 ± 8.617	0.470
Max. incisor. 2	7	2.14 ± 0.378	2.50 ± 0.500	0.158
Max.Pm.1	7	16.21 ± 5.032	15.52 ± 8.821	0.859
Max.Pm.2	7	19.786 ± 6.6324	15.536 ± 6.3450	0.244
Max.Pm. 3	7	15.36 ± 5.360	11.36 ± 5.534	0.195
Max.Molar.1	7	15.000 ± 5.1235	10.929 ± 3.5611	0.110
Max.Molar. 2	7	8.571 ± 4.0123	7.571 ± 3.8126	0.641
Mand. Incisor.1	7	38.14 ± 7.755	34.52 ± 8.010	0.406
Mand. Pm.1	7	26.36 ± 9.159	27.71 ± 14.731	0.839
Mand. Pm.2	7	10.66 ± 4.194	12.00 ± 3.175	0.513
Mand.Molar.1	7	10.12 ± 2.599	10.66 ± 3.959	0.770
Mand.Molar. 2	7	7.77 ± 3.275	9.00 ± 4.010	0.541

DISCUSSION

The dento-facial abnormality may cause psychological disturbances in children. It is therefore, important to understand the etiological factors responsible for the developmental defects of dental tissues. Few drugs identified in the previous literature are definitely teratogenic in human dentition.

The study was conducted to investigate and gain a better understanding of the gross morphological consequences on the teeth and the treatment needs of this condition. The developmental defects of teeth, expected to be caused by our selected drug was thoroughly searched and studied in the published literature.

Seymour RA, reported that the mouth and associated structures had been the frequent targets for unwanted effects arising from systemic drug therapy.[1] Hypothyroidsm may develop in Lithium treated patients and could effect in childhood e.g. the teeth may fail to erupt, although tooth formation may not be impaired.[19] A single intrauterine exposure to a drug can affect the fetal structures undergoing rapid development at the time of exposure.[20]

The prevalence of enamel defects in primary dentition indicated that the enamel opacity mostly affected the upper and lower second primary molars. Enamel hypoplasia mostly affected the maxillary and mandibular primary incisors and the maxillary first primary molars.[21]

In this study the maxillary central incisors, second and third premolars and maxillary first molars appeared comparatively smaller in treated groups as compared to the control group. In the mandibular teeth only the incisors were reduced in size. These results, regarding the effect on the particular type of dentition are in accordance with the previous studies.[7,8,21.]

The effects of fetal exposure to nicotine on dental development, revealed that the overall length and width of the molar is laid out similarly between experimental and control groups.[22]

According to a study maxillary incisors were wider, while mandibular incisors were wider in wild-type mice.[23] These results were not in response to any drug treatment.

Studies of the effects of lithium are very limited. The variation in the dimensions of the teeth in response to the fetal exposure of this drug has not been reported. This study fills this gap in the knowledge of the effects of Lithium on dental tissues.

Lithium treatment also resulted in a decrease in bone mineral content occurring within the first 6 months of Lithium treatment.[24] The most affected teeth were the second molars (44.4 %), followed by the first molars (23.5 %).[7]

The prevalence of enamel defects in the first permanent molars among children has been reported to be high, particularly in the European countries. Possible risk factors for enamel defects remains to be tested.[8]

The "mood-stabilizing" agents are particularly used in European countries, so it was hypothesized that the drug could possibly cause teratogenic effect in any of the developing body tissues.

In this study the data were collected to assess the effects of Lithium on the dimensions of teeth. The variations in the dimensions of the teeth in response to the fetal exposure of this drug have not been published. As described above, such data have previously not been reported. There are very large variations in the sample population for each of the control and treatment groups. This is supported by the large standard deviations observed for most of the parameters of interest while conducting the statistical analysis.

A variety of factors, i.e. general health, malnutrition and febrile diseases might also be involved. The typical way of improving statistical significance is to increase the sample size.

CONCLUSION

It can be concluded that the incisors and molars are esthetically and functionally compromised teeth. The nature of the insult is unlikely to be determinable. These results are generally not in accordance with the predicted outcome. A variety of factors might also have implications for the development of teeth, i.e. general health, malnutrition and febrile diseases.

However, malformations caused by the drugs are important because their exposure may be prevented.

The drugs used for various problems in pregnancy, are well known in the medical field and should be used by doctor's prescription only. Self-medication during pregnancy could ultimately result in teratogenic effects on the dentition of the new born.

ACKNOWLEDGEMENT

I am grateful to Dr. Abdul Hakeem Arain, BDS, DPD (UK) Associate Professor of Community Dentistry, Baqai Dental College / Baqai Medical University, Karachi, for his guidance in the preparation of this manuscript.

REFERENCES

1 Seymour RA, and Rudralingham M. Oral and dental adverse drug reactions. Periodontology. 2008; 46: 9-26

2 Potter WZ, and Hollister LE. Antipsychotic Agents & Lithium. In: Basic and clinical Pharmacology (Katzung BG (ed). 2007; 10th edition; 457-474. The Mc Graw-Hill companies USA

3 Baldessarini RJ, and Tarazi FJ. Drugs and treatment of Psychiatric Disorders. In: The Pharmacological Basis of Therapeutics. (Hardman JG, Limbird LE, Gillman AG, (eds). 2001; 10th edition; 485-520. The McGraw-Hill Companies USA

4 Bhattacharya SK, Sen P, and Ray A. Geriatric, Paediatric and Perinatal Pharmacology. In: Pharmacology. (Das PK,(ed). 2003; 2nd edition; 501-23.

5 Foley MR. Drug Use During Pregnancy. Women's Health Issues. The Merck Manuals. 2007

6 Abdollahi M, Rahimi R, and Radfar M. Current opinion on drug-induced oral reactions: a comprehensive review. J Contemp Dent Pract. 2008; 9 (3):1-15

7 Lunardelli SE, and Peres MA. Prevalence and distribution of developmental enamel defects in the primary dentition of preschool children. Braz Oral Res. 2005; 19 (2): 144-49

8 Arrow P. Prevalence of developmental enamel defects of the first permanent molars among school children in Western Australia. Aust Dent J. 2008; 53 (3): 250-59.

9 Thomas SV, Nair RR, Jose M, and Sarma PS. Risk of major congenital malformations in the offsprings of women with epilepsy is not related to family history. Epilepsy Research. 2009; 83: 52-57

10 Rubin P. Drug treatment during pregnancy. BMJ. 1998; 317: 1503-06

11 Rubin PC. Prescribing in Pregnancy. Medical Practice. British Medical Journal. 1986; 293

12 Nal.Geog.Com / Magazine Sep. 2009; New York

13 Neurolith® SR. (Reg. No. 015620). One tablet contains Lithium Carbonate B.P. 400 mg. Manufactured by Adamjee Pharmaceuticals (Pvt.) Ltd. Karachi Pakistan

14 Casarett LJ. Toxicology Evaluation. In: Toxicology. The Basic Science of Poisons. Casarett LJ, and Doull J. (eds). 1975; 1st edition; 11-25. Macmillan Publishing Co., Inc. USA

15 Fuller JL. Introduction and Nomenclature. In: Concise Dental Anatomy and Tooth Morphology. Fuller JL, and Denehy GE, (eds). 2006; 3rd edition; 2-20

16 Rouge M. Dental Anatomy of rabbits. 2002

17 Weisbroth SH, and Ehrman L. Malocclusion in rabbit: A model for the study of the development, Pathology and Inheritance of Malocclusion. Journal of Heredity.1967; 58: 245-46

18 Johnston N. Tooth numbering in other species (rabbit). The Modified Tradian System. Based on image supplied by David Crossley. Veterinary Dentistry. Basics. 2002; eMedia Unit RVC

19 Neville BW, Damm DD, Allen CM, and Bouquot JE. Oral Manifestations of Systemic Diseases. In: Oral and Maxillofacial Pathology.(Neville BW, Damm DD, Allen CM, and Bouquot JE. (eds). 2007; 2nd edition; 705-740. Saunders, Philadelphia, Pennsylvania

20 Koren G. Special aspects of Perinatal & Pediatric Pharmacology. In: Basic and clinical Pharmacology. (Katzung BG, (ed) 2007; 10th edition; 971-982. The McGraw-Hill companies USA

21 Zheng S, Deng H, and Bao Y. The study on the clinical manifestation of developmental enamel defects in primary dentition. Hua Xi Kou Qiang Yi Xue Za Zhi. 2003; 21 (3): 200-04

22 Chowdhury IG, and Bromage TG. Effects of Fetal Exposure to Nicotine on Dental Development of the Laboratory Rat. The Anatomical Record. 2000; 258: 397-405.

23 Risnes S, Peterkova R, and Lesot H. Distribution and structure of dental enamel in incisors of Tabby mice. Arch Oral Biol. 2005; 50(2): 181-84

24 Plenge P, and Rafaelsen OJ. Lithium effects on calcium, magnesium and phosphate in man: effects on balance, bone mineral content, faecal and urinary excretion. Acta Psychiatr Scand.1982; 66 (5): 361-73