*EXCLI Journal 2021;20:1028-1032 – ISSN 1611-2156*
*Received: March 26, 2021, accepted: May 27, 2021, published: June 07, 2021*

## Letter to the editor:

# RECENT UPDATE ON BARBITURATE IN RELATION TO BRAIN DISORDER

Sachchidanand Pathak[1,*], Gaurav Gupta[1], Lakshmi Thangavelu[2], Sachin K. Singh[3], Kamal Dua[4], Dinesh Kumar Chellappan[5], Ritu M. Gilhotra[1]

[1] School of Pharmacy, Suresh Gyan Vihar University, Mahal Road-302017, Jagatpura, Jaipur, India
[2] Department of Pharmacology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, India
[3] School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, 144411, India
[4] Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney, NSW 2007, Australia
[5] Department of Life Sciences, School of Pharmacy, International Medical University, Bukit Jalil 57000, Kuala Lumpur, Malaysia

* **Corresponding author:** Sachchidanand Pathak, School of Pharmacy, Suresh Gyan Vihar University, Mahal Road-302017, Jagatpura, Jaipur, India.
E-mail: sachchidanand.pathak904@gmail.com

http://dx.doi.org/10.17179/excli2021-3687



***Dear Editor,***

Barbiturate is a potent substance which forms a quintessential part of the NDPS Act. The substance is categorized under the psychoactive groups of drugs and is essentially a drug that possesses both hypnotic and sedative properties. The precursor for barbiturate is barbituric acid which is a condensation product of malonic acid and urea. However, barbituric acid itself is not a centrally acting depressant. Diethylbarbituric acid (Veronal) is the first ever barbiturate with hypnotic properties that was used as early as 1903 (Hadjihambi et al., 2020). The drug induced sleep both in human and animals. The substance was also called as barbital. Later in the year 1912, a second barbiturate drug, phenobarbitone was introduced into clinical practice which had both sedative and hypnotic properties. The phenomenal success of both these drugs announced the beginning of the barbiturate era. Their influence as the pre-eminent sedative-hypnotic agents was felt for over half a century. Although several so-called non-barbiturate drugs attempted to displace the barbiturates from their pinnacle from time to time, it was not until 1961 when a substance named chlordiazepoxide was introduced into the market that their position was seriously challenged (Velle et al., 2021). Several earlier studies have reported the characteristic features and the severity of the barbiturate withdrawal syndrome. In cases of mild withdrawal syndrome, symptoms like apprehension, hyperexcitability, mild tremors, loss of appetite and piloerection were observed. An intermediate withdrawal syndrome exhibited tightness in the muscles, extreme tremors, sudden loss of body weight, altered motor activity, ex-

EXCLI Journal 2021;20:1028-1032 – ISSN 1611-2156
Received: March 26, 2021, accepted: May 27, 2021, published: June 07, 2021

cessive nausea, and vomiting (Sharpe et al., 2020). The hallmarks of a severe withdrawal syndrome are convulsions, delirium or hallucination and hyperthermia or unusually high fever. The severity of withdrawal syndrome has been shown to depend on the frequency of drug administration and the duration of action of the drug. We review recent research on the role of barbiturates in brain disorders in this letter (Table 1).

**Table 1:** Recent study on the role of barbiturates in brain disorders

| Brain disorder | Key findings | Reference |
|---|---|---|
| Epilepsy | Brandt et al. reported several key advantages of bumepamine over bumetanide in targeting the nervous system. Some of these are; the potential of bumepamine to regulate diuresis, ability to render the drug more permeable and causing increased efficacy of the drug which in turn enhances the antiepileptic potential of phenobarbital. | Brandt et al., 2018 |
| | Klein et al. showed that both carbamazepine and phenytoin produced a far lesser therapeutic effect against focal nonconvulsive seizures, whereas valproate and levetiracetam revealed a moderate activity and phenobarbital and diazepam demonstrated marked anti-seizure effects. In addition, all AEDs are shown to restrain generalized convulsive seizures. | Klein et al., 2015 |
| | The antiepileptic activity of phenobarbital was enhanced when compared with bumetanide. Observations in the rat kindling model, namely BUM5 (N,N-dimethylaminoethylester) were reported to justify this finding. | Töllner et al., 2014 |
| | The findings from this study have shown that N-methylation completely diminishes the Pgp affinity of barbiturates. | Mairinger et al., 2012 |
| | The results obtained from the investigations suggested that, phenobarbital potentiates the activity of glutapyrone and sodium valproate, thereby significantly minimizing their doses, and reducing the risk of side effects when these drugs are administered in higher doses and for a longer duration. | Murphy et al., 2020 |
| Neonatal seizure | The children who were not administered daily with phenobarbital had reported a higher incidence of epileptic episodes. However, these were primarily observed to be febrile seizures. The occurrence of pre-seizures and other abnormalities were also seen to be relatively high. | Sakuma et al., 2020 |
| | Findings from this study have shown that the predisposing factors in infant subjects were oxygen deprivation, nerve related problems, and earlier barbiturate administration. Interestingly, in premature neonate extreme apnea was reported to be a predisposing factor. | Specchio and Pietrafusa, 2020 |
| | The results from this study had pointed out that prenatal PHB affected the anatomical maturation of the hippocampal architecture. Therefore, administration of PHB in management of such conditions is questionable. | Schizodimos et al., 2020 |
| | Thyroidal secretions were observed to be decreased in neonates administered with phenobarbitone. In addition, neural deficiencies and structural irregularities in neuronal tissues were seen in phenobarbitone use. Neuronal studies further revealed decreased sensitivity of DBA in subjects who were administered with phenobarbitone. The authors also elaborated on the existence of interactions between several genotypes as the nervous system developed. | Hadjihambi et al., 2020 |
| | Administration of barbiturate drugs in infants for seizure preventive measures is not often recommended for normal clinical procedures, as incidences of death were reported in several | Young et al., 2016 |

| | | |
|---|---|---|
| | studies. Lack of suitable supporting studies have made it further challenging. | |
| Brain tumor | Two separate groups were studied. The findings suggest no drastic changes or differences among the study cohorts, in terms of adverse events. In addition, there were no fatalities due to BCT. The conclusions suggested efficient monitoring of refractory intracranial hypertension (RICH) after surgery. | Ryu et al., 2019 |
| | From the findings of the study, it was evident that the strategy was focused to improve extreme deficiency of potassium in the blood. The findings also were strategized to prevent paroxysmal, fatal, rebounding potassium levels in the blood. Inspite of such efforts, the subjects who received the Barbiturate coma therapy (BCT) still reported and presented with having low grade hyperkalaemia. | Tat et al., 2017 |
| | Two major groups, namely the intervention group and the control group were studied. The findings suggested no significant differences in controlling epileptic episodes in the brain tumor subjects. Subjects who were on antiepileptic medications carried a higher risk of developing complications. These findings however may not be applied for drugs other than phenytoin, phenobarbital, and divalproex sodium. | Tremont-Lukats et al., 2008 |
| | Administration of phenobarbital may result in grave anatomical alterations in the architecture of the microtubules. Phenobarbital is also known to cause the destabilization of c-Jun, Akt and ERK proteins during the signaling process. To conclude, the observations reveal that the migratory and proliferation mechanisms of pentobarbital are arrested due to the disturbances in the microtubule function. The suggested mechanisms involve the ERK, c-Jun MAPK and PI3K/Akt pathways. | Xie et al., 2009 |
| | The study reports that subjects with brain tumors may not benefit from seizure preventive medications if they did not have a past-history of convulsions. | Forsyth et al., 2003 |
| Status epilepticus | The study reports that, compared to barbiturates, propofol can control RSE and shorten ATIPT in a more competent and appropriate manner. Moreover, the study also suggests that the drug does not increase the occurrence of hypotension and CFR. | Zhang et al., 2019 |
| | The study reported that the recurrence rate for late seizures was 13.6 % after having a strong influence with antiseizure drugs (ASD) in subjects having new onset status epilepticus (NOSE). The study also highlights that the probability of the convulsions to reoccur may be high in subjects with refractory status epilepticus (RSE) who were on barbiturate therapy. Further detailed and in depth studies are required to arrive at a proper conclusion. | Chakraborty and Hocker, 2019 |
| | The study reports that VPA (valproate) and PB (phenobarbital) were more effective than PHT (phenytoin/fosphenytoin) in subjects with SE (status epilepticus). However, PHT is not proven to be effective and is also expensive, which is a drawback when compared to its rivals. | Sánchez Fernández et al., 2019 |
| | The authors show that moderate-dose parenteral PB (phenobarbital) was efficient in attaining considerable seizure management in non-comatose refractory SE patients. None of the patients required ventilatory support. The authors conclude that PB dosages beneath those in recent guidelines may be sufficient to stop SE without clinically significant cardiopulmonary complications. | Hocker et al., 2018 |

| | | |
|---|---|---|
| | The study reported that PB (phenobarbital) at a dose greater than 100 µg/ml was found to be beneficial in adult subjects with refractory status epileptic (RSE). Furthermore, therapeutic plasma exchange has no effect on the amount of PB found in plasma. | Wang et al., 2018 |
| Intracranial pressure | The findings from this study indicate that barbiturates, when used in a modern NICU (neurointensive care unit), serves as a promising strategy to safely reduce intracranial pressure without causing any extreme adverse effects in younger population who suffer from refractory intracranial hypertension (RICH) with potential long-term benefits. | Velle et al., 2019 |
| | The observations from this study discuss about the significance of hypothermia which was caused by pentobarbital. The findings suggest that a combination of barbiturates with other suitable prescribed medication would be beneficial in post-operative refractory intracranial hypertension. This may also be effective in overcoming the effects of intraoperative cranial inflammation in younger patients with brain injury. | Mansour et al., 2013 |
| | The study reports that, unlike short-acting barbiturates, drugs like phenobarbital which have sustained pharmacological action may not be an appropriate choice of drugs when it comes to surgical induction. Phenobarbital may be helpful to decrease the metabolism in the brain and thereby decrease the intracranial pressure. However, phenobarbital causes several untoward actions, the principal one being hypotension. This may tilt the balance negatively wiping off the beneficial effects. | Lewis and Adams, 2021 |
| | According to Shein et al. intracranial pressure was observed to be lowered after phenobarbital administration. However, hypertonic saline was seen to have more merit as the first-line drug for treating intracranial hypertension, as it regulated the sympathetic cerebral hemodynamics and produced the fastest resolution of intracranial hypertension. | Shein et al., 2016 |
| | In this study, the authors showed that intracranial pressure fell after administration of HTS (hypertonic saline), mannitol, or barbiturates, which showed continued improvement after 2 hours. | Colton et al., 2014 |

### *Conflict of interest*

The authors declare no conflict of interest.

## REFERENCES

Brandt C, Seja P, Töllner K, Römermann K, Hampel P, Kalesse M, et al. Bumepamine, a brain-permeant benzylamine derivative of bumetanide, does not inhibit NKCC1 but is more potent to enhance phenobarbital's anti-seizure efficacy. Neuropharmacology. 2018;143:186-204.

Chakraborty T, Hocker S. Weaning from antiseizure drugs after new onset status epilepticus. Epilepsia. 2019;60:979-85.

Colton K, Yang S, Hu PF, Chen HH, Bonds B, Scalea TM, et al. Intracranial pressure response after pharmacologic treatment of intracranial hypertension. J Trauma Acute Care Surg. 2014;77:47-53.

Forsyth PA, Weaver S, Fulton D, Brasher PM, Sutherland G, Stewart D, et al. Prophylactic anticonvulsants in patients with brain tumour. Can J Neurol Sci. 2003;30:106-12.

Hadjihambi A, Karagiannis A, Theparambil SM, Ackland GL, Gourine AV. The effect of general anaesthetics on brain lactate release. Eur J Pharmacol. 2020;881:173188.

Hocker S, Clark S, Britton J. Parenteral phenobarbital in status epilepticus revisited: Mayo Clinic experience. Epilepsia. 2018;59(Suppl 2):193-7.

Klein S, Bankstahl M, Löscher W. Inter-individual variation in the effect of antiepileptic drugs in the intrahippocampal kainate model of mesial temporal lobe epilepsy in mice. Neuropharmacology. 2015;90:53-62.

Lewis CB, Adams N. Phenobarbital. StatPearls. Treasure Island (FL): StatPearls Publishing, 2021.

Mairinger S, Bankstahl JP, Kuntner C, Römermann K, Bankstahl M, Wanek T, et al. The antiepileptic drug mephobarbital is not transported by P-glycoprotein or multidrug resistance protein 1 at the blood-brain barrier: a positron emission tomography study. Epilepsy Res. 2012;100:93-103.

Mansour N, deSouza RM, Sikorski C, Kahana M, Frim D. Role of barbiturate coma in the management of focally induced, severe cerebral edema in children. J Neurosurg Pediatr. 2013;12:37-43.

Murphy L, Wolfer H, Hendrickson RG. Toxicologic confounders of brain death determination: A narrative review. Neurocrit Care. 2020;2020:1-18.

Ryu JA, Jung W, Jung YJ, Kwon DY, Kang K, Choi H, et al. Early prediction of neurological outcome after barbiturate coma therapy in patients undergoing brain tumor surgery. PLoS One. 2019;14(4):e0215280.

Sakuma H, Horino A, Kuki I. Neurocritical care and target immunotherapy for febrile infection-related epilepsy syndrome. Biomed J. 2020;43:205-10.

Sánchez Fernández I, Gaínza-Lein M, Lamb N, Loddenkemper T. Meta-analysis and cost-effectiveness of second-line antiepileptic drugs for status epilepticus. Neurology. 2019;92:e2339-e48.

Schizodimos T, Soulountsi V, Iasonidou C, Kapravelos N. An overview of management of intracranial hypertension in the intensive care unit. J Anesth. 2020;34: 741-57.

Sharpe C, Reiner GE, Davis SL, Nespeca M, Gold JJ, Rasmussen M, et al. Levetiracetam versus phenobarbital for neonatal seizures: A randomized controlled trial. Pediatrics. 2020;145(6):e20193182.

Shein SL, Ferguson NM, Kochanek PM, Bayir H, Clark RS, Fink EL, et al. Effectiveness of pharmacological therapies for intracranial hypertension in children with severe traumatic brain injury - results from an automated data collection system time-synched to drug administration. Pediatr Crit Care Med. 2016;17: 236-45.

Specchio N, Pietrafusa N. New-onset refractory status epilepticus and febrile infection-related epilepsy syndrome. Dev Med Child Neurol. 2020;62:897-905.

Tat YB, Hassan W, Chuen TY, Ghani ARI. Life-threatening dyskalaemia after barbiturate coma therapy: The strategy of management. Malays J Med Sci. 2017;24: 100-5.

Töllner K, Brandt C, Töpfer M, Brunhofer G, Erker T, Gabriel M, et al. A novel prodrug-based strategy to increase effects of bumetanide in epilepsy. Ann Neurol. 2014;75:550-62.

Tremont-Lukats IW, Ratilal BO, Armstrong T, Gilbert MR. Antiepileptic drugs for preventing seizures in people with brain tumors. Cochrane Database Syst Rev. 2008(2):Cd004424.

Velle F, Lewén A, Howells T, Enblad P, Nilsson P. Intracranial pressure-based barbiturate coma treatment in children with refractory intracranial hypertension due to traumatic brain injury. J Neurosurg Pediatr. 2019:1-9;epub ahead of print.

Velle F, Lewén A, Howells T, Nilsson P, Enblad P. Temporal effects of barbiturate coma on intracranial pressure and compensatory reserve in children with traumatic brain injury. Acta Neurochir (Wien). 2021; 163:489-98.

Wang SN, Gu CP, Liu GH, Lin ZZ, Zheng P, Pan SY, et al. The effectiveness of phenobarbital in patients with refractory status epilepticus undergoing therapeutic plasma exchange. Neuroreport. 2018;29:1360-4.

Xie J, Li Y, Huang Y, Qiu P, Shu M, Zhu W, et al. Anesthetic pentobarbital inhibits proliferation and migration of malignant glioma cells. Cancer Lett. 2009; 282:35-42.

Young L, Berg M, Soll R. Prophylactic barbiturate use for the prevention of morbidity and mortality following perinatal asphyxia. Cochrane Database Syst Rev. 2016 (5):Cd001240.

Zhang Q, Yu Y, Lu Y, Yue H. Systematic review and meta-analysis of propofol versus barbiturates for controlling refractory status epilepticus. BMC Neurol. 2019;19(1):55.