International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2016): 79.57 | Impact Factor (2015): 6.391

The Therapy Profile of Anti-Epilepsy Drugs in Spastic Cerebral Palsy of Indonesian Subject

Anidar[1], Irawan Mangunatmadja[2], Setyo Handryastuti[3], Cissy Rachiana B. Kartasasmita[4], Tuti Wahmurti A. Sapiie[5], Nelly Amalia Risan[6]

[1]Division of Pediatric of dr. Zainoel Abidin Hospital, Medical Faculty, Syiah Kuala University, Banda Aceh-Indonesia

[2, 3]Division of Pediatric Cipto Mangunkusumo Hospital, Medical Faculty, University of Indonesia, Jakarta-Indonesia

[4, 6]Division of Pediatric Hasan Sadikin Hospital, Medical Faculty, Padjajaran University, Bandung-Indonesia

[5]Division of PsychiatryHasan Sadikin Hospital, Medical Faculty, Padjajaran University, Bandung-Indonesia

Abstract: ***Background: Generally epilepsy may occur in children as well as patients with cerebral palsy. Epilepsy in children with cerebral palsy is difficult to control, therefore a regular evaluation of treatment response is required. Epilepsy treatment in cerebral palsy pediatric children requires the administration of long-term anti-epilepsy drugs either monotherapy or polytheraphy with a success indicator that patients are seizure-free for more than one year. Objective: To describes anti-epilepsy drug therapy on spastic cerebral palsy. Method: The study started by conducting exploration of research data through medical record study from 125 subjects who experienced spastic cerebral palsy with epilepsy, age range of subjects 1-18 years, then the findings were analyzed descriptively based on character from: subject, therapy, free from seizure, and application of medicine anti epilepsy for cerebral palsy epilepsy. Results: The type and comorbidity of spastic cerebral palsy are as follows: tetraplegia 52% (as dominant type), diplegia 28%, and hemiplegia 20%. The most frequent epilepsy is general tonic clonic epilepsy as much as 40%, followed by general tonic epilepsy as much as 30,4%, and last is partial complex as much as 11,2%. The application of valproic acid(81.6%) is the most treatment as anti-epilepsy which isadministratedthrough monotherapy application (64%). The results also showed a seizure-free condition dominated by: more than 1 year (13.6%). Conclusion: The type of tetraplegia as the most dominant form with epilepsy comorbidity, monotherapy therapy is more widely used and seizure free is known to be low.***

Keywords: Anti-epilepsy drugs, Epilepsy, Spastic cerebral palsy

1. Introduction

Cerebral palsy is a state of destruction of persistent and non-progressive brain tissue, this occurs at an early age so that it will interfere with brain development characterized by changes in muscle tone and movement and the presence of abnormalities in posture.[1,2]In various countries, the incidence rate cerebral palsy has varied between 1.2 and 2.5 per 1000 of live birth rates.[1] In general, cerebral palsy is divided into 4 types: spastic, atetoid, ataxia, and mixtures. Approximately 70% -80% of cases of cerebral palsy are spastic type.[3,4]

Epilepsy is one of the many neurological manifestations that can be found in cerebral palsy patients. Epilepsy is a symptom of frequent brain dysfunction that can cause brain damage when seizures persist for a long time.[5] All abnormalities that interfere with the brain and brain neurons are known to cause seizures or epilepsy seizures. Cortical or sub cortical lesions, the particular thalamus may become epileptogenic which may lead to epileptic conditions in the neurons around which potentially cause epilepsy.[6] Meanwhile, the condition of cerebral spastic palsy has more severe brain damage and involves the cerebral cortex, causing epilepsy to be more common in this type. Several studies have reported that about one-third of children with cerebral palsy have epilepsy.[7]

Epilepsy prevalence in cerebral pediatric children has a very wide percentage range of about 15% -90%, therefore it is still interesting to examine it. The Kulak W et. al [7], found that the incidence of epilepsy in cerebral pediatric children was 41.4%. Epilepsy events in spastic tetraplegia are known with a high percentage of 65.6% and 60% intractable epilepsy occurrences of spastic tetraplegia cerebral palsy. Singhi P et.al [8] reported that the incidence of epilepsy in children with cerebral palsy was 35.4%, furthermore it was also reported that spastic hemiplegic epilepsy was higher than that of spastic tetraplegi that was 60% vs. 46.2%.

The principle of epilepsy treatment in spastic cerebral children is similar to the treatment for generalized epilepsy, starting with conducting and establishing a diagnosis and determining the type of epilepsy.[5] Treatment is generally performed by long-term anti-epilepsy treatment in monotherapy and politerapi by evaluating the patient's response periodically. The response to epilepsy treatment is considered successful if the patient is seizure-free for more than one year. Wibowo et al have reported that 75.3% of epilepsy patients in cerebral palsy are administered anti-epileptic drugs in monotherapy.[9] While Bruck has found that the one-year seizure rate is 53.2% .[10] Understanding of anti-epilepsy treatment in cerebral pediatric children spastic is an important focus for obtaining better therapeutic patterns by minimizing excess seizure effects. This study aims to examine the profile of anti-epilepsy drug therapy in cerebral spastic children.

2. Material and Method

Ethical clearence

This research already has ethical clearance approval from ethics commission of Meical Faculty,University of Indonesia with letter No. 233 / UN2.F1 / ETHICS / 2015 dated March 30, 2015. A total of 125 subjects identified as epilepsy with cerebral spastic palsy (type hemiplegia, diplegia, and tetraplegia) and epilepsy type (general tonic clonic, general tonic, partial complex, focal, myoclonic, atonic) and history of anti-epilepsy drug therapy.

Sample Collection

Samples were collected retrospectively via consecutive sampling by tracking the medical record of spastic cerebral palsy patients with epilepsy that matched the inclusion and exclusion criteria. The study inclusion criteria were patients aged 1-18 years, had been diagnosed with cerebral spastic palsy at less and equally 3 years of age. Exclusion criteria were patients with cerebral spastic palsy with congenital metabolic abnormalities and genetic syndromes (Down syndrome, Turner syndrome, Klinefelter syndrome), patients with symptoms of motor disorder, posture, and tone after 3 years of age.

Data analysis

Research data obtained through the editing process which means the examination and preparation of data. Then performed the process of coding which means the data obtained are given a specific code to facilitate the reading. Then the data tabulated which means the data entered into the table according to their respective categories in order to be analyzed according to the purpose of the study. Thereafter, data are processed for data presentation and analysis, which means subject characteristics and history of anti-epilepsy drug therapy are presented descriptively.

3. Results

The subjects consisted of 54.4% male and 45.6% female. In general, the spastic cerebral palsy found in this study was 52% tetraplegia, followed by 25% diplegia, and 30% of hemiplegia. Meanwhile, the most common epilepsy in spastic cerebral palsy was epilepsy tonic clonic (40%), followed by general tonic epilepsy (30.4%) and last was a complex partial (11.2%). subject characteristics can be seen in Table 1 below.

Table 1: Characteristics of epileptic subjects with spastic cerebral palsy type

Subject Characteristic	*N*	*%*
Sex/ Gender		
Male	68	54.4
Female	57	45.6
Type of Spastic Cerebral Palsy		
Hemiplegia	25	20
Diplegia	35	28
Tetraplegia	65	52
Type of Epilepsy		
General tonic Clonic	50	40
General Tonic	38	30.4
Complex partial	14	11.2
Focal	8	6.4
Mioclonic	11	8.8
Atonic	3	3.2

Epilepsy treatment in spastic cerebral pediatric children with anti-epilepsy monotherapy treatment is known as 80 subjects or 64%. Then it was found that 17 subjects or 13.6% of subjects of cerebral spastic palsy with epilepsy were seizure-free while the subject was still seizures, known as 39.2%. Therapy and seizure-free with spastic cerebral palsy type can be seen in the following table.

Table 2: Therapy and seizure-free with spastic cerebral palsy type

Parameter	Type of spastic cerebralpalsy			N	%
	Hemiplegia	Diplegia	Tetraplegia		
Theraphy application					
Monotheraphy	16	23	41	80	64
Polytheraphy	9	12		45	36
Duration of seizure					
≤1 year	16	14	29	59	47.2
≥ 1 year	3	6	8	17	13.6
Still seizured	6	15	28	49	39.2

The findings of this study show that the most widely used anti-epilepsy drug for epilepsy therapy in spastic cerebral palsy is valproate acid where this usage has shown 102 subjects or 81.6% (Table 3).

Table 3: Types of anti-epilepsy in subjects with spastic cerebral palsy epilepsy

Type of Anti-Epilepsy	Type Of Epilepsy On Spastic Cerebral Palsy						N	%
	GTC	GT	CP	F	MC	AT		
Valproat Aci	39	33	11	6	9	4	102	81.6
Phenobarbital	21	10	2	5	3	2	43	34.4
Carbamazepin	4	2	6	0	1	1	14	11.2
Fenitoin	7	0	0	0	0	4	11	8.8
Klonazepam	2	1	3	0	1	0	7	5.6
Levetiracetam	1	0	1	0	0	0	2	1.6
Topiramat	1	1	1	2	1	0	6	4.8

Note:
GTC : General Tonic Clonic
GT : General Tonic
CP : Complex Partial
F : Focal
MC : Mioclonic
AT : Atonic

4. Discussion

The results of this study indicate that spastic cerebral palsy with epilepsy is more common in male than in female. This result shows the incidence ratio between men and women is 1.2:1 (Table 1). Compared with reports in 2010 which have reported that the ratio between male and female is 1.4:1[11]Thus, the results of this study showed a decrease in the incidence rate based on sex category. Meanwhile, the results showed that tetraplegia wasregular type of cerebral spastic palsy (52.3%). This type is also shown as the type with the most severe motoric disorder. As known, tetraplegia is a type of motoric disorder where the process has involved all extremities of the body. This type is also linked to intellectual disability and seizures as a result of wider brain damage compared to other types.[1,12] These results show different results with Kulak (2003) that stated a lower percentage or about 32.3 % and Grace (2010) that have

reported about 67% are epilepsy. This difference is due to differences in categorization of spastic cerebral palsy type. The study has categorized spastic types into 5 subtypes: hemiplegia, diplegia, quadriplegia, extrapyramidal and mixed forms.

This study showed the most frequent epilepsy in cerebral palsy is tetraplegia. This result has in line with previous reports that stated the incidence rates of tetraplegia which is frequwntly type in epilepsy of cerebral palsy is 65.6%[7], 42.6%[8], and 32.1%.[13]Gururaj et.al obtained a lower result due to different categories of types which is divided the division of cerebral palsy type into 6 groups: hemiplegia, diplegia, quadriplegia, extrapyramidal, ataxia and mixed type.[13]Meanwhile, this result unsimilar as research reported in 2011 that stated the most frequent type of epilepsy is epilepsy type hemiplegia.[14] Various studies have reported that in spastic cerebral palsy, both types quadriplegia and hemiplegic are the types that can cause more severe brain damage, therefore may lead increasing risk of epilepsy.[1,8,15]

The results of this study indicate that cerebral palsy with diplegia type is a type of epilepsy more frequent than hemiplegia (Table 1). The epilepsy of cerebral palsy indicated by varied results may be due to periventricular damage occurring rarely involving the cortical and subcortical structures of the brain.[6] In addition, it is also known that the cause factor of epilepsy of cerebral palsy is multifactor, whereby one factor may influence by other factors. Gurses (1999) study in Turkey reported that 47% of children with periventricular leukomalacia will become epilepsy and about 78% of them are intractable epilepsy.[16]

The clinical manifestations of epilepsy in spastic cerebral palsy depend on the position and degree of brain damage. In this study, it was found that 40% general tonic clonic epilepsy and 30.4% were general tonic (Table 1). This is closely related to the type of tetraplegia as the most frequent type of cerebral palsy. This type known as type of extensive cortical damage. Previous research reported mention that the percentage of this case is equal to 68.5%,[7] and 38.1% is general tonic clonic epilepsy with cerebral palsy type is hemiplegia.[8]Unmatched result also confirmed where 39.3% of partial epilepsy is quadriplegia type.[13] This difference indicates that the cause of epilepsy in cerebral palsy is multifactor, which may occur at prenatal, perinatal or postnatal.[17]

In this study 81.6% subjects were given monotherapyas anti epilepsy treatment (Table 2), similar with Wibowo[9], that reported treatment by monotherapy equal to 75.3%. Other research also found that most epilepsy patients in cerebral palsy were given the same application.[10]This is due to the fact that the pathogenesis and the response to seizures is related to the severity of cerebral palsy.[18] Additionally, epilepsy in children with cerebral palsy mostly difficult to control while there brain damage or may be related to the presence of an syndrome of epilepsy.[15,19]

Epilepsy treatment for children with cerebral palsy will be more difficult to stop, and it may take longer to achieve seizure-free for 1-2 years than children with epilepsy without cerebral palsy. Anti epileptic cessation may be performed if the patient has been seizure-free for 2 years.[20] In this study it was found after treatment that 49 subjects or 39.2% spastic cerebral palsy with epilepsy still seizured (Table 2). As much 17 subjects or 13.6% after treatment were seizure-free more than one year. Similarly, result research in 2012 stated that 49.5% of children with spastic cerebral palsy still have seizures after therapy with anti-epilepsy drug, while this research also reported that children with spastic cerebral palsy free from seizures are 20.6%.[9] This result is also in line with a study conducted in 1998, which mentions that 42% children of cerebral palsy with epilepsy have seizure-free for more than one year.[21]

Selection of anti-epilepsy drugs for spastic cerebral palsy was not different from common epilepsy with the seizure type as an indicator.[17] In this study, 102 subjects or 81.6% found using valproate acid as most anti-epilepsy drugs. This is in line with the frequent epilepsy that found isgeneral tonic clonic, where this type represents 40% (Table 3). This result is similar to previous study which states that about 70.1% of subjects use valproic acid.[9] As known, Valproic acid is the first choice for epilepsy general tonic clonic and general tonic. Other alternative anti-epileptic drugs that may be used are phenobarbital and phenytoin. In this study the use of phenobarbital was 34.4%. Assuming the first treatment fails, the second treatment given through titration method. The results showed that 36% politerapi mechanism was found, this result is not different with research conducted in 2012 which states that about 24,7% of patient use mechanism of polytheraphy.[9] Similarly, research reports conducted in 1998 was stated that partial epilepsy with a higher percentage of 37.5% compared with general epilepsy is only 28%.[21] Meanwhile, it also known that the application of polytheraphy which is 25% has been given with a second choice of anti-epilepsy drugs namely vigabatrin, lamotrigine, clonazepam, klobazam and gabapentin.

5. Conclusion

This study can be concluded that epilepsy is frequenly occurs in children with cerebral spastic palsy tetraplegia. Frequent epilepsy founded is generaltonic clonic epilepsy. The application of valproic acid is the most treatment as anti-epilepsy which isadministratedthrough monotherapy application to children whose spastic cerebral palsy in seizure-free condition equal to or more than 1 year.

6. Acknowledgement

Thanks to CiptoMangunkusumo Hospital (RSCM) and Fatmawati Hospital, and Harapan Kita Hospital-Jakarta Indonesia which has facilitated us, especially the access to subject and medical record.

References

[1] Swaiman KF, Wu Y. Cerebral palsy. Dalam: Kenneth F. Swaiman, Stephen Ashwal, Ferriero DM, penyunting. Pediatric neurology principles & practice. Edisi ke-5. Philadelphia: Mosby Elsevier; 2012. h. 492-501.

[2] Berker N, Yalcin S. The HELP guide to cerebral palsy. Edisi ke-2. Washington: Merril corporation; 2010. h. 7-14.
[3] Green L, Greenberg GM, Hurwitz E. Primary care of children with cerebral palsy. ClinFamPract 2003;5:467-91.
[4] Koman LA, Smith BP, Shilt JS. Cerebral palsy. The Lancet 2004;363:1619-31.
[5] Sankar R, Koh S, Wu J, Menkes JH. Paroxysmal disorders. Dalam: Menkes JH, Sarnat HB, Maria BL, penyunting. Child Neurology. Edisi ke-7. Lippincott Williams & Wilkins: Philadelphia; 2006. h. 858-943.
[6] Rho JM, Stafstrom CE. Neurophysiology of epilepsy. Dalam: Kenneth F. Swaiman, Stephen Ashwal, Ferriero DM, penyunting. Pediatric neurology principles & practice. Edisi ke-5. Philadelphia: Mosby Elsevier; 2012. h. 991-9.
[7] Kulak W, Sobaniec W. Risk factors and prognosis of epilepsy in children with cerebral palsy in north-eastern Poland. Brain Dev. 2003;25:499-506.
[8] Singhi P, Jagirdar S, Khandelwal N, dkk. Epilepsy in children with cerebral palsy. J Child Neurol. 2003;18:174-9.
[9] Wibowo AR, Saputra DR. Prevalensdanprofilklinispadaanakpalsiserebralspatikdenganepilepsi. Sari Pediatri. 2012;14:1-7.
[10] Bruck I, Antoniuk SA, Spessato A, de Bem RS, Hausberger R, Pacheco CG. Epilepsy in children with cerebral palsy. ArqNeuropsiquiatr 2001;59:35-9.
[11] Rahmat D, Mangunatmadja I, Tridjaja B. Prevalence and risk factors for epilepsy in children with spastic cerebral palsy. PaediatrIndonesia. 2010;50:11-7.
[12] Johnston MV. Encephalopathies. Dalam: Berhman RE, Kliegman RM, Arvit AM, penyunting. Nelson's textbook of pediatrics. Edisi ke-18. Philadelphia: Saunder; 2008. h. 2494-5.
[13] Gururaj AK, Sztriha L, Bener A, Dawodu A, Eapen V. Epilepsy in children with cerebral palsy. Seizure. 2003;12:110-4.
[14] Mert GG, Incecik F, Altunbasak S, Herguner O, Mert MK, Kiris N, dkk. Factors affecting epilepsy development and epilepsy prognosis in cerebral palsy. Pediatric Neurology 2011, 45 :89-94.
[15] Carlsson M, Olsson I, Hagberg G, Beckung E. Behaviour in children with cerebral palsy with and without epilepsy. Dev Med Child Neurol. 2008;50:784-9.
[16] Gurses C, Gross DW, Andermann F. Periventrikulerleucomalacia and epilepsy. Neurology. 1999;52:341-5.
[17] Aisen ML, Kerkovich D, Mast J. Cerebral palsy: clinical care and neurological rehabilitation. Lancet Neurol. 2011;10:844-52.
[18] Camfield PR, Camfield CS. Pediatric epilepsy: An overview. Dalam: Swaiman KF, Ashwal S, Ferriero DM, penyunting. Pediatric neurology: principles and practice. Edisi ke-4. St. Louis: Mosby; 2006. h. 981-9.
[19] Aicardi J. Epilepsy in brain-injured children. Dev Med Child Neurol 1990;32:191-202.
[20] Delgado MR, Riela AR, Mills J, Pitt A,Browne R. Discontinuation of antiepileptic drug treatment after two seizure-free years in children with cerebral palsy. Pediatrics 1996;97:192-7.
[21] Kwong KL, Wong SN, So KT. Epilepsy in children with cerebral palsy. PediatrNeurol 1998;19:31-6.

Author Profile

Anidar.Lecturer at Medical Faculty, University of Syiah Kuala and Consultant of Pediatric Neurology Division of Pediatric-dr. Zainal Abidin Hospital (Rumah Sakit Umum dr. Zainal Abidin), Banda Aceh-Indoensia.

IrawanMangunatmadja, Consultant of Pediatric Neurology, Division of Pediatric Cipto Mangunkusumo Hospital (RSCM), Medical Faculty, University of Indonesia, Jakarta-Indonesia

SetyoHandryastuti, Consultant of Pediatric Neurology, Division of Pediatric Cipto Mangunkusumo Hospital (RSCM), Medical Faculty, University of Indonesia, Jakarta-Indonesia,

Nelly AmaliaRisan, Consultant of Pediatric Neurology, Division of Pediatric Hasan Sadikin Hospital (Rumah Sakit Hasan Sadikin), Medical Faculty, Padjajaran University, Bandung-Indonesia.

Cissy Rachiana B. Kartasasmita, Professor of Pediatric Respirology Medical Faculty, Padjajaran University, Bandung-Indonesia and Consultant of Pediatric RespirologyDivision of Pediatric Hasan Sadikin Hospital (Rumah Sakit Hasan Sadikin), Bandung-Indonesia.

Tuti Wahmurti A. Sapiie, Professor of pediatric psychiatry Medical Faculty, Padjajaran University, Bandung-Indonesia and Consultant of Pediatric psychiatry, Division of psychiatry Hasan Sadikin Hospital (Rumah Sakit Hasan Sadikin), Bandung-Indonesia.