VALPROIC ACID-INDUCED HYPERKALEMIA: PATHOPHYSIOLOGICAL INSIGHTS AND CROSS-TAMPERING THERAPEUTIC STRATEGIES IN EPILEPSY AND PROXIMAL HUMERUS FRACTURE MANAGEMENT

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ABSTRACT

Encorate chrono is the brand of sodium valproate and valproic acid is a Anticonvulsant or Anti-seizure drug. Usually Hyonatremia is common Adverse drug reaction caused by this drug ,In this case hyperkalemia is caused for the elder patient and it should be monitored closely because it may cause cardiotoxicity.A 67 year old male patient was admitted with the complaints of pain over in left shoulder and lower back . He has a past history of Epilepsy with Rx of Tab.Encorate chrono (Sodium valproate and valproic acid). The potassium level was increased since first day of admission because of this VPA drug.The potassium level was increased for four days so the drug stoped and simultaneously add carbamazepine drug by cross tampering therapeutic strategy , the potassium level were resolved by adding the drug K.BIND SACHET(CALCIUM POLYSTYRENE SULPHONATE POWDER). A Probable relationship was indicated by the causality score of , which was determined by applying the Naranjo scale.This Tab.Encoratr chrono (Sodium valproate and valproic acid) might result from the impairment of potassium excretion caused by decreased mineralocorticoid function or abnormalpotassium reabsorption in the renal tubules cause hyperkalemia. Optimizing patient safety requires ongoing re-evaluation of therepy.

Key words: Electrolyte dysregulation, Mitochondrial dysfunction, Renal tubular handling, Bone remodeling, Antiseizure pharmacotherapy

INTRODUCTION:

A chronic brain disorder, epilepsy is characterized by a persistent (i.e., ongoing) propensity to have seizures that is not triggered by an instantaneous injury to the central nervous system, as well as the neurobiological, cognitive, psychosocial, and social repercussions of seizure recurrences. Epilepsy affects people of all ages and genders and is found all over the world.[1] Valproic acid (VPA), a medication *approved* to treat migraine, bipolar disorders, and epileptic seizures, increases the amount of gamma-aminobutyric acid (GABA) in the brain by competitively blocking GABA transaminase. This increases the availability of GABA at synapses and improves GABA-mediated responses.[2] Abnormalities in electrolytes are a potential side effect of valproic acid, which is a medication that is used to treat seizures. In a number of reports, hyponatraemia that is related with valproic acid has been described. However, there was no evidence of hyperkalaemia related with valproic acid in the published research.[3] A plasma potassium (K+) concentration more than 5.0 or 5.5 mEq/l is often referred to as hyperkalemia; however, the upper range of normal varies depending on the publication and standards.[4]We report a case of hyperkalaemia caused by valproic acid during a seizure following initial administration.

CASE DESCRIPTION:

A 67 year old male patient was admitted in the orthopedic department with history of RTA slip and fall while riding two wheeler and initially went to private hospital clinic and then came here for further management with the complaints of pain over (Left)shoulder and pain over left lower back .The surgical history was found to be Right femur fracture 2 year back plating for right femur.The past medical history was found to be Epilepsy since 30 years on regular medication . The past medication history was found to be Tab. Encorate chrono in the dose of 500mg.ORIF with plating (Left) proxinal humerus procedure done for him on the first day of admission.The diagnosis of this case was found to be Fracture and Proximal humerus .On the examination of vital sign ,the blood pressure ,pulse rate,SPO2,temperature was found to be normal in all days was given in table 1 .On examination of laboratory investigation in Hematology - Red Blood Cell ,Hemoglobin,Hematocrit aws decreased in level

and Mean corpuscular hemoglobin,Red blood distribution width,WBC was increased in level was given table 2 While in Biochemistry- Blood glucose fasting , Glucose random was increased in level and Bloog glucose post prandial was normal in level was given in table 3. In Liver function test- Bilirubin total, Bilirubin direct, Globulin was increased in level and A/G ratio was decreased in level was given in table 4. In Electrolytes - Potassium level was increased in first 5 days and remaining 3 days the Potassium level was normal in level was given in table 5 .The patient was treated with TAB.ENCORATE CHRONO-500MG,INJ.XONE-1G,INJ.PARA-1G,INJ.PAN-40MG,

TAB.CHYMODAC FORTE,TAB.K-BIND,TAB.FOLICACID-5MG,INJ.ZOSTOM-1.5G,

INJ.EMESET-4MG,INJ.DUCLO-1AMP,TAB.SHELCAL-500MG,TAB.VITC-500MG,INJ.LMWH-0.4,INJ.METRO-500MG,TAB.ZEPTOL-200MG,TAB.HYDROCORT-10MG,INJ.ZOSTUM-1.5MG,

TAB.ECOSPRIN-AV-75/40MG,TAB.CEFAKIND-500MG was given in table 6. In this case the patient potassium level was increased in level know as hyperkalemia caused by

T.ENCORATE CHRONO -500MG so switched the drug by TAB.ZEPTOL-200MG by **Cross-Tampering Therapeutic Strategy** and this strategy was explained here ;

Figure 1: **Cross-Tampering Therapeutic Strategy**

T.ENCORATE CHRONO((SODIUM VALPROATE AND VALPROIC ACID) was switched to TAB.ZEPTOL and the potassium level were resolved by adding the drug K.BIND SACHET(CALCIUM POLYSTYRENE SULPHONATE POWDER)After potassium was reduced to normal and the patient was discharged with improved patient compliance and discharged with the medication :TAB.CEFAKIND-500 MG, TAB. ECOSPRIN - 75/10 MG, TAB.PAN - 40 MG, TAB.PARA-1G,TAB.SHELCAL-500 MG,TAB.VITAMIN C, TAB.CHYMORAL FORTE- 300 MG,TAB.ENCORATE CHRONO-300MG,TAB.ZEPTOL-200MG,TAB.HYDROCORT-10MG was given in table 7

Table 1:VITAL SIGN[7 6]

PARAMETER	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7	DAY 8	NORMAL VALUE
BLOOD PRESSURE	120/70mg/dl	120/70mg/dl	120/80mg/dl	140/90mg/dl	120/70mg/dl	120/80mg/dl	120/60mg/dl	130/90mg/dl	120/80mg/dl[6]
PULSE RATE	76 b/min	76 b/min	72b/min	84b/min	86b/min	78b/min	98b/min	78b/min	60 to 100 beats per minute[6]
SPO2	98%	98%	99%	99%	96%	96%	98%	96%	95-100%[6]
TEMPERATURE	98.1F	98.1F	97.4F	96F	97.8F	96.8F	97.1F	97F	97.8 degrees Fto 99 degrees F[7]

TABLE 2: HEMATOLOGY[5]

S.NO	PARAMETER	OBSERVED VALUE	NORMAL VALUE
1.	RED BLOOD CELL	3.60million/cumm	4.7-6.2million/cumm[5]
2.	HEMOGLOBIN	12.0gm/dl	14-17g/dl[5]
3.	HEMOTOCRIT-HCT	34.3%	42-52%[5]
4.	MEAN CORPUSCULAR HEMOGLOBIN	33.3pg/cell	26-34pg/cell[5]
5.	RED BLOOD DISTRIBUTION WIDTH	14.4	11.6-14%[5]
6.	WHITE BLOOD CELL	13000mm3	5000-10000/mm3[5]

TABLE 3: BIOCHEMISTRY[5]

S.NO	**PARAMETER**	**OBSERVED VALUE**	**NORMAL VALUE**
1.	BLOOD GLUCOSE FASTING	102mg/dl	**70-100mg/dl**[5]
2.	GLUCOSE RANDOM	143mg/dl	**70-140mg/dl**[5]
3.	BLOOD GLUCOSE POST PRANDIAL	117mg/dl	**70-140mg/dl**[5]

TABLE 4: LIVER FUNCTION TEST[5]

S.NO	PARAMETER	OBSERVED VALUE	NORMAL VALUE
1.	BILIRUBIN-TOTAL	1.4 mg/dl	0.3-1.0mg/dl[5]
2.	BILIRUBIN-DIRECT	0.6mg/dl	0.1-0.3mg/dl[5]
3.	GLOBULIN	3.8gm/dl	2.5-3.5mg/dl[5]
4.	A/G RATIO	1.0	1.2-1.5 ratio[5]

TABLE 5: ELECTROLYTE[5]

PARAMETER	DAY 1	**DAY2**	**DAY3**	**DAY4**	**DAY5**	**DAY6**	**DAY7**	**DAY8**	NORMAL VALUE
POTASSIUM	5.9mmol/L	5.5mmol/L	5.3mmol/L	5.8mmol/L	5.4mmol/L	4.7mmol/L	4.5mmol/L	4.1mmol/L	**3.5-5Meq/L**[5]

TABLE 6: THERAPEUTIC CHART

S.NO	DRUG NAME	DOSE	FREQUENCY
1.	T.ENCORATE CHRONO(SODIUM VALPROATE AND VALPROIC ACID)	500MG	BD
2.	INJ.CEFTRIAXONE	1G	**BD**
3.	INJ.PARACETAMOL	1G	TDS
4.	INJ.PANTOPRAZOLE	40MG	BD
5.	TAB.TRYPSIN +CHYMOTRYPSIN		BD
6.	K-BIND(CALCIUM POLYSTYRENE SULPHONATE POWDER)	15g	BD (INCREASED FREQUENCY)
7.	K.BIND(CALCIUM POLYSTYRENE SULPHONATE POWDER)	15g	TDS
8.	TAB.FOLIMED	5MG	BD
9.	INJ.SULBACTAM +CEFEPERAZONE	1.5MG	BD
10.	INJ.ONDANSETRON	4MG	BD
11.	INJ.DICLOFENAC SODIUM	1AMP	SOS
12.	TAB.CALCIUM +VITAMIN D3	500MG	OD
13.	TAB.ASCORBIC ACID	500MG	OD

14.	INJ.LMWH	0.4MG	OD
15.	INJ.METRONIDAZOLE	500MG	TDS
16.	K.BIND SACHET(CALCIUM POLYSTYRENE SULPHONATE POWDER)	15g	TDS(decrease the frequency BD,OD)
17.	TAB.CARBAMAZEPINE	200MG	½-0-½
18.	TAB.HYDROCORTISONE SODIUM SUCCINATE	10MG	OD
19.	TAB.ATORVASTATIN +ASPIRIN	75/40MG	OD
20.	TAB. CEFUROXIME AXETIL	500 MG	BD

TABLE 7: DISCHAREGE MEDICATION

S.NO	**DRUG NAME**	**DOSAGE**	**FREQUENCY**	**B/A FOOD**
1.	TAB.CEFUROXIME AXETIL	500MG	1-0-1	AF
2.	TAB. AVATORVASTATIN +ASPIRIN	75/10MG	1-0-1	AF
3.	TAB.PANTOPRAZOLE	40MG	1-0-0	BF
4.	TAB.PARACETAMOL	1G	1-0-1	AF
5.	TAB.CALCIUM +VITAMIN D3	500MG	1-0-0	AF

6.	TAB.ASCORBIC ACID	500MG	1-0-0	AF
7.	TAB.TRYPSIN +CHYMOTRYPSIN		1-1-1	BF
8.	TAB.CARBAMAZEPINE	200MG	1-0-1	AF
9.	TAB.HYDROCORTISONE SODIUM SUCCINATE	10MG	1-0-0	AF

DISCUSSION:[1]

There have been reports of hyperkalemia while using valproic acid in this literature.In this instance, hyperkalemia only became apparent after valproic acid was administered; it then improved after VPA was stopped.[3]Changes in electrolyte levels, especially potassium levels, provided evidence for the link between hyperkalemia and VPA.[3].Notably, the patient received T.ENCORATE CHRONO (Valproic acid) in recent days after being diagnosed with epilepsy; prior to hyperkalemia, the patient did not get any medicine.[3].The patient's serum potassium level appeared to be elevated at admission.[3]

The mechanism underlying the association between hyperkalemia and valproic acid still remian unclear[8].Recent literature suggest that valproic acid has an inhibitory action on histone deacetylases[8].The inhibition of histone deacetylase can further attenuate the transcriptional activity of the mineralocorticoid receptor through its acetylation.[3]

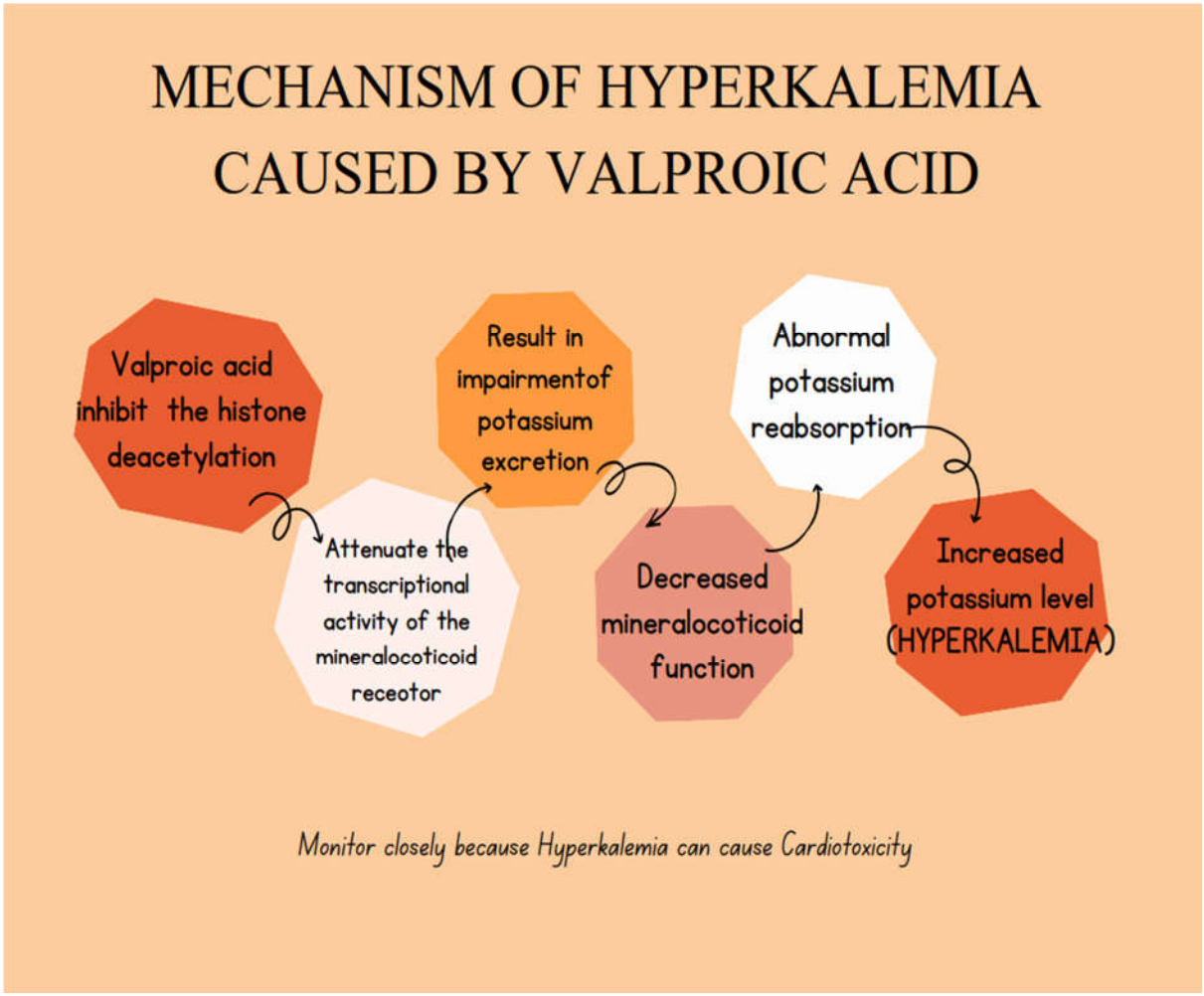

Figure 2: Mechanism of hyperkalemia caused by valproic acid[3 8]

The association between hyperkalemia and valproic acid might result from the impairment of potassium excretion caused by decreased mineralocorticoid function or abnormal potassium reabsorption in the renal tubules.[3]

In this case the potassium level were resolved by adding the drug K.BIND SACHET(CALCIUM POLYSTYRENE SULPHONATE POWDER) and the drug TAB.ENCORATE CHRONO(VALPROIC ACID) was changed to TAB.ZEPTOL(CARBAMAZEPINE) by **Cross-Tampering Therapeutic Strategy** and this strategy was explained briefly in case description. After this the potassium level was reduced to normal and the patient was discharged with improved patient compliance.

Since hyperkalemia is cardiotoxic and typically a medical emergency, it is always crucial to detect it early in the clinical context. When an elderly patient is on valproic acid, the clinician should also be extremely cautious about monitoring the serum potassium level.[8]

ABBREVIATION

VPA - Valproic acid

CONFLICT OF INTEREST

There is no conflict of interest

CONCLUSION

In conclusion, the development of hyperkalemia in an older patient with epilepsy and a proximal humerus fracture is an uncommon but potentially harmful side effect of valproic acid treatment. As part of a cross-tapering therapeutic approach, the patient's increased potassium levels were quickly detected and treated by stopping valproic acid and utilizing carbamazepine in addition to potassium-binding drugs. For patient safety and a positive result, early detection, prompt action, and careful electrolyte status monitoring were essential. Because hyperkalemia can be cardiotoxic and is a medical emergency, this case emphasizes the necessity for clinicians to continuously monitor serum potassium in elderly patients with valproic acid.

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