Nutmeg and Phenytoin toxicity in an infant

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3 month old male infant presented with

- Acute onset of multiple episodes of seizures – 2 days duration
- Seizure type – vacant stare with tonic posturing of limbs, lasting for a few seconds associated with loss of consciousness
• Treated with parenteral drugs at 2 other hospitals prior to admission at our institute

• Treatment details not available

• No preceding fever, cranial trauma, ear discharge or bleed from any site

• The baby had been fed paste made from nutmeg (*jadikkai*), prior to onset of seizures
• 1st born to 3rd degree consanguineous parentage

• Born at 36wks, forceps delivery, IUGR, birth weight 2.4 kg

• Normal antenatal and postnatal period

• Developmentally normal
On examination

• Afebrile
• No neurocutaneous markers
• Vitals stable
• CNS: drowsy, pupils were normal & reacting equally to light, no meningeal signs, AF level, no deficits, fundus – normal
• CVS: Grade 3/6 systolic murmur 2\textsuperscript{nd}, 3\textsuperscript{rd}, 4\textsuperscript{th} ICS
• RS & PA: Normal
Investigations

• Sepsis screen – Negative

• Blood sugar, calcium, magnesium, RFT, LFT, serum electrolytes – Normal

• EEG and MRI brain – Normal

• ECHO – Bicuspid aortic valve, mild aortic stenosis
Course in hospital

• After admission – 8 to 10 episodes of GTCS with lip smacking
• Two half loading doses of phenytoin given
• Seizures were controlled only after starting phenobarbitone and midazolam infusion
• Phenobarbitone and phenytoin maintenance continued
• Baby was noted to have nystagmus, extrapyramidal movements and shrill cry
• Did not follow light; sluggish pupillary reactions
• Did not focus upon or smile at the mother
In view of

- Multiple hospital admissions
- H/o administration of multiple injections
- Recurrence of seizures
- Nystagmus
- Extrapyramidal movements

Phenytoin toxicity suspected
• Serum phenytoin levels – >40 µg/ ml (toxic range)  
  normal – 10 -20 µg/ ml 

• Phenytoin was withdrawn and phenobarbitone continued
• Nystagmus – resolved within 48 hours

• Involuntary movements started improving within 72 hours

• Vision improved, in that baby could focus on and smile at mother, in about a week

• Repeat serum phenytoin – 17.7 µg/ml (therapeutic range; done after a week of stopping the drug)
At discharge

• Seizure free
• No involuntary movements or nystagmus
• Visual dysfunction persisted (did not follow light)
• VEP – P 100 latency suggestive of anterior visual pathway defect
• Discharged on oral phenobarbitone
Follow up after 2 weeks

- Baby was focusing and smiling at his mother
- He was able to follow light
- Pupillary reactions were normal

- Serum phenytoin level – < 0.5 µg/ ml
Discussion

- Proximate cause for acute symptomatic seizures – probably nutmeg (*jadikkai*) ingestion
- Anti diarrheal and carminative agent
- Active component – Myristicin; weak MAO inhibitor with CVS and CNS effects
- Hallucinogen
- Poisoning causes convulsions, delirium and blurred vision
- Assay not widely available

*Simple and rapid determination of myristicin in human serum. Dawidowicz AL, Dybowski MP. Forensic toxicology 2012*
• Phenytoin is a commonly used AED; iatrogenic toxicity is also common
• Factors responsible for dose related toxicity
  ✓ Narrow therapeutic index
  ✓ Complex pharmacokinetics
  ✓ Inter individual variability in metabolism and clearance
  ✓ Drug interactions
  ✓ Improper dosing
Phenytoin pharmacokinetics in infancy

- Neonates and early infancy – reduction in the activity of rate controlling enzymes of phenytoin biotransformation

- Increased free phenytoin fraction in plasma and tissues
Dose related toxicity:

- 20 - 25 µg/ dl – Nystagmus on lateral gaze
- 30 µg/ dl – Ataxia and diplopia
- >30 µg/ dl – Dysarthria, seizures
- >40 µg/ dl – lethargy, drowsiness, rarely asterixis
Clinical manifestations of Phenytoin toxicity

- GIT – nausea, vomiting, abdominal distension, ileus
- CVS – tachycardia, arrhythmias
- Renal failure
CNS toxicity

- Dizziness, vertigo, lethargy, altered mental status
- Dysdiadochokinesia, ataxia
- Choreoathetosis, dystonia
- Dysarthria
- Seizures
- Opsoclonus, cerebellar atrophy
- Reversible focal neurological deficits
Ocular toxicity due to phenytoin

• Blurred vision, visual loss (reversible)
• Xanthopsia
• Colour blindness
• Concentric visual field constriction
• Nystagmus
• Diplopia
• External ophthalmoplegia
• Sluggish pupillary reflexes
Patient Information
ID No.: 4696
Sex: Male
Age: 30
Height: 175 cm
Weight: 70 kg
Refer Dept.: Pvt
History: N/C Seizures

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Treatment of phenytoin toxicity

• Symptomatic
• Seizures managed with benzodiazepines
• Plasmapheresis
• Hemodialysis
• Hemoperfusion

Follow up:
MRI brain after 6 months to look for cerebellar atrophy
Take Home Message

- Nutmeg, a spice, can cause significant CNS toxicity in infants
- Phenytoin can cause refractory seizures at toxic levels
- Phenytoin has a narrow therapeutic range hence serum levels should be monitored after loading doses and while on therapy
- Reversible visual dysfunction can occur due to acute phenytoin toxicity.
References


2) Phenytoin induced status epilepticus. Ali H. Al-Khulaif, S.S. Asaad, Neurosciences 2010; vol.15(2)

3) Total external ophthalmoplegia induced by phenytoin: A case report and review of literature. Vinod Puri, Neera Chaudhry, Neurology India Sept 2004; vol 52 issue 3


6) Acute phenytoin intoxication in a 4yr old mimicking viral meningo-encephalitis, Amlin Shukla, Jhuma Sankar, Ankit Verma, Nankishore Dubey

7) Phenytoin toxicity presenting as acute meningo-encephalitis in children, Vijay Gupta, Tribhuvan P Yadav, Anita Yadav, BMJ case report 2011; vol 59, issue 1


THANK YOU