# Histological Studies Of The Effects Of Oral Administration Of Artesunate On The Superior Colliculus Of Adult Wistar Rats

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**Citation**

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**Abstract**

The histological effect of oral administration of artesunate commonly used for the treatment of Malaria on one of the visual relay centres namely the superior colliculus (SC) 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 (n=6) groups. The rats in the treatment group 'A' received 4mg/kg body weight of artesunate base dissolved in distilled water daily for 3 days, through orogastric tube. The animals in groups 'B' and 'C' received 4mg/kg body weight of artesunate base dissolved in distilled water for the first day and thereafter received 2mg/kg body weight daily for six and thirteen days through the same route respectively, while that of the control group D, received equal volume of distilled water daily during the period of the experiment. 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 four, eight and fifteen of the experiment. The Superior colliculus 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 Superior colliculus showed some varying degree of cell clustering, cellular hypertrophy, and intercellular vacuolations appearing in the stroma of the superior colliculus. Varying dosage and long administration of artesunate may have some deleterious effects on the neurons of the intracranial visual relay centre and this may probably have some adverse effects on visual sensibilities by its deleterious effects on the cells of the superior colliculus of adult Wistar rats. It is therefore recommended that further studies aimed at corroborating these observations be carried out.

## INTRODUCTION

Malaria remains one of the world's most significant health problems despite increasing research and control efforts[1]. 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[2].

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 dehyroartemisinin[3]. Artemisinin-type compounds reduce malaria parasitemia more rapidly than any other known antimalarial drugs and are effective against multi drug resistant malaria parasites[4,5]. Artesunate is highly effective against multi-drug resistant strains of plasmodium falciparum hence its increasingly wide usage for the treatment and management of malaria[6]. 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[7,8,9]. Artesunate have been reported to cause gait disturbances, loss of spinal cord and pain response mechanisms in animals[10,11].

The superior colliculus and lateral geniculate body constitute the intracranial visual relay centres. The superior colliculus has a critical role in visual localization, orientation tracking movements, accommodation and pupiliary reflex[12]. An analysis of effective connectivity demonstrated that the search-dependent variance in the activity of the superior colliculus was significantly influenced by the activity in a network of cortical regions including the right frontal eye fields and bilateral parietal and occipital cortices[13].

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

The effects of artesunate on the intracranial visual 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 vision such as dizziness may be due to direct effect of artesunate on this visual relay centre. This present study was to elucidate the histological effects of artesunate on the superior colliculus 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 marsh 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 superior colliculus was quickly dissected out and fixed in10% formal saline for routine histological techniques.

HISTOLOGICAL STUDY: The tissue was 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 deparaffinized sections were stained routinely with haematoxyline and eosin (H&E) method[15]. 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 superior colliculus (SC) 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).

The sections of the superior colliculus from the treatment (A, B, & C) groups showed some varying degree of cell clustering, cellular hypertrophy, and intercellular vacuolations appearing in the stroma (Figure 2, 3 &4)

### Figure 1

Figure 1 (Group D): Control section of the superior colliculus (Mag. x400)

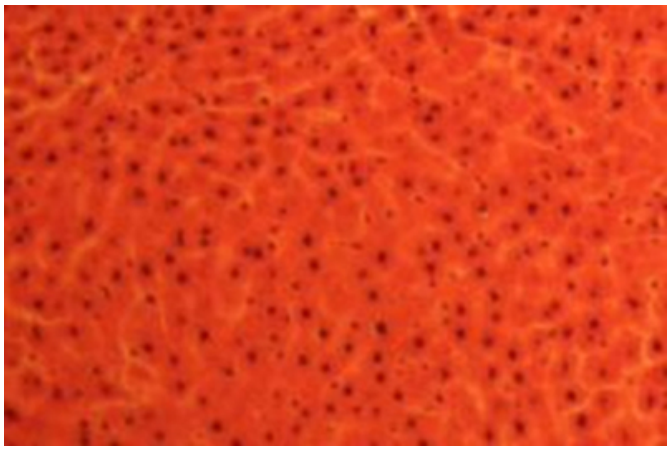


**Figure 2**

Figure 2 (Group A): Treatment section of the superior colliculus (group A) that received 4mg/kg of artesunate for 3 days (Mag. x400)

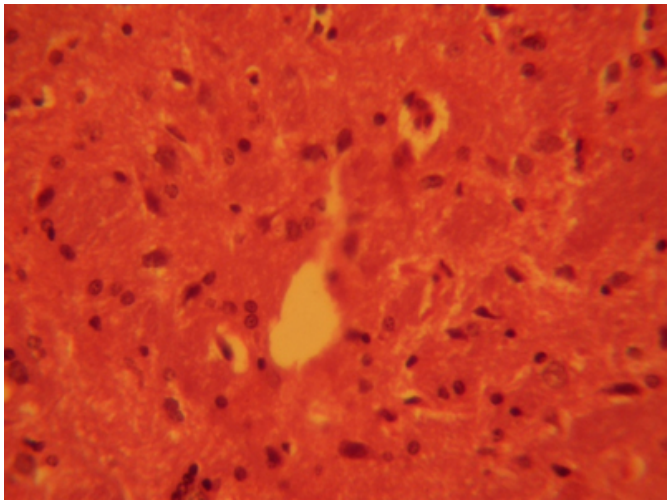


**Figure 3**

Figure 3 (Group B): Treatment section of the superior colliculus (group B), that received 4mg/kg 1st day and thereafter 2mg/kg for 6 days of artesunate. (Mag.x400)

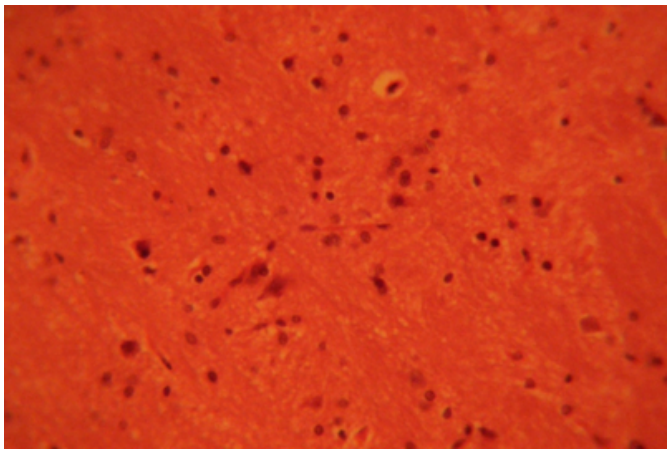
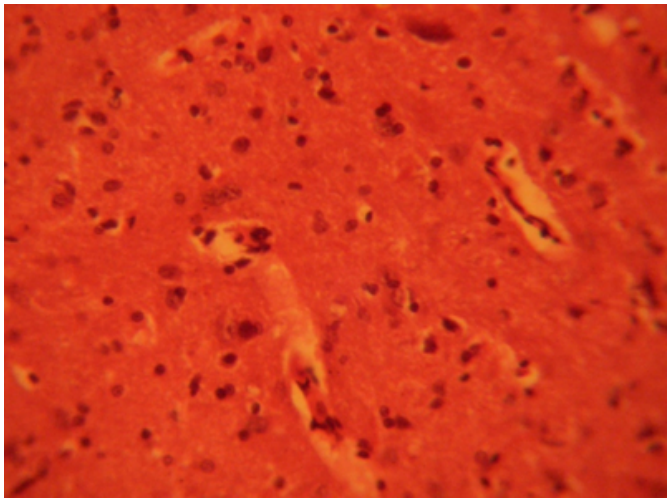


**Figure 4**

Figure 4 (Group C): Treatment section of the superior colliculus (group C), that received 4mg/kg 1st day and thereafter 2mg/kg for 13 days of artesunate (Mag. x400)



## DISCUSSION

The results (H & E) revealed that administration of artesunate showed some varied degree of cellular degenerative changes, cellular hypertrophy, clustering of cells and intercellular vacuolations appearing in the stroma of the treatment groups compared with the control section of the superior colliculus of the adult Wistar rat. 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[16]. 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[17]. It was reported that cell death in response to neurotoxins might trigger an apoptotic death pathway within brain cells[18].

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[19]. There is the need to further investigate the actual mechanism by which artesunate induced neuronal degeneration in the superior colliculus of adult Wistar rat in this study.

Extensive cell death in the central nervous system is present in all neurodegenerative diseases[18]. The type of nerve cell loss and the particular part of the brain affected dictate the symptoms associated with an individual disease[18]. In this

study artesunate may have acted as toxin to the cells of the superior colliculus, 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.[20] The principle holds true for toxicological insult to the brain and other organs[19]. The prime candidates for inducing the massive cell destruction observed in neurodegeneration are neurotoxins[18]. The latter when present at a critical level can be toxic to the brain cells they normally excite[18]. It is inferred from this results that prolonged and high dose of artesunate resulted in increased toxic effects on the SC. [21, 22].

The vacuolations observed in the stroma of the superior colliculus 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[23]. The cellular hypertrophy observed in this experiment may be due to the adverse effects of artesunate on the superior colliculus. This study may underlie the possible neurological 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[7,8,9].

## CONCLUSION

Our study revealed that high doses and long term administration of artesunate caused some varied degree of cellular degenerative changes, cellular hypertrophy, clustering of cells and intercellular vacuolations in the superior colliculus of adult Wistar rats. These results may probably affect the functions of the superior colliculus in visual sensibility in adult Wistar rats.

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