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TOXIC EFFECTS OF ERGOTAMINE ON THE KIDNEY TISSUES AND BLOOD OF ALBINO RATS

N. M. Ghanem[1]*, Aly Khan[2], F. M. Bilqees[3] and Y. M. Rizki[4]

[1]Dept. of Microbiology, University of Karachi, Karachi-75270.
[2]Crop Disease Research Institute, P. A. R. C; University of Karachi, Karachi-75270.
[3]Dept. of Parasitology, Faculty of Health Science, Baqai Medical University, Karachi.
[4]B-24/12. Gulberg, F. B Area-Karachi.

ABSTRACT

Ergotamine tends to produce a pattern of subjective effects that varies as a function of dose. Male albino rats were employed in this study as animal model and three different drug dosages of ergotamine were orally administrated. The higher dose of ergotamine caused severe damage to the kidney tissue. When treated with a dose of 0.03 mg/0.5 ml of ergotamine slight changes in the interstitium and glomeruli and inflammation with increased in the cellularity of the glomeruli was obvious. At an acute dose (1.25 mg/3 ml), destruction of the glomerular structure and Bowman's capsule was seen. Slight changes on haematological parameter were observed, no bacteremia was detected and faecal samples were also normal. In *vitro* studies, ergotamine slowly induces well-sustained vasoconstriction that can not be eliminated with drug washout.

Key words: Ergotamine, Albino rats, Kidney, histopathology, haematology, faecal examination.

INTRODUCTION

The term "ergot" is generally used to describe species of the genus *Claviceps*, the sclerotia formed by the fungi specifically *Claviceps purpurea*, and the wide range of unique alkaloids produced by the fungi following infestation of grain. The ergot alkaloids are derivatives of the tetra cyclic compound 6-methylergoline (Berde and Sturmer, 1978). There simply is no such single entity as ergot from the pharmacologic, toxicological, biological, or clinical point (Berde, 1978).

The "classic" natural ergot alkaloid is ergotamine, first purified from ergot in 1918 by Stoll, it continues to be used as a treatment of vascular headache (Rall, 1990), producing constriction of both veins and arteries (Berde and Sturmer, 1978; Miller-Schweiniter and Weidmann, 1978), and extensively metabolized in the liver. Reduction in liver function may lead to accumulation and may sequester in various tissue, which probably accounts for its long-lasting effects. Contraindications to the use of ergotamine tartrate include renal or hepatic failure; coronary, cerebral, and peripheral vascular disease; and sepsis. Based upon several reports, (Andersson, 1975; 1988), detoxification is frequently carried out through rapid discontinuance rather than slow, gradual reduction. The *in vitro* studies, ergotamine slowly induces well-sustained vasoconstriction that can not be eliminated with drug washout (Mikkelsen *et al.*, 1981; Ostergaard *et al.*, 1981). The aim of the present study was the histopathological, haematological and faecal examination of chronic and acute doses of ergotamine on the tissues and blood of albino rat.

MATERIALS AND METHODS

Drug and Dosage:

Ergotamine tartrate (Novartis Pharma) at three different dosages were selected to be administered to the animals. The dosages were calculated so as to match the dosages given to the human beings according to their body weights. The dosages were given to the animals via oral route through gastric feeding needle.

Histopathological Evaluation:

The rats were anesthetized with chloroform. 3 cc Blood was drawn via heart puncture using sterile syringe from these anesthetized animals. This blood was used for haematological and microbiological tests. . An incision was made in the abdomen and incised up to neck. Gross section of the tissues kidney was observed, and then the tissues were taken and cut in longitudinal and transverse pieces and proceded as described below:

1. Tissue Processing
2. Block Making
2. Sectioning/Mounting
4. Staining
5. Microscopic Observation
6. Photography

*part of Ph. D thesis of the first Author.

Haematological Evaluation,.

Following haematological parameters were evaluated:

1. Haemoglobulin…….. (Hb)
2. Total Red Blood Cells Count…….(RBC)
3. Erythrocyte Sedimentation Rate …(ESR)
4. P.V.C…….. (Hct)
5. Total White Blood Cells Count…..(WBC)
6. Differential Leucocytes Count ……(DLC)
7. Platelet Count

Microbiological Evaluation:

The study protocol comprised of:

Blood Culture of un-treated and treated animals.

Fecal culture of un-treated and treated animals.

RESULTS AND DISCUSSION

The test animals were monitored continuously throughout the test period and during this period none of them showed any marked abnormal behavior or signs of illness whatsoever and all were normal. However, the animals that were given acute doses of ergotamine showed marked changes. Histopathology of the Kidney tissues reveals that, interstitium and glomeruli were affected. Higher doses caused greater damage to the glomeruli, which resulted in abscess formation. At a dose of ergotamine (0.03 mg/0.5 ml), there were slight changes in the interstitium and glomeruli. At this dose, the parietal layer of the glomeruli inside the Bowman's capsule was intact, glomerular spaces were reduced and the mesangium was obliterated. Inflammation with increase in the cellularity of the glomeruli was obvious (Fig **1**). At an acute dose of ergotamine (1.25 mg/3 ml), the glomerular structure destroyed and lesions consisting of polymorphonuclear leukocytes, lymphocytes, plasma cells and macrophages replaced Bowman's capsule. Interstitium was also indistinguishable (Fig.**2**).

Table 1. Mean values of haematological findings of rats treated with different doses of ergotamine.

Animal Groups	Hb g/dL	Total RBC Count 10^6/mm^3	ESR mm/ Hr	PCV Vol%	Platelet Count 10^3/mm^3	Total WBC Count 10^3/mm^3	Differential Leucocytes Count					
							N %	L %	M %	E %	B %	Abnormal Immature Cells
	11.5-16.1	6.76-9.75	3-7	37.6-50.6	150-460	6.6-12.6	17-38	47-91	1-4	3-8	0-3	
***E1**	14.9	4.9	06	45	220	10.2	48	49	01	02	00	**NIL**
***E2**	16.4	5.2	05	49	196	9.0	23	75	01	01	00	**NIL**
***E3**	13.9	4.6	04	42	195	9.7	45	52	02	01	00	**NIL**
***EA**	10.9	5.9	04	37	160	14.2	20	75	01	02	00	**NIL**
***C**	15.2	7.2	04	48	250	11	33	65	01	01	00	**NIL**

Hb Haemoglobin
RBC Red Blood Cells
PCV Packed Cell Volume
WBC White Blood Cells
N Neutrophile
EA The animal group has given acute dose of 1.25 mg\3ml of ergotamine.
L Lymphocytes
M Monocyte
B Basophile
E Eosinophile
E1 The animal group given 0.03 mg/0.5 ml of ergotamine.
E2 The animal group given 0.06 mg/1.5 ml of ergotamine.
E3 The animal group given 0.09 mg/3 ml of ergotamine.
C Control
* There were three replicates for each observation

Haematological analysis of blood tests for control and treated animals are presented in (Table 1). Microbiological analysis of blood test for control and treated animals revealed no bacteria growth (Table 2). Likewise, feces of the treated animals did not show presence of any pathogenic bacteria and the microbial contents were the same as for the control (untreated), (Table 3). Long-term large dose of ergotamine can induce marked peripheral vasoconstriction and pain (Glazer *et al*., 1966). Ergotamine causes temporary narrowing of blood vessels

throughout the body. Ergotamine induced valvular disease were documented pathologically. It also reduces distensibility of the common ceratoid artery (Barenbrock *et al*., 1996). Human coronary artery is contracted by the action of ergotamine (Brink *et al*., 1998). Naturally, when blood supply is impaired and toxicity is present the functioning of the organs is badly affected which is the end result of the tissue damage that can lead to fatal consequences.

Ergotamine is extensively metabolized in the liver resulting in impaired normal hepatic metabolism and hepatic function (Perrin, 1985); it is supported by the present observation on the affected kidney of rat at various doses. Higher the dose, the more severe tissue damages.

The manifestation described by various authors for such kidney problems, poor circulation, high blood pressure due to ergotism are actually the end result of tissue damage.

In our studies, great tissue damage has been observed due to ergotamine. Toxic effects in the glomeruli were obvious with complete obliteration of glomerular spaces and shrinkage and atrophy of the glomerulus mass creating large spaces in the glomerular capsule. In some glomerular, spaces reduced, visceral epithelium destroyed, and the parietal epithelium at the outer margin was intact. The convoluted tubules were dilated. In severe condition, sclerosis and disintegration of glomerulus and partial epithelium occurred with obliteration of glomerular spaces. All the above mentioned conditions show the deteriorating effects of ergotamine.

Table 2. Mean values of microbiological findings of blood samples of rats treated with different doses of ergotamine.

Media	**ANIMAL GROUPS**					**ORGANISM ISOLATED**
	ERGOTAMINE					
	***E1**	***E2**	***E3**	***EA**	***C**	
NA	-	-	-		-	**NIL**
BA	-	-	-		-	**NIL**

E1 The animal group has given dose of 0.3 mg/0.5 ml of ergotamine; **E2** The animal group has given dose of 0.6 mg/1.5 ml of ergotamine.
E3 The animal group had given dose of 0.9 mg/3 ml of ergotamine; **EA** The animal group has given acute dose of 1.25 mg/3 ml of ergotamine; **C** Control animal were given distilled water; **NA** Nutrient Agar; **BA** Blood Agar
- Negative, No growth; * There were three replicates for each observation.

Table 3. Mean values of microbiological findings of fecal samples of rats treated with different doses of ergotamine.

Media	**ANIMAL GROUPS**					**MAJOR ORGANISM ISOLATED**
	ERGOTAMINE					
	***E1**	***E2**	***E3**	***EA**	***C**	
NA	+	+	+	+	+	***E. coli, Lactobacilli***
BA	+	+	+	+	+	*S. aureus*
Mac	+	+	+	+	+	*E. coli*
EMB	+	+	+	+	+	*E. coli*
BHI	+	+	+	+	+	*B. subtilis*
SDA	-	-	-	-	-	NIL
SSA	-	-	-	-	-	NIL
BSA	-	-	-	-	-	NIL
SMA	+	+	+	+	+	*Lactobacilli*

E1 The animal group has given dose of 0.3 mg/0.5 ml of ergotamine; **E2** The animal group has given dose of 0.6 mg/1.5 ml of ergotamine.
E3 The animal group has given dose of 0.9 mg/3 ml of ergotamine; **EA** The animal group has given acute dose of 1.25 mg/3 ml of ergotamine; **C** Control animal given distilled water; **NA** Nutrient Agar; **BA** Blood Agar
Mac MacConkey's Agar; **EMB** Eosin Methylene Blue Agar; **BHI** Brain Heart Infusion Agar; **SDA** Sabarose Dextrose Agar
SSA Salmonella Shigella Agar; **BSA** Bismuth Sulphite Agar; **SMA** Skimmed Milk Agar;
- Negative, No growth; + Positive, Present; * There were three replicates for each observation

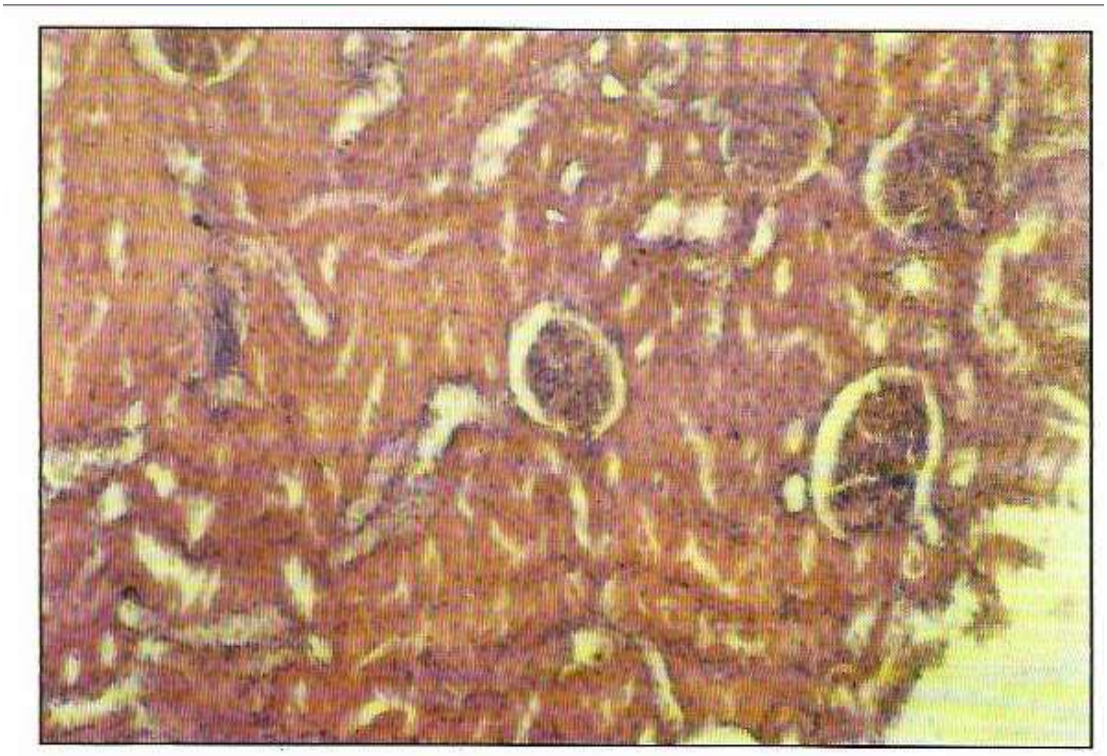

Fig.1. Longitudinal section of the kidney tissue of orally treated albino rat with 0.03 mg/0.5 ml ergotamine showing intact parietal epithelium of glomerular capsule especially on juxtaglomerular (J) granules and on the afferent glomerular arteriole. (X50). (H&E stain).

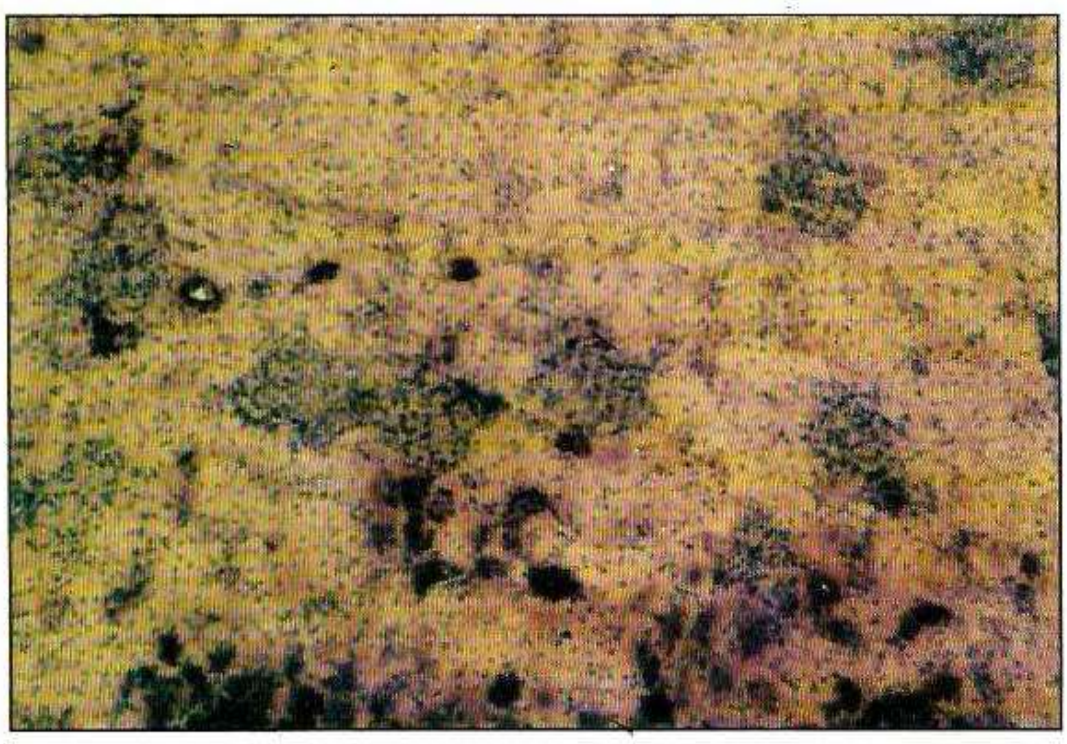

Fig.2. Transverse section of the kidney tissue of orally treated albino rat with 1.25 mg/3 ml ergotamine, showing that the structure of glomerular (G) capsules is destroyed, undifferentiated and appears as a mass of cells. (X50). (H&E stain).

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