Original Article

Effects of amlodipine besylate on testicular histology, sperm cells count, morphology and motility in adult male Wistar rats

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Abstract

Aims/Introduction: Amlodipine besylate (5 or 10 mg daily) is a long-acting calcium-channel blocker used in men for the treatment of hypertension and angina. This study tested the hypothesis that administration of amlodipine besylate impairs fertility in adult male Wistar rats. **Materials and Methods:** Twenty-nine normotensive adult male Wistar rats (weighing 150-250 g) were employed in the study. Rats of Control Group I received physiological saline while rats of experimental Groups II-VI received 5, 10, 15, 20 and 40 mg/kg BW of amlodipine besylate respectively for 56 to 65 days. **Results:** Histological analyses showed dose-dependent anomalies of the testes such as scanty seminiferous tubules, wider tubular lumen and significantly reduced sperm cells in rats that received 20 and 40 mg/kg BW of amlodipine besylate. Dose-dependent anomalies of sperm morphology such as sperms with arrow or pin head and double tail as well as significantly reduced sperm cells count and motility ($P \leq 0.05$) were observed in rats of the experimental groups. **Conclusion:** This study observed impaired fertility in adult male rats treated with 15 mg/kg BW and higher doses of amlodipine besylate.

Key words: Amlodipine besylate, adult male Wistar rats, sperm cells

INTRODUCTION

High blood pressure and hypertrophy of cardiac muscles occur in hypertension when the resistance against which the left ventricle must pump becomes elevated over a long period. Such a resistance could be due to arteriosclerosis, thickening of intima media of arteries, hypertrophy of smooth muscles, reduced compliance of arterial walls and vascular stenosis (Tripathi, 2003; Nicholas *et al.*, 2006; Guyton and Hall, 2011). Similarly, angina could result from focal coronary artery spasm and/or coronary vasoconstriction (Tripathi, 2003; Nicholas *et al.*, 2006; Guyton and Hall, 2011). These cardiovascular anomalies in hypertension and angina are directly related to excitation-contraction coupling and contractions of vascular smooth muscles (Tripathi, 2003; Nicholas *et al.*, 2006; Guyton and Hall, 2011).

The increased intracellular entry of calcium ion results in formation of calcium–calmodulin complex, phosphorylation of myosin light chain, activation of

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myosin light chain kinase (MLCK) and contractions of vascular smooth muscles (Tripathi, 2003; Nicholas *et al.*, 2006; Aguilar *et* al., 2010; Guyton and Hall, 2011). Relaxation of vascular smooth muscles, however, occurs following the release of calcium ions and activation of myosin phosphatase which splits the phosphate from the myosin light chain (Tripathi, 2003; Nicholas *et al.*, 2006; Aguilar *et al.*, 2010; Guyton and Hall, 2011).

Amlodipine besylate is a calcium ion antagonist which inhibits trans-membrane influx of calcium ion into cardiac and vascular smooth muscles. It inhibits calcium intracellular entry through voltage-gated channels and activation of the actin–myosin complex leading to muscular relaxation (Tripathi, 2003; Nicholas *et al.*, 2006; Guyton and Hall, 2011). It relieves ischemic burden through dilation of peripheral arterioles and reduced total peripheral resistance resulting in declined stress of the left ventricular wall, reduced myocardial energy consumption, reduced oxygen requirements, direct relaxant effects on vascular smooth muscles and reduced blood pressure (Tripathi, 2003; Nicholas *et al.*, 2006; Guyton and Hall, 2011). In angina, amlodipine besylate relieves coronary artery spasm and vasoconstriction through dilation of peripheral arterioles and reduced total peripheral resistance resulting in increased blood flow to the heart muscle and increased myocardial oxygen delivery (Tripathi, 2003; Nicholas *et al.*, 2006; Guyton and Hall, 2011).

Calcium ions have a ubiquitous presence in somatic and germ cells (Latif *et al.*, 2008; Latif *et al.*, 2009a). Calcium ions are, therefore, directly involved in the regulation of the following key processes that regulate or determine male fertility: blood testicular barrier (Cheng *et al.*, 2002; Lui *et al.*, 2003), testosterone synthesis by Leydig cells (Latif *et al.*, 2012), hormonal regulation of Sertoli cells function (Gorczyńska-Fjälling, 2004), secretion of products by Sertoli cells (Latif *et al.*, 2008; Latif *et al.*, 2009a), capacitation of sperm cells (Almeida *et al.*, 2000), sperm motility (Guyton and Hall, 2011), spermatogenesis (Gorczyńska-Fjälling, 2004; Latif *et al.*, 2009a; Latif *et al.*, 2009b), penetration of oocytes by sperm cells, prevention of polyspermy and gene expression (Latif *et al.*, 2008; Latif *et al.*, 2009b); Guyton and Hall, 2011). However, increased intrasperm concentration of calcium ions was determined to correlate negatively with sperm viability (Kumar *et al.*, 2008).

Hypertension is a global health concern which affects all races, sexes and different age groups; though it is more prevalent in the adults. It affects 20% of people living in the world, a third of which is unaware of their condition. Hypertension is usually treated with calcium-channel blockers (Tripathi, 2003; Nicholas *et al.*, 2006; Guyton and Hall, 2011). There have been contradictory observations concerning the effects of calcium-channel blockers on testosterone concentrations (Latif *et al.*, 2008), while concern over the possible adverse effects of calcium-channel blockers on male fertility remains (Latif *et al.*, 2012). For further considerations of the possible effects of amlodipine besylate as a calcium-channel blocker on male fertility, this study tested the hypothesis that the administrations of 5 mg and higher doses of amlodipine besylate impair fertility in adult male Wistar rats.

MATERIALS AND METHODS

Ethical Approval

Ethical approval was sought and received from the ethical committee of the Department of Anatomy of the University of Ilorin, Ilorin, Kwara State, Nigeria, and experimental procedures were carried out in accordance with the 'Principles of laboratory animal care' of NIH publication number 85-23 and revised in 1985.

Animal Care and Feeding

Twenty-nine adult male Wistar rats weighing 150-250 g obtained from the colony breed of the animal house of the Department of Anatomy, Obafemi Awolowo University, Ile-Ife, Osun State and the Department of Veterinary Physiology, University of Ibadan, Oyo State, Nigeria, were used in the study. The rats aged ten (10) to twelve (12) weeks. They were housed in individual cages in a well-ventilated and fumigated room with ambient temperature and good lighting. All rats were fed with standard pellet diet (Sesco Feeds Ikenne, Ogun State, Nigeria) and received water *ad libitum*. The rats were acclimatised for 7 days before the start of experimental procedures. The weight of each rat was taken daily. Furthermore, each rat was examined daily for possible behavioural and gross morphological changes.

Administrations of Drugs

Rats of Control Group I (comprising of four rats) received daily oral administration of 4 ml of normal saline. In an adult 70 kg man, the treatment regimen of amlodipine besylate for the treatment of hypertension or angina is 5 or 10 mg daily. 5 mg Amlodipine besylate (NORVASC) was dissolved in 333 ml of normal saline effectively without any residue. Therefore, rats of Experimental Groups II-VI (each comprising of five rats) received daily corresponding oral administration of 5, 10, 15, 20 and 40 mg/kg bodyweight of amlodipine besylate respectively for 56 to 65 days. Oral administration of drugs was done with the use of a 5 ml syringe and a long flexible feeding tube.

The average weight of rats employed in the study was determined as 200 g. In an adult 70 kg man, the treatment regimen of amlodipine besylate is 5 or 10 mg daily. Therefore, to determine the amounts of amlodipine besylate to be administered to each rat, the corresponding

dosage (X mg) for a 200 g rat was calculated as follows: X mg = (200 g × 5 mg)/70,000 g = 0.014 mg of amlodipine besylate.

If 5 mg amlodipine besylate was dissolved in 333 ml of normal saline solution, the volume (X ml) of the amlodipine besylate/normal saline solution that would contain 0.014 mg of amlodipine besylate was determined as follows:

X ml = (0.014 mg × 333 ml)/5 mg = 4.662 ml/5 = 0.93 ml (approximately 1 ml of amlodipine besylate/normal saline solution.

Therefore, rats of Experimental Groups II-VI (each comprising of five rats) received 1, 2, 3, 4 and 8 ml of amlodipine besylate/normal saline solution as corresponding doses of 5, 10, 15, 20 and 40 mg/kg bodyweight of amlodipine besylate, respectively. Volumes of drugs solutions that were more than 2 ml were given two or four times daily to rats of Groups IV, V and VI for eased ingestion. This was in consideration of the maximum 3.4 ml volume capacity of the stomach of adult rats (McConnell *et al.*, 2008) and the more likelihood of individuals who abuse amlodipine besylate to take doses of the drug two or more times daily. Rats of the Control Group I correspondingly received 4 ml of normal saline solution.

Excision and Fixation of the Testes and Epididymis

At the end of experimental procedure, each rat was sacrificed by cervical dislocation and the scrotal sacs opened. The whole testis was removed, taken out and fixed in 10% formal saline of at least five times its volume. The caudal epididymis was equally removed and put in normal saline of at least five times its volume. The testes and epididymis were put in separate containers and labelled appropriately.

Histological Analyses of the Testes

After complete fixation of the testes, blocks were embedded in paraffin wax and 5 μm thick sections were cut. The tissue sections were stained with haematoxylin and eosin and mounted in Canada balsam. Microscopic examination of the sections was then carried out under the Olympus light microscope to determine possible cytoarchitectural changes of the testes following administrations of drugs.

Analyses of Morphology, Quantification and Motility of Sperm Cells

The caudal epididymis was removed and cut in many sections to open up the tube and placed in 0.5 ml of physiological saline (0.85% NaCl). After about 5 minutes, the pipette was used to draw solutions of the semen on slides for observation under the light microscope. Motility of spermatozoa was observed with the magnification of ×400.

For morphological analyses, one drop of eosin staining solution was added to the semen and the sperm cells were viewed under the binocular Olympus light microscope to determine the presence or absence of normal shapes/structures of the head (hook shape) and tail (single), and abnormal shapes/structures of the head (curved, round, arrow, pin or double) and tail (double, coiled or detached) (Shetty and Narayana, 2007). Under the light microscope, living sperm cells appeared darkish or colourless while dead sperm cells appeared pinkish (after picking up the colour of the eosin stain).

For sperm cells count analyses, semen was drawn from the caudal epididymis into a culture dish to which variable amounts of prepared 200 ml of Monica's fluid (50 g $NaHCO_3$ and 10 ml formalin up to 1 litre of distilled water) was added and viewed on a haemocytometer. Sperm cells that fell into the centre box and two edges of the haemocytometer were counted and the result was multiplied by 32,000 and the dilution factor. The readings were then recorded in millions of sperm cells per millilitre.

RESULTS

Histological Analyses of the Testes in Rats of Control and Experimental Groups

Analyses of Sperm Cells Morphology, Quantification and Motility

Rats of Control Group I showed normal testicular histology [Figure 1a], sperm morphology and adequate quantity of sperm cells [Table 1 and Figure 2a]. Rats of experimental groups II - IV which received 5, 10 and 15mg/kg bodyweight of Amlodipine Besylate had normal testicular histology [Figure 1a-d] while those of Groups V and VI treated with 20 and 40mg/kg bodyweight of Amlodipine Besylate had abnormal testicular histology with dose-dependent reduced quantities of seminiferous tubules and sperm cells [Figure 1e-f].

Rats of Groups II - VI which received 5 mg and higher doses of Amlodipine Besylate were observed to have reduced quantity of sperm cells with normal morphology such as hook head, long and short tails [Figure 2b-f] and significantly increased percentage ($P \leq 0.05$) of sperm cells with abnormal morphology (arrow or pin head and double tail) in a dose-dependent manner [Table 1]. Statistical analyses of sperms cells count and motility showed dose-dependent significant decreases ($P \leq 0.05$) in rats treated with 5, 10, 15 and 20mg/kg bodyweight of Amlodipine Besylate and no sperm cells in rats treated with 40mg/bodyweight of Amlodipine Besylate [Tables 2 and 3]. Summarized graphical chart of percentages of sperm cells with normal morphology and motility (million cells per ml) in rats of the Control

and Experimental Groups (Groups I–VI) are as shown in [Figures 3 and 4].

DISCUSSION

Results have shown that the cytoarchitectural components of the testis were normal with adequate quantity of sperm cells in the lumina of the seminiferous tubules of rats of Control Group I and Experimental Groups II–IV [Figure 1a-d]. In contrast, cytoarchitectural components of the testis were disrupted with progressive or marked reduction in the quantities of seminiferous tubules in rats that received 20 or 40 mg/kg bodyweight of amlodipine besylate [Figure 1e-f]. Some seminiferous tubules were destroyed while some seminiferous tubules have wider tubular lumina with few or no sperm cells in their lumina in rats that received 40 mg/kg bodyweight of amlodipine besylate [Figure 1e-f].

Similarly, there was dose-dependent significantly reduced quantities and percentages of sperm cells with normal morphology [Figures 2d-f and 3],

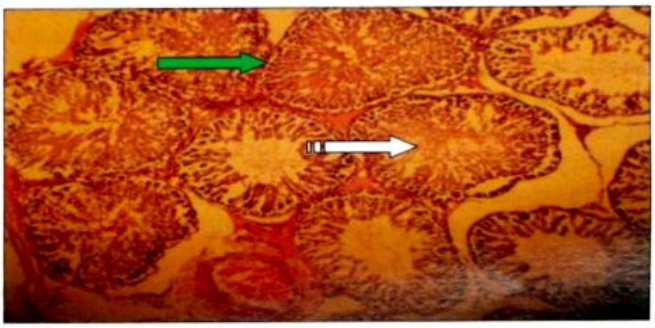

Figure 1a: Photomicrograph sample of the testis of rats of control Group I which received 4 ml of normal saline (haematoxylin and eosin ×100). Solid green arrow = seminiferous tubule; Broken arrow = lumen of seminiferous tubule. The cytoarchitectural components of the testis appear normal. There is adequate quantity of sperm cells in the lumina of the seminiferous tubules

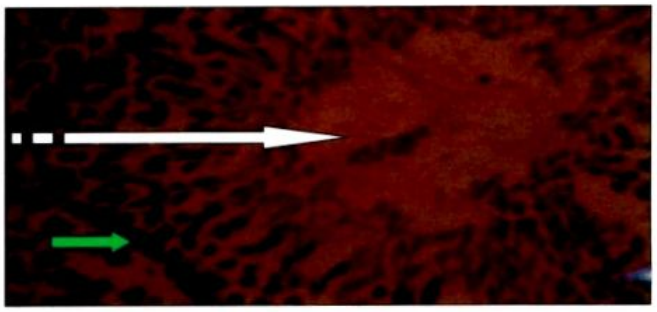

Figure 1c: Photomicrograph sample of the testis of rats of experimental Group III which received 10 mg/kg bodyweight of amlodipine besylate (haematoxylin and eosin ×200). Solid green arrow = seminiferous tubule. Broken arrow = lumen of seminiferous tubule. The cytoarchitectural components of the testis appear normal. There is adequate quantity of sperm cells in the lumina of the seminiferous tubules

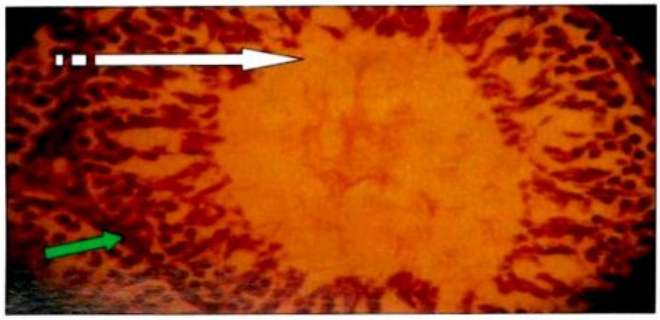

Figure 1b: Photomicrograph sample of the testis of rats of experimental Group II which received 5 mg/kg bodyweight of amlodipine besylate (haematoxylin and eosin ×200). Solid green arrow = seminiferous tubule. Broken arrow = lumen of seminiferous tubule. The cytoarchitectural components of the testis appear normal. There is adequate quantity of sperm cells in the lumina of the seminiferous tubules

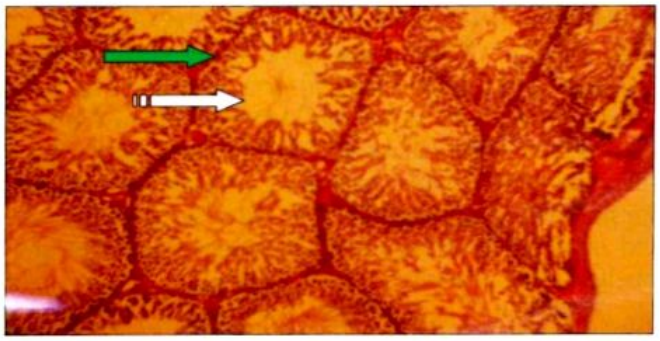

Figure 1d: Photomicrograph sample of the testis of rats of experimental Group IV which received 15 mg/kg bodyweight of amlodipine besylate (haematoxylin and eosin ×100). Solid green arrow = seminiferous tubule. Broken arrow = lumen of seminiferous tubule. The cytoarchitectural components of the testis appear normal. There is adequate quantity of sperm cells in the lumina of the seminiferous tubules

Table 1: Percentages of normal and abnormal sperm cells with their morphological descriptions in rats of control and experimental groups

Doses of drugs	Hook head (%)	Long tail (%)	Short tail (%)	Percentage of sperm cells with normal morphology	Morphological anomalies	
					Arrow/Pin head (%)	Double tail (%)
Normal saline	90	65	35	90	10	0
5 mg/kg bw amlodipine	90	50	50	90	10	0
10 mg/kg bw amlodipine	85	50	50	85	15	0
15 mg/kg bw amlodipine	85	44	45	84	5	11
20 mg/kg bw amlodipine	71	22	50	43	29	28
40 mg/kg bw amlodipine	No visible sperm cells	No visible sperm cells	No visible sperm cells	0	No visible sperm cells	No visible sperm cells

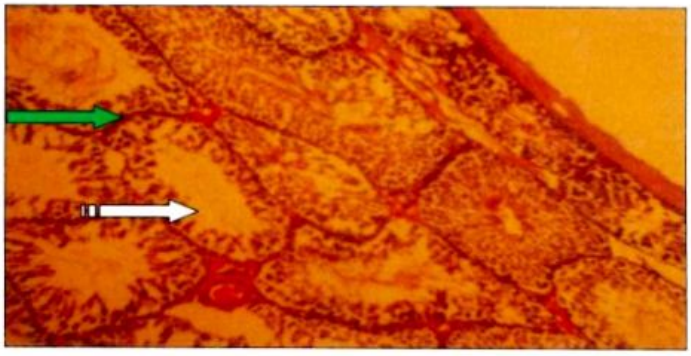

Figure 1e: Photomicrograph sample of the testis of rats of experimental Group V which received 20 mg/kg bodyweight of amlodipine besylate (haematoxylin and eosin ×100). Solid green arrow = seminiferous tubule. Broken arrow = lumen of seminiferous tubule. The cytoarchitectural components of the testis appear normal. Reduced quantity of sperm cells in some lumina of seminiferous tubules was observed

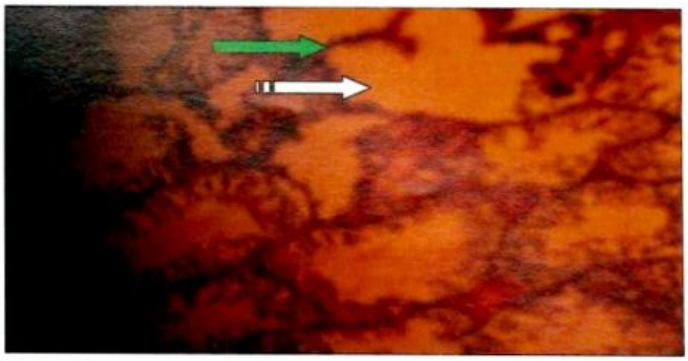

Figure 1f: Photomicrograph sample of the testis of rats of experimental Group VI which received 40 mg/kg bodyweight of amlodipine besylate (haematoxylin and eosin ×400). Solid green arrow = seminiferous tubule. Broken arrow = lumen of seminiferous tubule. The cytoarchitectural components of the testis appear disrupted. There is marked reduction in the quantities of seminiferous tubules and sperm cells are absent in some lumina

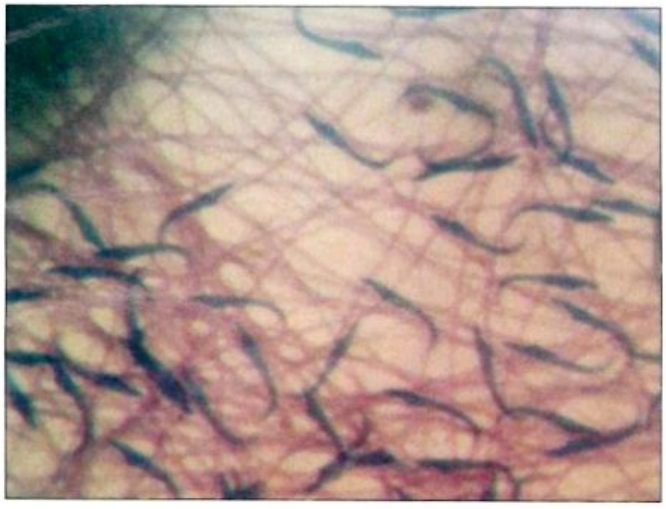

Figure 2a: Normal morphology and quantity of sperm cells of rats of control Group I which received 4 ml of normal saline solution (×400)

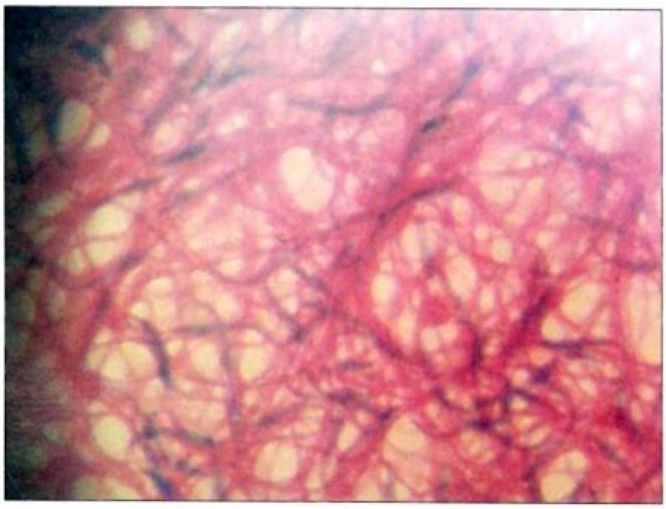

Figure 2b: Normal morphology and quantity of sperm cells of rats of experimental Group II which received 5 mg/kg bodyweight of amlodipine besylate (×400)

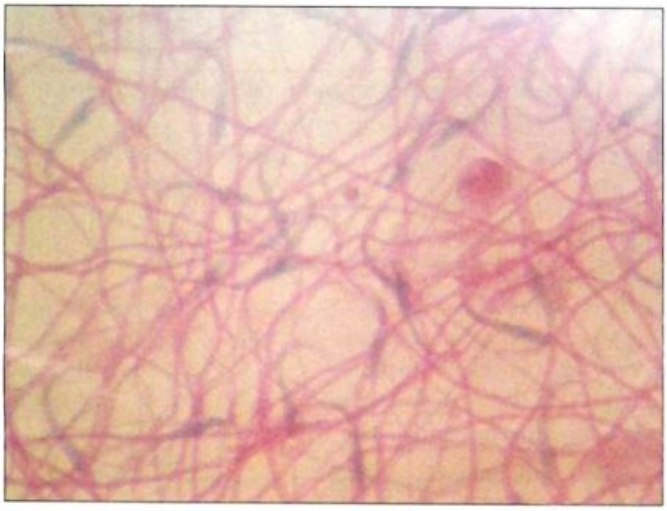

Figure 2c: Normal morphology and quantity of sperm cells of rats of experimental Group III which received 10 mg/kg bodyweight of amlodipine besylate (×400)

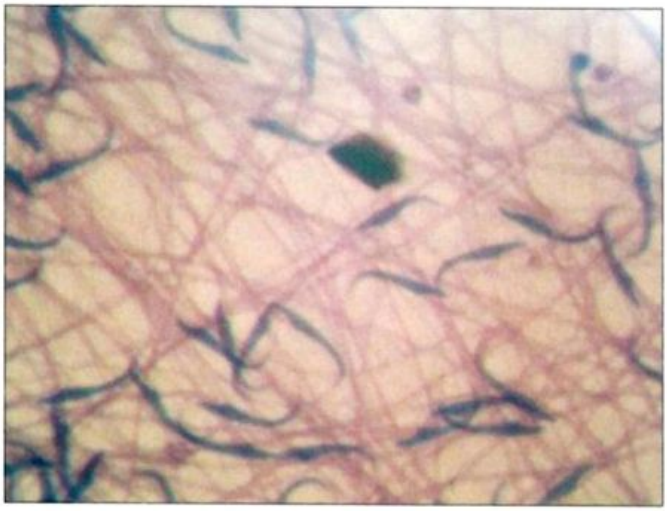

Figure 2d: Reduced percentage and quantity of sperm cells with normal morphology in rats of experimental Group IV which received 15 mg/kg bodyweight of amlodipine besylate (×400)

sperm cells count [Figure 4] and motility [Table 3] in rats that received 15, 20 or 40 mg/kg bodyweight of amlodipine besylate. In contrast, adequate quantities and percentages of sperm cells with normal morphology [Figures 2a-c and 3], sperm cells count [Figure 4] and motility [Table 3] were observed

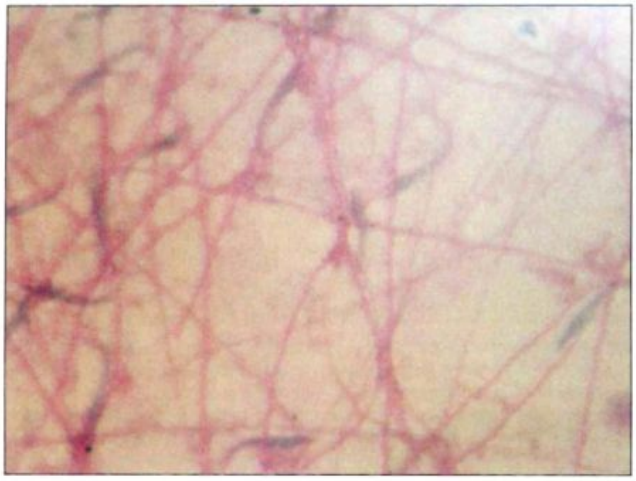

Figure 2e: Marked significantly reduced percentage and quantity of sperm cells with normal morphology in rats of experimental Group V which received 20 mg/kg bodyweight of amlodipine besylate. (×400)

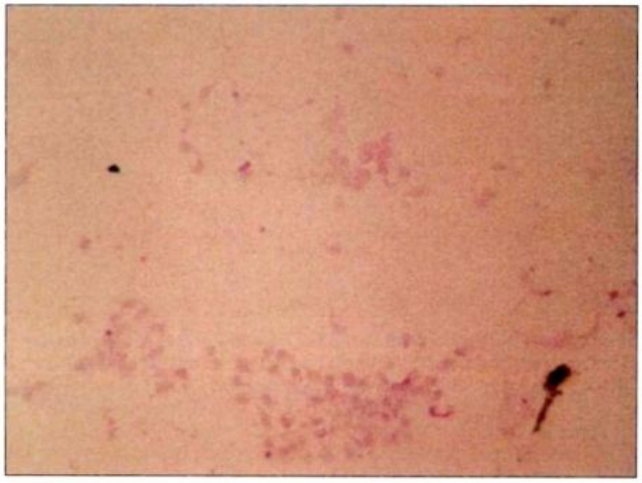

Figure 2f: Dead sperm cells which appeared pinkish after picking up the colour of the eosin staining solution in rats of experimental Group VI which received 40 mg/kg bodyweight of amlodipine besylate (×400)

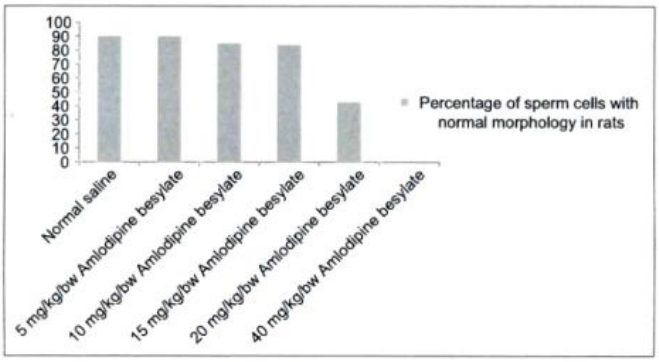

Figure 3: Percentages of sperm cells with normal morphology in rats of the control and experimental groups. Analyses of quantifications of sperm cells

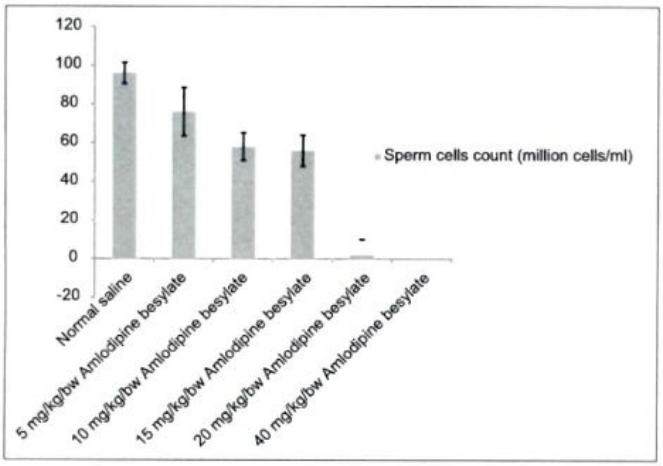

Figure 4: The graphical analyses of sperm cells count (million cells per ml) in rats of control and experimental groups . Analyses of motility of sperm cells

Table 2: Analyses of sperm cells count in rats of control and experimental groups. ($P \leq 0.05$)

Doses of drugs	Sperm cell count (million cells/ml)	Statistical significance at $P \leq 0.05$ (Group I vs Groups II–V)
Normal saline	96+5.5	
5 mg/kg bw amlodipine besylate	76+12.5	Significant decrease
10 mg/kg bw amlodipine besylate	58+7.2	Significant decrease
15 mg/kg bw amlodipine besylate	56+8.0	Significant decrease
20 mg/kg bw amlodipine besylate	2.0+8.0	Significant decrease
40 mg/kg bw amlodipine besylate	No visible sperm cells	No visible sperm cells

Table 3: Analyses of motility of sperm cells in rats of control and experimental groups

Doses of drugs	Sperm cell motility	Statistical significance at $P \leq 0.05$ (Group I vs Groups II–VI)
4 ml Normal saline	75% +++	
5 mg/kg bw of amlodipine besylate	35% ++	Significant decrease
10 mg/kg bw of amlodipine besylate	25% ++	Significant decrease
15 mg/kg bw of amlodipine besylate	5% +	Significant decrease
20 mg/kg bw of amlodipine besylate	0% –	Significant decrease
40 mg/kg bw of amlodipine besylate	0% –	No visible sperm cells

in rats that received normal saline, 5 or 10 mg/kg bodyweight of amlodipine besylate.

The roles of calcium ions in the regulations of several processes that determine fertility in males such as steroidogenesis (Latif *et al.*, 2012), hormonal control of Sertoli cells function (Gorczyńska-Fjälling, 2004), secretion of products by Sertoli cells (Latif *et al.*, 2008; Latif *et al.*, 2009a) and spermatogenesis (Gorczyńska-Fjälling, 2004; Guyton and Hall, 2011) could possibly have been impaired by the calcium ions blocking functions of amlodipine besylate which led to the observed adverse effects on the microscopic anatomy of the testes [Figure 1e-f], the quantities and percentages of sperm cells with normal morphology [Figures 2d-f and 3], sperm cells count [Figure 4] and motility [Table 3] in rats that

received 15, 20 or 40 mg/kg bodyweight of amlodipine besylate.

Furthermore, the testes are the main organs of male fertility which imply that the observed anomalies of testicular histology would adversely affect all processes involved in spermatogenesis. Anomalies of spermatogenesis would have been responsible for the observed anomalies of sperm cells count, morphology and motility in rats that received 15, 20 or 40 mg/kg bodyweight of amlodipine besylate. These observations are in agreement with previous studies that reported low sperm count (Almeida *et al.*, 2000), reduced height of germinal epithelium and significantly reduced seminiferous tubular diameter (Latif *et al.*, 2009a) and suppressed spermatogenesis (Latif *et al.*, 2009a, 2009b) in rats treated with amlodipine besylate.

This study observed anomalies of testicular histology, sperm cells count, morphology and motility in adult male Wistar rats treated with 15, 20 or 40 mg/kg bodyweight of amlodipine besylate. The observations of significantly decreased sperm cells count and motility in rats of Experimental Groups II–III when compared with Control Group I were not sufficient enough to affect male fertility [Figures 1b-c; 2b-c and Table 1]. This could possibly imply that 5 or 10 mg/kg bodyweight daily usage of amlodipine besylate in man is probably safe. However, administration of 15 mg/kg bodyweight or higher doses of amlodipine besylate to achieve assumed accelerated relief of hypertension by drug abusers could have adverse effects on testicular histology, sperm cells count, morphology and motility.

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