"No Carbs!" Managing refractory seizures – A case study

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Literature Review

Tuberous sclerosis complex (TSC) is a rare genetic condition involving tumour (or tuber) growth across multiple organs. Approximately 75-90% of people with TSC have tubers in the central nervous system which can cause epilepsy, the main type of which is focal seizures [1].

Management of refractory seizures secondary to TSC includes antiepileptic drugs (AEDs), vagal nerve stimulation, ketogenic diet (KD), mTOR inhibitors and/or cannabidiol. Studies from the international Tuberous Sclerosis registry (TOSCA) demonstrated that using one or more of these interventions controlled focal seizures in 58.2% (n=713) of patients [2]. From 2011 to 2015, 11.8% (n=28) of TOSCA patients being treated for focal seizures were prescribed a KD [3]. KDs involve reducing carbohydrates (CHO) and increasing fat intake to over 70% of calories to induce chronic ketosis. Despite lack of efficacy data for KDs in TSC and refractory status epilepticus populations, the traditional KD can reduce seizures by more than half in 22-70% of adults with epilepsy [4].

Hypotheses for the KD's mechanism of action include ketone bodies exerting an antiepileptic effect, 'starving' neurones reduces synaptic excitability, and ketosis increasing synthesis of GABA [5].

Objective

To describe pharmacological management in a patient with refractory status epilepticus secondary to Tuberous Sclerosis Complex.

Clinical Features

- 41F with TSC and secondary cognitive impairment, seizures, Stage 3 CKD, hypertension and hypothyroidism
- Presented to ED with atypical seizures (usually exhibits focal jerking and symmetrical tonic seizures). Transferred with super refractory status epilepticus to a tertiary hospital ICU for continuous EEG monitoring and maintenance of mechanical ventilation
- Day 13 of hospitalisation: KD prescribed, targeting ketones 2.5 – 5.0 mmol/L

Interventions

Medication	Considerations	Pharmacist suggestions for KD
Carbamazepine NG 400mg BD	• 200mg IR tablets: nil CHO • Oral liquid: sorbitol 175mg/mL, flavouring, propylene glycol	Use the tablets, crushed
Clonazepam NG 2mg BD + IV 1mg q4h PRN	• Paxam® tablets: maize starch, lactose • IV Rivotril®: propylene glycol	Continue as charted. Review if ketosis not achieved in several days
Coloxyl & Senna® NG 2 nocte	Maize starch & maltodextrin	Change to Movicol®
Lamotrigine NG 150mg BD	• Chewable tablets: starch glycollate and flavouring • Regular tablets: starch glycollate and lactose	Use regular tablets (chewable likely to have more sugars for flavouring)
Levetiracetam NG 1500mg BD	Generic Health tablets: maize starch	Change to IV (1:1) while in the acute stage
Vigabatrin NG 2000mg BD	• Sachets: nil CHO • Tablets: starch	Continue on current sachets
Fentanyl IV infusion	Nil CHO	Currently diluted in sodium chloride 0.9%; ensure nurses avoid glucose
Propofol IV infusion	Propofol infusion syndrome and glycerol	Switched to midazolam and dexmedetomidine. Do not re-start propofol

Dosing guidance

Day 24 of hospitalisation: Everolimus (Afinitor®) was initiated for TSC.
The pharmacist suggested a starting dose of 8mg/m^2, due to carbamazepine-induced clearance of everolimus via CYP3A4/5 [6].
TDM guidance was provided for everolimus and AEDs.

Case Progress & Outcomes

All the KD suggestions were actioned by the medical team and handed over to nursing staff. NG feeds were switched to KetoCal® 4:1. Ketosis was transiently achieved – ketones ranged from 0.9 to 2.7 mmol/L during the KD.

AEDs were titrated to wake and extubate the patient. Seizures transiently worsened (hemiclonic), then improved along with alertness. With no continuous events for several days, the patient was safely extubated. Upon ICU discharge, the KD was ceased to facilitate speech pathologist assessment.

Discussion

With multiple treatment modalities, it was difficult to assess the efficacy of the KD in this case. However, KDs are easy to monitor and maintain in the ICU, with effects potentially apparent after several days [7], and has the benefit of not affecting haemodynamic parameters – unlike anaesthetic agents used in refractory status epilepticus [4]. A multidisciplinary effort is required to initiate and maintain a KD; complete CHO elimination is not always possible. Adherence to the KD would be difficult for TSC outpatients with behavioural and intellectual impairment alongside epilepsy [2].

In conclusion, refractory seizure management requires concurrent treatments which can include AEDs and KD, where pharmacist intervention helps to optimise dosing and minimise CHO intake through comprehensive medication review.

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PHOTO: Pharmaceutical Drugs On The Blue Background, Concept Of Complex Treatment by Alina Kholopova from NounProject.com