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Potential risks of maternal administration of Mucophylline on the pups of albino rats during lactation

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ABSTRACT

The present study was undertaken to evaluate the potential risks of the mucolytic and broncholytic drug, Theophylline derivatives (Mucophylline) maternally administered on the pups. The nursing rats orally administered from 1st postpartum day (PPD) to 21th PPD with two different doses 30.83 mg/kg (low dose) and 66.61 mg/kg (Human equivalent dose (HED)). On the 21th PPD, the postnatal developmental signs, skeletal malformation and the histopathology of neonatal liver, kidney and brain were examined. Our results showed that Mucophylline induced a significant reduction in the neonatal weight and length, delayed, weak and incomplete ossification, wavy ribs and the neonatal liver revealed histopathological changes, pyknotic hepatocytes, cytoplasmic vacuolization, dilated sinusoid and necrotic area. Kidney revealed alternation changes, enlargement of the glomerulus, renal tubules degeneration and lymphatic infiltration. Brain (cerebral cortex and cerebellum) showed neurodegenerative changes, vacuolization of neuropil, congested and dilated blood vessel and dark stain neurons. Our results showed that the activities of non-enzymatic (GSH) and enzymatic (GST, CAT) antioxidants were insignificantly decrease in both neonatal brain and liver tissues of rats administered with 30.83 mg/kg and 61.66 mg/kg of Mucophylline and insignificant increase in MDA levels in both neonatal brain and liver tissues. However, significant reduction ($P \leq 0.05$) in the content of GR was recorded in neonatal brain tissue of rats administered with 30.83 mg/kg and 61.66 mg/kg of Mucophylline during lactation period in comparison with control. These support and proof the potential risks of the maternal administration of Mucophylline on pups.

1. Introduction

Mucophylline (Bromhexine hydrochloride 4 mg/5 ml and Acephylline piperazine 100 mg/5 ml) acts on the bronchial tree clearing it from the viscid sputum and relaxing its constricted muscles providing an efficient symptromatic treatment in most respiratory ailments. Acephylline piperazine is Piperazine 7-theophyllineacetat. Theophylline is related to methulexanthine group that used as medication for asthma (Antiasthmastics). Acephylline piperazine. The other active ingredient in Mucophylline is a theophylline derivative with a direct bronchodilator action. It has the advantages over theophylline in being far less toxic and by producing minimal gastric irritation.

The main classes of antiasthmatic drugs are: (a) bronchodilators, such as β adrenergic agonists and Theophyllines, and (b) prophylactic or anti-inflammatory agents such as corticosteroids (oral or inhaled) and sodium cromoglycate.

In clinical use, Mucophylline used in Cough specially when associated with bronchospasm in such conditions as: asthma, emphysema, acute & chronic bronchitis, chronic inflammatory lung diseases & inhalation of irritants, etc.

Lactation is the result of powerful coordination between two mechanisms, endocrine and neuroendocrine. This cooperation stimulates secretion of milk in the mother and supplies the offspring with several nutritive materials Whitworth (1988).

In fact, without any question, the best source of nutrition for infants is the human milk. The advantages of breastfeeding have been documented in the neonatal period and extend throughout childhood and into adulthood Lawrence (2000). Breast milk contains powerful immune factors that help infants fight against infections Oddy (2001) and it contains growth factors that appear to influence brain development. Breastfeeding builds a powerful bond between a mother and her child, and this bond enhances

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Table 1
Showing effect of mucophylline on change in pup weight, length, tail length from 1st–21th day of lactation. Values are expressed as Mean ± SEM. The statistical differences were analyzed by ANOVA followed by independent samples T test. a = P ≤ 0.05 compared with control and b = P ≤ 0.05 compared with other treated group.

Group	Pup weight (P.WT)(g)	Pup length (P.L)(cm)	Tail length (T.L)(cm)
Control A	17.36 ± 0.48	4.29 ± 0.06	4.16 ± 0.04
GB(0.3 ml)	14.09 ± 0.51[a,b]	4.15 ± 0.07[b]	4.13 ± 0.43[b]
GC (0.6 ml)	11.91 ± 0.33[a,b]	3.64 ± 0.06[a,b]	3.84 ± 0.04[a,b]

Fig. 1. A Photograph of pups at 21th day of lactation showing growth retardation. 1 = control, 2 = 30.83 mg/kg and 3 = 61.66 mg/kg.

health and well-being across the generations. There are also clear health benefits to the mother Labbok (2001).

There are limited well-designed studies about asthma drugs during breastfeeding. No human data were available for effects of theophylline on or via lactation Health Council of the Netherlands (2013).

Due to insufficient information about the Mucophylline especially and asthma drug generally in a mammalian species, the aim of the present study was to determine the potential risks of Mucophylline in the neonates when nursing rats orally administered during lactation period (1st-21th PPD).

2. Materials and methods

2.1. Experimental design

The present experimental study is carried out on the albino *Wistar* rat (*Rattus norvegicus*). The *Wistar rat* is an outbred albino rat. The *Wistar* rat is currently one of the most popular rats used for laboratory research. It is characterized by its wide head, long ears, and having a tail length that is always less than its body length. The standard guidelines of The Institutional Animal Care and Use Committee (IACUC) were implemented in handling the animals. The rat is preferred in teratological studies because it has short duration of pregnancy (about 21 days), high fertility rate and large number of litters, genetic stability and a very low rate (about 0.1%) of spontaneous malformation (Banerjee and Durloo, 1973; Tuchmann-Duplessis, 1966, 1977; Wilson, 1973). The animals were selected from a pure strain so that the genetic influence was kept at a constant and uniform level. Females of 11–13 weeks old were selected for the present study and vaginal smears were prepared every morning and examined under the light microscope (according to the method of Snell (1956) for 5 days to select the female with regular estrus. Two females were selected and caged together with one male over night under controlled environmental condition of temperature (25 ± 2 °C), humidity (60 ± 20%) and light (12 light-12 dark cycles). The first day of gestation was determined by the presence of sperms in the vaginal smear McClain and Becker (1975). Following observation of a sperm plug, pregnant rats were housed individually in plastic cages. The day of parturition was designated as day 1 of lactation.

Mucophylline was purchased from Misr Co. For Pharm. Ind. S.A. E.—Egypt.

Drug orally administrated daily from 1st to 21th PPD. The animals were divided into three groups with 10 animals in each.

Group A: Control rats received distilled water orally.

Group B: Rats orally administered with 30.83 mg/kg of body weight of mucophylline.

Group C: Rats orally administered with 61.66 mg/kg of body weight of mucophylline.

2.2. Developmental observations

At the 21th day of lactation the neonates of the treated groups (B&C) were sacrificed. Neonatal body weight, body length, tail length and external malformation were recorded.

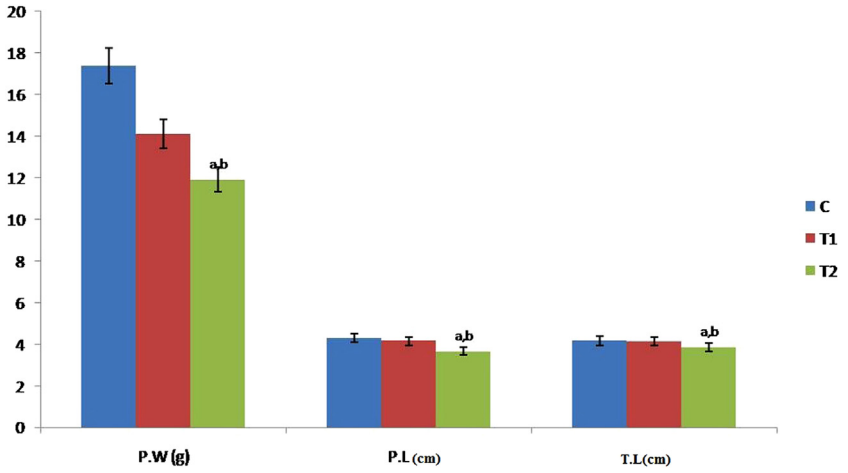

Fig. 2. Histogram showing effect of mucophylline on change in pup weight (P.W) (g), puplength (P.L)(cm) and tail length (T.L)(cm) 1st–21th day of lactation. Values are expressed as Mean. The statistical differences were analyzed by ANOVA followed by independent samples T test. a = P ≤ 0.05 compared with control and b = P ≤ 0.05 compared with other treated group.