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Effects of Antiepileptic Monotherapy with Clobazam, Phenobarbital, Carbamazepine, and Levetiracetam on Thyroid Hormone Profiles in Children Aged 2–16 Years

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Abstract

Background: Antiepileptic drugs (AEDs) constitute the cornerstone of epilepsy management in children. However, accumulating evidence suggests that certain AEDs may alter endocrine function, particularly the hypothalamic–pituitary–thyroid axis. Given the critical role of thyroid hormones in growth and neurodevelopment, clarifying the endocrine safety profile of these agents in pediatric populations is clinically essential.

Objective: To evaluate the effects of carbamazepine, phenobarbital, clobazam, and levetiracetam on serum thyroid hormone levels (TSH, FT4, and T3) in children aged 2–16 years over a 6-month treatment period.

Methods: In this prospective before-and-after interventional study, 80 children with epilepsy receiving monotherapy (20 per drug group) were enrolled. Baseline demographic and anthropometric characteristics were comparable across groups. Serum TSH, FT4, and T3 levels, along with weight and height, were measured at treatment initiation and after 6 months. Within-group changes were analyzed using paired t tests, and between-group differences were assessed using one-way analysis of variance (ANOVA). Statistical significance was defined as $P < 0.05$.

Results: After 6 months, significant alterations in FT4 and T3 levels were observed exclusively in the carbamazepine group ($P < 0.05$), with mean hormonal changes differing significantly from those in the other treatment groups. No significant thyroid hormone changes were detected in the phenobarbital, clobazam, or levetiracetam groups. Although weight and height increased significantly in all groups ($P < 0.01$), the magnitude of growth changes did not differ between treatments.

Conclusion: Carbamazepine was associated with measurable alterations in thyroid hormone levels over 6-month, whereas phenobarbital, clobazam, and levetiracetam demonstrated relative short-term endocrine stability. Ongoing thyroid function monitoring may be warranted, particularly in children receiving conventional enzyme-inducing AEDs.

Key Words: Antiepileptic drugs, Carbamazepine, Epilepsy, Levetiracetam, Pediatric, Thyroid function.

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1- INTRODUCTION

Epilepsy is among the most common chronic disorders of the central nervous system and is characterized by recurrent unprovoked seizures caused by abnormal, excessive neuronal electrical activity in the brain (1, 2). It is diagnosed when an individual experiences at least two unprovoked seizures occurring more than 24 hours apart, or a single seizure with a high likelihood of recurrence in the future (3). In children, epilepsy may be accompanied not only by seizures but also by cognitive impairment, learning difficulties, behavioral problems, and developmental delay, particularly when seizures are frequent or inadequately controlled (4).

The prevalence of epilepsy in developed countries has been estimated at approximately 3.2–5.5 per 1,000 children, whereas in some regions of developing countries, it may be as high as 44 per 1,000 children (5). Recent population-based analyses estimated that, in 2021, more than 18.15 million children and adolescents worldwide were living with epilepsy, corresponding to a global prevalence of approximately 688.4 per 100,000 population among those aged 0–19 years (6). In Iran, epilepsy is likewise considered a major public health concern. Epidemiological studies have reported a lifetime prevalence of approximately 16.6 per 1,000 population and an active prevalence of approximately 9.5 per 1,000 population, both exceeding the global average (7).

The treatment of epilepsy in children is primarily based on pharmacotherapy, with the main goals being seizure control, improvement of quality of life, and minimization of drug-related adverse effects (8). The selection of antiepileptic medication is determined by several factors, including seizure type, epilepsy syndrome, patient age, and the drug's adverse effect profile (9). Phenobarbital, one of the oldest antiepileptic drugs, exerts its anticonvulsant effect by enhancing the activity of gamma-aminobutyric acid (GABA) receptors and is still widely used in many regions. Carbamazepine is also considered a first-line treatment for focal seizures in children and primarily acts through the inhibition of voltage-gated sodium channels. Clobazam, a benzodiazepine derivative, is commonly prescribed as adjunctive therapy in certain types of epilepsy. In contrast, newer antiepileptic agents such as levetiracetam have gained widespread use in the management of pediatric epilepsy in recent years due to their lower potential for drug interactions and more favorable safety profile (9).

One of the major concerns in the long-term management of epilepsy in children is the potential impact of antiepileptic drugs on endocrine function, particularly the hypothalamic–pituitary–thyroid (HPT) axis (10). Thyroid hormones play a crucial role in growth, brain development, and metabolic regulation in children, and any disruption in thyroid function may lead to developmental, cognitive, and metabolic complications (11).

The use of conventional antiepileptic drugs such as carbamazepine and phenobarbital has been associated with a reduction in Free T4 levels accompanied by a compensatory increase in TSH, which may indicate subclinical hypothyroidism (12-14).

In contrast, levetiracetam has not demonstrated a significant effect on thyroid function in most studies, although mild biochemical alterations have been reported in some patients (15, 16). Based on these findings, several researchers have recommended periodic evaluation of thyroid function in children with epilepsy who are receiving long-term antiepileptic therapy (17-19).

Despite existing research, sufficient data regarding the effects of certain antiepileptic drugs on thyroid function in children remain limited, and the findings of previous studies have sometimes been inconsistent (20). In particular, clinical evidence regarding clobazam in the pediatric population is limited, and most studies have been conducted on small samples or mixed age groups. Given that thyroid dysfunction can significantly affect growth, development, and metabolic status in children, investigating the effects of different antiepileptic drugs on thyroid hormones is of considerable importance. Therefore, the present study was conducted to determine the effects of four antiepileptic drugs-clobazam, phenobarbital, carbamazepine, and levetiracetam-on the levels of TSH, Free T4, and T3 hormones, as well as body mass index (BMI), in children.

2- MATERIALS AND METHODS

This clinical trial was conducted on 80 children aged 2–16 years with epilepsy who were referred to the clinic of Bu-Ali Educational and Therapeutic Center, affiliated with Ardabil University of Medical Sciences. The study was carried out from April to November 2025. Simple random sampling was performed among eligible patients, and participants were subsequently allocated into four groups (n=20 per group) using a random number table. The patients were assigned to monotherapy groups receiving levetiracetam, carbamazepine, clobazam, or phenobarbital.

The sample size was calculated using the formula for comparing means, assuming a 95% confidence level, 80% power, a standard deviation (SD) of 10 in both groups, and means of 50 and 41.1. The minimum sample size was estimated at 20 participants per group, resulting in a total of 80 children enrolled in the study.

Inclusion criteria consisted of children aged 2–16 years diagnosed with epilepsy who were receiving monotherapy with one of the four medications: clobazam, phenobarbital, carbamazepine, or levetiracetam. Furthermore, patients were required to have no pre-existing thyroid disorders or developmental disabilities. Exclusion criteria included the need for polytherapy, a history of head trauma or neurosurgery, chronic kidney disease, metabolic disorders, the requirement for dose escalation during the study, and withdrawal of consent. No participants were excluded from any drug group throughout the study period.

The required data were collected using a researcher-designed checklist and by reviewing the patients' medical records. The recorded data included demographic characteristics, type of seizure, type and dosage of antiepileptic medication, and hormonal laboratory results. Blood samples were obtained at baseline and six months after initiation of treatment to measure TSH, FT4, and T3 hormone levels, and all laboratory analyses were performed at the laboratory of Bu Ali Hospital. In addition, patients' height and weight were measured at the beginning and at the end of the study, and BMI was calculated.

Data were analyzed using SPSS software version 26. Descriptive statistics were presented as mean, standard deviation, frequency, and percentage. The chi-square test, paired t-test, and analysis of variance (ANOVA) were used to compare variables between groups. A p-value of less than 0.05 was considered statistically significant.

3- RESULTS

The comparison of sex distribution among the drug groups before the intervention showed no statistically significant difference ($P > 0.05$), indicating that the groups were comparable in terms

of baseline sex characteristics. Similarly, no significant differences were observed among the groups regarding age, baseline weight, or baseline height (P > 0.05), confirming that the groups were comparable with respect to baseline growth indices (Table 1).

Table-1. Baseline growth indices and sex distribution among the four drug groups before intervention.

Drug Group	Age (mean ± SD)	Weight Before (mean ± SD)	Height Before (mean ± SD)	Male n (%)	Female n (%)
Carbamazepine	6.9 ± 5.10	30.8 ± 20.43	120.50 ± 32.51	8 (40.0%)	12 (60.0%)
Phenobarbital	6.15 ± 4.11	23.92 ± 14.36	113.0 ± 25.61	11 (55.0%)	9 (45.0%)
Levetiracetam	6.90 ± 4.10	28.1 ± 17.03	116.75 ± 25.74	8 (40.0%)	12 (60.0%)
Clobazam	5.90 ± 4.54	25.45 ± 17.97	115.0 ± 27.81	11 (55.0%)	9 (45.0%)
P-value	0.852	0.621	0.744	0.61	

The findings of this study demonstrated that only carbamazepine resulted in significant changes in thyroid hormone levels. Levels of Free T4, TSH, and T3 decreased after treatment in this group. In contrast, no significant changes in thyroid hormones were observed in the phenobarbital, clobazam, or levetiracetam groups.

However, in all four drug groups, weight, height, and BMI increased significantly following treatment. Overall, the results indicate that only carbamazepine had a significant impact on thyroid function, while all medications contributed to increased physical growth.

In the carbamazepine group, significant reductions were found in Free T4 (P = 0.002), TSH (P = 0.001), and T3 (P = 0.013), confirming a meaningful effect of carbamazepine on thyroid hormones and growth indices (Table 2).

Table-2. Mean ± SD of thyroid hormones and growth indices before and after treatment in the four drug groups.

Drug	Time	Free T4 (mean ± SD)	TSH (mean ± SD)	T3 (mean ± SD)	Weight (mean ± SD)	Height (mean ± SD)	BMI (mean ± SD)
Carbamazepine	Before	2.00 ± 1.06	3.12 ± 1.35	2.72 ± 1.45	30.80 ± 20.43	120.50 ± 32.51	18.65 ± 3.35
	After	1.71 ± 0.93	2.71 ± 1.09	2.30 ± 1.32	33.09 ± 21.51	122.73 ± 32.55	24.56 ± 10.2
	P-value	0.002	0.001	0.013	<0.001	<0.001	0.002
Phenobarbital	Before	1.53 ± 0.77	2.72 ± 1.37	2.57 ± 1.00	23.92 ± 14.36	113.00 ± 25.61	16.97 ± 3.3
	After	1.46 ± 0.89	3.13 ± 1.72	2.51 ± 0.83	25.80 ± 15.13	115.45 ± 25.72	20.8 ± 7.8
	P-value	0.589	0.262	0.797	<0.001	<0.001	0.004
Clobazam	Before	1.70 ± 0.76	2.66 ± 1.50	2.11 ± 0.87	25.45 ± 17.97	111.50 ± 27.81	18.1 ± 3.8
	After	1.74 ± 0.73	2.81 ± 1.40	2.25 ± 0.82	26.76 ± 18.39	113.60 ± 28.17	21.59 ± 9.1
	P-value	0.814	0.265	0.245	<0.001	<0.001	0.017
Levetiracetam	Before	1.84 ± 1.28	3.98 ± 4.33	2.90 ± 1.55	28.10 ± 17.03	116.75 ± 25.74	18.63 ± 3.6
	After	1.83 ± 1.10	4.03 ± 4.48	3.13 ± 1.45	30.08 ± 17.75	118.40 ± 25.12	23.7 ± 8.9
	P-value	0.948	0.851	0.192	<0.001	0.007	0.002

The results showed that the mean changes in Free T4 differed significantly among the drug groups (P = 0.036), as did the changes in T3 (P = 0.016), indicating that the greatest reduction in both hormones occurred in the carbamazepine group. However, the mean changes in TSH did not differ significantly among the four drug groups (P = 0.32). Therefore, in the present study, the four antiepileptic drugs carbamazepine, phenobarbital, levetiracetam, and clobazam did not show a statistically significant difference in terms of changes in TSH levels (Table 3).

Post hoc pairwise comparisons demonstrated that, for T3, the mean change was significantly greater in the carbamazepine group than in the levetiracetam group (P = 0.017) and the clobazam group (P = 0.04). Similarly, for Free T4, the mean change differed significantly between the carbamazepine and clobazam groups (P = 0.04). However, no statistically significant pairwise differences were observed among the drug groups for TSH (P > 0.05) (Table 4).

Table-3. Comparison of mean changes in thyroid hormones across the four drug groups.

Variable	Drug Group	N	Mean Change	SD	P-value (Inter-group)
Free T4 Change	Carbamazepine	20	−0.36	0.32	0.036
	Phenobarbital	20	−0.06	0.53	
	Levetiracetam	20	−0.005	0.36	
	Clobazam	20	+0.03	0.60	
TSH Change	Carbamazepine	20	−0.18	0.34	0.32
	Phenobarbital	20	+0.40	1.56	
	Levetiracetam	20	+0.04	1.08	
	Clobazam	20	+0.15	0.60	
T3 Change	Carbamazepine	20	−0.53	0.73	0.016
	Phenobarbital	20	−0.06	1.06	
	Levetiracetam	20	+0.23	0.76	
	Clobazam	20	+0.13	0.51	

Table-4. Pairwise comparison of mean changes in thyroid hormones among the four drug groups.

Variable	Reference Group	Comparison Group	Mean Difference	P-value
T3 Change	Carbamazepine	Phenobarbital	−0.46	0.25
		Levetiracetam	−0.76	0.017
		Clobazam	−0.67	0.04
	Phenobarbital	Carbamazepine	+0.46	0.25
		Levetiracetam	−0.29	0.65
		Clobazam	−0.20	0.82
Free T4 Change	Carbamazepine	Phenobarbital	−0.30	0.18
		Levetiracetam	−0.36	0.08
		Clobazam	−0.40	0.04
	Phenobarbital	Carbamazepine	+0.30	0.18
		Levetiracetam	−0.06	0.97
		Clobazam	−0.098	0.91
TSH Change	Carbamazepine	Phenobarbital	−0.56	0.25
		Levetiracetam	−0.23	0.88
		Clobazam	−0.34	0.70
	Phenobarbital	Carbamazepine	+0.59	0.25
		Levetiracetam	+0.35	0.67
		Clobazam	+0.25	0.86

4- DISCUSSION

In the present interventional study, conducted on 80 children with epilepsy who received six months of monotherapy with carbamazepine, phenobarbital, clobazam, or levetiracetam, the findings indicated that, except for carbamazepine, the other medications did not produce significant changes in the levels of TSH, FT4, or T3 ($P > 0.05$). The results showed that the mean changes in Free T4 differed significantly among the drug groups ($P = 0.036$), as did the changes in T3 ($P = 0.016$). However, the mean change in TSH among the four drug groups was not statistically significant ($P = 0.32$). Therefore, it can be concluded that in this study, the four antiepileptic drugs- carbamazepine, phenobarbital, levetiracetam, and clobazam- did not demonstrate a statistically significant difference in terms of changes in TSH levels.

Although no study was identified that simultaneously compared these four medications within a single clinical trial design, the available evidence suggests that findings regarding the hormonal effects of antiepileptic drugs (AEDs) are inconsistent and appear to depend on the specific drug used (20). According to the results of a comprehensive meta-analysis, the use of AEDs, particularly classic agents such as carbamazepine and phenytoin, has been associated with reduced levels of T4 and FT4 and increased TSH levels compared with control groups (21).

Regarding phenobarbital, the findings of the present study are consistent with some previous reports. In the study by Aygün, phenobarbital showed limited effects on thyroid hormones compared with other antiepileptic drugs (22). Likewise, in another study conducted in Iran on neonates, phenobarbital use was not associated with significant changes in T4 or TSH levels (23, 24). However, other studies have reported conflicting results, showing that phenobarbital may lead to significant reductions in T3 and T4 levels (25), as well as increases in TSH (24, 25).

With respect to levetiracetam, our findings are in agreement with more recent evidence. A study by Seymen in 2025 reported that although minor changes in TSH were observed, hormone levels remained within the normal range, and FT4 did not change significantly (26). Similarly, the study by Isojärvi found no significant alterations in FT4 or TSH levels following levetiracetam treatment (27). These findings suggest that, unlike conventional enzyme-inducing antiepileptic drugs, levetiracetam lacks a major hepatic enzyme–inducing effect and is therefore less likely to cause hormonal disturbances.

Regarding carbamazepine, the findings of the present study are consistent with the existing body of evidence. Numerous studies have demonstrated that carbamazepine therapy is associated with reductions in T4 and Free T4 levels (18, 28-29). In another investigation evaluating the effects of various antiepileptic drugs on thyroid function, patients receiving carbamazepine exhibited significantly lower Free T4 levels compared with those treated with non-enzyme-inducing agents (22).

Furthermore, a meta-analysis confirmed that carbamazepine and phenytoin show the strongest association with reductions in T3 and T4, whereas phenobarbital appears to exert a more pronounced effect on FT3, and levetiracetam demonstrates the least impact on thyroid hormone parameters (10). However, not all studies are fully concordant. For example, Morten et al. reported that TSH levels were not significantly affected by carbamazepine therapy (30).

One of the most critical determinants underlying discrepancies among studies

appears to be the duration of treatment. Investigations with longer follow-up periods (12 months or more) more frequently report reductions in FT4 and elevations in TSH. For instance, in a large-scale study with 12 months of follow-up, patients receiving valproate, phenobarbital, carbamazepine, and oxcarbazepine exhibited decreased FT4 and increased TSH, whereas levetiracetam did not produce significant changes (16).

In contrast, shorter-term studies (6–9 months) have yielded less consistent findings. One such study reported a gradual increase in TSH among patients treated with valproate, while changes in FT4 and T3 were inconsistent (31). This pattern suggests that alterations in thyroid function may not become fully apparent during the early months of therapy, particularly when patients remain clinically euthyroid despite biochemical fluctuations.

The discrepancies observed across studies may be attributed to several factors, including differences in age groups, drug dosage, the use of monotherapy versus polytherapy, and the presence of underlying diseases (32). Variations in the timing of hormonal assessments, for example, differences between evaluations conducted at 3, 6, or 12 months, may also contribute to the inconsistent findings reported in the literature (16). In addition, the presence or absence of a healthy control group can influence the interpretation of results, as comparisons with healthy individuals may make subtle biochemical changes more apparent.

Overall, the analysis of the present findings alongside existing evidence suggests that biochemical hormonal changes, even when remaining within the normal reference range, may represent early metabolic alterations. Such changes, particularly during long-term treatment with classical enzyme-inducing antiepileptic drugs, highlight the importance of regular monitoring of thyroid function in pediatric patients receiving these medications (10, 21, 33).

4-1. Limitations

Despite its prospective design and regular follow-up, the present study has several limitations that should be considered when interpreting the findings. First, the relatively small sample size in each treatment group may have limited statistical power and reduced the generalizability of the results. Second, the absence of a healthy control group restricted direct comparison between physiological age-related hormonal changes and those potentially attributable to antiepileptic drug exposure. Third, pubertal status was not systematically assessed or incorporated into the analysis. Given that puberty is associated with significant endocrine changes and may influence thyroid hormone profiles, residual confounding cannot be excluded. In addition, the lack of interim hormonal measurements prevented evaluation of the temporal trajectory of hormonal changes during treatment. Finally, the relatively short follow-up period of six months may not have been sufficient to detect delayed or cumulative effects of long-term antiepileptic therapy on the hypothalamic–pituitary–thyroid axis. Future studies with larger cohorts, longer follow-up durations, and consideration of pubertal stage are warranted to confirm and extend these findings.

5- CONCLUSION

In this prospective study of children with epilepsy receiving antiepileptic monotherapy, phenobarbital, clobazam, and levetiracetam were not associated with significant changes in serum TSH, FT4, or T3 levels during the six-month follow-up period. In contrast, carbamazepine treatment was associated with significant alterations in thyroid hormone profiles, suggesting a greater

potential for endocrine effects compared with the other agents evaluated. Although increases in height and weight were observed across all treatment groups, these changes are most likely attributable to normal growth and development during childhood rather than treatment-related endocrine effects.

Overall, the findings suggest that newer-generation antiepileptic drugs, particularly levetiracetam, may have a more favorable short-term thyroid safety profile. However, given the study limitations, including the modest sample size and relatively short follow-up duration, the results should be interpreted with caution. Larger longitudinal studies are needed to clarify the long-term effects of antiepileptic drugs on thyroid function and to determine the clinical significance of the observed hormonal changes.

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7- ETHICAL STATEMENT

Throughout all stages of the study, the confidentiality of patients' information was maintained. After explaining the objectives of the study, written informed consent was obtained from the parents or legal guardians. This study was approved by the Ethics Committee of Ardabil University of Medical Sciences (Ethics code:IR.ARUMS.MEDICINE.REC.1403.467) and was registered in the Iranian Registry of Clinical Trials with the code IRCT20250622066215N1.

8- CONSENT FOR PUBLICATION

All authors consent to the publication of the manuscript and findings.

9- DATA AVAILABILITY STATEMENT

The raw data analyzed during this study are available from the corresponding author upon reasonable request.

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