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PREVENTION OF EPILEPSY BY LOW-DOSE ARTESUNATE + ESOMEPRAZOLE-FUROSEMIDE SEQUENTIAL THERAPY.

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ABSTRACT

Very recent findings indicate an important neuromodulatory role for astrocytes in altering neural circuit activity and behaviour. Artesunate, esomeprazole and furosemide are now verified agents that modulate noxious agents-induced hazardous orchestra via ATP- P2X7R-P2YI-NLRP3-A2AR signalling in astrocytes. Their mechanisms of action converge on down-regulating hyperglutamatergic excitotoxicity-and caspase-I-induced pyroptosis. They are therfore in a position to down-regulate inflammatory-related oxidative stress implicated in the mechanisms of chronic CNS diseases such as type 2 diabetes-induced complications, epilepsy and Alzheimer's disease. Importantly, these agents, which also exhibit anti-malarial activities, may become significant alternatives to present AEDs which are associated with short-comings such as drug resistance, cognitive decline, oxidative stress and even metabolic syndrome. In the present study, the effect of intermittent low-dose artesunate + esomeprazole and furosemide sequential therapy was investigated for their anti-epileptic effects. In children, intermittent use of these agents over a period of 4 months significantly ($P < 0.05$) abrogated seizure recurrence in six patients with epilepsy and status epilepticus studied. Episodes of fever were also reduced in those who were placed on the sequential combination therapy. The drugs deserve careful attention in our locality where malaria, other infections and birth injuries have co-operated to maintain, at least, a sustained prevalence rate of epilepsy and related illnesses.

KEYWORDS: Artesunate, Esomeprazole, Furosemide, Excitotoxicity, Seizures, Attenuation.

INTRODUCTION

The prevalence of active convulsive epilepsy in sub-saharan Africa (7.8-14.8/1,000 people) is higher than in other parts of the world.[1] Communicable and non-communicable disorders such as malaria, neuro-cysticercosis; malnutrition, hypertension, abnormal ante-natal periods, cerebral palsy and birth injuries are the main culprits.[2] There are cyanogenic glycosides in cassava, one of the staples in some areas and cyanide detoxification is impaired by protein deficiency.[3] Malaria-associated febrile convulsions/acute seizures may progress to epilepsy and status epilepticus in children.[2][4] The issue of drug resistance/side-effects associated with the use of present anti-epileptic drugs make the case for the interest in new remedies pressing and warranted. A goal of current antiepileptic research is the identification of additional and safer molecules targeting novel molecular mechanisms involved in neuronal excitability control.[5][6]

Artemisins and analogues are the most potent anti-malarial drugs presently available. They act by inhibiting the sarcoplasmic Ca^{2+}-ATPase (SERCA) orthologue, pfATP6, outside the food vacuole of *Plasmodium falciparum* after activating iron. Their potency here is similar to that of thapsigargin, another sesquiterpene- lactone, that has more specificity for SERCA.[7] They also inhibit the p-type ATPase of the parasite. Chelation of iron by desferrioxamine inhibits the activity ofartemisinins.[7][8] The activity of the artemisinins is substantially enhanced under conditions which enhance intra-cellular iron concentration such as hypoxia and inflammation. These endoperoxide bridge-containing compounds, discovered by Chinese scientists in 1972 from *Artemisia annua L.*, inhibit ferrous-dependent bacteria such as *H. pylori*, oncogenic viruses, trematodes such as *S. haematobium*, protozoa, cancer cells to promote their eradication. In the presence of heme which is released after malaria-induced haemolysis of red blood cells, the endoperoxide bridge undergoes reduction decomposition to form a free radical and electrophilic intermediates.[9][10] The role of iron, an important regulator of immune effector function, immune cell proliferation and cytokine expression, in infection is controversial. Iron may shift the Th_1/Th_2 differentiation to a Th_2 reaction, antagonise the IFN-gamma induced expression of MHC II, iNOS and TNF-alpha. It also, as noted above, supports bacterial growth.[11][12]

Furosemide and esomeprazole possess anti-malarial actions

Furosemide inhibits plasmodial surface anion channels (PSAC) and resistance to anti-malarials like furosemide targeting PSAC may be harder to acquire than to drugs targeting less constrained targets inside the parasite compartment.[13] Additionally, furosemide inhibits the facilitative nucleobase transporters (fNBT) and the new permeation pathways (NPP) which partly mediate uptake of purines and other nutrients in *Plasmodium falciparum*-infected human erythrocytes.[14] Not the least, furosemide enhances Akt phosphorylation and eNOS which may contribute to its anti-plasmodial effect.[15][16]

Esomeprazole and artesunate combination may be beneficial in anti-malarial effects. Via upregulation of the insulin signalling pathway, heme oxygenase-I levels and parasite death, they both contribute to halting the growth of *Plasmodium falciparum, increasing anti-oxidant genes* and thereby decreasing epileptogenesis by decreasing oxidative stress.[17][18] Esomeprazole inhibits the v-ATPase of the malaria parasite. The combination of PPIs with artesunate may decrease incidence of resistance to malaria since they both inhibit the multi-drug resistance proteins (MRP (1-6) of the parasite and even cancer cells.[19][20][21] mTOR inhibitors and AMPK pathway activators such as artesunate and esomeprazole that enhance mitochondrial biogenesis, induce autophagy and upregulate heme oxygenase-I enhance resistance to malaria.[22]

Artesunate, esomeprazole and furosemide signal to the ATP-P2X7-NLRP-3 inflammasome axis in astrocytes.

The common diuretic, furosemide, decreases renal interstitial ATP levels.[23] It also inhibits Ca^{2+}-dependent glutamate release from astrocytes which may enhance ATP signalling to P2X7 or P2YI receptors; with resultant suppression of excitotoxicity. P2X7 receptor (mainly) or P2YI receptor signaling activate the nucleotide binding oligomerisation domain, leucine-rich repeat and pyrin domain-containing 3 (NLRP-3) inflammasome which finally cause the processing of IL-I beta, IL-18 and IL-33 via increased caspase-I.[24][25][26][27][28] NLRP-3 inflammasome activation confers resistance to loop diuretics and has a role in angiotensin-II induced podocyte injury.[29][30][31]

Neuroinflammation is a fundamental innate immune response.[24] Toll-like receptor ligands alone or synergistically with ATP enhance IL-I beta-dependent Th_{17} activation. Neuromodulators signal through astrocytes to alter neural circuit activity and behaviour.[32]

Brain noxious stimuli/cellular stress trigger sustained increase of extra-cellular ATP release from astrocytes.[21] This cellular stress leading to excessive ATP release may be caused by low PH such as exists in the tumor micro-environment, hypoxia as caused by ischaemia, osmotic changes, thermal/mechanical stress, toxins and crystalline substances such as urate. Lytic or non-lytic release of ATP from acidic organelles such as mitochondria, lysosomes and endosomes, gap junctions (-like) channels (connexions, pannexin), cystic fibrosis transmembrane conductance regulator (CFTR) and plasmalemmal voltage-dependent anion channels occur. Once released, ATP is rapidly broken down by ecto-nucleotidases. ATP fulfills different roles as a neurotransmitter and neuromodulator in astrocyte-to- neuron communication. It helps in propagating astrocytic signals and in formatting microglia responses. High levels of extra-cellular ATP, ROS and K^+ activate the purinergic P2 receptor P2X7 (gate-keeper of inflammation) signaling to adenosine A_{2A} receptor axis which activate the NLRP-3 inflammasome, leading to increased cytokine processing.[33]

The P2X7 receptor has graduated as a key point of communication between the nervous, immune and cardiovascular diseases. Neuroprotection is provided by blockade of NF-kappa B, P2X7, P2YI, NLRP3/1 and A_{2A} receptor signalling.[34][35]

Importantly, the main target of the PPIs is the NLRP-3 inflammasome. PPIs such as esomeprazole down-regulate the ATP-gated P2X7 receptor signalling to NLRP-3 leading to inhibition of TNF-alpha and IL-I beta.[36] Esomeprazole may antagonise this P2X7 receptor signalling and this is important for anti-epileptogenesis and anti-ictogenesis and prevention of inflammatory-cell death (pyroptosis) via caspase-I.[37][38]

In the same vein, artemisinins, a pannexin-I blocker, inhibit the NLRP-3 inflammasome activation to decrease glutamate and cytokine release.[24][39][40][41] Modulation of cytokine release mediated by artesunate, esomeprazole and furosemide may explain their additive contribution to attenuation of seizures.[42][43][44] Importantly, artemisinins and analogues such as artesunate increase gephrin stabilisation and trafficking to enhance surface expression of GABA-$_A$ receptor.[45] GABA-$_A$ receptor is essential for anti-epileptogenesis, insulin secretion, mitochondrial biogenesis and immune function.

Aim of the Study

The aim of the study was to investigate the effect of the sequential use of low-dose artesunate + esomeprazole or omeprazole, and low-dose furosemide on seizure prevention/attenuation in children aged 7-15 years.

METHODS

Study was done over a period of 4 months at Oseghale Oriaifo Medical Centre/Oriaifo Medical Centre, Ekpoma/Uromi in Edo State. 6 children aged 7-15 years in each group with febrile convulsions were studied. Frequency of seizures was studied for 4 months in controls and in those with sequential use of artesunate + esomeprazole and furosemide. Artesunate + esomeprazole was given for 2 weeks, followed by 10 or 20mg of furosemide for two weeks. This sequential dosing may achieve two objectives: helping to reduce the risk of resistance and risk of any side-effect.

Inclusion Criteria

Children with infection-related febrile convulsions were studied. Body temperatures> 38.3^{o}C increase risk for febrile convulsions in children 9 months to 5 years which in some case (< 5%) progress to status epilepticus. (NIH)[2][4] These children had normal inter-ictal skull X-rays and EEG. They were not exposed to convulsion-provoking agents such as camphor, cyanide and pesticides. They had normal inter-ictal FBC, serum electrolytes and urea.[46]

Exclusion Criteria

Children with psychogenic non-epileptic seizures (PNES) were excluded. Also, children with severely abnormal inter-ictal skull X-rays and EEGs were excluded.

RESULTS

Results show that sequential combination dosing as described reduced the number of seizures over a 4-month period than furosemide alone which acted as the control (Table I). Number of febrile episodes also were less with the sequential dosing. The combination therapy stands to be more anti-malarial. Artesunate, the most effective anti-malaria agent at present, in combination acted most potently against the most common neurological disease, epilepsy. Not only this, we have noted that a child on the combination therapy who had Down's syndrome features and was profoundly deaf (suspected John Langdon Down syndrome) started to talk and respond properly after the combination therapy for 3 weeks. This may not

be too surprising since there may be increased amyloid-beta peptide expression in Down's syndrome as in Alzheimer's disease.

Table 1: Effect of artesunate + esomeprazole and furosemide sequential therapy on seizures.

	Furosemide	Combination
Febrile episodes	1.10	0.18
Number of seizures	2.80	1.10
Over 4 months	±2.02	±1.05
Duration of seizures (mins)	1.62	0.26
	±0.35	±0.16

Table 1: Sequential therapy with artesunate + esomeprazole and furosemide had more significant effect ($P < 0.05$) in prevention and attenuation of seizures.

DISCUSSION

We have reported from our Laboratory that artesunate may exhibit similar roles with metformin in neuropsychiatric and cardio-metabolic disorders.[46] [47] Also, furosemide has been reported by our team to possess significant anti-epileptic effects, and to be reliable in reversing cognitive deficits.[6][17] Recently, we also observed the significant effect of esomeprazole in preventing pre-eclampsia and noted the possibility of mitochondrial function –enhancing drugs such as artesunate and esomeprazole in the prevention of mitochondrial dysfunction due to malaria-induced oxidative stress.[22]

Present report may seem like an extension of our previous observations. Present study shows a significant effect of artesunate + esomeprazole and furosemide sequential therapy in the prevention or attenuation/abrogation of epileptic seizures and status epilepticus in some Nigerian children where malaria is commonly the cause of febrile convulsions which may progress to epileptic seizures.[4]

Induction of heme oxygenase-I and inhibition of amyloid-beta peptide cause decreased NLRP-3 inflammasome activation. The result is decreased cytokine activation, abrogation of mitochondrial dysfunction and decreased epileptogenesis. This mechanism may be common to furosemide, esomeprazole and artesunate,[42][43][44][45][48][49][50][51] and helps to explain present results. Increased Nrf-2 and induction of HO-I suppress neuronal inflammatory cell death (neuronal apoptosis).[52][53] The NLRP-3 inflammasome is activated in Alzheimer's disease. Alzheimer's disease and Down's syndrome may both share this aetiopathogenesis in having increased amyloid-beta peptide and mitochondrial dysfunction. This may explain the

observation in one of the children that had attenuation of the profound deafness.[54]] Artesunate may act similarly to coenzyme Q(10) in enhancing DNA repair mechanisms and decreasing mitochondrial oxidant stress to be useful in attenuating the cognitive deficits in Down's syndrome.[55][56]

Whereas present AEDs may induce cognitive dysfunction, metabolic syndrome/vascular stress,[57][58][59] our present report shows that sequential therapy with artesunate + esomeprazole and furosemide may enhance cognition most probably by decreasing markers of vascular stress and preventing the metabolic syndrome which may upregulate epileptogenesis. This effect may largely be explained by these agents upregulating mitochondrial biogenesis.[60][61][62] The issue of drug resistance by alterations in GABA-$_A$ receptor and increased MDR especially in temporal lobe epilepsy may also be significantly addressed by this sequential drug combination therapy.[62][63] For example, artesunate and the PPIs may inhibit P-glycoprotein (P-gp) or multi-drug resistance protein-I.[21]

CONCLUSION

Present evidence indicates that institution of the artesunate + esomeprazole and furosemide sequential combination therapy stands as an attractive cheap alternative to present anti-epileptic drug therapy especially in sub-saharan Africa.

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