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EFFECT OF ANTICONVULSANT DRUGS ON MONOVALENT CATIONS

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ABSTRACT :

Sixty patients receiving anticonvulsant drugs like tegretol 9 Carbamazepine) and 61 age-matched controls were studied to determine the disturbances in sodium and potassium. levels There was a significant difference in sodium level the mean serum sodium levels of the subjects (138.8± 0.6 mEq/L) and the controls (141.7± 0.4 mEq/L). Thirteen (21.7%) of the subjects, but none of the controls, had sodium levels 135 mEq/L. But the mean values of potassium (4.3 ± 0.02 mEq/L), were not significantly changed as compared to controls. The risk of hyponatremia increased with age (subjects 30 years old had four times the prevalence of hyponatremia as those < 30 years old.

INTRODUCTION :

Tegretol (Carbamazepine) induces antidiuresis and hyponatremia[1,2,3]. but there are few uncontrolled studies[4] of the prevalence of this effect in patients under-going prolonged therapy. Data about risk factors for individuals are conflicting. Association of potassium levels with tegretol treatment has not so far been reported in the literature. The identification of several patients who had hyponatremia un-explained by any factor other than tegretol and potassium alterations if any, was the impetus for this study of the electrolyte changes in patient who received tegretol.

MATERIALS AND METHODS :

Sixty subjects (Group 1) taking tegretol (Carbamazepine) were randomly selected form a list of all patients taking tegretol and alternately matched for age with 31 (group II) taking with no history of taking any anticonvulsant drugs. All subjects were mentally retarded. Patients with history of cardiovascular or renal problems or uncorrected hypothyroidism were excluded from study.

Fasting morning blood samples were drawn for determination of sodium, potassium and BUN levels. Sodium and potassium levels measured by flame photometer Corning 410C and BUN levels were measured by Boehringer Mannheim. GmbH kit method. The independence of variables and Mean differences were determined by Student's T test.

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RESULTS :

There were significant differences between the groups in age, sex and percentage of children (Table 1). Subjects in group I tended to be taken more anti-convulsants per person (Mean = 2.8 : 67% were taking three or more). There were no significant differences in anti-convulsant use with respect to individual anti-convulsants (Phenytoin, Phenobarbital, Mephobarbital, Primidone or Valproate). Characteristics of Tegretol (Carbamazepine) use are listed in Table II.

TABLE I : CHARACTERISTICS OF GROUPS

Groups	Nos	Sex		Age Yrs.	Children*		Phenytoin use	
		M	F	(Mean ± SE)	No.	%	No.	(%)
Group I (On Tegretol)	60	42	18	24.97 ±1.213	(22%)		30(50%)	
Group II (On other Anticonvulsants)	31	16	15	24.99 ± 1.4	7	(23%)	19	(61%)
Group III	30	22	8	2.52 ± 2.2.	8	(27%)		N.A.

*Child defined as < 18 years old : N.A. = Not applicable.

TABLE II : CHARACTERISTICS OF TEGRETOL USE IN GROUP I THE VALUES ARE GIVEN IN MEAN = S.D. WITH RAGE.

Daily dose (mg/day)	1244 ± 568	(300-2600)
Daily dose (mg/kg/day)	24.1 ± 9.9	(6.8 - 46.1)
Duration of therapy (months)	42.6 ± 25.7	(5 - 96)
Tegretol monotherapy*	7/60 (11%)	

No. of anticonvulsants per person 2.8 ± 1.0 (67% on 3 or more)
*For which the number and percent are given.

There was a small but significantly lower mean sodium levels in Group I compared with values in each control group (Table III), but the control group II & III did not differ significantly from each other. Thirteen (21.7%) of 60 subjects taking tegretol had hyponatremia (defined as sodium level <135meq/L), while no control subject had an abnormally low level. Differences in BUN levels were not significant. There was also no significant difference in potassium levels between group I and controls, even the control groups did not differ significantly from each other regarding potassium levels.

TABLE III : LEVELS OF MONOVALENT CATIONS IN VARIOUS GROUPS

Group	Nos.	Sodium (mEq/L) Mean ± S.E. (Range)	Hyponatremia* No. (%)	Potassium (mE1/L) Mean ± S.E. (Range)
I	60	138.8 ± 0.6 (129 -144)	13 (12.7)	4.1 ± 0.01 (3.7-5.4)
II	31	141.2 ± 0.5 ** (135-151)	0	4.3 ± 0.02 (3.6 - 5.0)
III.	30	142.2 ± 0.5 ** (137 - 148)	0	4.5 ± 0.2 (3.6 - 4.9)

* Defined as serum sodium level < 135mEq/L

** P<001 compared combined groups II & III with group I.

Within group I, there was no significant relationship between sex, tegretol dose, duration of tegretol therapy, phenytoin use or phenytoin dose and hyponatremia or mean sodium level. There was too few subjects < 18 years old to compare the prevalence of hyponatremia between children and adults but one out of 13 children had hyponatremia. Similarly, there were few subjects taking tegretol alone to compare the effects of single therapy and poly therapy. Three of 7 subjects taking tegretol alone had sodium level <135 mEq/L ; 10 out of 53 subjects taking multiple anticonvulsants also had hyponatremia.

Age co-related negatively with sodium level (r = -0.403). The risk of hyponatremia increased 40% in those >30 years old (Table-IV). There was also a negative correlation between age and sodium level in group II (r = -0.446), although no one in group II was hyponatremic. No similar association was found in group III (who were taking no anticonvulsant).

The table IV also indicates that the correlation between tegretol and sodium levels approached significance (r = -0.201), and when the analysis was restricted to adults (> 18 years old), the correlation was significant (r = -0.267).

TABLE-IV : ASSOCIATION OF AGE WITH SODIUM STATUS IN GROUP -I

	Age < 30 years	Age > 30 years
Hyponatremia No. (%)	6/47 (12.8%)	7/13 (57.8%)*
Sodium level	(Age yrs) Mean ± S.E.	
<135 mEq/L	33.0 ± 3.1	
> 135 mEq/L	22.7 ± 1. 1 **	

* P < 0.05 **P < .001

DISCUSSION :

This study revealed a high prevalence (21.7%) of hyponatremia in patients taking tegretol. Other studies[5] have reported rates ranging from 6% to 31%. Difference in these results may reflect differences between the populations in terms of age, group mean daily tegretol dosages or serum levels, rates of monotherapy or polytherapy, or the use of different additional anticonvulsants (e.g., phenytoin has been reported to reverse the antidiuretic action of tegretol).[2] However, the use of phenytoin was not a significant factor in this study, nor was the number of anticonvulsants per subject. The current subjects were all mentally retarded and may have had other central nervous system abnormalities that predisposed them to the development of hyponatremia. Nevertheless. O'Hare et al[6] reported in a similar study of a different patient population that 12.7% of their patients had sodium levels <132mEq/L; in the present study, 11.6% had comparable levels. In a recent study of 12 psychiatric patients taking tegretol for affective disorders, the incidence was 33.3%.

Although the potassium levels were low in subjects receiving tegretol as compared to control groups, but the difference was not significant statistically (Table III). The difference in potassium values was again not significant between the control groups (Group II and Group III). Association of potassium status with the anticonvulsant drugs has not been reported in the available literature, so it is not debatable.

Some studies[4,6] have reported a positive correlation between hyponatremia and age, although, again some have not.[7] Helin et al[4] and Koivikko and Valikangas[8] found no hyponatremia in their studies of pediatric patients, although Koivikko and Valikangas[8] did report one case. It appears that the incidence is much lower in children, which suggests a tegretol age interaction. The negative correlation between sodium level and age in group II (anticonvulsants other than tegretol) was surprising. This correlation did not appear in group III (taking no anticonvulsants and with no history of epilepsy). Such a finding might be the result of a particular anticonvulsant, anticonvulsants in general, epilepsy itself, or a peculiarity of the population of patients with epilepsy studies. In this study, no anticonvulsant other than tegretol was associated with lowered blood sodium levels. Given the study design, the other possibilities could not be tested.

Phenytoin might be expected to lessen or prevent the antidiuretic action of tegretol. In the present study, the proportion of patients with hyponatremia who were taking phenytoin (seven of 13) was the same as in the group as a whole (30 of 60). Others have reported similar results.[5] None of the patients in the current study was obviously water intoxicated, but most would be incapable of reporting symptoms. Water intoxication has been reported in associated with tegretol therapy[1,3] and anyone with psychogenic polydipsia would be particularly at risk. The effect of hyponatremia on seizure control was not studied. If severe enough, hyponatremia can induce seizures in patients who are not epileptic, and water balance has been shown to effect seizure control in the epileptic.[3] It is possible that less severe hyponatremia might interfere with seizure control.

Tegretol therapy may result in the development of hyponatremia; the risk is greater

in the older patients. Patients taking tegretol should receive monitoring of their electrolyte levels. Hyponatremia should be considered in any patient who develops lethargy, confusion or other symptoms consistent with water intoxication, or suffers increased seizure frequency while taking adequate stable or increasing doses of tegretol.

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