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Synergistic and antiseizure effects of pure histamine: clinical and experimental correlations

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ABSTRACT

Background: Fever commonly leads to vomiting in children and their mothers commonly in our society give them non-prescribed antihistamine. Allergy is commonly associated with histamine, thus antihistamines are commonly applied in therapy. It may not be uncommon to have interplay of seizure and allergy where antihistamines are concurrently administered with antiseizures. Histamine, however, has been shown to influence seizure inhibitory activity in experimental animals.

Aim: To demonstrate antiseizure and, or synergistic antiseizure activity of pure histamine in experimental animals.

Method: A total of 45 adult albino rats of average weight of 130grams were used as animals. The animals were divided into 9 groups (A-I) of 5 animals per group while a two-stage experiment was done. At the first stage animals in groups A-G were used to test for antiseizure activity of pure histamine, valproic acid and phenytoin. Positive convulsive models controls were given either Pentylenetetrazole (PTZ) or Picrotoxin (PIC) while negative control group was given only drinking water. At the second stage, group H was given 10mg/kg of histamine and 5mg/kg of phenytoin at intervals of 15minutes while group I, was given 10mg/kg of histamine and 10mg/kg of valproic acid also at intervals of 15minutes. Seizure was induced with PTZ and PIC post 30 minutes time lapse. Evidence of convulsion was noted when observed. Time onset of seizure and, or death were noted. Results were analysed statistically using SPSS version 16.0.

Results: The positive controls, groups D and E exhibited average seizure onset time of 7.0minutes post convulsion induction and died at an average time of 10.2±0.2 and 10.5±0.1 minutes respectively. Pure histamine extended PTZ and PIC-induced seizure onset-time from average of 7.0 to 22. 2 and 21.2 respectively. Their death times were equally extended to average of 30.2 and 31.2 also respectively. Antiseizure activity was however, much lower than Phenytoin and Valproic acid. At the second stage of the experiment, animals on pure histamine plus phenytoin though had seizure onset of 52.4minutes, recovered from seizure attack and remained alive for over 8hours post seizure induction. On the hand animals on pure histamine plus valproic acid remained with no seizure signs and, or death for over 8hours. Non-treated (drinking water only) animals exhibited same pattern with rats on valproic acid/histamine.

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Conclusion: Histamine has antiseizure activity in both PTZ and PIC induced. Its synergistic activity is more with absence seizure when extrapolated to man. Concurrent administration of antihistamines in febrile state with allergy must be done cautiously if not avoidable. While the risk/benefit ratio with the use of antihistamines in known or potential epileptic must be re-evaluated. We recommend increase in education of mothers to avoid giving antihistamine to febrile children. Continuous education should be encouraged to educate doctors and other health workers.

Keywords: - Febrile seizures, Antihistamines, Allergy, Epilepsy, Seizures, Histamine.

1. INTRODUCTION

Febrile seizures are the most common convulsive events in childhood, occurring in 2%–5% of children younger than 5 years of age. They are age-dependent and are uncommon before 9 months and after 5 years of age. The peak age of onset is approximately 14–18 months. A strong family history of febrile convulsions in siblings and parents suggests a genetic predisposition (Zolaly, 2012). The pathogenesis of febrile convulsions is not clear even today. Viral infections of the upper airways, exanthema subitum, acute otitis media, infection of the urinary tract, and febrile reactions after vaccination are the most frequent precipitating factors (Zolaly, 2012). Our unpublished reports from two tertiary health centres in Anambra State, South East, Nigeria indicate that many parents patronize patent medicine and pharmacy shops where they purchase most ethical drugs at will. Our experience shows that most children who in their febrile state come down with vomiting are given antihistamine by their mothers. Usually at the second or third day of recurring episodes of vomiting and antihistamine dosing, the children go into fits necessitating their being brought to hospital.

Histamine is naturally produced from histidine and primarily stored in mast cells but, released on activation of mast cells. L-histidine, which is a precursor of histamine, naturally increases the neurotransmitter activity of histamine and also exhibits a neuronal protective activity against seizure (Noszal et al., 2004). Historically, histamine (β-aminoethylimidazole) parallels that of acetylcholine. Both being synthesized out of chemical curiosities before their biological significance evolved. They were first detected as uterine stimulants in ergot extracts from which they were subsequently isolated and proved to be contaminants of ergot derived from bacterial action (Randal et al,. 2006). Histamine is a biogenic amine and an important neurotransmitter-neuromodulator in the central nervous system that has been implicated in a variety of biological functions including thermo- and immunoregulation, food intake, seizures, arousal, anxiety, reward and memory (Dere *et al*., 2010).

The histaminergic neurons originate from the tuberomamillary nucleus of the posterior hypothalamus and send projections to most parts of the brain. The effects of neuronal histamine are mediated via G-protein-coupled H_1 to H_4 receptors. The prominent role of histamine as a wake-promoting substance has drawn interest to treat sleep-wake disorders (Seifert et al. 2010). Histamine-receptor, H_2 is located peripherally in the gastrointestinal tract while $H_{1,3}$ and the recently discovered H_4 are predominantly centrally acting (Nuutinen and Panula, 2010; Broderick and Masri, 2011). Again while H_1 and $_3$ appear to be essentially inhibitory, H_4 is predominantly involved in inflammation and excitation (Seifert et al,. 2010) and while the central level of histamine is lowered in Alzheimer disease, convulsion and seizures it is markedly raised in Parkinson and schizophrenia (Nuutinen and Panula, 2010; Alvarez, 2009).

The depletion of hypothalamic neuronal histamine induced by antihistamines may increase neuronal excitability, thereby increasing seizure susceptibility in patients with febrile seizures especially in children (Takano et al., 2010). Presently, novel findings suggest that H_1 receptors play a pivotal role in the regulation of seizure intensity and duration as well as seizure-induced neuronal damage in the immature P9 mice (Kukko-Lukjanov et al., 2006). With fore goings, the physiologic role of histamine is not in doubt both as inhibitory and excitatory central transmitter particularly in the pathogenesis of allergy, inflammation, Parkinson and schizophrenia. A problem of influence of antihistaminic drugs upon the convulsive threshold and effectiveness of antiepileptic drugs appears significant because of the increasing prevalence of allergic and inflammatory diseases in 21st century which results in significant intake of anti-histaminergic drugs (Ferenc and Czuczwar, 2008). The widely used histamine H_1 antagonists have a potential to induce seizures, although clinical evaluation is scarce except for a few case reports (Miyata et al., 2011). Histamine, apart from its various activities, takes also part in the inhibition of seizures via H_1 histamine receptors. H_1 receptor antagonists (antazoline, ketotifen, astemizole), especially when administered chronically, impaired the anticonvulsant activity of some antiepileptic drugs (phenobarbital, phenytoin, valproate) against maximal electroshock-induced convulsions in mice. Valproate was however, resistant to this hazardous effect of antihistaminic drugs (Ferenc and Czuczwar, 2008).

Earlier in literature, endogenous histamine has been demonstrated to exhibit a natural protection against seizure (Li-san et al., 2003). The combination of clobenpropit with pyridoxine appears to exhibit beneficial pharmacodynamic

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interaction for the prevention of electric shock (ES)-induced seizures, which might not be mediated by the histaminergic mechanisms (Uma et al., 2011). Intake of diets low in histamine lowered seizure development in pentylenetetrazol (PTZ)-induced kindling in rats (Chun-Lei et al., 2005). Cyproheptadine, an appetite enhancer which blocks serotonergic and histaminergic pathway/receptors in the brain has however, been shown to lower seizure threshold in experimental animals (Singh and Goel, 2010). But, diphenhydramine, a $H_{1,}$ antagonist that is commonly used in treatment of allergic reactions, colds and cough, and as a sleep aid induced status epilepticus in over dosage (Jang et al., 2010). One may be tempted to believing that the seizure protective effect of histamine will have no peripheral relationship but, an intravenous injection of cefazedone and famotidine (H_2 antagonist) for the preoperative preparation of left varicocele resulted in anaphylatic shock in a 23 year old man (Kim et al., 2010). As an aid in the actual site of histamine in the brain, Chun-Lei et al, (2008) gave a 14-day low histamine feed to mice and recorded the accumulation of histamine in the cortex, hippocampus and hypothalamus thus justifying the excitatory-memory function of histamine as well as its antiseizure activity.

2. MATERIALS AND METHODS

Phenytoin and Valproic acid were bought as tablet form from the Madonna University Teaching Hospital Pharmacy and used far before their expiry dates. Pure histamine was bought as histamine granules from a chemical shop at Onitsha, South-East, Nigeria. A total of 45 adult albino rats of average weight of 130grams were bought from Madonna University's animal's house and divided into cages (A-I) of 5animals per cage. All animals were allowed three day-group acclimatization before the commencement of the experiment. They were fed rats/mice pellets (Pfizer Nigeria PLC) and allowed free access to pure drinking water (*ad libitum.*) throughout the experimental period but, no feed. Shortly to commencement of study, the animals were individually weighed. Pentylenetetrazole (PTZ-90mg/kg) and Picrotoxin (PIC-8.0mg/kg) were administered intraperitoneally, while pure histamine (10mg/kg) was administered intramuscularly. Valproic acid and Phenytoin were given orally. The actual study was carried in two stages. The first stage of the experiment, involved animals of groups A-G; Groups A and B were given 10mg/kg of histamine only. Group C was given 5mg/kg of phenytoin while group D was given 200mg/kg of valproic acid. Groups E and F were used as the convulsion positive control models and were given 90mg/kg and 8.0mg/kg of PTZ and PIC respectively. Titration for optimal seizure doses was earlier determined. The negative controls, group G received orally 2ml/kg of pure drinking water. Thirty minutes post antiseizure or pure histamine administrations, PTZ and PIC were separately administered to a group each of those on histamine.

PIC was used to induce convulsion in animals on phenytoin while valproic acid rats received PTZ of same dosage with positive control. Seizure signs were taken as myoclonic (whole body spasm or jerks), hind limb extension and, or death and time of onset were noted for each case. At the second stage, groups H and I were used. Group H received 10mg/kg of histamine and 5mg/kg of Phenytoin at intervals of 15minutes while the last group I was given 10mg/kg of histamine and 200mg/kg of valproic acid also at intervals of 15minutes. Seizure was induced as in the first stage with the positive and negative controls also applicable. Time onset of seizure and, or death time were taken as convulsive signs and ability to prolong either or both were taken as anti seizure activity. Absence of either or both for up to 6 to 8hours post seizure induction was taken as absolute inhibition or abolishment of seizure. Results were analysed statistically using SPSS 16.0 version and presented as mean± standard error of mean. Comparative statistics of P-value less than 0.05 was considered significant.

3. RESULTS

Contrary to the work of Oliveria et al., (2008) that achieved seizure at 80mg/kg of PTZ, this study achieved significant seizure and death in PTZ-positive control at 90mg/kg. The positive controls, groups D and E exhibited average seizure onset time of 7.0minutes post convulsion induction and died at an average time of 10.2±0.2 and 10.5±0.1 minutes respectively (Table 1). Pure histamine extended PTZ and PIC-induced seizure onset-time from average of 7.0 to 22. 2 and 21.2 respectively. Their death times were equally extended to average of 30.2 and 31.2 also respectively. Antiseizure activity was however, much lower than Phenytoin and Valproic acid (Table 1).

At the second stage of the experiment, animals on pure histamine plus phenytoin though had seizure onset of 52.4minutes, recovered from seizure attack and remained alive for over 8hours post seizure induction. On the hand animals on pure histamine plus valproic acid remained with no seizure signs and, or death for over 8hours (Table 2). Non treated animals exhibited same pattern with rats on valproic acid/histamine.

4. DISCUSSION

The present study has demonstrated the seizure inhibitory activity of pure histamine in experimental animals. Histamine extended seizure onset and death time compared to positive control ($P<0.01$). Histamine exhibited a profound synergistic seizure inhibitory activity with valproic acid against PTZ induced seizures and compared with

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Table 1

Seizure inhibitory effects of pure histamine and standard anticonvulsants

Drugs	No of Animals	Weight (grams)	Dosage Mg/kg	Onset Time/Min	Death Time/Min
PTZ	5	129	90	7.0±0.3	10.2±0.2
PIC	5	130	8.0	7.0±0.1	10.5±0.1
HIS/PTZ	5	131	10/90	22.2±0.2	30.2±0.2
HIS/PIC	5	131	10/8.0	21.2±0.5	31.0±0.4
VAL/PTZ	5	130	200/90	90.4±0.2	179.8±0.4
Phy/PIC	5	130	5/8.0	49.0±0.7	60.4±0.5
Water	5	131	2ml/kg	Nil	>2880

Table 2

Synergistic seizure inhibitory effects of pure histamine

	No of Animals	Weight (grams)	Dosage Mg/kg	Onset Time/Min	Death Time/Min
PTZ	5	129	90	7.0±0.3	10.2±0.2
PIC	5	130	8.0	7.0±0.1	10.5±0.1
His+Val	5	130	10+200	Nil	>2880
His+Phy	5	129	10+05	52.4	>2880
Water	5	131	2ml/kg	Nil	>2880

Key:

PTZ = Pentylenetetrazole.
PIC = Picrotoxin
HIS = Histamine
VAL = Valproic acid
Phy = Phenytoin

positive control (P<0.001). Death was also completely abolished through a synergistic activity of histamine and phenytoin against picrotoxin induced seizure and compared with control (P<0.001). All histamine receptors are G-protein coupled receptors. H_1 couples to Gq/11 to activate PLC-IP3-Ca2+ pathway thus activating calcium ions as well as protein kinase and phospholipase A_2. H_2 is linked to Gs to activate adenylyl cyclase-cyclic AMP-protein Kinase A (PKA) pathway. H_3 and H_4 however act via Gi/o thus inhibit adenylyl cyclase. Though activation of H_4 also mobilizes calcium ions from some cells (Randal et al,. 2006). H_1 and H_2 have been shown to improve memory thus a prove point case of its excitatory activity (Li-san et al., 2003).

One would normally suggest from the above receptors actions that seizure protective activity of histamine is based on its neuro-inhibitory activity via H_3 and, or H_4 but, this appears not completely to be the case as some data suggest that the seizure protective effect is more via H_1 and less via H_3. Recent literatures perhaps have elucidated this small confusion. Histamine has more affinity for H_4 and H_1 is intrinsically coupled onto H_4 which is predominantly involved in inflammation and excitation (Seifert et al., 2011). In kainic acid (KA)-treated slices, the H_3 receptor antagonist thioperamide enhanced the neuroprotective effect of histaminergic neurons, whereas the H_1 receptor antagonists, triprolidine and mepyramine dose-dependently decreased the neuroprotection of H_1 (Kukko-Lukjanov et al., 2006). The above results suggest that histaminergic neurons protect the developing hippocampus from KA-induced neuronal damage, with regulation of neuronal survival being at least partly mediated through H_1 and H_3 receptors. However, the importance of histaminergic neurons in seizure-induced cell damage is poorly known (Ferenc and Czuczwar, 2008).

Another very recent work adds that histamine receptors act like GABA and are involved in chloride conductance to activate GABA-like activity mediate inhibitory activity of histamine (Fleck et al., 2012). It has been demonstrated that increased histamine levels elevate the seizure threshold and reduce the severity and duration of seizures, whereas decreased histamine levels have the opposite effect. Of the four histamine receptors, the histamine-1 (H_1) and histamine-3 (H_3) receptors are suggested to be of importance in decreasing seizure activity. The first-generation H_1 receptor antagonists, such as ketotifen and chlorpheniramine, elicit epileptiform activity. The H_3 receptor

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antagonists, which block H_3 autoreceptor function, are believed to decrease seizure activity by increasing histamine release.

Our present work adds two major contributions to existing data. First and most importantly is the fact that it demonstrated synergistic seizure inhibitory activity of histamine and tested standard anticonvulsant. Pure histamine however because of its pharmacological effect may not be used in therapy. Its blockade has been proven therefore to decrease the effectiveness of antiseizures drugs. Secondly, the work has demonstrated the seizure inhibitory activity of pure histamine. Mechanisms that underlie this action most likely relates to our earlier and above analysis on histamine.

4. CONCLUSION

Histamine has antiseizure activity in both PTZ and PIC induced. Its synergistic activity is more with absence seizure when extrapolated to man. Concurrent administration of antihistamines in febrile state with allergy must be done cautiously if not avoidable. While the risk/benefit ratio with the use of antihistamines in known or potential epileptic must be re-evaluated. We recommend increase in education of mothers to avoid giving antihistamine to febrile children. Continuous education should be encouraged to educate doctors and other health workers.

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