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RESEARCH ARTICLE

PHENYTOIN AND SODIUM VALPROATE INTOXICATION AND MANAGEMENT, A CASE REPORT

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Abstract

Phenytoin Toxicity Is Challenging Due To Its Pharmacokinetic Properties And Narrow Therapeutic Index. Serum Values In Valproate Toxicity Do Not Correlate With Its Side Effects. In This Case Report, Patient Consumed 100 Tablets Of Phenytoin And 15 Tablets Of Sodium Valproate Causing Her Serum Levels Of Phenytoin And Valproate Rise To 100mcg/ML And 1.4mcg/ML Respectively. Her Conditioned Worsened And Suffered Cardiac Arrest On 9th Day Of Admission During Supportive Therapy. Plasma Pheresis Was Done As Rescue Measure Which Decreased Phenytoin Levels. Her Neurological Condition Improved And Was Discharged After 40 Days Of Hospital Stay.

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Introduction:-

Phenytoin Sodium And Sodium Valproate Are Few Of The Commonly Used Antiepileptics. Overdosage Of These Drugs Occurs Due To Suicidal Intent Or Inadequate Monitoring Of The Therapy. Phenytoin At Lower Doses Follows First Order Kinetics And At Higher Doses Follows Zero Order Kinetics. Henceforth Management Of Its Toxicity Is Challenging As Its Removal From The Body Takes Longer Duration.^[1] Few Side Effects Of Sodium Valproate Toxicity Includes Hyperammonemia, Raised Hepatic Transaminases And Pancreatitis.^[2] We Report A Case Of Suicidal Consumption Of 100 Phenytoin Tablets Each Of 100mg And 15 Tablets Of 200 Mg Sodium Valproate.

Case Report:-

A 28 Year Old Female Presented 10 Hours After Consumption Of 100 Tablets Of 100 Mg Phenytoin And 15 Tablets Of 200 Mg Sodium Valproate. She Was Treated At Local Hospital 2 Hours After Consumption With Gastric Lavage And Shifted To Our Hospital. At Presentation, She Was Conscious, Oriented With Nystagmus, Diplopia And Slurring Of Speech. Electrocardiogram Showed Prolonged Qtc Interval (580msec). Serum Phenytoin, Ammonia And Sodium Valproate Levels Were >100mcg/ML, 40mmol/L And 1.4mcg/ML Respectively With Sgot Of 57iu/L And Sgpt Of 76iu/L. She Was Shifted To Icu, Where She Became Drowsy, Irritable After 6 Hours. She Was Treated Conservatively With Lipid Emulsion For Prolonged Qtc Interval. She Was Intubated And Ventilated In View Of Low Gcs (Glasgow Coma Scale). Her Serum Ammonia Increased To 56mmol/L Where As Serum Phenytoin Level Came Down To 33.70 Mcg/ML. Percutaneous Tracheostomy Was Performed On Day 8 In View Of Neurological Status And Prolonged Ventilator Support. Tracheal Secretions Showed Acinetobacter And Was Treated With Appropriate Antibiotics. Mri Of Brain Showed Normal Study With Global Cerebral Dysfunction On

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EEG. Serum Phenytoin Levels On 9th Day Of Admission Increased To 50.90 Mcg/ML And Patient Remained Irritable And Not Obeying Commands. Patient Suffered A Cardiac Arrest, And Hypothermia Was Instituted On Day 9. Plasmapheresis Was Planned In An Attempt To Decrease Phenytoin Levels Due To Progressive Worsening. Her Serum Phenytoin Levels Decreased To 27.3mcg/ML Post Plasma Pheresis. A Day After Cardiac Arrest Patient Showed Spontaneous Eye Opening With Persistent Nystagmus. Serum Phenytoin Levels Were Monitored Regularly And Were 8.2mcg/ML On Day 21. Serum Ammonia Level Also Decreases From 125mmol/L To 64mmol/L. In View Of Repeated Episodes Of Abdominal Distention Sodium Valproate Induced Acute Pancreatitis Was Suspected. Serum Amylase And Lipase Levels Were Elevated 257 U/L And 788u/L Respectively. Sigmoid Decompression Was Done On 16th Day Of Admission For Recurring Episodes Of Abdominal Distention. As Her Irritability Decreased, Sensorium Improved, Ventilator Support Weaned And Was Decannulated On 28th Day Of Admission. Patient Was Shifted Out Of Icu And Was Later Discharged After 40 Days Of Hospital Stay.

Discussion:-

After Consumption, Phenytoin Precipitates In Acid Environment Of Stomach And This Plays An Important Role In Over Dosage. It Is Metabolized By Hepatic Microsomal Enzymes And Is Highly Protein Bound. Only Free Unbound Phenytoin Is Biologically Active. Peak Blood Levels Are Seen 3-12 Hours After Ingestion. Phenytoin Levels In Cns Are Higher Than Plasma Levels Henceforth Serum Phenytoin Levels May Underestimate Cns Concentration Levels.^[3] This Might Be The Reason In Our Patient Too. Cns Toxicity May Lead To Damage To Cerebellum Manifesting As Cerebellar Atrophy. Ataxic Gait, Nystagmus And Mental Status Changes Are Early Signs Of Toxicity Which Were Noted In Our Patient.[Table 1]

Table 1:- Serum Phenytoin Level And Toxicity.

Serum Phenytoin Level	Signs And Symptoms
10-20 Mcg/ ML	Therapeutic Range
20-30 Mcg/ML	Nystagmus
30-40 Mcg/ML	Ataxia, Slurred Speech, Nausea And Vomiting
40-50 Mcg/ML	Lethargy And Confusion
Higher Than 50 Mcg/ML	Coma And Seizures

Management Includes Prolonged Supportive Care And Treatment Of Secondary Infections. Case Reports Regarding Use Of Multiple Doses Of Activated Charcoal Exists But Nausea And Vomiting May Occur, Leading To Aspiration Pneumonia.^[4] Usage Of Charcoal Hemoperfusion Decreased Serum Phenytoin Levels In Paediatric Case Reports.^[5] In Presence Of Activated Charcoal, Hemoperfusion Causes Bound Phenytoin To Dissociate From Albumin And Gets Adsorbed To It.^[6] Molecular Adsorbent Recirculating System Has Been Shown To Cause Reduction Of Phenytoin Levels Across Charcoal Column Indicating Main Site Of Removal Of Drug Bound To Albumin.^[7] But Usage Of Mars Has Been Limited By Its Availability And High Costs. Use Of Plasmapheresis Resulted In Drop Of Protein Bound Drug In Some Studies.^[8] Our Patients Gcs Improved And Showed A Significant Drop In Phenytoin Levels From 50.90 To 27.30 Mcg/ML Post Plasmapheresis. Phenytoin Induced Inhibition Of Cardiac Sodium Channels Especially At Phase 0 Causing Inward Intracellular Sodium Currents Leading To Slowing Of Conduction And Widening Of The Qrs Complex Has Been Attributed As A Cause For Bradyarrhythmia's.^[9] In Our Case This Could Have Been The Cause Of Bradycardia And Cardiac Arrest As The Levels Of Phenytoin Have Also Been High (50.90) At The Same Time. Intravenous Lipid Emulsion Therapy Can Be Considered For Toxicity Of Lipophilic Drugs Causing Prolonged Qtc Interval.^[10] Drugs Like Phentoin And Valproic Acid Are Highly Lipid Soluble. Henceforth Lipid Emulsion Was Used In Our Case.

Valproic Acid Is Rapidly Absorbed After Consumption And Is 90% Protein Bound. Peak Serum Concentrations Can Be Varying From 1 To 20 Hours After Consumption Depending Upon The Type Of Preparations. There Are Reports That Over Dosing Of Enteric Coated Valproate Sodium May Result In Delayed Toxicity.^[11] Two Mechanisms Were Proposed For Hyperammonemia, A Complication Of Valproate Overdose. The First Mechanism Commonly Seen In Young Individuals With Neurological Illness Is Due To An Idiosyncratic Reaction To Sodium Valproate Causing Liver Injury.^[12] Second Mechanism Is By Inhibiting Enzymes Of The Urea Cycle In Patients With Normal Liver Functions And Without Any Liver Injury.^[13] Patient's Drowsiness Is Related To High Serum Ammonia Levels. Studies Have Shown That Blood Ammonia Levels Do Not Correlate With Blood Levels Of Valproic Acid As Seen In Our Case.^[14] Acute Pancreatitis Had Also Been Reported As A Very Rare Complication Of Valproic Acid Overdose With An Incidence Of 1:40,000.^[15] The Exact Mechanism Of Valproate Induced Pancreatitis Is Unknown.

Conclusion:-

Antiepileptic Drugs Intoxication Can Be Suicidal Or Accidental. Among Them, Management Of Phenytoin Intoxication Is Challenging. Only Supportive Care Plays An Important Role, Plasmapheresis Can Be Helpful In Scenarios Where Improvement Is Not Evident. In Valproic Acid Overdose, Though The Initial Serum Values Of Drug Is Normal, Complications Like Hyperammonemia And Pancreatitis Should Always Be Suspected.

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