J. Expt. & Clin. Anat. 9 (2):44-46

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Amlodipine Besylate Is Testes Friendly

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ABSTRACT

Amlodipine besylate is a relatively new antihypertensive drug with potential as a choice chemotherapy in future. Commonly prescribed as a single oral dose, it can be used in all forms of elevated blood pressure and has a high cure rate. Eleven (11) male Wistar rats of 250g average body weight were used to determine the effect of Amlodipine besylate on the testes. Three dose levels (0.5, 1.0 and 10mg/kg) were used. The rats were all sacrificed on the eighth day following treatment and the testes examined morphologically and histologically after fixing with 10% formaldehyde. The results obtained revealed active seminiferous tubules where the processes of spermatogenesis and spermiogenesis were seen occurring. This study strongly suggests that there was no toxicological effect on the testes even at dose level as high as 10mg/kg. It could be deduced that Amlodipine besylate is a very safe drug which is highly recommended.

Key words: Hypertention, Amlodipine besylate, Testes, Spermatogenesis, Spermiogenesis

Hypertension is an important worldwide public health challenge because of its high prevalence and the concomitant increase in risk of cardiovascular and renal disease. For example, 8 million Nigerians suffer from hypertension of which 2.8 million fall on the mild category while 0.8 million and 0.6 million fall into the moderate and severe categories respectively (Akinkugbe 1999).

Hypertension may be caused by factors such as Cushing's syndrome, phaeochromocytoma, primary aldosteronism, trauma, and tumour to name but a few. However, these conditions most of which can be treated surgically account for only 10% of all cases of hypertension; the other 90% of the cases are due to essential or primary hypertension (Bergston 1996).

Calcium ions (Ca^{2+}) are vital in many biological processes, hence, the development of drugs that interfere with the entry of Ca^{2+} into cells (Ca^{2+} channel blockers). The contraction process in all muscle types is decisively influenced by the Ca^{2+} concentration in the vicinity of the contractile elements (Ebashi and Endo, 1958, Ebeigbe 1982a). Furthermore, myoplasmic Ca^{2+} depends ultimately on the entry of Ca^{2+} into the cell, and understanding of this process requires an appreciation of the electrical activity of cardiac cells (Carmillet, 1980). Normal cardiac contraction and relaxation are critically dependent on precisely timed modulations of myoplasmic Ca^{2+} and abnormalities in its influx can affect myocardial performance.

Drugs classified as Ca^{2+} entry blockers belong to a class of compounds that act predominantly in the cardiovascular system where they cause relaxation of the vascular smooth muscle, inhibit contractile force of cardiac muscle and damp the Ca^{2+} dependent activity of cardiac pacemaker (Fleckenstein 1977, Ebeigbe 1987).

A wide variety of Ca^{2+} entry blockers actions have been reported (Fleckenstein 1977, Dede et al 1992, Ebeigbe 1988). These agents, including Amlodipine, represent a heterogeneous group of compounds where precise overall relationship between chemical structure and pharmacological activity cannot be readily defined (Ebeigbe 1987).

Amongst the three subclasses of Ca^{2+} entry blockers (Spedding 1984), namely, dihydropyridines, diphenylalkalamines and drugs that operate by allosteric mechanism, amlodipine belongs to the dihydropyridine class. The predominant action of Ca^{2+} blockers is mediated via selective inhibition of Ca^{2+} entry through voltage dependent channels (Fleckenstein 1997, Godfraind 1983, Godfraind et al 1986)

Amlodipine besylate is a dihydropyridine derivative, which acts as a calcium ion influx inhibitor. It is indicated for the first line treatment of hypertension in the majority of patients. It is contraindicated in patients with known sensitivity to dihydropyridines. Its effect on testis has not been adequately established, hence, this investigation

was done to evaluate the toxicological effect of amlodipine besylate on the testes of Wistar rats.

MATERIALS AND METHODS

Eleven male Wistar Rats (*Rattus norvegicus*) were procured and bred in the experimental animal house of the College of Health Sciences, University of Port Harcourt Nigeria. The rats were fed with grower's mash (Sanders feed, Port Harcourt) and tap water was provided *ad libitum* until they weighed 200g-300g.

The rats were divided into four groups, two in group A and three each in group B, C & D respectively. The first group (Group A) which was the control group was given distilled water. The second to fourth groups (i.e Groups B, C and D) were given 0.5, 1 and 10mg/kg orally by means of syringes respectively at twenty four hour intervals for seven days.

The rats were then monitored and sacrificed on the eighth day and the testes dissected out and fixed in 100% formal saline. The tissue were sliced and dehydrated with different increasing concentrations (50, 70, 80, 95 and 100%) of ethanol for about 24hrs. The tissues were then cleared with xylene to remove the alcohol and improve their refractive index; they were then imbedded in the molten paraffin wax and allowed to solidify in the wax. The resultant blocks were sectioned and slides were later obtained after sectioning. The slides were stained with heamatoxylin/eosin solution and the stained testes slides were examined for histopathological lesions using a binocular Olympus light microscope. The testes were then dissected out and were fixed with 10% formaldehyde and then processed accordingly for histopathological examination.

RESULTS

Gross Morphology

There was no obvious difference in the shape and colour of the testis in the four groups when rats were observed with the naked eye.

Histology

Figures 1-4 show micrographs of the effect of Amlodipine on the histology of the testes for the various groups. No histological changes were seen in the testes. At the highest dose of 10mg/kg/day, active seminiferous tubules with the processes of spermatogenesis and spermiogenesis were evident.

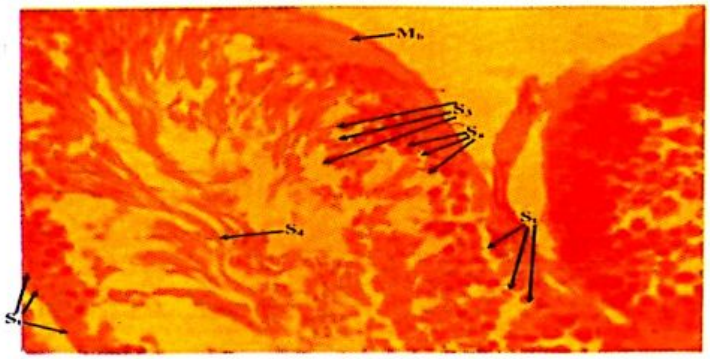

Fig.1 The transverse section of the testes of untreated (control) rats. The arrows show the basement membrane (M_b), spermatogonia a (S_a), spermatids (S_3), spermatozoa (S_4) and Sertoli cells (S_t).

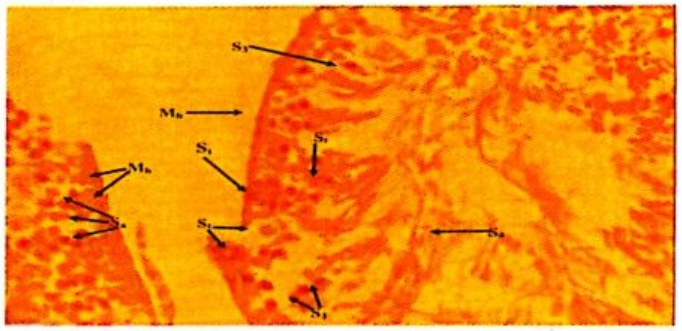

Fig. 2 Effect of Amlodipine besylate (0.5mg/kg) on the rat testes The section shows the basement membrane (M_b) containing several layers of spindle-shaped fibromyocytes (myoid cells) which are responsible for the production of collagen and elastin fibres in the lamina propria. It also shows the Sertoli cells (S_t), spermatogonia type A, (S_a), spermatozoa (S_4) and spermatids (S_3)

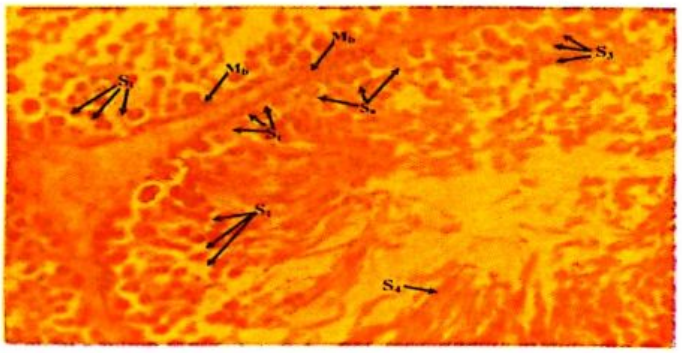

Fig. 3 Testis from Amlodipine besylate (1mg/kg) treated rat shows the basement membrane with myoid cells (M_b), sertoli cells (St), Type A spermatogonia (S_a), primary spermatocyte (S_1), spermatids (S_3) and spermatozoa (S_4).

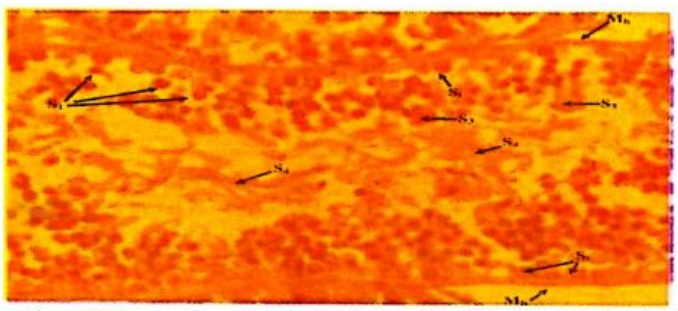

Fig. 4 Testis from Amlodipine besylate (10mg/kg) treated rat.

The process of spermatogenesis and spermiogenesis are synchronized, with waves of activity occurring sequentially along the length of the tubule. Basement membrane and the myoid cells (M_b), Sertoli cells (S_1), spermatids (S_3), primary spermatocytes and spermatozoa (S_4) are visible.

DISCUSSION

Amlodipine Besylate is a relatively new anti-hypertensive drug with potentials to be the choice chemotherapy in future. It is commonly prescribed as a single oral dose. It can be used in all forms of elevated blood pressure and has a high cure rate (Amlodipine, Wikipedia).

In this study, Amlodipine was given as a single dose, once daily in an attempt to simulate the manner of administration for Amlodipine besylate chemotherapy in humans.

Pilot study and LD_{50} determination was done; the calculation informed the decision that LD_{100} and LD_{50} of the drug is greater than 200mg/kg, this goes to confirm that the drug has a high therapeutic index.

Furthermore, the micrographs taken revealed active seminiferous tubules where the processes of spermatogenesis and spermiogenesis were seen occurring. Waves of activity were occurring sequentially along the length of the seminiferous tubules. It has been shown that Amlodipine maleate has no effect on the fertility of rats treated orally and that no evidence of teratogenicity or other embryo/foetal toxicity has been found with pregnant rats. This is in agreement with our result which strongly suggests that Amlodipine has no toxicological effect on the testes even at dose level as high as 10mg/kg.

In conclusion, it could be deduced from this study that Amlodipine besylate is a very safe drug which is highly recommended. Furthermore, there is need to carry out a chronic toxicity study on Amlodipine with the aim of ascertaining the long term effect of use of Amlodipine on the testes of Wistar rats, this will be to ascertain precautions that high blood pressure patients should take as they have to be on long term therapy.

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