Section: Pediatrics

Original Research Article

THERAPEUTIC SERUM PHENOBARBITAL CONCENTRATIONS IN INDIAN CHILDREN WITH SEIZURE DISORDERS: A CLINICAL AND PHARMACOKINETIC STUDY

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ABSTRACT

Background: Phenobarbital remains a widely used first-line antiepileptic drug in developing countries, yet limited data exists on therapeutic serum concentrations in Indian paediatric populations. This study aimed to determine optimal phenobarbital serum levels for seizure control in Indian children and correlate these levels with clinical efficacy and adverse effects. **Materials and Methods:** A prospective observational study was conducted at King George's Medical College, Lucknow, from May 1991 to April 1992. Seventy children aged less than 12 years presenting with generalized or focal seizures were enrolled. Phenobarbital therapy was initiated at 3 mg/kg/day, and steady-state serum concentrations were measured in 20 patients using homogeneous enzyme immunoassay (EMIT). Clinical efficacy, adverse effects, and pharmacokinetic parameters were analysed. **Result:** The study included 53 males and 17 females (ratio 3:1). Generalized seizures predominated (55.7%) over focal seizures (44.3%). Secondary epilepsy was more common (60%) than idiopathic epilepsy (40%), with infectious aetiologies being prevalent. Overall seizure control was achieved in 97.1% of patients. Mean serum phenobarbital concentration in the controlled group was 20.81 ± 1.431 µg/ml compared to 11.53 ± 1.202 µg/ml in the uncontrolled group ($p<0.05$). Drowsiness occurred when serum levels exceeded 25 µg/ml. **Conclusion:** Indian paediatric patients achieved higher serum phenobarbital concentrations than reported Western populations at similar doses, suggesting potential differences in drug metabolism. A therapeutic threshold of approximately 15 µg/ml appears necessary for seizure control in this population.

INTRODUCTION

Epilepsy represents one of the most prevalent neurological disorders affecting children worldwide, with an estimated incidence of 20-40 million people globally. In India, approximately 6 million individuals are affected by epilepsy, making it a significant public health concern. The condition disproportionately affects paediatric populations, with most forms of epilepsy manifesting during childhood years.[1-3]

Phenobarbital, introduced as an antiepileptic agent by Hauptmann in 1912, remains the oldest and most widely prescribed antiepileptic drug globally. Despite the availability of newer antiepileptic medications, phenobarbital continues to serve as a first-line therapy in developing countries due to its proven efficacy, excellent safety profile, and cost-effectiveness. The drug demonstrates broad-spectrum activity against various seizure types, including generalized tonic-clonic seizures and focal seizures, while exhibiting relatively low toxicity compared to other antiepileptic agents.[4-6]

The therapeutic effectiveness of phenobarbital is closely correlated with serum drug concentrations, making therapeutic drug monitoring an essential component of optimal seizure management. Western literature suggests therapeutic serum concentrations ranging from 15-40 µg/ml for adequate seizure control. However, significant inter-individual variability exists in drug metabolism, distribution, and elimination, particularly among different ethnic populations and in varying nutritional states.[7-9]

Indian paediatric populations present unique challenges in epilepsy management due to factors including malnutrition, parasitic infestations, subclinical infections, and socioeconomic constraints. These conditions may potentially alter drug pharmacokinetics through modifications in absorption, distribution, hepatic metabolism, and renal clearance. Despite widespread use of phenobarbital in Indian clinical practice, limited data

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exists regarding optimal therapeutic serum concentrations in Indian paediatric populations.[10,11] The pharmacokinetics of phenobarbital in children differs significantly from adults, with faster hepatic metabolism necessitating higher weight-adjusted doses. Indian children may require different dosing strategies compared to well-nourished Western populations due to environmental and genetic factors affecting drug handling. Furthermore, the aetiology of childhood seizures in developing countries often differs from developed nations, with infectious causes being more prevalent.[12,13]

This study was designed to address these knowledge gaps by investigating serum phenobarbital concentrations in Indian children with seizure disorders, correlating these levels with clinical efficacy and toxicity, and establishing therapeutic guidelines appropriate for this population.[14,15]

MATERIALS AND METHODS

Study Design and Setting: This prospective observational study was conducted in the Department of Paediatrics at King George's Medical College, Lucknow, India, over a one-year period from May 1991 to April 1992. The study was carried out in collaboration with the Clinical Pharmacological Unit for Rational Care of Patients. All procedures were conducted in accordance with institutional ethical guidelines.

Study Population: The study included 70 children aged less than 12 years presenting with either generalized or focal seizures to the outpatient department or admitted to the children's hospital. Patients were enrolled from both indoor and outdoor departments, representing a diverse socioeconomic spectrum typical of the Indian paediatric population.

Inclusion Criteria

- Children aged 0-12 years
- Either sex
- Presenting with documented seizure disorders (generalized or focal)
- Consent for participation from parents/guardians

Exclusion Criteria

- Patients with encephalopathy
- Those with significant hepatic or renal dysfunction
- Children receiving other antiepileptic drugs concurrently
- Patients with known hypersensitivity to phenobarbital

Clinical Assessment: Comprehensive clinical evaluation included detailed history taking covering antenatal events, birth history, developmental milestones, and family history of seizure disorders. Physical examination encompassed general, systemic, and detailed neurological assessments. Seizure classification followed the International League Against Epilepsy (ILAE) criteria established in 1989.

Diagnostic Investigations: Routine investigations included complete hemogram, serum protein and albumin levels. Electroencephalography (EEG) was performed in all patients, while computerized tomography (CT) scanning was conducted when clinically indicated. Additional investigations such as cerebrospinal fluid examination, chest X-ray, and tuberculin testing were performed based on clinical suspicion.

Treatment Protocol: All patients received phenobarbital monotherapy at an initial dose of 3 mg/kg/day administered orally as a single bedtime dose. The medication used was Gardenal (phenobarbital) manufactured by May & Baker Pharmaceuticals, Rhone Poulenc India Ltd. Dose adjustments were made when necessary based on clinical response and serum drug levels.

Serum Concentration Measurement: Steady-state serum phenobarbital concentrations were measured in 20 patients after 10 days of consistent therapy. Blood samples (2 ml non-oxalated) were collected 5-8 hours after oral administration. Serum phenobarbital levels were determined using homogeneous enzyme immunoassay (EMIT, Syva Co., California) on a Vitalab 32 analyser (Vital Scientific, Netherlands).

Statistical Analysis: Data analysis was performed using appropriate statistical methods. Continuous variables were expressed as mean ± standard error. Student's t-test was used for comparing means between groups. Chi-square test was applied for categorical variables. A p-value <0.05 was considered statistically significant.

RESULTS

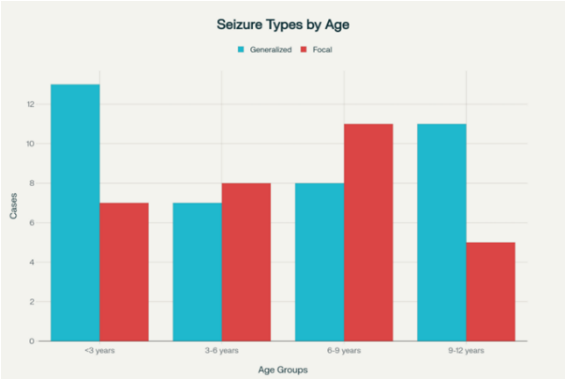

Figure 1: Age-wise distribution of seizure types in pediatric patients (n=70)

Demographic Characteristics: The study enrolled 70 children with seizure disorders, comprising 53 males (75.7%) and 17 females (24.3%), yielding a male-to-female ratio of 3:1. Age distribution showed relatively uniform representation across all pediatric age groups: children under 3 years constituted 28.6% (n=20), 3-6 years represented 21.5% (n=15), 6-9 years comprised 27.5% (n=19), and 9-12 years accounted for 22.8% (n=16) of the study population.

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Socioeconomic analysis revealed that 80% of patients belonged to lower socioeconomic strata, while 20% represented middle-class families. Nutritional assessment demonstrated that 75.7% of children had normal nutritional status, with the remaining 24.3% showing varying degrees of malnutrition according to standard pediatric growth charts.

Seizure Characteristics and Etiology: Generalized seizures were more prevalent, affecting 39 patients (55.7%), while focal seizures occurred in 31 patients (44.3%). Etiological analysis revealed secondary epilepsy in 60% of cases, surpassing idiopathic epilepsy (40%). Among secondary causes, infectious etiologies predominated, with chronic granulomatous lesions accounting for 21.5%, pyogenic meningitis for 18.5%, tuberculosis-related seizures for 11.5%, and cerebral palsy for 8.5% of cases.

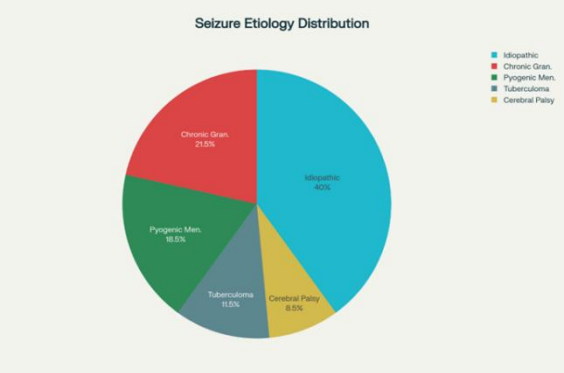

Figure 2: Seizure Etiology Distribution

Diagnostic imaging provided valuable insights into underlying pathology. CT scanning demonstrated abnormalities in 51.4% of examined patients, while EEG abnormalities were detected in only 17.1% of cases, suggesting CT scanning as a more sensitive diagnostic modality for identifying structural brain lesions in this population.

Clinical Efficacy: Phenobarbital monotherapy demonstrated excellent clinical efficacy, with overall seizure control achieved in 68 out of 70 patients (97.1%). The majority of patients (81.5%) achieved adequate seizure control with the standard dose of 3 mg/kg/day, while 10.0% required 4 mg/kg/day, 5.8% needed 5 mg/kg/day, and only 2.7% required the maximum dose of 6 mg/kg/day.

Serum Phenobarbital Concentrations: Steady-state serum phenobarbital concentrations were measured in 20 patients, revealing considerable inter-individual variability ranging from 9.22 to 31.82 µg/ml. Patients with controlled seizures (n=17) demonstrated significantly higher mean serum concentrations (20.81 ± 1.431 µg/ml, range 13.93-31.82 µg/ml) compared to those with uncontrolled seizures (n=3) who had lower concentrations (11.53 ± 1.202 µg/ml, range 9.22-13.36 µg/ml). This difference was statistically significant ($p<0.05$), establishing a clear correlation between serum drug levels and therapeutic efficacy.

Adverse Effects and Toxicity: Adverse effects were minimal and dose-related. Drowsiness was the most commonly observed side effect, occurring primarily in patients with serum phenobarbital concentrations exceeding 25 µg/ml. Notably, this threshold was lower than the 30 µg/ml reported in Western pediatric populations, suggesting increased sensitivity to phenobarbital-induced sedation in Indian children. No serious adverse events or signs of phenobarbital toxicity were observed during the study period.

Pharmacokinetic Considerations: The study revealed that Indian pediatric patients achieved higher serum phenobarbital concentrations compared to Western populations receiving similar dosages. Mean serum concentrations in our controlled group (20.81 µg/ml) exceeded Western pediatric literature reports of 15 µg/ml at comparable doses. This finding suggests potential differences in drug metabolism, possibly related to variations in hepatic enzyme activity, nutritional status, or concurrent subclinical conditions prevalent in this population.

Analysis of drug clearance showed no significant correlation with serum concentrations, indicating potential alterations in hepatorenal drug elimination pathways. The relationship between blood pH and serum phenobarbital concentrations showed a significant positive correlation ($p<0.01$), with higher pH values associated with increased drug concentrations.

DISCUSSION

This study provides valuable insights into phenobarbital pharmacokinetics and therapeutic efficacy in Indian paediatric populations. The predominance of male patients (75.7%) aligns with previously reported epidemiological data from developing countries, where cultural factors may influence healthcare-seeking behaviour and reporting of seizure disorders in female children.[16]

The higher incidence of secondary epilepsy (60%) compared to idiopathic cases represents a significant departure from Western paediatric populations, where primary epilepsy typically predominates. This pattern reflects the increased burden of infectious diseases, malnutrition, and perinatal complications in developing countries. The prevalence of infectious aetiologies, particularly tuberculosis-related seizures and chronic granulomatous lesions, underscores the impact of endemic diseases on paediatric neurological health in India.[17-19]

Our findings demonstrate that CT scanning provides superior diagnostic yield compared to EEG in identifying structural brain abnormalities, with abnormal CT findings in 51.4% versus 17.1% abnormal EEGs. This observation supports the value of neuroimaging in the evaluation of childhood seizures, particularly in populations with high rates of infectious and structural brain lesions.[20,21]

The therapeutic efficacy of phenobarbital in our study (97.1% seizure control) exceeded reported rates in

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Western literature, possibly reflecting differences in seizure aetiology, patient selection, or adherence patterns. The majority of patients achieved control with relatively low doses (3 mg/kg/day), suggesting adequate therapeutic response despite the challenging clinical circumstances.[22]

A critical finding of this study is the higher serum phenobarbital concentrations achieved in Indian children compared to Western paediatric populations at equivalent doses. Our controlled group demonstrated mean concentrations of 20.81 µg/ml, substantially higher than the 15 µg/ml typically reported in Western literature. This discrepancy suggests important pharmacokinetic differences that may be attributed to several factors.[23]

Malnutrition, subclinical infections, parasitic infestations, and altered protein binding may contribute to modified drug distribution and metabolism in Indian children. Reduced hepatorenal clearance capacity, potentially related to nutritional deficiencies or concurrent illnesses, could explain the higher achieved serum concentrations. Additionally, genetic polymorphisms in drug-metabolizing enzymes may influence phenobarbital pharmacokinetics in different ethnic populations.[24]

The occurrence of drowsiness at serum concentrations exceeding 25 µg/ml, compared to 30 µg/ml in Western populations, suggests increased sensitivity to phenobarbital's sedative effects in Indian children. This finding has important clinical implications, indicating that therapeutic drug monitoring may be particularly valuable in this population to optimize efficacy while minimizing adverse effects.[25]

The positive correlation between blood pH and serum phenobarbital concentrations reflects the drug's weak acid properties and pH-dependent tissue distribution. This relationship may have clinical relevance in patients with acid-base disturbances, potentially affecting drug efficacy and toxicity.

Our study limitations include the relatively small sample size for serum concentration measurements (n=20) and the single-centre design, which may limit generalizability. Additionally, the study did not evaluate long-term developmental outcomes or detailed cognitive assessments, which are important considerations in paediatric antiepileptic drug therapy.

The implications of these findings for clinical practice are significant. Indian paediatric patients may require lower phenobarbital doses than currently recommended to achieve therapeutic serum concentrations while minimizing adverse effects. Therapeutic drug monitoring should be considered, particularly in patients with poor seizure control or signs of toxicity. Future research should investigate the underlying mechanisms responsible for altered phenobarbital pharmacokinetics in Indian children and establish population-specific therapeutic guidelines.

CONCLUSION

This study establishes important benchmarks for phenobarbital therapy in Indian paediatric populations with seizure disorders. Key findings include excellent therapeutic efficacy (97.1% seizure control) with phenobarbital monotherapy, predominantly at doses of 3 mg/kg/day. Indian children demonstrated higher serum phenobarbital concentrations than reported Western populations at equivalent doses, suggesting altered pharmacokinetics possibly related to nutritional, genetic, or environmental factors.

The therapeutic threshold for seizure control appears to be approximately 15 µg/ml in this population, while adverse effects, particularly drowsiness, occurred at concentrations exceeding 25 µg/ml. These findings suggest that Indian children may be more sensitive to phenobarbital effects compared to Western populations.

The higher prevalence of secondary epilepsy, particularly from infectious causes, reflects the unique disease patterns in developing countries and emphasizes the importance of comprehensive diagnostic evaluation. CT scanning proved more valuable than EEG for identifying structural abnormalities in this population.

Future research should focus on larger multicentre studies to validate these findings, investigate the underlying mechanisms of altered phenobarbital pharmacokinetics, and develop population-specific therapeutic guidelines. The potential for lower dosing strategies in Indian children warrants further investigation to optimize cost-effectiveness while maintaining therapeutic efficacy.

These findings contribute to the growing body of evidence supporting personalized medicine approaches in paediatric epilepsy management and highlight the importance of considering population-specific factors in therapeutic decision-making.

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