

# Headache and self-aggression as paradoxical reactions to diazepam: Case reports and review of the literature

Dr. S.E. Oriafio

Department of Pharmacology and Therapeutics, Ambrose Ali University, Ekpoma, Nigeria

## Abstract

Two cases of paradoxical reactions to diazepam are presented. In case 1, patient presented with moderate headache and restlessness after 10mg of diazepam. In case II, patient presented with addiction to diazepam and cannabis though the diazepam addiction started earlier. The addiction resulted in suicidal ideations, which progressed to attempted suicide. The literature on the GABA receptor is reviewed to elucidate the actions of diazepam; and to explain the basis of the paradoxical actions of diazepam which may be most likely due to down-regulation of the receptor by diazepam. That the paradoxical actions could have genetic basis is highlighted.

**Keywords:** Paradoxical actions, diazepam, GABA receptor, headache, self-aggression.

## INTRODUCTION

### The Gaba Receptor

The sedative-hypnotic, diazepam, is an agonist at the  $\gamma$ -Aminobutyric acidA (GABAA) receptor. GABA, the major inhibitory neurotransmitter in the brain, exerts its action via ionotropic GABAA and metabotropic GABAB receptors (Olsen and Sieghart, 2008). Agonists of the GABAB receptor such as baclofen have been found to be associated with escalated aggression (Takahashi et al., 2010). The GABAA receptor is one of the two ligand-gated ion channels responsible for mediating the effects of GABA. GABA controls brain excitability by exerting inhibitory functions on neuronal membranes by altering their permeability to specific ions (Tornberg, 2006). Binding of GABA to the GABAA receptor increases the permeability of neuronal membranes to chloride ions (Russel, 2000; Uusisaari, 2002; Grob et al., 2005).

Native GABAA receptors are formed from at least 19 related subunits. The subunits are group into  $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ ,  $\epsilon$ ,  $\eta$ , and  $\rho$  families (Olsen et al., 2008). The most prevalent combination of GABAA receptor is a stoichiometric combination of the  $2\times\alpha$ ,  $2\times\beta$ . and  $1\times\gamma$  subunits, with the remaining subunits relegated to substituting for the  $\gamma$  subunit during specific development expression or in highly specific brain region localization. The adult brain predominantly expresses the  $\alpha 1$ ,  $\beta 2$ ,  $\gamma 2$  subunit combination (Benke et al., 1991) with  $\alpha 2$ ,  $\beta 3$ ,  $\gamma 2$  and  $\alpha 3$ ,

$\beta n$ ,  $\gamma 2$  subunits comprising the majority of the remaining receptors. The relative effects of GABA are influenced by the GABAA receptor subunit expressed in a specific brain region or neuronal circuit (Atack, 2003).

The allosteric modulators have distinct sites on the GABA receptor channel, sites separate and unique from the site that recognizes GABA. The most notable of the positive allosteric modulators are the benzodiazepines (Hanson et al., 2008) while flumazenil, an inverse agonist, is a notable negative allosteric modulator (Lader and Morton, 1992) which may cause agitation and may be used for treatment of diazepam post-withdrawal symptoms.

### GABAA Interactions

It is now recognized that the cation– chloride co-transporter, isoform 2 of the potassium-chloride-cotransporter (KCC2) establishes the fast hyperpolarizing inhibitory responses mediated by GABAA (Russel, 2000; Kakazu et al., 1999; Sipila, 2006; Ben- Ari et al., 2006; Diykov, 2007). Also dysfunction or under expression of KCC2 can turn GABAA from being inhibitory to becoming excitatory (Tornberg, 2006; Kakazu et al., 1999; Nabekura et al., 2002; Chen and Sun, 2005).

Maintenance of an optimal intracellular chloride [Cl<sup>-</sup>]

concentration determines the cross-talk between GABAA and the cation-chloride co-transporters (CCC) (Malek et al., 2003; Schomberg et al 2003; Palma et al., 2008).

Serotonin receptors modulate GABAA receptor channels through activation of anchored protein kinase C (Feng et al., 2001) and regulates extra-cellular GABAA level in the prefrontal cortex (Abi-Saab et al., 1999). On the other hand, GABAB receptor mediates inhibition of serotonin release in the rat brain (Schlicker et al., 1984).

Activation of presynaptic GABAA receptor also influence glutamate release onto noradrenergic neurons while glutamate receptor activation in hippocampal neurons may cause sustained depolarizing shift of the GABAA reversal potential (Kitamura et al., 2005). Also, chronic modulation of the GABAA receptor complex regulates Y1 receptor gene expression in the medial amygdala of transgenic mice (Oberto et al., 2000).

Taken together, these serve to confirm the findings by Gellman et al (1993) that GABAA inhibitory interneurons may themselves be modulated by dopaminergic, serotonergic and noradrenergic inputs, and some GABAA neurons may even receive a convergence of all three of these monoaminergic afferent fibre systems. With these interactions, it is not surprising that GABAergic hypofunction may be a cause of the up-regulation of the dopaminergic and serotonergic systems.

While the majority of GABAA receptors (those containing  $\alpha 1$ ,  $\alpha 2$ ,  $\alpha 3$  or  $\alpha 5$  subunits) are benzodiazepine sensitive (DS) (Pym et al., 2005), there exists a minority of GABAA receptor ( $\alpha 4$  or  $\alpha 6$ -subunit containing) which are insensitive to classical 1,4-benzodiazepines like diazepam (Derry et al., 2004) but instead are sensitive to other classes of GABAergic drugs such as the neurosteroids, the imidazobenzodiazepines for which bretazenil is an example and alcohol.

### Diazepam and the GABAA Receptor

Benzodiazepine actions are mediated by specific gamma-aminobutyric acid (A) receptor subtypes (Rudolph et al., 2000). Diazepam is a classical benzodiazepine because it binds to GABAA receptor containing  $\alpha 1, \alpha 2$ ,  $\alpha 3$  or  $\alpha 5$  subunits that are labeled as diazepam-sensitive receptors (Pym et al., 2005). Diazepam accelerates GABA association to its receptor (Lavole and Twyman, 1996) and there is no age-related change in GABA binding.

The  $\alpha 1$  GABAA receptors mediate the sedative action of diazepam (Tobler et al., 2001). The  $\alpha 2$  GABAA receptor is necessary for anticonvulsant activity (Fredley et al., 2007). The anxiolytic-like, myorelaxant, motor impairing and ethanol-potentiating effects are attributed to the  $\alpha 2$ ,  $\alpha 5$  subunits found in the limbic system (Rudolph et al., 2000).

Mutations in the GABAA receptor can occur (Tornberg, 2006; Korpi and Seeburg, 1993) and affect

diazepam activity (Marini et al., 2003).

### Diazepam as Essential Drug

Diazepam is a core medicine in the World Health Organization's Essential Drugs list, which is a list of minimum medical needs for a basic health care system (WHO Model list, 2000). It is used for its anxiolytic, sedative, myorelaxant and amnestic properties (Diazepam, Pubchem, 2006; Diazepam MeSH, 2006). It may also be used for alcohol withdrawal and benzodiazepine withdrawal because of its long half-life of 40-200 hours (Ashton, 2000). It also finds a place in anaesthetic practice (Whitwam, 1995) and can be a drug of abuse (Poulos and Zack, 2004) which is a patterned use of a substance in which the user consumes the substance in amounts or with methods neither approved nor supervised by medical professionals. Diazepam like alcohol, anabolic steroids and cocaine is a key drug of abuse that can escalate the development of aggression and violent behaviour.

### CASE REPORT 1

Mrs. W.B. is a 35 years old housewife living in Ekpoma. She presented to Oseghale Oriafio Medical Centre, Ekpoma on January 2011 with headache and restlessness since she took two (10mg) of diazepam on 14th of January 2011 for sleeplessness. The headache was bitemporal, throbbing in nature, accompanied with generalized heaviness of the head. It was not incapacitating. She says she has noticed this for eight years now, that when she takes diazepam she is restless and has headache, but the intensity has remained the same.

On examination, she was normotensive with BP 120/70mm. Hg. Pulse was 70/min. Temperature was 36.7°C. Physical and neurological examinations, including ophthalmologic examination, were normal. These other investigations were done to rule out other causes of secondary headache.

- Complete blood count, which was normal.
  - Urinalysis, which was normal.
  - Serum electrolytes and urea, which were normal.
  - Malaria parasite test, which was negative.
  - Widal test which was negative.
  - Ultrasound of blood vessels of neck, which was normal.
  - Skull x-ray, which revealed no abnormality.
- The headache responded to intravenous paracetamol and promethazine tablets.

She was rechallenged on 28th of January 2011 (with her consent) by administering 10mg of diazepam. The headache and restlessness recurred two hours after the rechallenge. This challenge and rechallenge with

diazepam to produce the headache is confirmatory as it is known that the patient's history is the key to diagnosis. This diazepam – induced headache was different in symptomatology from the primary headaches of tension headache, migraine headache, cluster headache and chronic daily headache. Patient has remained headache-free since the diagnosis.

## CASE REPORT II

Mr. O.B. is a 22 -years old secondary school graduate from Ekpoma.

He presented to Oseghale Oriaifo Medical Centre, Ekpoma on 16th of March 2010 with attempted suicide by laceration of the wrist. He was brought by the relations who complained that it happened after he ingested seven tablets of 5mg diazepam and smoked cannabis (Omigbodun et al., 2004) heavily in the night. According to them, and confirmed by the patient himself, the suicidal thoughts started five years earlier in 2005 after the patient became addicted to diazepam. Things got worse in 2007 when patient also started taking cannabis. He would some times talk of killing himself, become loose and refused to read for higher education.

On examination, there was transverse laceration on left wrist with involvement of flexor tendons but sparing the left radial artery. Patient was normotensive with a clear sensorium. He had good insight but appeared anxious. Tendon repair was done using 2-0 silk by author. During the period of management, efforts were made to wean him from the drug habit and-, on discharge, attempts to refer him to a psychiatrist failed as they took him for tradomedical healing (Coring and Murphy, 1979). Since then, he has been lost to follow-up.

## DISCUSSION

The two cases demonstrate that diazepam is capable of paradoxical reactions as previously reported (Marrosu et al 1987, Michel et al., 2003: Berman et al., 2005, Miczek et al., 2007).

### In Causing Headache, Diazepam is Exhibiting Paradoxical Actions

In case report I, the patient exhibited headache and heightened anxiety after diazepam. This is a paradoxical reaction. Single exposure to diazepam can have significant effects on GABAA receptor function as noted by Holt et al (1999) who reported decreased GABA enhancement of benzodiazepine binding after a single dose of diazepam. Also, mutation at any of the subunits ( $\alpha 1$ ,  $\alpha 2$ ,  $\alpha 3$ ,  $\alpha 5$ ) necessary for diazepam sensitivity can

alter the action of diazepam on GABA binding and give paradoxical results. Furthermore, mutation of the KCC2 channel can give unexpected paradoxical reactions. Mice with a point mutation in the GABAA receptor subunit  $\alpha 1$  are insensitive to low-dose diazepam-induced sedation and motor impairment (Rudolph et al., 1999; Crestani et al., 2000) confirming that the majority of diazepam-induced sedation is mediated through the activation of the  $\alpha 1$  sub-unit-containing GABAA receptors. Also genetically modified mice with altered expression of KCC2 (KCC2 deficient mice) show several behavioral abnormalities including increased anxiety-like behaviour (Tornberg, 2006; Tanaka et al., 2000). The heterogeneity of the GABAA receptor makes mutations more probable.

### Diazepam can be a Cause of Aggression

In case Report II, diazepam is strongly associated with the self- aggressive behaviour exhibited. This action of diazepam may be synergistic with the action of cannabis since cannabis acts through central benzodiazepine receptors (Sethi et al., 1986). Clinically relevant diazepam doses may be associated with self- aggressive behaviour at levels that do not significantly impair basic cognitive processes or psychomotor performance (Berman et al., 2005; Miczek, 2007). Apart from possible mutation of the GABAA receptor and KCC2; down-regulation of GABAA receptor, calcium-dependent calmodulin protein kinase II $\alpha$  (CaMKII $\alpha$ ) and brain-derived neurotrophic factor (BDNF) can be induced by diazepam. Down-regulation of CaMKII $\alpha$  decreases the inhibitory synaptic potential of GABAA (Licata and Rowlett, 2008). GABAA receptor down-regulation (impairment) which leads to decrease in allopregnanolone expression plays a pivotal role in the expression of aggressive behaviour (Pinna et al., 2005). Gabaergic inputs on mesocortical serotonin circuits that control escalated aggression and violence may be deficient (Miczek et al., 2007) and this may be related to alteration of GABAA receptor density in relevant sections of the brain (McCleod et al., 2008). The rate for aggressive behaviour with diazepam is low but this can be of concern since diazepam can cause simple behavioral disinhibition, feeling of invulnerability, to serious crimes like homicide. In a study of effect of psychotropic drugs on aggression in a prison environment, diazepam-use was associated with most of the cases of aggression reported by Workman and Cunningham (1975). Diazepam can, at times too, be associated with delusional, manic, confusional or depressive states (Michael and Lang, 2003) and could potentiate other aggression-provoking drugs such as the performance enhancing anabolic-androgenic steroids (AAS) that may also down-regulate the GABAA signal transduction (Pinna et al., 2005).

## CONCLUSION

All prescribers need to be aware of the side-effects of diazepam especially the rare paradoxical side-effects such as (self-) aggression and escalated violence. Voluntarily induced disinhibition has to be carefully differentiated from diazepam induced disinhibition. Even the milder paradoxical headache has to be recognized to prevent unnecessary increase in dosage and loss in man-hours. It is also of interest to prescribers to realize that these paradoxical actions could have genetic basis.

## REFERENCES

- Ashton CH (2001). Reasons for a diazepam taper. Retrieved from [www.Benzo.org.uk](http://www.Benzo.org.uk).
- Abi-Saab WM, Bubser M, Roth R (1999). 5-HT<sub>2</sub> receptor regulation of extracellular GABA levels in the prefrontal cortex. *Neuropsychopharmacology*. 20:92-96.
- Atack JR (2003). Anxiolytic compounds acting at the GABA<sub>A</sub> receptor benzodiazepine-binding site. *Neurological disorders*. 2(4):213-32.
- Berman ME, Jones GD, McCloskey MS (2005). The effects of diazepam on human self-aggressive behaviour. *Psychopharmacology (Berl)*. 178(1):100-6.
- Benke D, Mertens S, Trzeciak A, Gillissen D, Mohler H (1991). GABA<sub>A</sub> receptors display association of  $\gamma 2$  subunits with  $\alpha 1$  and  $\beta 2/3$  subunits. *J. Biol. Chem.* 266:4478-4483.
- Ben-Ari Y, Galarsa J, Tyzio R (2006). GABA: A pioneer transmitter that Excites Immature Neurons and Generates Primitive Oscillations. *Physiol. Rev.* 87:1215-1284.
- Crestani F, Martin JR, Mohler H, Rudolph U (2000). Resolving differences in GABA<sub>A</sub> receptor: mutant mouse studies. *Nat. Neurosci.* 3:1059.
- Chen H, Sun D (2005). The role of Na-K-Cl co-transporter in cerebral ischaemia. *Neurological Res.* 27:280-286.
- Corin E, Murphy HBM (1979). Psychiatric perspectives in Africa. *Transcultural Psychiatry*. 16:147-178.
- Diakov D (2007). Changes in GABAergic mechanism and cation-Chloride co-transporters in the albino visual cortex. Doctoral thesis. Retrieved from <http://www.ub.ruhr-uni-bochum.de/DigiBib/DissListen>.
- Diazepam Medical subject Headings (MeSH). National library of Medicine (2006). Retrieved from <http://www.nlm.nih.gov/cgi/mesh>.
- Derry JM, Dunn SM, Davis M (2004). Identification of a residue in the gamma- amino butyric acid type A receptor alpha subunit that differentially affects diazepam sensitive and insensitive benzodiazepine site binding. *J. Neurochem.* 8(6): 1431-8
- Diazepam Pubchem. National Institute of Health. National library of medicine (2006). Retrieved from [pubchem.ncbi.nlm.nih.gov](http://pubchem.ncbi.nlm.nih.gov).
- Fredly R, Guscott M, Bull S (2007). Differential contribution of GABA<sub>A</sub> receptor sub types to the anticonvulsant efficacy of benzodiazepine site ligands. *J. Psychopharmacol.* 21:384-6
- Feng J, Cai X, Zhao J, Yan Z (2001). Serotonin Receptors modulate GABA<sub>A</sub> Receptor channels. *J. Neurosci.* 21(17):6502-6511.
- Grob M, Mougnot F (2005). Heterogeneous Chloride homeostasis and GABA responses in the median preoptic nucleus of the rat. *J. Physiol.* 569(3):885-901.
- Gellman RL, Aghajanian GK (1993). Pyramidal cells in piriform cortex receive a convergence of inputs from monoamine activated GABAergic interneurons. *Brain Res.* 600:63-73.
- Hanson DM, Czaikowski, C (2008). Structural mechanisms underlying benzodiazepine modulation of the GABA<sub>A</sub> receptor. *J. Neurosci.* 28(13):3490-9.
- Holt RA, Bateson AN, Martin IL (1999) Decreased GABA enhancement of benzodiazepine binding after a single dose of diazepam. *J Neurochem.* 72:2219-22
- Kakazu Y, Akaike N, Komiyama S, Nabekura J (1999). Regulation of intracellular Chloride by co-transporters in developing lateral superior olive Neurons. *J. Neurosci.*, 19(8):2843-2851.
- Kitamura A, Ishibashi H, Watanabe M (2008). Sustained depolarizing shift of the GABA reversal potential by glutamate receptor activation in hippocampal neurons. *Neurosci. Research*. 62( 4):270-277.
- Korpi ER, Seeburg PH (1993). Natural mutation of GABA receptor alpha 6 subunit alters benzo-diazepine affinity, *Eur. J. Pharmacol.* 247:23-7.
- Lader MH, Morton SV (1992). A pilot study of the effects of flumazenil on symptoms persisting after benzodiazepine withdrawal. *J. Psychopharmacol.* 6(3):357-363
- Lavole RM, Twyman RE (1996). Direct evidence for diazepam modulation of GABA receptor microscopic affinity. *Neuropharmacol.* 35(9-10):1383-92.
- Licata, S. C., Rowlett, J. K. (2008). Abuse and dependence liability of benzodiazepines: GABA receptor modulation and beyond. *Pharmacol Biochem Behav.* 90(1):74-89
- Malek SA, Coderre E, Stys PK (2003). Aberrant Chloride Transport contributes to anoxic/ischemic white matter injury. *J. Neurosci.* 23(9):38326-3837.
- Marrosu F, Marrosu G, Rachel MG, Bigglo G (1987). Paradoxical reactions elicited by diazepam in children with classic autism. *Funct. Neurol.* 2 (3):355-61.
- Michael L, Lang JP (2003). Benzodiazepine and Forensic aspects. 1: *Encephale*. 29(6):479-85.
- Miczek KA, de Almedia RMM, Kravitz EA, Rissman EF, de Boer SF, Raine A (2007). Neurobiology of escalated Aggression and violence. *J Neuroscience*. 27(44):11803-11806.
- Marini C, Harkin LA, Wallace RH (2003). Childhood absence epilepsy and febrile seizures: a family with a GABA<sub>A</sub> receptor mutation. *Brain*. 126(1): 230-240.
- Nabekura J, Ueno T, Okabe A (2002). Reduction of KCC2 expression and GABA<sub>A</sub> receptor mediated excitation after in vivo axonal injury. *J. Neurosci.* 22:4412-4417.
- Oslen RW, Sieghart W (2008). International Union of Pharmacology LXX. Subtypes of  $\alpha$ -Aminobutyric Acid Receptors. Classification on the basis of subunit composition. Pharmacology and function, update IUPHAR Nomenclature report on line. *Pharmacol Rev.* 60:243-260.
- Oberto A, Pan Zica G, Altruda F, Eva C (2000). Chronic Modulation of the GABA<sub>A</sub> receptor complex regulate Y1 receptor gene expression in the amygdala of transgenic mice. *Neuropharmacology*. 39(2):227-234.
- Omigbodun OO, Babalola O (2004). Psychosocial dynamics of psychoactive substance misuse among Nigerian adolescents. *Annals of African Medicine*. 3(3):111-115.
- Palma E, Annicim M, Sobrero F, Spinelli G, Angelantonio SD, Ragozzino D (2008). Anomalous levels of [Cl<sup>-</sup>] transporters in the hippocampal subiculum from temporal lobe epilepsy patients make GABA excitatory. *PNAS*. 103(22):8465-68.
- Pinna G, Costa E, Guidotti A (2005). Changes in brain testosterone and allopregnanolone biosynthesis elicit aggressive behaviour. *PNAS*. 102(6):2135-2140
- Pym LJ, Cook SM, Rosahi T (2005). Selective labeling of diazepam-insensitive GABA<sub>A</sub> receptors in vivo using (3H) RO 15-4513. *British J. Pharmacol.* 146:817-825.
- Poulos CX, Zack M (2004). Low-Dose diazepam primes motivation for alcohol-related semantic networks in problem drinkers. *Behav Pharmacol.* 15(7):503-12.
- Russell JM (2000). Sodium-Potassium-Chloride co-transport. *Physiological Reviews*. 80(1):211-276.
- Rudolph U, Crestani F, Benke D (2000). Benzodiazepine action mediated by specific gamma-aminobutyric acid (A)receptor subtypes. *Nature*. 404(6778):629.
- Sipila S (2006). Cellular and network mechanisms generating spontaneous population events in the immature rat hippocampus, Academic Dissertation. Retrieved from <https://helda.helsinki.fi/bitstream/handle>
- Schomberg SL, Bauer J, Kintner DB, Flemmer A, Forbush B, Sun D (2003). Cross-talk between the GABA<sub>A</sub> receptor and the Na-K-Cl co-

- transporter is mediated by intracellular  $[Cl^-]$ . *J. Neurophysiol.* 89:159-167
- Schlicker E, Classen K, Gothers M (2004). GABAB receptor-mediated inhibition of serotonin release in the rat brain. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 326(2):99-105.
- Sethi BB, Trivedi JK, Kumai P (1986). Anti-anxiety effect of cannabis: involvement of central benzodiazepine receptors. *Biol Psychiatry*. 21(1):3-10.
- Takahashi A, Shimamoto A, Boyson CO, DeBold JF, Miczek KA (2010). GABAB receptor modulation of serotonin neurons in the dorsal raphe nucleus and escalated aggression in mice. *J. Neurosci.* 30(35):11771-11780
- Tornberg J (2006). Generation and Characterization of the Cation-Chloride co-transporter KCC2 in Hypomorphic mouse. Academic Dissertation. Retrieved from <http://e-thesis.helsinki.fi>.
- Tanaka M, Yoshida M, Emoto H, Ishii H, (2000). Noradrenaline systems in the hypothalamus, amygdala and locus coeruleus are involved in the provocation of anxiety. *Basic studies, Eur. J. Pharmacol.*, 405:397-406.
- Tobler I, Kopp C, Deboe T (2001). Diazepam-induced changes in sleep: Role of the  $\alpha$  GABAB receptor subtype. *PNAS*. 2001.
- Uusisaari M (2003). GABAergic mechanisms of excitation and hypersynchrony in adult rat hippocampus. Academic Dissertation. Retrieved from <http://e-thesis.helsinki.fi>.
- WHO model list of Essential Medicines. World Health Organization. (2005). Retrieved from <http://www.who.int/medicines/publications/essentialmedicines>
- Whitwam JG (1995). Fumazenil and Midazolam in anaesthesia. *Acta Anaesthesiologica Scandinavica Suppl.* 108:15.
- Workman DG, Cunningham DG (1975). Effect of psychotropic drugs on aggression in a prison setting. *Can. Fam. Physician*. 21(11): 63-66