

Table of Content

Table of Content.....	I
Dedication.....	III
Acknowledgements.....	IV
Abstract (Arabic).....	V
Abstract.....	VII
List of Figures.....	IX
List of Tables.....	X
Introduction.....	1
Objectives.....	3
1. Literature Review.....	4
1.1 Chemistery of Amphetamines.....	4
1.2 Pharmacological effects.....	4
1.3 Tolerance and dependance.....	9
1.4 Pharmacokinetics aspects.....	11
1.5 Clinical use and unwanted effects.....	12
2. Materials and Methods.....	15
2.1 Animals and Housing.....	15
2.2 Collecting of blood samples.....	15
2.3 Chemicals and drugs.....	15
2.4 Haematological methods.....	16
2.5 Serobiochemical methods.....	16
2.6 Experimental design.....	12
2.7 Statistical Analysis.....	12

3. Results	24
3.1 Signs of toxicity.....	24
3.2 Organ: body weight ratio.....	24
3.3 Biochemical studies.....	24
3.4 Haematological studies.....	25
3.5 Testicular effect of amphetamine.....	30
4. Discussion.....	39
5. Conclusion and Recommendations.....	44
4. References.....	45

DEDICATION

*This Thesis is dedicated to my late father, my
mother, wife and children with love.*

ACKNOWLEDGEMENTS

I am very grateful to the Minister of Interior and Police Commissioner of Sudan for allowing me to do this work in Sudan University for Science and Technology.

I am indebted to my supervisors professors Osman Saad Mohamed and Abdel Gadir Musa Homeida for their close supervision and constructive criticism throughout the years it took to complete this thesis.

Special thanks to Gadoura and Gailani for the encouragement and confidence they bestowed upon me and for being great friends.

My gratitude is also for my friends Dr. Mustafa Osman Ismail, Professor Abdallatif Ashmaeg, and Professor Awad Mahagoub for their moral support.

Thanks are due to Mohamed Al-fatah and Sulaiman Yassin for technical assistance.

I wish to give my family the biggest acknowledgment. My wife, Tahani, always supported me. I had to leave her alone with kids. Thanks to her and to my daughters Salma, Sulafa, and sons Awab and Osama for their love and support they gave me.

الملخص

تعتبر الامفيتامينات من مجموعة أمينات الجهاز الثمبتاوي الغير مباشرة. فهو منه قوي للجهاز العصبي المركزي ويتسبب في التعود والإدمان. إن سمية الامفتمين في الإنسان والحيوان لم يثبر غورها كاملاً. لذا فقد تم في هذه التجارب إجراء بعض الدراسات الدوائية والسمية للامفتمين في الجرذان. إن إعطاء الامفتمين بالفم ولمدة شهر بجرعة مقدارها 8 ملجم للكيلو جرام للجرذان نتج عنه أعراض قلق وهياج. لقد تسبب المركب في انخفاض تركيز انزيمات جلوتاميل (AST) والباروفيت اوكسالو استيت في الكبد (ALS). وكان هنالك تغيرات طفيفة في المعايير الدموية والبيوكيميائية للدم بالمقارنة مع الشاهد. لقد تسبب إعطاء الامفتمين للجرذان ولمدة 60 يوماً في انخفاض في تركيز الأنزيمات الدالة على نشاط الخصى مثل السوربتول ديهيدروجينيز والإسيد فوسفيتيز. لكن زاد نشاط أنزيمات الاكتك ديهيدروجينين والجاما جلوتاميل تراتسبيتاديز والبيتا جلوكويورنديز. لقد تم ملاحظة انخفاض أعداد الحيوانات المنوية وبطء حركتها وزادات الأعداد غير الصحية فيها. لقد تسبب إعطاء الامفتمين للجرذان الحوامل في الفترة بين 6 إلى 15 يوم من الحمل إلى تغير في سلوك المواليد الحركي إذ صارت أكثر حساسية. كما أدى إعطاء الامفتمين إلى زيادة في تركيز النورادرينالين والسيروتونين وانخفاض في تركيز انزيم المونو امين أوكسديز في المخ مقارنة مع الشاهد. تبين هذه النتائج أن

الامفتمين يعتبر سام للجرذان بجرعة مقدارها 8 ملجم للكيلو جرام ويؤدي إلى تسمم خفيف للكبد. ويؤدي أيضاً إلى ضعف في الخصية حيث تم نقصان في أعداد الحيوانات المنوية وحركتها وحالتها الصحية. وأدى أيضاً إلى زيادة في تركيز مجموعة الأمينات في المخ حيث نتج عن ذلك الإثارة والتهيج في الكبار بل ونتج عن ذلك تغير في سلوك الصغار.

ABSTRACT

Amphetamines are indirect sympathomimetic amines with potent stimulant action on central nervous system. These compounds produce tolerance and dependence. Full exploitation of amphetamine toxicity in man and animal is still lacking. Therefore, this study was carried out to investigate some of the pharmacotoxicity of amphetamine in rats. Administration of 8mg/kg of amphetamine sulphate orally to rats for a month produced signs of restlessness and hyperexcitability and caused decreased activity of liver glutamic oxaloacetate and pyruvic oxaloacetate transaminases compared to controls. Marginal effects were observed in haematological and serobiochemical parameters. Amphetamine given for 60 days to rats significantly caused decreased activity of marker testicular enzyme such as sorbitol dehydrogenase and acid phosphatase but the activity of testicular lactic dehydrogenase, gamma-glutamyl trans peptidase and beta glucuronidase were significantly increased. A decrease in epididymal sperm count and motility and increased in percentage spermatozoa abnormality was also noticed. Further, daily intraperitoneal administration of d-amphetamine sulphate at a dose of 8 mg/kg, body weight to rats during 6-15 days of gestation has resulted in significant effect on sensory and motor reflexes of their pups. These pups have shown increased righting and rotating reflexes and cliff avoidance activity. Significant

increase in brain noradrenaline, 5-hydroxytryptamine and decrease in monoamine oxidase activity was observed in these pups and their mothers compared to their control counterparts. These results show that the amphetamine was toxic to rats at the dose of 8mg/kg producing mild, hepatotoxicity, testicular atrophy indicated in decreased sperm count and sperm abnormalities, increased brain catecholamine that was associated with hyperexcitability and causing disturbed behavioural activity in the neonates.

List of Figures

ITEM	DESCRIPTION	PAGE No.
Fig (1)	Effect of perinatal amphetamine administration on the mean (seconds) righting reflex of rat pups	35
Fig (2)	Effect of perinatal amphetamine administration on the mean (seconds) cliff avoidance activity of rat pups.	36
Fig (3)	Effect of perinatatal amphetamine administration on the mean (seconds) rotating reflex of rat pups.	37

List of tables

ITEM	DESCRIPTION	PAGE No.
Table (1)	Relative organ: body weight rations (g) of male and female rats following treatment with amphetamine	26
Table (2)	Liver biochemical changes in male and female rats following treatment with amphetamine (8mg/g) for 30 days.	27
Table (3)	Serum biochemical changes in male and female rats following treatment with amphetamine (8mg/kg)	28
Table (4)	hecmatological observations in male and female rats following treatment with amphetamine (8mg/kg)	29
Table (5)	Effect of treatment with amphetamine on the marker testicular enzyme in rats treated for 60 days.	31
Table (6)	Effect of treatment with amphetamine on sperm motility and total epididymal sperm count in rats treated for 60 days.	32
Table (7)	Effect of treatment with amphetamine on different types of morphological abnormalities in spermatozoa in rats treated for 60 days.	33
Table (8)	Mean brain concentrations of noradrenaline, 5-hydroxytryptamine, 5-hydroxyindole acetic acid and 5-hydroxyquinolone in amphetamine treated mothers and their pups.	38