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## HISTOLOGICAL STUDIES OF THE EFFECTS OF ORAL ADMINISTRATION OF ARTESUNATE ON THE MEDIAL GENICULATE BODY OF ADULT WISTAR RATS.

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### ABSTRACT:

The histological effect of oral administration of artesunate, commonly used for the treatment of Malaria on the medial geniculate body (MGB) of adult wistar rat was carefully studied. The rats of both sexes (n=24), average weight of 210g were randomly assigned into three treatment (n=18) and control (n6) groups.

The rats in the treatment group 'A' received 4mg/kg body weight of artesunate base dissolved in distilled water for 3 days. The animals in groups 'B' and 'C' received 4mg/kg body weight of artesunate dissolved in distilled water for the first day and thereafter received 2mg/kg body weight daily for six and thirteen day respectively. The control group D, received equal volume of distilled water daily using the Orogastric tube. The rats were fed with grower's mash obtained from Edo Feeds and Flour Mill Ltd, Ewu, Edo State, Nigeria and were given water liberally. The rats were sacrificed on day fourth, eight and fifteenth of the experiment. The medial geniculate body was carefully dissected out and quickly fixed in 10% formal saline for histological studies.

The histological findings after H&E method indicated that the treated section of the medial geniculate body showed some decreased cellular population, degenerative changes, cellular hypertrophy, with some vacuolations appearing in the stroma.

Varying dosage and long administration of artesunate may have some deleterious effects on the neurons of the Medial geniculate body and this may probably have some adverse effects on auditory sensibilities by its deleterious effects on the cells of the medial geniculate body of adult wistar rats. It is therefore recommended that further studies aimed at corroborating these observations be carried out.

**Key words:** Artesunate, medial geniculate body, decrease cellular population, vacuolation.

**RESUMEN: ESTUDIO HISTOLÓGICO DE LOS EFECTOS DE LA ADMINISTRACIÓN ORAL DE ARTESUNATO EN CUERPO GENICULADO MEDIO DE RATAS WISTAR ADULTAS**

El efecto histológico de la administración oral de artesunate, comúnmente utilizado para el tratamiento de la malaria en el cuerpo geniculado medio (MGB) de ratas wistar adultas, fue cuidadosamente estudiado. Ratas de ambos sexos (n = 24), con peso promedio de 210 g fueron distribuidas de forma aleatoria en tres grupos de tratamiento (n = 18) y control (n = 6).

Las ratas del grupo de tratamiento "A" recibieron 4mg/kg peso corporal de artesunate base, disuelto en agua destilada, durante 3 días. Los animales en los grupos "B" y "C" recibieron 4mg/kg peso corporal de artesunate disuelto en agua destilada el primer día y posteriormente recibieron 2mg/kg peso corporal al día durante seis y trece días respectivamente. El grupo control D, recibió igual volumen de agua destilada al día, utilizando sonda nasogástrica. Las ratas fueron alimentadas con pienso de Edo Feeds y Flour Mill Ltd, Ewu, Estado de Edo, Nigeria y se les proporcionó agua libremente. Las ratas fueron sacrificadas en el día cuarto, octavo y décimo quinto de la prueba. El cuerpo geniculado medio fue cuidadosamente disecado y rápidamente fijado en el 10% de solución de formol salina para el estudio histológico.

Los hallazgos histológicos observados en secciones del cuerpo geniculado medio, teñidas con H&E indicaron que el tratamiento disminuye la población celular, con cambios degenerativos, hipertrofia celular, y aparecen en el estroma algunas vacuolizaciones.

Variando la dosis y tiempo de administración de artesunate, pueden verse algunos efectos perjudiciales sobre las neuronas del cuerpo geniculado medio y pueden probablemente tener algunos efectos negativos sobre la sensibilidad auditiva por sus efectos nocivos sobre las células del cuerpo geniculado medio de las ratas wistar adultas. Por consiguiente, se recomienda realizar nuevos estudios para corroborar estas observaciones.

**Palabras Clave:** Artesunate, cuerpo geniculado medio, disminución de población celular, vacuolización.

**INTRODUCTION**

Malaria remains one of the world's most significant health problems despite increasing research and control efforts<sup>1</sup>. The occurrence of malaria during pregnancy exposes the mother and infants to serious risks. It is therefore imperative that pregnant women be protected against malaria; and that pregnant women with malaria receive treatment as soon as possible<sup>2</sup>.

Artesunate is one of the numerous drugs for malaria intervention in Nigeria. It is a semi synthetic derivative of artemisinin, the active compound of the Chinese herb *Artemisia annua* which consist of the sodium succinyl salt of dehydroartemisinin<sup>3</sup>. Artemisinin-type compounds reduce malaria parasitemia more rapidly than any other known antimalarial drugs and are effective against multi drug resistant malaria parasites<sup>4-5</sup>. Artesunate is highly effective against multi-drug resistant strains of *Plasmodium falciparum* hence its increasingly wide usage for the treatment and management of malaria<sup>6</sup>. Artesunate is well tolerated at therapeutic doses; therefore a lot of people, pregnant women inclusive take the drug.

Several studies have shown that high doses of artesunate can produce neurotoxicity such as selective damage to brainstem centres in mice and rats<sup>7-9</sup>. Artesunate have been reported to cause gait disturbances, loss of spinal cord and pain response mechanisms in animals<sup>10-11</sup>.

The Inferior colliculus and Medial geniculate body constitute the intracranial auditory relay centres. The medial geniculate body is the target of ascending projections from the inferior colliculus and descending input from the auditory cortex; this is the obligatory synaptic target in the thalamus for hearing. It contains interleaved and overlapping tonotopic and aural bands<sup>12</sup>. The cerebral cortex strongly affects the medial geniculate body through descending projections which are thought to consist primarily of small areas with slow conduction velocities<sup>13</sup>.

Cerebral nuclei such as the medial and lateral geniculate bodies, inferior and superior colliculi have higher glucose utilization than other structures. There is also a correlation between functional activity and metabolic rate such as in the visual and auditory system<sup>14</sup>.

The effects of artesunate on the intracranial auditory relay centre may not have been documented, but there have been reports that it may be implicated in varied symptoms of dizziness, itching, vomiting, abdominal pain, headaches, diarrhea, tinnitus, increase hearing loss, macular rash, neutropenia and convulsion. It is probable that the adverse effects of artesunate on hearing such as tinnitus may be due to direct effect of artesunate on this auditory relay centre. This present study was to elucidate the histological effects of artesunate on the medial geniculate body of adult wistar rats.

## MATERIALS AND METHODS

### ANIMALS:

Twenty-four (24) adult wistar rats of both sexes with average weight of 210g were randomly assigned into four groups A, B, C and D of (n=6) in each group. Groups A, B, and C of (n=18) serves as treatments groups while group D (n=6) is the control. The rats were obtained and maintained in the Animal holdings of the Department of Anatomy, School of Basic Medical Sciences, University of Benin, Benin city, Nigeria. They were fed with grower's mash obtained from Edo feed and flour mill limited, Ewu, Edo state) and were given water liberally. The rats were allowed to gain maximum acclimatization before the actual commencement of the experiment. The Artesunate tablets were obtained from the University of Benin Teaching Hospital Pharmacy, Benin City, Edo state, Nigeria.

### ARTESUNATE ADMINISTRATION:

The rats in the treatment groups (A, B, & C) received 4mg/kg body weight of Artesunate base dissolved in distilled water for the first day. Animals in the treatment group 'A' continued with this dosage for the next two days, while animals in groups B & C received 2mg/kg once daily for six and thirteen days respectively. The control group D received equal volume of distilled water using orogastric tube. The treated rats in groups A, B, and C were sacrificed by cervical dislocation on the 4th, 8th and 15th day of the experiment respectively, while that of the control group D was sacrificed at the end of the experiment. The skulls were opened using bone forceps to expose the brain of the rat, and the medial geniculate body was quickly dissected out and fixed in 10% formal saline for routine histological techniques.

### HISTOLOGICAL STUDY:

The tissue were dehydrated in an ascending grade of alcohol (ethanol), cleared in xylene and embedded in paraffin wax. Serial sections of 7 microns thick were obtained using a rotatory microtome. Some of the deparaffinised sections were stained routinely with haematoxyline and eosin (H&E) method<sup>15</sup>. The digital photomicrographs of the desired sections were made in the Department of Anatomy research laboratory, University of Benin, Nigeria for further observations.

## RESULTS

The sections of the medial geniculate body (MSG) from the control group showed normal histological features with the neurons appearing distinct and the glial cells normal without vacuolation in the stroma (Figure 1).

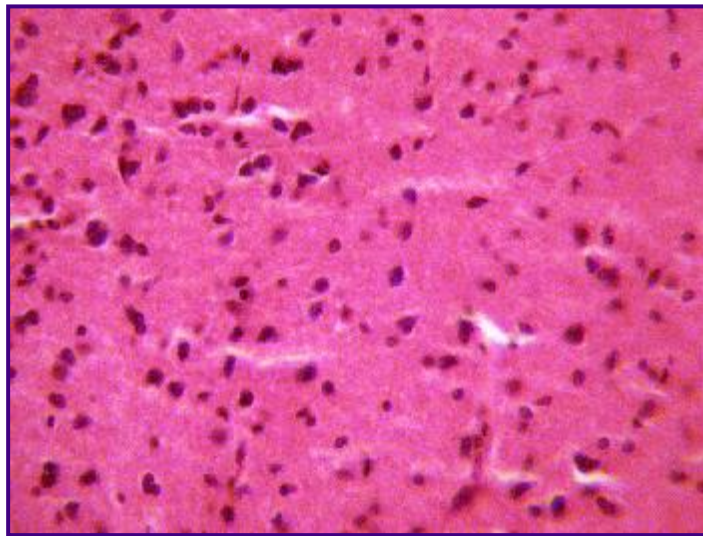
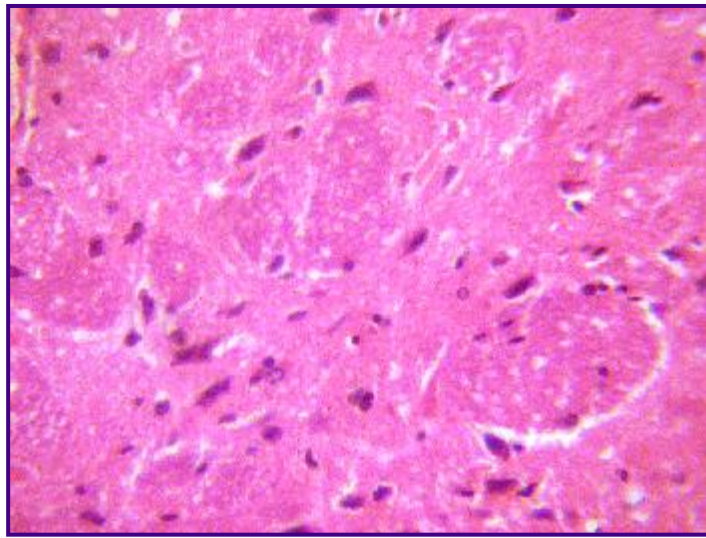
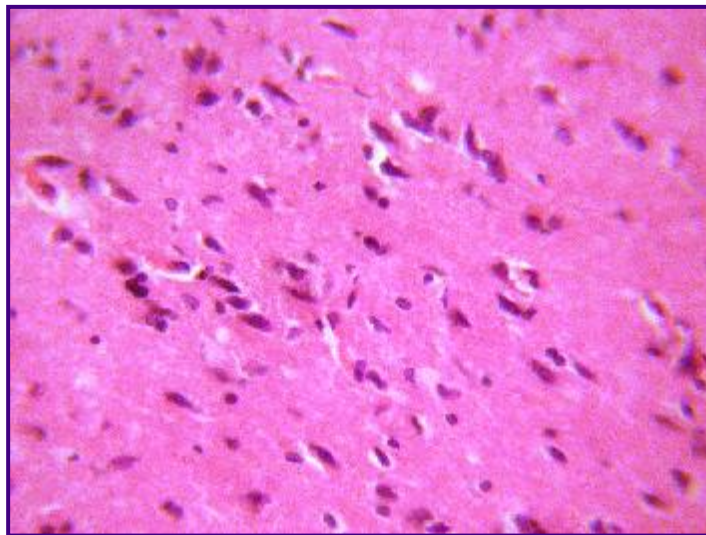


Figure 1 (GROUP D): Photomicrograph representing the control section of the medial geniculate body (Original magnification x 400).

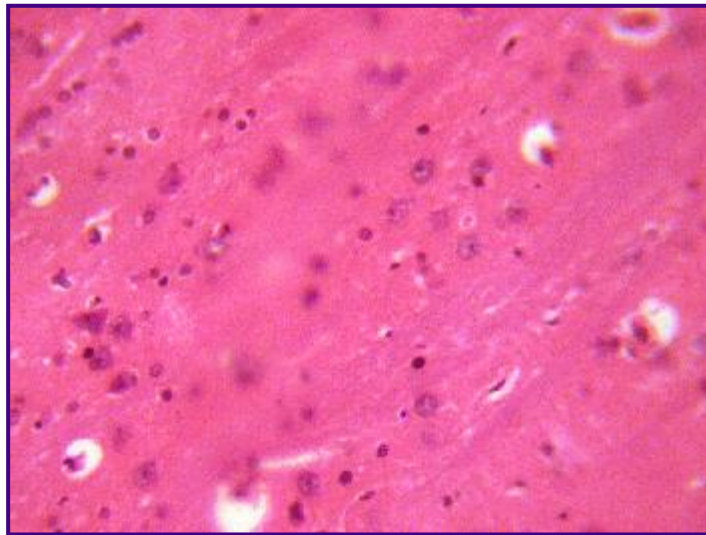
The sections of the medial geniculate body from the treatment (A, B, & C) groups showed some decrease in cellular population, degenerative changes, cellular hypertrophy and vacuolations appearing in the stroma (Figure 2, 3 & 4).



**Figure 2 (GROUP A):** Photomicrograph representing the treatment section of the medial geniculate body (group A), that received 4mg/kg of artesunate for 3 days. (Original magnification x 400).



**Figure 3 (GROUP B):** Photomicrograph representing the treatment section of the medial geniculate body (group B) that received 4mg/kg 1st day and thereafter 2mg/kg for 6 days of artesunate. (Original magnification x 400).



**Figure 4 (GROUP C):** Photomicrograph representing the treatment section of the medial geniculate body (group C),



that received 4mg/kg 1st day and thereafter 2mg/kg for 13 days of artesunate. (Original magnification x 400).

All the rats in each group were affected equally, with the rats in group C more severe than groups A and B. Affection of the rats in group A was mild and Group B appears to be moderate.

## DISCUSSION

The results (H & E) revealed that administration of artesunate showed some decreased cellular population, degenerative changes, cellular hypertrophy and vacuolations which appeared in the stroma of the treatment groups compared with the control section of the medial geniculate body. Neuronal degeneration has been reported to result in cell death, which is of two types, namely apoptotic and necrotic cell death. These two types differ morphologically and biochemically<sup>16</sup>. Pathological or accidental cell death is regarded as necrotic and could result from extrinsic insults to the cell such as osmotic, thermal, toxic and traumatic effects<sup>17</sup>. It was reported that cell death in response to neurotoxins might trigger an apoptotic death pathway within brain cells<sup>18</sup>. Cell death in response to neurotoxins occurs as a controlled event involving a genetic programme in which caspase enzymes are activated<sup>18</sup>.

The process of cellular necrosis involves disruption of the membranes structural and functional integrity. Cellular necrosis is not induced by stimuli intrinsic to the cells as in programmed cell death (PCD), but by an abrupt environmental perturbation and departure from the normal physiological conditions<sup>19</sup>. There is the need to further investigate the actual mechanism by which artesunate induced neuronal degeneration in the medial geniculate body of adult wistar rat in this study.

Extensive cell death in the central nervous system is present in all neurodegenerative diseases<sup>18</sup>. The type of nerve cell loss and the particular part of the brain affected dictate the symptoms associated with an individual disease<sup>18</sup>. In this study artesunate may have acted as toxin to the cells of the medial geniculate body, affecting their cellular integrity and causing defect in membrane permeability and cell volume homeostasis.

In cellular necrosis, the rate of progression depends on the severity of the environmental insults. The greater the severity of the insults the more rapid the progression of neuronal injury<sup>19</sup>. The principle holds true for toxicological insult to the brain and other organs<sup>20</sup>. The prime candidates for inducing the massive cell destruction observed in neurodegeneration are neurotoxins<sup>18</sup>. These may be substances present in small amounts in the environment, or even naturally occurring chemicals such as glutamate used by the brain as transmitter's substances<sup>18</sup>. The latter when present at a critical level can be toxic to the brain cells they normally excite<sup>18</sup>. It is inferred from this results that prolonged and high dose of artesunate resulted in increased toxic effects on the MGB. The decrease in cellular population observed in this study may have been as a result of cell death caused by the toxic effect of artesunate. In the same way, it has been reported that chronic administration of chloroquine resulted in the cellular degenerative changes, sparse cellular population and vacuolation appearing in the stroma with some autophagic vacuoles in the medial geniculate body and inferior colliculus of adult wistar rats<sup>21-22</sup>. Chloroquine intoxication has been reported to result in the accumulation of lysosomal membranes rich in phospholipids and gangliosides due to the inhibition of lysosomal enzymes<sup>23</sup>.

The vacuolation observed in the stroma of the medial geniculate body in this experiment may be due to artesunate interference, since it has been reported that artesunate may be neurotoxic to the developing nervous system of wistar rats<sup>24</sup>. The cellular hypertrophy observed in this experiment may be due to the adverse effects of artesunate on the medial geniculate body. This study may underlie the possible neurogenic symptoms such as dizziness and tinnitus for high doses of artesunate has been reported to produce neurotoxicity such as selective damage to brainstem centres in mice and rats<sup>7-9</sup>.

## CONCLUSION

Our study revealed that high doses and long term administration of artesunate causes spares cellular population, cellular degenerative changes, cellular hypertrophy and vacuolation in the medial geniculate body of adult wistar rats. These results may indicate that the functions of the medial geniculate body in auditory sensibility may be adversely affected.

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**Comment of the reviewer Prof Pilar Muñiz Rodríguez, PhD. Titular del Área de Bioquímica y Biología Molecular de la Facultad de Ciencias de la Universidad de Burgos. España**

Artemisinins are the fastest acting antimalarials, and they are being increasingly deployed in the global fight against falciparum malaria. These compounds are also being developed for use against other parasites and in cancer chemotherapy. The artemisinins are sesquiterpine lactones characterized by possession of an endoperoxide ring. Animal studies have consistently revealed a unique pattern of artemisinin induced brainstem injury, and concerns have lingered over possible neurotoxicity in humans.

Eweka and Adjene studied the histological effect of oral administration of artesunate, on the medial geniculate body of adult Wistar rat. They observed that long administration or high doses may be neurotoxic to developing cellular hypertrophy and degenerative changes in the medial geniculate body. The present work undoubtedly is a valuable addition to more detailed studies of the neurotoxicity of artesunate.

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**Comment of the reviewer Erhan Süleymanoglu. PhD. G.U.E.F., Department of Pharmaceutical Chemistry, Gazi University. Gazi Mahallesi, Ankara. Turkey**

The present study examines effects of orally administered antimalarial Artesunate on the medial geniculate body of adult wistar rats.

Certain morphological alterations found, could further be used in establishing dose-dependent deleterious effects of the drug on this body neurons. The basic features of Artesunate, the objective of this study, as well as the experimental design are well presented. Undoubtedly, this work is another contribution to the efforts of understanding the cellular mechanisms of Artesunate induced neuronal degeneration and cell death in animal models, and thus deserves to be published.

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