Full Length Research Paper

Selective antiseizure activity of synthetic morpholine in experimental animals

Azikiwe C. C. A.[1]*, Siminialayi I. M.[1], Brambaifa N.[2], Ifezulike C.C.[2], and Nwankwo M. J.[3], [4]Amazu LU.

[1]Department of Pharmacology, College of Health Sciences, University of Port Harcourt, Nigeria.
[2]Department of Paediatrics, Anambra State University, Uli, Nigeria.
[3]Department of Medical Rehabilitation, Nnamdi Azikiwe University. Nnewi, Nigeria.
[4]Department of pharmacology, Imo State University, Orlu. Imo State. Nigeria.

More than two third of epileptic patients have inadequate control of seizure as no drug has been found to be truly antiepiletogenic, a process through which a normal neuron becomes epileptic. Morpholine is an alkaloid and an active constituent of *Crinum jagus*, a medicinal plant used in the treatment of all forms of convulsive seizures in traditional medicine. Antiseizure activity of morpholine was investigated. Convulsion was induced using maximum electric shock (MEST), pentylenetetrazole(PTZ), strychnine and picrotoxin in the appropriate animal models. Seizures onset time and death time were used as standard convulsive signs while prolongations of these features were taken as anticonvulsant activity of standard drugs/morpholine. Results were analyzed using SPSS-16.0 version. Acute toxicity (LD$_{50}$) of morpholine was found to be 2.21 mg/kg (IP in mice) based on the arithmetic method of Karbar. Morpholine exhibited a dose dependent antiseizure activity against PTZ induced seizure (P<0.001). The antizeizure activity of morpholine was higher than that of valproic acid (P<0.001), a standard drug used in absence seizure. Morpholine showed no statistically significant antiseizure activity against MEST, strychnine and picrotoxin induced seizures. Synthetic Morpholine is though very toxic but, has potent selective antiseizure as well as antiepileptogenic activity which if well controlled could be used in the treatment of absence seizure and its complications in man. It is highly recommended that a further characterization of the extracts of *C. jagus* being carried out as well as clinical trial of a less toxic form of morpholine be carried out in man.

Key words: Morpholine, *Crinum jagus*, medicinal plants, seizure, epilepsy, epileptogenesis, antiepileptogenesis.

INTRODUCTION

Seizure is coined from the Latin word *Sacire* "To take possession of". Seizure (Convulsion) is therefore a paroxysmal event due to abnormal, excessive hyper-synchronous discharges from aggregates of central (Cerebral) neurons (Lowenstein, 2010).

Although, a variety of factors influence the incidence and prevalence of seizures, approximately, 5 to 10% of the population will have at least one seizure during their life time with the highest incidence occurring during early childhood and late adulthood and because seizure is common, this clinical condition is encountered frequently during medical practice in a variety of settings(Lowenstein, 2010).

Seizures could occur in a variety of clinical settings, including febrile convulsion that is common in children, head injury, enclampsia in pregnancy, frank epilepsy, septicaemia, tetanus, meningitis, stroke, metabolic disorders and could be of different kinds (Allen, 2010). Seizure in epilepsy is unprovoked, intractable and reoccurring unlike seizures in other settings that could be secondary (Lowenstein, 2010; Clarke, 2009), thus not all seizures are epileptic.

Most epileptic patients do not only suffer from stigmatization, they usually suffer from depression, mus-

*Corresponding auhor. E-mail: ccazikiwe@yahoo.com.
Tel: 2348037203029.

cular spasm, strange sensations, abnormal behavioural changes, convulsions, loss of consciousness and are highly prone to suicide and sudden, unexpected death(Boison, 2007). Epilepsy affects natural intelligence among a studied group of Nigerian epileptics (Sunmonu et al., 2008). Recurrent excitatory activity or increased latency period of convulsion results in neurosis and dementia, as glutamate damages the brain cells(Levite and Ganor 2008).

Current drug therapy tends to target certain strategies in the pathogenesis of seizure. The dentate gyrus (DG) is a gateway that regulates seizure activity in the hippocampus.   Lamotrigine when used as an anticonvulsant, blocks both AMPA and NMDA receptors of glutamate (Lee et al., 2008). During seizures, electrical impulses are distributed from one neuron in the brain to another through ion channels. Major ion channels include Sodium and Calcium. Therapeutic drugs in current use are therefore employed to block these ions thus correct the spread of seizure. Notable examples are phenytoin and carbamazepine that block Sodium ions and are thus used for grandmal seizures. Ethosuximide and valproic acid that block calcium ions in T-channel receptor, are used for Petitmal seizures. A counter action of gamma amino butyric acid (GABA) which is inhibitory to the excitatory effect of glutamate/aspartate is employed in therapy. This includes the use of benzodiazepines or barbiturates as GABA-enhancers, gabatin, pregabalin and gabapentin as GABA analogues and vigabatrin or tiagabin as GABA hydrolysis inhibitors. Direct blockade of glutamate receptors is also employed in therapy. Lamotrigine acts in this manner (Lee et al., 2008).

These drugs/strategies however bring about only symptomatic relief as they do not control epileptogenesis, the process by which the brain develops epileptic(Kumaria et al., 2008; Costa et al., 2011).

Current research into antiseizure therapy is looking into the possibility of synthesizing drugs that can block the gliotransmission of ATP (adenosine tri-phosphate). This transmission in astrocyte-glia cells leads to astrocyte-calcium wave generation. Blockade of ATP signaling will not only decrease the frequency of epilepsy, it will make more adenosine available through further hydrolysis of ATP [Kumaria A et al., 2008]. The list of anti seizures has even tripled in the 21 first century but, epilepsy remains a big clinical burden as no definite cure/control without devastating adverse effects appears to be in sight (Costa et al., 2011)

More than one third of patients with epilepsy have inadequate control of seizures with drug therapy, as most drugs in current use are largely palliative and there currently exist no drug that has eliminated or prevented reoccurrence of epilepsy (Antiepileptogenic) (Allen, 2010).

An intriguing possibility is to control acquired epilepsy by preventing epileptogenesis, a process by which the brain becomes epileptic. A number of antiepiletics have been evaluated in clinical trials to test whether they prevent epileptogenesis in humans, but to date no drug has been shown to be effective in such trials. Thus, there is a pressing need for drugs that are truly antiepileptogenic to either prevent epilepsy or alter its natural course (Costa et al., 2011)

Morpholine; a synthetic alkaloid of *Crinum jagus* (*C.jagus*).

Out of the three main active component of *C. jagus* morpholine appears to be the only specific components. Other active components of *C. jagus* hamayne and lycorine are not only found in other plants (Berkov et al., 2007), they are found in most other species of *Crinum* (Houghton et al., 2004).

Morpholine extract from *C. jagus* is liquid at room temperature and above but as crystalline solid at temperatures below 14-15^{0}C. It has a strong smell of ammonia, slimy and colourless (Edema and Okanieimen, 2002). Its other names are diethylenimide oxide and 1,4-oxazinane tetrahydro-1,4 oxazine (Klaus et al., 2003).

The Chinese originally obtained morpholine from some plants but, many companies today rely on the synthetic form. Dilutions usually, 1-5% of morpholine are used in treatment of seizures and other ailments in China (Emily Fans, 2009). Morpholine has a chemical structural formula of C_4H_9ON while structurally it can be represented (Figure 1).
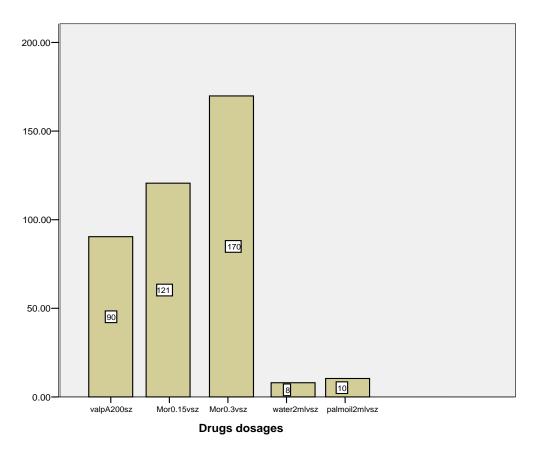
Synthetic morpholine is soluble in water and most other solvents. It has a boiling point of 128.4, melting point of 4.6 and igniting (firing point of 310). It has the same relative density with water, has strong smell of ammonia and interlaced soft sweet smell typical of amines (Klaus et al., 2003). It can be synthesized in the Laboratory by neutralizing ethanolamine with sulfuric acid (Klaus et al., 2003). Morpholine is used as a chemical emulsifier in waxing of fruits and as structural building block in the preparation of certain antibiotic like linezolide (Klaus et al., 2003). But, morpholine is classified as a toxic chemical (Klaus et al., 2003).

Morpholines have been shown to block T-receptors of calcium ion channels (Ku et al., 2006). Morpholines also have been shown to possess antienzymes activity against some parasites including plasmodium falciparum as well as inhibition of cyclooxygenase (Khan et al., 2005). Methoxy and hydroxyl morpholine derivatives of phencyclidine have recently been shown to exhibit analgesic/pain perception activity in rats (Ahmadi et al., 2011).

MATERIALS AND METHODS

Animals

Total number of animals used for the study consisted of 53 Wister Albino Mice, 20 adult Wister Albino Rats and

Figure 1. Mean seizure onset time in PTZ induced seizure.ValpA200mgdth stands for valproic acid (standard positive control) 5 mg/kg.), Mor0.15dth stands for death time of low dose morpholine (0.221 mg/kg), Mor0.3dth stands for death time of high dose morpholine (0.442 mg/kg), Water2mldth stands for negative control (Water-2 ml/kg), Palmoil2mldth stands for transport vehicle (TV) control (palm oil-2 ml/kg).

20 day-old Chicks. Previous work showed that different animal models exhibit varying degree of sensitivity to seizures induction models thus our choice of animals. Drugs consisted of convulsant models and standard anticonvulsants.

Morpholine

Bought as a synthetic product from Anhuie Hermann Chemical Company, China and used as such.

Animal study: Acute toxicity (LD$_{50}$) study)

Lorke's 1983 method and as used by Azikiwe et al., 2007; Akhila et al., 2007 and Azikiwe et al., 2009, involved the use of 13 animals and divided into two stages. At the first phase, a total of 9 male mice of average weight of 20.5 grams were used.

The animals were divided into 3 groups (A-C) of 3 animals per group. Morpholine was administered intraperitoneally to the mice at doses of 10mg/kg,

100mg/kg and 1000mg/kg. All animals had unrestricted access to water and animal feed and were then observed in their cages for 24hours. The animals were observed for possible signs of toxicity **(**anorexia, drowsiness, apnoea, immobility, twitches and irritation**)** and, or death. All dead animals were immediately removed from the cage as soon as possible once death was observed, counted and recorded.

All animals died within 24 hours thus by Lorke's definition, morpholine was too toxic to be used in man.

Acute toxicity based on karber's method

Karber's method became necessary because Lorke's method could not be employed for morpholine.

An initial pilot study was carried out using a total of 4 mice of average weight of 20.5g. The animals were divided into four cages (A-D) with an animal per cage and given 10mg/kg, 1000mg/kg, 5000mg/kg and 10,000mg/kg of morpholine intraperoteneally respectively. All animals were then observed for 24 hours for any sign of acute toxicity.

Table 1. Morpholine acute toxicity (Karber's Method).

Doses mg/kg	No. Dead	Dose difference (a)	Mean Mortality (b)	a x b
0.5	Nil	Nil	0	0
1.0	Nil	0.5	0	0
1.5	Nil	0.5	0	0
2.0	4	0.5	2	1
2.5	4	0.5	4	2.0
3.0	5	0.5	4.5	2.25
4.0	6	1.0	5.5	5.5

LD50 of Karber is got Arithmetical method of Karber. The interval mean of the number dead in each group of animals was used as well as the difference between doses for the same interval. The product of interval mean and dose difference was obtained. The sum of the product was divided by the number of animals in a group and the resulting quotient was subtracted from the least lethal dose to all animals in a group in order to obtain LD50 value. Therefore LD50 = 4 minus the quotient (1.79) which is equal to 2.2083333mg/kg. LD50 of morpholine based on Karber's method is therefore 2.208 or approximately 2.21mg/kg(IP) in mice.

All animals that received morpholine died thus necessitating another pilot study in which 1mg/kg, 4mg/kg, 6mg/kg and 8mg/kg of morpholine was administered intraperitoneally respectively, to another set of four mice. All animals were again observed for 24 hours.

The main study commenced subsequently, with 48 mice of average weight of 20.5g. The mice were divided into 8 groups (A-H) of 6 mice per group. Animals in group G received 1ml/kg of water for injection intraperitoneally, and thus served as negative control.

Morpholine was administered in doses of 0.5mg/kg, 1.0mg/kg, 1.5mg/kg, 2.0 mg/kg, 2.5 mg/kg, 3.0mg/kg and 4.0 mg/kg, respectively to mice in groups A to G.

All animals had unrestricted access to drinking water and animal feed throughout the 24-hour duration of the experiment. All animals were observed for signs of toxicity as described earlier. Dead animals were counted and recorded against the dosage group.

The interval mean of the number dead in each group of animals was used as well as the difference between doses for the same interval. The product of interval mean and dose difference was obtained. The sum of the product was divided by the number of animals in a group and the resulting quotient was subtracted from the least lethal dose to all animals in a group in order to obtain LD_{50} value [Akhila JS et al., 2007].

LD50 = The apparent least dose lethal to all in a group–
$\square$ (a x b)

N
where N is the number of animals in each group, **a** is the dose difference and **b** is the mean mortality.

Convulsion induction models

Convulsion was induced in different animal models using maximum electric shock (MEST), pentylenetetrazole(PTZ), strychnine(Sty) and picrotoxin(Picro). While maximum electric shock was used in 25 day old chicks, PTZ was used in 25 adult rats and Sty and Picro were used each in 25 adult mice. The methods employed standard methods (Edema and Okanieimen, 2002; Azikiwe et al., 2009; Ode et al., 2010). Warm red palmoil(2ml/kg) was used as transport vehicle control to account for its use by traditional healers. Pure drinking water (2ml/kg) was used as negative control.

RESULTS

LD_{50} of Karber was obtained by the Arithmetic Method of Karber. The interval mean of the number dead in each group of animals was used as well as the difference between doses for the same interval. The product of interval mean and dose difference was obtained. The sum of the product was divided by the number of animals in a group and the resulting quotient was subtracted from the least lethal dose to all animals in a group in order to obtain LD_{50} value.

LD50 = The apparent least dose lethal to all in a group –
$\square$ (a x b)

N
where N is the number of animals in each group, **a** is the dose difference and **b** is the mean mortality (Table 1).
$\square$ (a x b)
    N

Table 2. Average Seizure onset time and Death time in minutes.(MEST).

Doses	Seizure onset time (Min)	Death time in minutes
Phenytoin-5 mg/kg	49.0±0.71 *	60.4±0.5*
Morpholine-0.221 mg/kg	8.2±0.21	9.4±0.24
Morpholine-0.442 mg/kg	8.2±0.2	9.4±0.24
Water-2 ml/kg	6.3±0.20	7.8±0.2
Palm oil-2 ml/kg	6.8±0.2	8.4±0.4

*indicates results with significant antiseizure activity compared with control(P value<0.01).

Table 3. Average PTZ Induced seizure onset time and death time in minutes.

Doses	Seizure onset time (Min)	Death time in minutes
Valproic acid-200 mg/kg	90.4±0.24 *	179.8±0.37*
Morpholine-0.221 mg/kg	120.6±0.2*	Nil (0000± 00)***
Morpholine-0.442 mg/kg	169.8±0.66*	Nil (0000± 00)***
Water-2 ml/kg	8.0±0.31	9.0±0.31
Palm oil-2 ml/kg	10.4±0.24	15.0±0.31

Indicates results with significant ant seizure activity compared with control(P value<0.001). *** indicates death completely abolished.

= 1 + 2 + 2.25 + 5.5 = 10.75. Quotient is 10.75 divided by 6 which is equal to 1.79 where
N = 6.
The least apparent dose lethal to all animals in the group = 4
Therefore LD50 = 4 minus the quotient (1.79) is equal to 2.2083333mg/kg.
LD50 of morpholine based on Karber's method is therefore 2.208 or approximately 2.21mg/kg (IP) in mice.

Anticonvulsant activity in day-old chicks (MEST)

Morpholine did not show any significant activity against MEST induced seizure. Both doses of morpholine had equal antiseizure activity and almost of the same effect with those of water and palm oil (*Table 3.02*). *C. jagus* like most medicinal plants formulation by traditional medicine healers is macerated in palm oil. The present study could not demonstrate any significant antiseizure activity of palm oil (Table 2).

Anticonvulsant activity against pentylenetetrazole (PTZ) induced seizure

Oliveria et al.,2008, achieved seizure at 80mg/kg. In the present study seizure was achieved at 90mg/kg from our earlier pilot study.
    With PTZ induced, there was mild statistically insignificant antiseizure activity of red palm oil. Morpholine on the other hand extended seizure onset time in a dose dependent fashion (P<0.001) but, completely abolished death at both dosages (Table 3 and

Figures 1 and 2). The animals though convulsed but rapidly recovered and remained alive through out the experimentation period.
    Those of Valproic acid which exhibited intermittent seizures, showed increase in seizure onset time but, later died at their final average time of 179.8mins. Antiseizure activity of morpholine was statistically more superior to that of valproic acid (P<0.001).

Anticonvulsant against seizure induced by strychnine (8mg/kg subcutaneously {SC}).
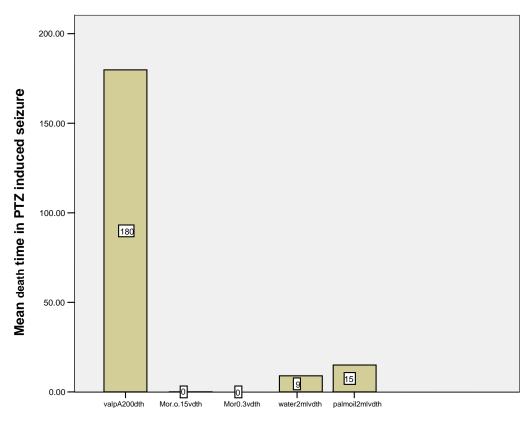
Morpholine had an insignificant extension of both seizure onset time and death time. Its results were similar to those of water and palm oil. Diazepam on the hand showed significant extension of both parameters (Table 4).

Anticonvulsant against seizure induced by Picrotoxin (6mg/kg SC)

The results of Strychnine and Picrotoxin induced seizures were similar. Morpholine again had no significant antiseizure activity against picrotoxin induced seizure (Table 5).

DISCUSSION

Among the objectives of the present study were to investigate the safety margin of morpholine, to investigate the anticonvulsant activity of morpholine, to find out the specific seizure type(s) that morpholine is most effective

Figure 2. Mean Death Time in PTZ induced seizure. Key to figure 2. ValpA200mgdth stands for valproic acid (standard positive control) 5 mg/kg.), Mor0.15dth stands for death time of low dose morpholine (0.221mg/kg), Mor0.3dth stands for death time of high dose morpholine (0.442 mg/kg), Water2mldth stands for negative control (Water-2 ml/kg), Palmoil2mldth stands for transport vehicle (TV) control (palm oil-2 ml/kg)

at controlling and to elucidate the specific mechanism(s) of its anticonvulsant activity.

The present study found that morpholine is oily in appearance and has specific and selective activity against PTZ induced seizure. Morpholine's seizure inhibitory activity was dose dependent and superior to that of valproic acid ($P<0.01$), a standard anticonvulsant against absence seizure in man.

Edema and Okaniemen, 2002, administered 200mg/kg of both the crude extract of *C. jagus* and morpholine fraction. They demonstrated seizure inhibitory activity of *C. jagus* against MEST-induced seizures but all the animals in their study died at 200 mg/kg of their morpholine fraction most probably due to lethal toxicity, rather than the inability of the morpholine fraction to inhibit MEST-induced seizures. The present study has gone ahead not only to demonstrate the safety dose of morpholine but, also the specific type of seizure inhibited by the morpholine fraction.

Earlier in history, (Dua et al.,1994), had demonstrated antiseizure activity of morpholine against PTZ and MEST induced seizure. The present study could not however

demonstrate significant activity against MEST induced.

As stated earlier in the methods, inhibition of MEST-induced seizures signifies anti-generalized tonic-clonic, myoclonic and atonic (grandmal) seizure while inhibition of PTZ-induced seizures implies inhibition of generalized non-convulsive (absence) seizures. Alkaloids and flavonoids have been shown to possess anticonvulsant activity (Oloyede et al., 2010; Faggion et al., 2011). Their mechanism of anti-seizure activity may be due to their antioxidant activity or through some vague means(Oloyede et al., 2010). Morpholine is an alkaloid of C. jagus and its antiseizure activity against PTZ-induced seizures may stem from its presence.

Morpholines have been shown to block calcium ions in T- and N-Channels of the neuron although it is more selective for T-channels (Ku et al., 2006). Blockade of calcium in T-channels is employed in drug therapy of seizures. Drugs like ethosuximide and valproic acid in particular, is used for the treatment of petitmal epilepsy (absence seizure) and acts via the above stated mechanism.

Recently too, prostaglandins have been demonstrated

Table 4. Average strychnine induced-seizure onset time and death time in minutes.

Doses	Seizure onset time(Min)	Death time in minutes
Diazepam-5 mg/kg	45.2±0.37*	50.6±0.24*
Morpholine-0.221 mg/kg	8.4±0.24	9.4±0.24
Morpholine-0.442 mg/kg	8.2±0.20	9.0±0.00
Water-2 ml/kg	6.2±0.20	8.4±0.24
Palm oil-2 ml/kg	7.4±0.24	8.6±0.24

Key: * indicates results with significant ant seizure activity compared with control. (P value<0.01).

Table 5. Average picrotoxin induced-seizure onset time and death time in minutes.

Doses	Seizure onset time(Min)	Death time in minutes
Diazepam-5 mg/kg	45.0±0.31 *	50.6±**0.4**ced*
Morpholine-0.221 mg/kg	8.2±0.37	9.2±0.20
Morpholine-0.442 mg/kg	8.4±0.24	9.8±0.37
Water-2 ml/kg	6.4±0.24	8.6±**0.4**
Palm oil-2 ml/kg	7.6±0.4	9.6±**0.4**

* indicates results with significant difference from negative control.(P value<0.01).

to decrease the seizure induction threshold of PTZ from 60mg/kg to 20mg/kg in rats (Oliveria et al.,2008). With the use of celecoxib (a COX_2 selective antagonist), these researchers buttressed the point that blockade of cyclooxygenase-$_2$, decreases the chance/frequency of seizures as well as decreases its latency period.

Morpholine blocks cyclooxygenase and has promising anti-inflammatory as well as analgesic effects (Khan et al., 2005; Ahmadi et al., 2011).

Adenosine has been clearly demonstrated as an inhibitory transmitter and decreases neuronal excitation induced by caffeine, glutamate and acetylcholine (Eugene, 2004).The secretory apparatus for these excitatory substances is intimately coupled to the Ca^{2+} channels (Eugene, 2004).

Mechanism of antiseizure activity of morpholine can be linked to possible dual effects of calcium ion blockade of the T-receptor and inhibition of cyclooxygenase enzyme. The calcium ion blockade may be at two sites, namely: (a) at the T-receptor and (b) an adenosine enhanced calcium blockade. Stimulation of adenosine release is currently being exploited in treatment of seizures/epilepsy [Kumaria et al., 2008).].

The most disturbing thing about seizures is epileptogenesis, the underlying cause of a previously healthy or non epileptic cerebral neuron becoming epileptic (Lowenstein, 2010; Allen, 2010; Kumaria et al., 2008).

Notable examples of epileptogenic substances or factors are deep head injury, stroke, prostaglandins, neurosyphilis and fever. Africa, most especially Nigeria and most other parts of the tropics/sub tropics live with

malaria and other infectious diseases that cause fever. Plasmodiasis is a major cause of malaria fever in Nigeria and other tropical countries (Amazu et al., 2010).

Fever is one of the major mediators of neuronal excitation in children, resulting in febrile seizure. Fever also has a relationship with prostaglandins in the pathogenesis of inflammation (Okada et al., 2006). Okada et al., 2006, reported that cytokines (mediators of inflammation) and cyclooxygenase are up-regulated in the brain of human epilepsy and animal models induced by electroconvulsive method (MEST). These authors demonstrated that prostaglandins tend to be more effective in post MEST-induced seizure. There is therefore a large volume of prostaglandins in the brain following the up-regulation of their synthetic enzymes. It follows from the foregoing that inflammation caused by prostaglandin upsurge could be epileptogenic as well as acting to sustain grandmal epilepsy in man. In summary prostaglandins appear to be the major "strong-hold" in seizure/epilepsy. Factors or substances that can initiate their synthesis and/or release will be epileptogenic while their accumulation will enhance recurrence and increase in latency periods of seizure.

This may be responsible for the recurrence and frequency of seizure-attacks experienced in epilepsy.

Morpholines have also been shown to possess anti-topoisomerase-1 activity against Leishmania donovani (Kuettel et al., 2007). Morpholine has activity against Hepatitis C virus (Khan et al., 2005), and some species of Trypanosomes (Kuettel et al., 2007), but, most importantly, against Plasmodium falciparum (Kuettel et al., 2007), a major cause of malaria fever in the tropics and

sub-tropics.

Malaria fever is perhaps the most common form of fever in the tropics and fever is epileptogenic. Successful control of febrile seizure with *C. jagus*, by traditional medicine practitioners may have arisen from the antimalarial and antiseizure activities of the plant. One can therefore state from the present study and existing literature that *C. jagus* via mainly its morpholine component also possess antiepileptogenic activity.

Physiologically, astrocytes down-regulate kinases by synthesizing kynurenic acid. kynurenic acid on the other hand down-regulates the activity of glutamate (Kumaria et al., 2008).

Dysfunction of astrocytes in brain injuries or in age-related neurodegenerative disorders or states is probably the hall mark of epileptogenesis as the excitatory activity of glutamate goes out of physiological regulation. Kynurenic acid although naturally found in the CNS of man, has now also been richly found in most medicinal plants and honey-bee (Turski et al., 2008). There is the possibility that kynurenic acid is not only present in *C. jagus,* but may have contributed to *C. jagus*' antiepileptogenic activity.

The synthetic morpholine, from our present study is very toxic and cannot easily be recommended to man but, its proven activity against absence seizure cannot be over-emphasized.

CONCLUSION

Synthetic Morpholine is though very toxic but, has potent selective antiseizure as well as antiepileptogenetic activity which if well controlled could be used in the treatment of absence seizure and its complications in man. It is highly recommended that a further characterization of the extracts of *C. jagus* should be carried out as well as clinical trial of a less toxic form of morpholine be carried out in man.

ACKNOWLEDGEMENT

REFERENCES

Lowenstein DH (2010). Seizures and Epilepsies. Ed in Harrison's principles of internal Medicine, Churchill Livingstone medical publications- McGraw-Hill access medicine, USA. Pp. 2124-2157.

Allen CMC, Lueck CJ, Dennis M (2010). Neurological disease. Eds in Davidson's principles and practice of medicine Churchill Livingstone Elsevier, Edinburgh. Pp 1131-1156.

Clarke CRA (2009). Neurological diseases. Ed in Kumar and Clark's Clinical Medicine, Saunders Elsevier. London. Pp. 1137-1145

Boison D (2007). The adenosine kinase hypothesis of epileptogenesis. Prog neurobiol., **11** (12) 234-239.

Sunmonu TA, Komolafe MA, Ogunrin AO, Oladimeji BY, Ogunnniyi A (2008). Intellectual impairment in patients with epilepsy in Ile-Ife Nigeria Acta Neurol Scand. **6** (11). 311-316

Levite M, Ganor Y (2008). Autoantibodies to glutamate receptors can damage the brain in epilepsy, systemic lupus erythematosus and encephalitis. Neuro., **56** (11) 1111-1117.

Lee CY, Fu WM, Chen CC, SU MJ, Liou HH (2008). Lamotrigine inhibits Post synaptic AMPA receptor and glutamate release in the dentate gyrus. Neuro., **56** (11) pg 910-916.

Kumaria A, Tolias CM, Burnstock G (2008). ATP signaling in epilepsy. Purinergic signal. Epilepsia; **44**(12) Pg. 11-14.

Costa J, Fareleira F, Ascencao R, Wiznitzer A (2011). Clinical comparability of the new antiepileptic drugs in refractory partial epilepsy: A systematic review and meta-analysis. Epilepsia; **52**(7):1280-91.

Berkov S, Codina C, Viladomat F, Bestida J (2007). Alkaloids from Galanthus nivalis. Phytochemistry, **68**(13): 1791-1798.

Houghton PJ, Agbedahunsi JM, Adegbulugbe A (2004). Choline esterase inhibitory properties of alkaloids from two Nigerian Crinum species. Phytochemistry **65**(21): 2893-2896.

Edema MO, Okanieimen FE (2002). Chemical and anticonvulsant screening of Crinum jagus bulbs: Nig. J. Chem. Res., **7**: 25-28.

Klaus W, Hans-jurgen A, Charlet RL, Hawkins S (2003). Oxidation products of ethylene. Industrial chemistry, 4th Edition, Wiley-VCH, Pp. 159-161.

Emily Fans (2009). Uses of morpholine in China: Oral communication Anhuie Hermann Chemical Company, China..Kindly provide page number

Ku IW, Cho S, Doddarrddy MR, Jang MS, Keum G, Lee JH, Chung BY, Kim Y, Rhim H, Kang SB (2006). Morpholin-2-one derivative as novel selective T type Ca^{2+} channel blockers. Bioorg Med Chem Lett, **16** (19) 5244-5248.

Khan RA, Afroz S, Ara A, Saify ZS (2005) Pharmacological activity of morpholino compounds. Pak J. Pharm Sci., **18**(3) 55-59.

Ahmadi A, Khalili M, Hajikhani R, Naserbakht M. (2011) New morpholine analogues of phencyclidine: chemical synthesis and pain perception in rats. Pharmacol. Biochem. Behav., **98** (2). 227-233.

Azikiwe CCA, Unekwe PC, Amazu LU, Nwankwo MJ, Affonne OJ, Chilaka K, Ezeani MC, Nwosu PJC (2007). Anticoagulation and Anti-thrombotic activity of Triclisia dictyophylla, Moonseed. J. Nat. Prod. Medic **11**, 26-29.

Akhila JS, Deepa S, Alwar MC (2007). Acute toxicity studies and determination of median lethal dose. CURRENT SCIENCE. **93,** (7): 917-920.

AZIKIWE CCA, Amazu LU, Unekwe PC, Nwaosu PJC, Ezeani MC, Siminialayi MI, Obidiya SO Arute JE (2009). Antidiabetic fallacy of Vernonia amygdalina in human diabetes. Asian Pacific J Tropical Med., **2**(5) 54-57.

Ode OJ, Nwaehujor CO, Onakpa MM (2010). Evaluation of antihaemorrhagic and antioxidant potentials of *Crinum jagus* bulb. Int. J. Appl. Biol. Pharm.Technol., **1**(3):1330-1336.

Oliveira MS, Furian Rambo LM, Ribeiro LR, Royes LF, Ferrira J, Calixto JB, Melio CF (2008). Modulation of pentylenetetrazole-induced seizure by prostaglandin E2. Neuroscience, 152(4):1110-1118.

Dua PR, Ahuja P and Anand N: p-Aminobenzene sulphonyl morpholine, compound 82/208 a new anticonvulsant agent. Indian J. Experim. Biol., 1994, 32(10) 729-731.

Oloyede KG, Oke MJ, Raji J, Olugbade T(2010). Antioxidant and anticonvulsant alkaloids in Crinum ornatum bulb extract. World J. Chem., **5**(1): 26-31.

Faggion SA, Cunha AO, Fachim HA, Gavin AS, dos Santos WF, Pereira AM, Beleboni RO (2011) Anticonvulsant profile of the alkaloids (+)-erythravine and (+)-11-α-hydroxy-erythravine isolated from the flowers of Erythrina mulungu Mart ex Benth (Leguminosae-Papilionaceae). Epilepsy Behav., 20(3):441-446.

Eugene SM (2004). Adenosine decreases both presynaptic calcium currents and neurotransmitter release at the mouse neuromuscular junction. J physiol., 135(6): 12-15.

Amazu LU, Azikiwe CCA, Njoku CJ, Osuala FN, Nwosu PJC, Ajuquo AO, Enye JC (2010). Anti-inflammatory activity of methanolic extract of the seed of Carica papaya in experimental animals. Asian Pac J Trop. Med., 12(6). 1-5.

Okada K, Yamashita U, Tsuji S (2006). Cyclooxygenase system contributes to the maintenance of post convulsive period of epileptic phenomena in the genetically epileptic El mice. UOEH, **28**(3):265-275.

Kuettel S, Zambon A, Kaiser M, Brun R, Scapozza L, Perozzo R (2007). synthesis and evaluation of antiparasitic activities of new 4-5 (4-phenoxyphenyl)-2H-pyrazol 3-yl) morpholine derivatives. Med. Chem., 50(23):833-839

Turski MP, Turska M, Zgrajka W, Kuc D, Turski WA (2008). Presence of kynurenic acid in food and honeybee products. Amino acids., **1**(30)12-19.