Antiepileptic Drugs In Pediatric Indoor: Widely Prescribed; Wisely Consumed?

Siddhartha Ghosh¹, Ayan Kumar Pati²

¹Associate Professor, Department of Pharmacology, IQ City Medical College & Hospital, Durgapur, West Bengal, India.
²Assistant Professor, Department of Pharmacology, IQ City Medical College & Hospital, Durgapur, West Bengal, India.

Received: June 2019
Accepted: July 2019

Copyright: © the author(s), publisher. Annals of International Medical and Dental Research (AIMDR) is an Official Publication of “Society for Health Care & Research Development”. It is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Seizure is a very common manifestation of a variety of disorders in pediatric age groups. The choice of antiepileptic drugs varies in different age groups in various doses, routes and frequencies. The perception of the care giver regarding proper use of medications is also equally important for success of pharmacotherapy. This study aimed to explore the prescribing pattern of seizure medications in pediatrics inpatients of a tertiary care hospital and assess the parent’s knowledge on drug intake simultaneously. Methods: A prospective observational study carried out with the prescription data of 107 children aged less than 18 years admitted in the pediatric department with the diagnosis of seizure and analyzed with descriptive statistics to obtain drug utilization indices. Results: A questionnaire survey was employed on the parents of the children to assess their knowledge. Results: Neonatal presentation with seizure was more common than older pediatric age group. Commonest causes of convulsions were birth asphyxia with its sequel (84.78 %), CNS infection (39.34%) and epilepsy (32.79%). Monotherapy was highly prevalent (73.80%) with phenobarbitone and phenytoin being the commonest drugs in neonatal and post-neonatal populations respectively. No newer generation antiepileptics were used. GENERIC prescribing was 28.03% with all the drugs being enlisted in essential medicine list. Average no. of anticonvulsants per prescription was 1.28. Parent’s knowledge about frequency of drug administration and food interaction was largely deficient. Conclusion: Monotherapy with older antiepileptics are preferred in pediatric indoor patients presenting with seizures. Parent education on appropriate use of medication is needed to rationalize the therapy.

Keywords: Antiepileptic drugs, drug utilization, epilepsy, pediatric, prescribing pattern.

INTRODUCTION

Seizure is one neurological disorder that frequently complicates childhood ailments. Up to 10% of people worldwide have one seizure during their lifetime. Around 50 million people worldwide have epilepsy and 80% of those live in low- and middle-income countries. Indian scenario also reflects this. Epileptic syndromes pose some greater challenges in the form of being chronic in nature and requiring, at times, lifelong drug therapy to maintain the quality of life. All of the commonly used anticonvulsants are having narrow therapeutic windows which require therapeutic monitoring of their plasma concentration throughout the treatment, particularly in vulnerable population like pediatric age groups.

Over the past few decades, successful drug development has strengthened the anticonvulsant armamentarium with a number of new antiepileptic drugs (AEDs) with better tolerability profile but at a higher cost. Previous studies showed that the older agents are popular, and they are still considered first line in standard treatment guidelines with newer ones having add-on benefit. This can be attributed to time-tested favor of the clinicians due to low cost, extensive post marketing surveillance and better research-driven evidence.

With so many choices available, the treatment must be individualized. Otherwise, irrational drug use may creep in, which contributes significantly towards unnecessary polypharmacy, unacceptable drug interaction, expensive treatment and inefficient utilization of resources. Also, as the sole care giver, parent’s knowledge about how to take the drugs in most safe and effective way is equally important factor contributing to children’s disease-free productive life.

In this context, investigating the utilization of antiepileptic drugs in different epileptic or non-epileptic seizure disorders as well as exploring the background knowledge of the care givers in a tertiary care government health facility will provide an overall picture and drive the necessary corrective steps to improve the health care delivery. Thus, the objectives of our study were to find out the

Name & Address of Corresponding Author
Dr. Ayan Kumar Pati,
Assistant Professor,
Department of Pharmacology,
IQ City Medical College & Hospital,
Durgapur, West Bengal, India.
prescribing pattern of antiepileptic drugs for different indication in various age group in pediatric ward of a tertiary care hospital.

MATERIALS AND METHODS

Study Design:
A hospital-based prospective observational study was conducted for 6 months in between the months of July and December 2018 in the department of pediatrics of IQ City Medical College and Hospital, a tertiary care private teaching hospital in Durgapur, West Bengal.

Study population & sample size:
Study population comprised of children aged less than 18 years admitted in the pediatric department with the diagnosis of seizure. Complete enumeration method was employed to include 107 patients.

Selection criteria:
Pediatric patients with seizures, who were prescribed an anti-epileptic drug, are included in the study. Children who received Antiepileptic drugs for non-seizure indications, children admitted with convulsion due to metabolic derangements (hypoglycemia, hypocalcemia etc.) and who were on ventilator, excluded from the study.

Study tools, techniques and data collection procedures:
All Bed Head Tickets (BHTs) were examined for various drug use parameters by 2 independent investigators. Patient particulars, diagnosis, investigations and drug data (generic prescription, dosage form, route of administration, drug from essential medicine list) were included on a customized data collection sheet. Basic drug indicators had been selected to analyze the prescribing patterns. An interviewer-administered questionnaire-based survey was also conducted on the parents of the patients.

Ethical Clearance & Confidentiality:
Prior approval from Institutional Ethics Committee (IEC) was obtained. Written informed consent and assent (where applicable) was obtained from the patients and parents. For the purpose of protection of privacy of the participants, anonymity was maintained throughout the study.

Statistical analysis:
Data was compiled in Microsoft office Excel 2016 and analyzed. Descriptive statistics was used to summarize the data. Categorical data was expressed as proportions while continuous data was expressed as mean and standard deviation as per normal distribution.

Reporting Guideline:
The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline was followed in the preparation of protocol and the manuscript[1].

RESULTS & DISCUSSION

A total of 107 BHTs were collected and analyzed from pediatric indoor of which 58.90% (n=63) were male and 41.40% (n=43) were female. The age distribution of all the patients is depicted in [Figure 1].

Figure 1: Age distribution of children presenting with convulsion

Among the patients presenting with convulsion anytime during admission, the disease distribution and affected age group is shown in [Table 1].

Table 1: Distribution of diagnosis of convulsion among pediatric age groups

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of cases (Percentages)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth asphyxia and its sequels</td>
<td>39 (84.78%) 0 (0%) 39 (36.40%)</td>
</tr>
<tr>
<td>CNS infection</td>
<td>24 (39.34%) 25 (23.40%)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>20 (32.79%) 20 (18.70%)</td>
</tr>
<tr>
<td>Febrile convulsions</td>
<td>10 (16.39%) 10 (9.30%)</td>
</tr>
<tr>
<td>Seizures associated with infections except CNS infections</td>
<td>4 (6.56%) 6 (5.6%)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>3 (4.92%) 7 (6.5%)</td>
</tr>
</tbody>
</table>

Use of a total of 6 anticonvulsants from different classes have been observed in this study: namely, phenobarbitone, phenytoin, diazepam, sodium valproate, clobazam and midazolam. The relative usage of each drug in both overall and in neonatal age group, percentages of cases where loading dose were used along with average loading and maintenance dose used is represented in [Table 2].

Monotherapy with single antiepileptics was noted in 73.80% (n=79) cases while 26.20% (n=28) cases required multidrug combination therapy. Among monotherapy, phenobarbitone (59.49%, n=47), phenytoin (30.38%, n=24), diazepam (7.59%, n=6) and valproate (2.53%, n=2) were most popular drugs. Most commonly used combinations were Phenytoin + diazepam (64.29%, n=18), followed by
phenytoin + valproate, phenytoin + phenobarbitone, phenobarbitone + diazepam (each 7.14%, n=2). Valproate + diazepam and diazepam + clobazam combination were used in 3.57% (n=1) cases each and only 2 cases (7.14%) required triple drug therapy with phenytoin + phenobarbitone + midazolam.

Analysis of prescriptions was done by WHO-INRUD drug use indicators, provided in [Table 3].

Out of the 6 most commonly used drugs, only diazepam and midazolam are prescribed by generic names. Regarding utilization of hospital formulary, phenobarbitone (96.23%, n=51), phenytoin (100%, n=48), diazepam (100%, n=28) and midazolam (100%, n=2) were procured from hospital supply and rest purchased from retail shops.

Details of dosing of individual agents are depicted in [Table 4].

Table 2: Pattern of usage of major antiepileptic drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Overall usages (%)</th>
<th>Usages in neonates (%)</th>
<th>Cases with loading dose administration (%)</th>
<th>Loading dose (mg/kg) mean ± SD</th>
<th>Maintenance dose (mg/kg) mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbitone</td>
<td>49.53</td>
<td>95.65</td>
<td>94.33</td>
<td>19.91 ± 0.44</td>
<td>2.47 ± 0.33</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>44.85</td>
<td>4.76</td>
<td>100</td>
<td>19.04 ± 3.11</td>
<td>2.45 ± 0.37</td>
</tr>
<tr>
<td>Diazepam</td>
<td>26.16</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.5 ± 0</td>
</tr>
<tr>
<td>Valproate</td>
<td>4.67</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2.6 ± 0.55</td>
</tr>
<tr>
<td>Clobazam</td>
<td>0.97</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2.5 ± 0</td>
</tr>
<tr>
<td>Midazolam</td>
<td>1.86</td>
<td>2.38</td>
<td>100</td>
<td>0.53 ± 0.65</td>
<td>0.21 ± 0.007</td>
</tr>
</tbody>
</table>

Table 3: WHO/INRUD- drug prescribing indicators

<table>
<thead>
<tr>
<th>Prescribing indicators</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average number of drugs per prescription: Mean ± SD</td>
<td>5.63 ± 1.08</td>
</tr>
<tr>
<td>Average number of antiepileptic drugs per prescription: Mean ± SD</td>
<td>1.28 ± 0.34</td>
</tr>
<tr>
<td>Percentage of prescriptions containing antiepileptic FDCs</td>
<td>0%</td>
</tr>
<tr>
<td>Percentage of drugs prescribed by generic name</td>
<td>28.03%</td>
</tr>
<tr>
<td>Percentage of drugs prescribed from NLEM</td>
<td>100%</td>
</tr>
<tr>
<td>Percentage of prescriptions with an injection prescribed</td>
<td>79.41%</td>
</tr>
</tbody>
</table>

Table 4: Pharmacokinetic attributes of major antiepileptic drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of administration no. (%)</th>
<th>Frequency of dosing no. (%)</th>
<th>Dosage form no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>oral (%)</td>
<td>BD (%)</td>
<td>Syrup (%)</td>
</tr>
<tr>
<td>Phenobarbitone</td>
<td>2 (3.77%)</td>
<td>0 (96.22%)</td>
<td>0 (2)</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>0 (100%)</td>
<td>47 (97.92%)</td>
<td>1 (2.08%)</td>
</tr>
<tr>
<td>Diazepam</td>
<td>1 (3.17%)</td>
<td>27 (96.43%)</td>
<td>27 (96.43%)</td>
</tr>
<tr>
<td>Valproate</td>
<td>5 (100%)</td>
<td>1 (3.75%)</td>
<td>5 (100%)</td>
</tr>
<tr>
<td>Clobazam</td>
<td>1 (100%)</td>
<td>3 (60%)</td>
<td>5 (100%)</td>
</tr>
<tr>
<td>Midazolam</td>
<td>2 (100%)</td>
<td>1 (50%)</td>
<td>1 (50%)</td>
</tr>
</tbody>
</table>

(IV; intravenous, PR; per rectal, BD; twice daily, TDS; thrice daily, SOS; as and when required)

Figure 2: Parent’s knowledge of antiepileptic drug consumption

The parent’s knowledge on consumption of administered drugs were also assessed and expressed in [Figure 2]. The perception of treatment satisfaction of the parents was recorded in a 4-point forced choice format scale and presented in [Figure 3].

Figure 3: Parent’s satisfaction with treatment

The commonest indication for AED use, extent of monotherapy, commonest AED used varies in neonatal and post-neonatal age groups as shown in [Table 5].
The disease burden of epilepsy and non-epileptic fits in children is high both globally as well as in India. Compared to older generation AEDs, newer drugs are expensive, although both classes are reported to have similar efficacy and safety profile. Recently new generation AEDs are increasingly utilized in other non-epileptic indication like psychiatric disorders, migraine and neuropathic pain etc. The prescribing pattern of AEDs along with their pharmacokinetic attributes in different convulsive disorders encountered in different pediatric age groups in a tertiary care center offers a glimpse of standards of care and extent of adherence to standard evidence-based treatment guidelines. Irrationality as well as medication errors can be minimized if caregiver’s knowledge about drug intake can be taken into account. Our study focused on these issues simultaneously.

In this study, neonates were found to be most susceptible to convulsive disorders than other pediatric age groups. Children more than 5 years of age are affected least. Similar results were reported by Aaberg and colleagues. There was no significant gender predominance in regard to the disease distribution. Birth asphyxia and its sequel (36.40%), central nervous system infections (23.40%) and epilepsy (18.70%) are found to be the 3 most common causes of convulsion overall in pediatric population. While birth asphyxia and its sequel were the single most common diagnosis in neonates, rest two were major contributors for morbidity in post neonatal group. Other causes were febrile convulsions (32.79%), seizures associated with non-CNS infections. No newer AEDs were found to be used in this study. Patel also reported that Conventional AEDs (78.95%) were prescribed more frequently than newer AEDs (21.05%) for epilepsy; while newer AEDs (68.10%) were frequently prescribed in patients suffering from non-epileptic conditions. Preference on conventional AEDs may be due to being p-drug for most of the clinicians in a healthcare setting and availability in the hospital supply, low cost as well as better quality evidence in the event of acute episodes. Phenytoin and midazolam are the most common AEDs used in neonate and post neonates respectively. This is unlike other studies where new generation AEDs were used predominantly, but similar to studies done in developing countries like India. Diazepam, clobazam and valproate were not used in neonates. Loading doses were administered in phenobarbitone (94.33%) and in all cases of phenytoin and midazolam receiving patients while rest of the drugs were given in maintenance doses. Monotherapy with single AED was preferred by clinicians in almost ¾th of cases, similar to trends found globally and in India. Phenobarbitone and phenytoin were the 2 most popular choices. In rest of the cases requiring multi drug combination therapy, Phenytoin with diazepam was used in majority while only 2 cases received 3 concurrent AEDs namely Phenytoin, phenobarbitone and midazolam. Monotherapy was noted to be more prevalent in neonates than post-neonatal age group (95.65% vs 75.40%).

While analyzing the prescribing indicators for AEDs, it was found that the average number of antiepileptic drugs per prescription was 1.28 which is similar to studies done in other parts of India and abroad. Generic prescribing was noted in 28.03 percent of overall cases with diazepam and midazolam, but rest drugs were prescribed in brands. Majority of the AEDs were provided from hospital supply. All the 6 drugs were included in National List of Essential Medicine (NLEM), 2015. 79.41% of the dosage form of anticonvulsants were injection. The pharmacokinetic attributes pertaining to the bioavailability of the drugs were analyzed. The commonest route of administration was intravenous (IV) followed by per rectal and oral routes. Phenytoin and midazolam were exclusively given via IV while valproate and clobazam via oral routes. Phenobarbitone was administered by IV and oral route and diazepam by rectal and IV routes. Syrups and injections were preferred dosage forms chosen. A questionnaire survey of the parent’s knowledge about the correct method to consuming the drug reveals that most of the parents lack the information of food interaction and frequency of intake of the drugs but were aware of timing and route of administration of the drugs. The satisfaction of the parents pertaining to the quality of care provided was assessed and most of them are not satisfied. Our study results are limited by the fact that the study was done in a tertiary healthcare setting whose result may not be generalizable universally. Also, larger sample size study will be warranted to find out the true pattern of prescribing.

**CONCLUSION**

The present study explored the utilization pattern of antiepileptic drugs in a tertiary care health facility as well as assessed the caregiver’s knowledge about basic facts regarding safe and effective consumption...
of these drugs. We found, newborns are most susceptible to convulsive episodes due to birth asphyxia and its sequel than other pediatric age groups. Monotherapy with phenobarbitone and phenytoin is most commonly administered but newer AEDs are not employed regularly. There is a significant lack of basic drug consumption information among the children’s parents which may contribute to serious medication errors.

REFERENCES


Source of Support: Nil, Conflict of Interest: None declared