

# Furosemide terminates generalised seizure status epilepticus in a woman with inter-ictal focal seizures

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**Status Epilepticus is an additional and life-threatening burden for patients living with epilepsy and their families. Extra precautionary measures attend the use of present medications available to treat the disorder. In this report, a 55-year old woman who presented with recurrent generalised tonic-clonic seizures and loss of consciousness between seizures had her attacks abated with 40mg of intravenously-administered furosemide. Her vital signs remained unperturbed and she regained consciousness in less than 30 minutes of the furosemide administration indicating that there was no evolution to subtle status epilepticus; after which there was post-ictal sleep which lasted about two hours. Also in this report, the mechanism of action of furosemide responsible for its seizure-terminating effects is discussed. The use of furosemide with its therapeutic efficacy, low cost and safety profile may stand to be a welcome addition to the armamentarium available to deal with status epilepticus.**

**Keywords:** Furosemide; Status Epilepticus; Generalised tonic-clonic seizures.

## INTRODUCTION

Status epilepticus (SE) is defined as a single clinical seizure lasting more than 30 minutes or repeated seizures over a period of more than 30 minutes without intervening recovery of consciousness (Knake et al., 2009). The first-line drugs for treatment of SE are the benzodiazepines, lorazepam and diazepam, which, if administered at the scene or pre-hospital setting, have been found to be associated with a greater likelihood of seizure termination. Phenytoin and fosphenytoin are

alternative first-line drugs, while valproic acid, levetiracetam and lacosamide are being tried as third-line drugs for refractory SE or failure of first-line drugs (Knake et al, 2009). Refractory SE may be an indication for coma induction with the traditional second-line drugs of narcotics and general anaesthetics comprising propofol, midazolam or barbiturates (pentobarbitone or thiopental). Other anaesthetics that may be tried for refractory SE include isoflurane, ketamine and lidocaine. Since current antiepileptic drugs (AEDs) do not provide cure nor prevent relapse and are associated with neurotoxic side-effects, there is need for an ideal antiepileptic drug with broad-spectrum activity, rapid onset of action, minimal side-effects, good oral bioavailability and low cost. A goal of current antiepileptic research is the identification of additional molecules targeting novel molecular mechanisms involved in neuronal excitability control.

Fresh insights are emerging into the mechanisms by which diuretics, which have been in use in treatment of SE and epilepsy control, might reduce susceptibility to seizures (Maa et al., 2011; Haglund and Hochman, 2005). Maa and his co-workers believe that it may be time to re-examine whether diuretics could serve as

## List of Abbreviations

SE: status epilepticus; GCSE: generalized convulsive status epilepticus; GTC: generalized tonic-clonic seizures; SPS: simple partial seizures; CPS: complex partial seizures; PWE: patients living with epilepsy; NKCC<sub>1</sub>: isoform 1 of the sodium-potassium-chloride co-transporter; KCC<sub>2</sub>: isoform 2 of the potassium-chloride co-transporter (neuron-specific); BDNF: brain-derived neurotrophic factor; CCB: calcium channel blocker; NPY: neuropeptide Y; ECS: extra-cellular space

adjunctive therapies in the treatment of refractory epilepsy. Low-dose furosemide is safe for maintenance treatment of epilepsy (Our unpublished report; Hesdorffer et al., 2001; Frewin et al., 1987).

### Case report

In March, 2010, a 55-year old woman living at Obeidu, Uromi was brought to us at Oseghale Oriaifo Medical Centre, Idumebo-Ekpoma at 8.00am with a history of recurrent convulsions which started at about 4.30 am in the morning of the 16<sup>th</sup>. It was also stated that she had lost consciousness since the attacks. The relations gave a history of similar attacks last year and 10 years ago and that an electroencephalogram (EEG) done earlier at a centre in Benin-City diagnosed complex partial seizures for which she has been on monotherapy with phenytoin but that, recently, there has been problems with drug procurement. Skull X-ray done at the same time was normal. Furthermore, there was no history of exposure to convulsion-provoking agents such as lidocaine, camphor, hypoglycaemic agents such as ethanol and insulin, toxic fumes, cyanide, heavy metals such as lead, pesticides (patient is a farmer), nicotine, cocaine, belladonna alkaloids such as atropine, chloroquine, mefloquine, tricyclic antidepressants, phencyclidine and sympathomimetics such as amphetamine. On examination, the attack was a dramatic series of generalized tonic-clonic seizures. Each seizure was discrete with the motor activity stopping abruptly. A gradual recovery was followed by the next seizure with no recovery of consciousness. The convulsions were sustained without pause until the end of each individual seizure, distinguishing the attacks from that of psychogenic non-epileptic seizure (PNES) where the motor activity is often punctuated by brief periods of rest. Also, there was evidence of lateral tongue-biting, wide opening of mouth in tonic phase and contraction of abdominal muscles during the seizures and there were no geotropic eye movements as seen in PNES (Shaibani and Sabbagh, 1998).

Her body temperature was normal (98.4°F) and the respiration was not labored with respiratory rate at 24/minute. Her blood pressure was 130/80mm.Hg and emergency blood glucose estimation was normal (88 mg/dl). She was not dehydrated and there were no external scarification marks. After blood was taken for laboratory tests, an intravenous infusion of dextrose-saline was commenced and then 40mg of furosemide was given intravenously as bolus; and the seizures ceased with the patient regaining consciousness in about 30 minutes indicating that there was no evolution to subtle status epilepticus; after which the patient slept for another 2 hours. Patient was continued on 40mg furosemide tablet daily for 14 days before another EEG was done.

Results of laboratory tests later showed that the full blood count and differential white blood cell count were

normal. Retroviral test was negative. The plasma calcium was normal and was not affected by furosemide administration. Plasma sodium and potassium concentrations were reduced by furosemide (from 141.0 to 140.0mmol/l for sodium, and from 3.9 to 3.8mmol/l for potassium). Bicarbonate increased from 29.0 to 30.5mmol/l while blood Urea was not affected.

Urinalysis was normal before and after furosemide treatment. Also, the post-admission EEG still diagnosed complex partial seizures.

The absence of fever, the negative retroviral test and the normal differential white blood cell count ruled out an infective cause for the convulsions such as meningitis or encephalitis. The normal blood glucose ruled out hypoglycaemia or hyperosmolar hyperglycaemic non-ketotic coma. The normal blood urea level would not support a diagnosis of uremic encephalopathy. The normal blood pressure and absence of any neurological deficit may rule out transient ischaemic attacks or stroke. The plasma sodium levels did not support hyponatraemia or hypernatraemia as likely culprits for the convulsions. The normal Skull X-ray and EEG would not support tumor or head trauma as culprits for the convulsions. The negative history for neuroleptics would not support a diagnosis of neuroleptic malignant syndrome or drug-induced dystonic reaction. And this is a patient we have known for more than 20 years. The most likely diagnosis was generalized seizure status epilepticus from a secondarily-generalised complex partial seizure which the EEG showed, especially when it is realized that this was not the patient's first episode and that the status epilepticus was most probably precipitated by drug withdrawal due to problems with drug procurement.

### DISCUSSION

Status Epilepticus (SE) is defined as recurrent or continuous seizure activity lasting longer than 30 minutes in which the patient does not regain baseline mental status or consciousness (Mitchell, 2002). SE is a common life-threatening neurologic disorder. It is essentially an acute prolonged epileptic crisis.

Etiologically, SE can represent exacerbation of a pre-existing seizure disorder; the initial manifestation of a seizure disorder or an insult other than a seizure disorder. In patients with known epilepsy, a change in medication is the commonest cause. Treiman (1994) classified SE into four types:

- . Generalised convulsive SE
- . Subtle SE
- . Nonconvulsive SE (including absence SE and complex partial SE)
- . Simple partial SE

Status Epilepticus is treated as a neurologic emergency and only later are the potential etiologies assessed (Bleck, 2010). The principles of treatment are

**Table 1.** Pharmacological Treatment of Status Epilepticus

Medication Class	Available Routes	Adverse Effects
Lorazepam	Intravenous      Rectal sublingual intramuscular	Respiratory depression Hypotension Decreased level of consciousness
Diazepam	Intravenous      Rectal Intramuscular	Respiratory depression Hypotension Decreased level of consciousness
Midazolam	Intravenous Intramuscular	Respiratory depression Hypotension Decreased level of consciousness
Phenytoin	Intravenous	Hypotension QT Prolongation Purple glove syndrome
Fosphenytoin	Intravenous Intramuscular	Hypotension Cardiac arrhythmias
Phenobarbital	Intravenous	Hypotension Respiratory depression Decreased level of consciousness. Manno EM New management Strategies in the treatment of SE
Clobazam(1,5- benzodiazepine)	Oral	Causes less cognitive impairment than the traditional 1,4- benzodiazepines such as diazepam.
Adjunctive use in non- convulsive SE	Intranasal	Tolerance develops quickly

to terminate the seizure while resuscitating the patient, treating complications and preventing recurrence. Causes of SE include anticonvulsant drug withdrawal, alcohol-related disorders, drug toxicity, CNS infection, tumor, metabolic derangement, anoxia and stroke (Lowenstein and Alldredge, 1993).

The increased risk of death in epilepsy (Walczak et al., 2001; Hitiris et al., 2007) is due to status epilepticus, suicide associated with depression, trauma from seizures and sudden unexpected death. Depression, anxiety disorders, migraine, infertility, hypoactive sexual desire and attention-deficit/hyperactivity disorder are diseases that may co-morbidly associate with epilepsy.

## Investigations

Skull X-ray, EEG, Neuro-imaging techniques such as computerized tomography, magnetic resonance imaging, positron emission tomography and single photon emission computerized tomography are used to confirm clinical diagnosis, to delineate the subtype of epilepsy (especially EEG-Video) and to diagnose cerebral atrophy and demyelinating diseases. A proportion of patients with epilepsy, particularly those who have frequent fits, show inter-ictal EEG abnormalities which are of diagnostic value (Ahmad et al., 1977). In Nigeria, diagnostic neuro-imaging studies are not yet widely available.

## Drug Treatment of Status Epilepticus

The first-line drugs are the 1,4-benzodiazepines, lorazepam and diazepam given intravenously (Manno, 2003). If 1,4-benzodiazepines fail, intravenous phenytoin or fosphenytoin is given. Midazolam (given

intramuscularly) and phenobarbitone are administered when above drugs fail and are second-line drugs (Knake et al., 2009) (Table1). The general anaesthetic combination of pentobarbitone and midazolam may be tried for recalcitrant cases

## The role of Furosemide in epilepsy and status epilepticus

It is evident that the anticonvulsants are the mainstay of treatment of seizure disorders. However, over 30% of people with epilepsy do not have seizure control (Beghi et al., 1986; Engel, 1996) even with the best available medication now used making the quest for newer non-sedating drugs urgent. The sodium-potassium-chloride co-transporter inhibitor, furosemide, has been found recently to possess a wide spectrum of activity which includes anticonvulsant activity. An emerging body of evidence points to the efficacy of furosemide in epilepsy (Hesdorffer et al., 2001; Hochman et al., 1995; Luszczki et al., 2007) and status epilepticus in man (Ahmad et al., 1976) and rodents (Holtkamp et al., 2003). Ahmad et al. (1977) found that 40mg of furosemide produced a marked and sustained decrease in spike frequency, which was not different from that produced by diazepam in reducing EEG spike discharges. In our laboratory (unpublished report), furosemide's effect in protecting mice against leptazol-induced seizures (Kielczewska-Mrozikiewicz, 1968) was comparable to that of phenytoin and significantly greater than that of diazepam. A primary mechanistic explanation for furosemide's ability to terminate seizures may be its ability to prevent sustained  $\text{Ca}^{2+}$  intracellular increases due to hyperglutamatergic excitotoxicity (Sanchez-Gomez et al., 2011), a property it now seems to share with other NMDA receptor antagonists such as the calcium

channel blockers (Palmer et al., 1993). Besides, furosemide, which induces BDNF release (Szekeres et al., 2010), may enhance the seizure terminating effect of neuropeptide Y (Binder et al., 2001) which is upregulated by BDNF. Furthermore, changes in chloride transporter expression contribute to human epileptiform activity (Huberfeld et al., 2007) with increased sodium-potassium-chloride cotransporter (NKCC1) and altered subcellular distribution of the neuron-specific potassium-chloride cotransporter (KCC2) (Aronica et al., 2007), and molecules such as furosemide acting on these transporters may be useful antiepileptic drugs. Modulation of electrical field interactions via the extra-cellular space (ECS) might also contribute to neuronal hypersynchrony and epileptogenicity and present evidence suggests that non-synaptic mechanisms play a critical role in modulating the epileptogenicity of the human brain. Furosemide and other drugs that modulate the extra-cellular space might possess clinically useful antiepileptic properties, while avoiding the side-effects (Table 1) associated with the suppression of neuronal excitability (Manno, 2003; Haglund and Hochman, 2005). Studies have also shown that furosemide can reversibly suppress low  $\text{Ca}^{2+}$ -induced and low  $\text{Mg}^{2+}$ -induced epileptiform activity. Amplitudes of evoked field potentials underwent an initial slight increase followed by a significant reduction after prolonged furosemide treatment. Additionally, stimulation-induced shrinkage of extracellular space-volume was reduced by furosemide (Gutschmidt et al., 1999). Furosemide more potently blocks epileptiform activity in vitro studies than many of the commonly prescribed antiepileptic drugs (Haglund and Hochman, 2005). Endogeneous field effects in the CNS play functional roles and they are thought to contribute to epileptogenesis (Weiss and Faber, 2010) and there is evidence for a role of field effects (ephaptic transmission) in rhythmogenesis in cortex and hippocampus (Buzsaki, 2002). The administration of furosemide suppresses epileptic activity potently in the human cortex probably by also reducing field effect interactions (ephaptic transmission) (Haglund and Hochman, 2005; Weiss and Faber, 2010; Dudek et al., 1989).

Recent studies have shown evidence that the persistently high levels of brain-derived neurotrophic factor (BDNF) engendered by ictal activity may be pro-necrotic through activation of NADPH oxidase (Kim et al., 2006; Park et al., 2006) and that the Bax blocker furosemide (Lin et al., 2005) which is anti-apoptotic may serve in this instance as a neuroprotective. Also since oxidative stress (Ikonomidou, 2002), inflammatory mediators and hyperglutamatergic excitotoxicity too underlie epileptogenesis and epileptic brain injury, antioxidants such as furosemide (Hamelink et al., 2005) may play a greater role in future in preventing neurodegeneration from being a cause (Vercueil, 2004; Koyama and Ikegaya, 2005) of and sequel of epilepsy.

Furosemide improves scores in a modified mini-mental

state examination (MMSE) (Our unpublished observation) and thus may be of help in the cognitive impairment which probably begins at the onset of epilepsy especially in children (Elger et al., 2004).

In conclusion, emerging evidence suggests that furosemide is protective (Hesdorffer et al., 2001; Kanner, 2002; Frewin et al., 1987) for unprovoked seizures and in this report, it terminated status epilepticus from secondarily-generalised complex partial seizures. Its low cost, long-term safety and tolerability warrants it being further explored.

## REFERENCES

- Ahmad S, Clarke L, Hewett AJ, Richens A (1976). Controlled trial of furosemide as an antiepileptic drug in focal epilepsy. *Br. J. Clin. Pharmacol.* 3(4): 621-625.
- Ahmad S, Perucca E, Richens A (1977). The effect of Furosemide, mexilente, (+)-propranolol and three benzodiazepine drugs on interictal spike discharges in the electroencephalogram of epileptic patients. *Br. J. Clin. Pharmacol.* 4: 683-688.
- Aronica E, Boer K, Redaku S, Spliet WGM, van Rijen PC, Troost D, Gorter JA (2007). Differential expression patterns of chloride transporters, Na-K-2Cl cotransporters and K-Cl cotransporters in epilepsy-associated malformations of cortical development. *Neuroscience*. 145: 185-196.
- Beghi E, di Mascio R, Tognoni G (1986). Drug treatment of epilepsy: Outlines, criticism and perspectives. *Drugs*. 31: 249-65.
- Binder DK, Croll SD, Gall C, Scharfman HE (2001). BDNF and epilepsy: Too much of a good thing. *Trends in Neurology*. 24(1): 47-53.
- Bleck TP (2010). Less common etiologies of status epilepticus. *Epilepsy Curr.* 10(2): 31-3.
- Buzsaki G (2002). Theta oscillations in the hippocampus. *Neuron*. 33: 325-340 cognition. *The Lancet Neurology*. 3(110): 663-672
- Dudek FE, Yasumura H and Rash JE (1989). Non-synaptic mechanisms in seizures and epileptogenesis. *Cell Biol. Int.* 22: 793-805.
- Elger CE, Helmstaedter C, Kurthen M (2004). Chronic epilepsy and Engel J. (1996). Surgery for seizures. *NEJM*. 334(10): 647-652
- Frewin DB, Radeski C, Guerin MD (1987). The effects of substituting furosemide for a thiazide diuretic in the drug regimens of patients with essential hypertension. *Euro. J. Clin. Pharmacology*. 33(11): 31-34.
- Gutschmidt KU, Stenkamp K, Buchherm K (1999). Anticonvulsant actions of furosemide in vitro. *Neuroscience*. 91(4): 1471-1481
- Haglund MM, Hochman DW (2005). Furosemide and mannitol suppression of epileptic activity in the human brain. *J. Neurophysiol.* 94: 907-918.
- Hamelink C, Hampson A, Wink DA, Eiden LE, Eskay RL (2005). Comparison of cannabidiol, antioxidants and diuretics in reversing binge ethanol-induced neurotoxicity. *JPET*. 314(2): 780-788
- Hesdorffer DC, Stables JP, Hauser WA (2001). Are certain diuretics also anticonvulsants. *Ann. Neurol.* 50: 458-462.
- Hitiris N, Mohanraji R, Norrie J, Brodie MJ (2007). Mortality in epilepsy. *Epilepsy and Behaviour*. 10: 363-376.
- Hochman DW, Baraban SC, Owen JWN, Schwartzkin PA (1995). Dissociation of synchronization and excitability in furosemide blockade of epileptiform activity. *Science*. 270(5233): 99-102.
- Holtkamp M, Matzen J, Buchheim K, Walker MC (2003). Furosemide terminates limbic status epilepticus in freely moving rats. *Epilepsia*. 4(9): 1141-1144.
- Huberfeld G, Wittner L, Clemenceau S, Baulac M, Kaila K, Miles R and Rivera C (2007). Perturbed chloride homeostasis and GABAergic signaling in human temporal lobe epilepsy. *J. Neuroscience*. 27(37): 9866-9873.
- Ikonomidou C (2002). Neurodegeneration and neuroprotection in the epileptic brain. *Annals of general psychiatry* 7(suppl 1): S73.
- International Society on Brain and Behaviour, 3<sup>rd</sup> International

- Congress on Brain and Behaviour; Thessalonika, Greece 28 Nov-2Dec.2002.
- Kanner AM. Diuretics as antiepileptic drugs (2002). *Epilepsy Curr.* 2(2): 39-40.
- Kielczewska-Mrozikiewicz D (1968). Experimental studies on the effect of lasix on the occurrence of cardiazol convulsions. *Przegląd Lekarski.* 24: 716-718.
- Kim SH, Won SJ, Sohn S, Kwon HJ, Lee JY, Park JH, Gway BL (2002). BDNF can act as a pro-necrotic factor through transcriptional and translational activation of NADPH oxidase. *JCB.* 159(5): 821-831.
- Knake S, Hamer HM, Rosenow F (2009). Status epilepticus: A critical review. *Epilepsy and Behavior.* 15: 10-14.
- Koyama R and Ikegaya Y (2005). To BDNF or not to BDNF: That is the epileptic hippocampus. *The Neuroscientist.* 11(4): 282-287
- Lin C-H, Lu Y-Z, Cheng F-C, Chu L-F and Hsueh C-M (2005). Bax-regulated mitochondrial translocation is responsible for the in-vitro ischaemia-induced neuronal cell death of Sprague-Dawley rats. *Neuroscience letters.* 387(1):22-27.
- Lowenstein DH, Alldredge BK (1993). Status epilepticus at an urban public hospital in the 1980s. *Neurology.* 43(3 Pt 1): 483-8
- Luszczki J, Sawicka K, Kozinska J, Borowiczka K (2007). Furosemide potentiates the anticonvulsant action of valproate in the mouse maximal electroshock seizure model. *Epilepsy research.* 76(1): 66-72.
- Maa EH, Kahle KT, Walcott BP, Spitz MC, Staley KJ (2011). Diuretics and epilepsy: Will the past and present meet? *Epilepsia.* 52(9): 1559-1569.
- Manno EM (2003). New management strategies in the treatment of status epilepticus. *Mayo Clin. Proc.* 78: 508-518
- Mitchell WG (2002). Status epilepticus and acute serial seizures in children. *J. Child Neurol.* 17(Suppl. 1): S36-43 .
- Palmer GC, Stagnitto ML, Ray RK, Knowles MA, Harvey R, Garske GE (1993). Anticonvulsant properties of calcium channel blockers in mice: N-methyl-D,L-aspartate and Bay K 8644-induced convulsions are potently blocked by the dihydropyridines. *Epilepsia.* 34(2): 372-80.
- Park J-H, Cho H, Kim H, Kim K (2006). Repeated brief epileptic seizures by pentyleneetetrazole cause neurodegeneration and promote neurogenesis in discrete brain regions of freely moving adult rats. *Neuroscience.* 140(2): 673-684.
- Sanchez-Gomez MV, Alberdi E, Perez-Navarro E, Alberch J, Matute C (2011). Bax and calpain mediate excitotoxic oligodendrocyte death induced by activation of both AMPA and Kainate receptors. *J. Neurosci.* 31(8): 2996-3006.
- Shaibani A, Sabbagh M (1998). Pseudoneurologic Syndromes: Recognition and Diagnosis. *Am. Fam. Physician.* 57(10): 2485-2494.
- Szekeres M, Nadasy GL, Turu G, Supeki K, Svidonya L, Buday L, Chaplin T, Clark A, Hunyady L (2010). Angiotensin 11-induced expression of BDNF in human and rat adrenocortical cells. *Endocrinology.* 151 (4): 1695-1703.
- Treiman DM (1994). Generalised convulsive, non-convulsive and focal status epilepticus. In: Feldman E, ed. *Current Diagnosis in Neurology.* St. Louis: Mosby-Year Book; 11-8
- Vercueil L (2004). Epilepsy and neuro-degenerative disorders in adults. *Epileptic Disorders.* 6(1): 47-57.
- Walczak JS, Leppik IE, D'Amelio M, Rarick J, So E, Ahman P, Ruggles K, Cascino GD, Annegers JF, Hauser WA (2001). Suicide and risk factors in sudden unexpected death in epilepsy: a prospective cohort study. *Neurology.* 56: 519-525.
- Weiss SA and Faber DS (2010). Field effects in the CNS play functional roles. *Front. Neural Circuits.* 4:15.doi:10.3389.