CVA and Seizures

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CVA AND SEIZURES

CVA Epidemiology, Diagnosis and Management

I. INTRODUCTION

A. Objectives

1. Describe the epidemiology and pathophysiology of acute stroke
2. Describe the clinical presentation of the various stroke syndromes
3. Delineate the current management of acute hemorrhagic strokes
4. Delineate the current management of acute ischemic strokes

B. Epidemiology of stroke

1. Third leading cause of death in the USA
2. 550,000 new strokes per year
3. 150,000 deaths per year
4. Leading cause of disability; 3 million people in the USA live with some disability resulting from stroke
5. Leading diagnosis for placement in long term care
6. Total direct cost is approx. $13 billion/year
7. Total indirect cost is approx. $17 billion/year
8. Most significant strokes initially present to the ED

C. Types of stroke

1. 85% of strokes are ischemic
   a. 2/3 thrombotic
   b. 1/3 embolic
2. 15% are hemorrhagic
   a. 2/3 intracerebral
   b. 1/3 subarachnoid

D. Mortality rates

1. For all strokes, 25% of patients over 70 years will die within 30 days
2. African Americans have 2x the incidence and mortality vs other groups
II. PATHOPHYSIOLOGY

A. Circulation

1. Normal blood flow is 40-60cc/100g brain/min
2. At < 20cc/100g/min neurons stop firing; membrane integrity is maintained
3. At < 10cc/100g/min membrane failure occurs
4. Collateral circulation leaves a large area with 10-20cc/100g/min. The area perfused between 10-20cc/100g/min is called the penumbra.
5. The penumbra becomes infarcted tissue as the ischemic time increases
   a. <2 hrs of ischemia: neuro deficits are reversible
   b. 2-6 hrs of ischemia: actively being investigated, recovery uncertain
   c. >6 hrs of ischemia: neuro deficits are irreversible
6. It is the preservation of the neurons in the penumbra that is the goal of therapies such as thrombolytics and neuroprotective agents.

B. The role of glutamate in neuronal death

1. Glutamate is an excitatory amino acid found in many neurons and acts on NMDA receptors
2. Ischemia causes the release of Glutamate which leads to calcium and sodium influx into the neuron
3. This decreases ATP as the cell tries to move the calcium and sodium extracellularly
4. Calcium is sequestered in the mitochondria
5. This causes uncoupling of oxidative phosphorylation and the production of oxygen free radicals
6. This leads to glial swelling which leads to worsening ischemia.

C. Glucose

1. Within 5 min ATP is depleted and lactate production increases leading to acidosis
2. If more glucose is given there is an increase in lactate through anaerobic metabolism
3. Thus it is important to have strict glucose control and avoid using D50W.
D. Pre-hospital issues in the treatment of stroke

1. Public education is a priority
   a. Average arrival time after the onset of symptoms is 12-24 hours
   b. Barsan et al found that arrival times after the onset of symptoms were different based on who the patient called first (911 vs. hospital vs. private physician)
   c. Kothari et al found that using 911, race (white) and living with someone were independently associated with arrival within 3 hours of the onset of symptoms

2. EMS response and assessment
   a. Porteous et al found that dispatchers classified calls in which “stroke” was used by the caller as “CVA” only 48% of the time. In 61 patients with documented stroke the EMS calls were retrospectively reviewed and the dispatch code of “CVA” was used in only 31% and ambulances were dispatched at “low priority” in 59%
   b. Kothari et al have validated their Prehospital Stroke Scale which uses 3 items from the NIH Stroke Scale (facial palsy, best motor arm, and best language)
   c. Kidwell et al have also developed a prehospital stroke screen

III. STROKE SYNDROMES

A. Anterior cerebral artery

1. Paralysis of the opposite leg, worse than the arm paralysis
2. Sensory deficit paralleling paralysis
3. Altered mental status; confusion
4. Bowel or bladder incontinence

B. Middle cerebral artery (most common)

1. Paralysis opposite body, arm, face, worse than legs
2. Sensory deficit paralleling paralysis
3. Blindness in lateral half of visual field (Hemianopsia)
4. Dysphasia
5. Agnosia (inability to recognize objects)

C. Posterior cerebral artery

1. Hemianopsias
2. 3rd nerve paralysis
3. Cortical blindness
4. Altered mental status

D. Vertebrobasilar artery

1. Vertigo, nystagmus
2. Facial numbness/paresthesias
3. Contralateral loss of pain and temperature
4. Bilateral spasticity
5. Syncope, drop attacks

E. Cerebellar infarction

1. Nausea and vomiting
2. Headache
3. Nuchial rigidity
4. Central vertigo
5. Drop attacks
6. 1/3 of ischemic infarcts develop cerebellar edema
7. Hemorrhagic cerebellar infarcts are a surgical emergency
8. Brainstem impingement leads to altered consciousness
9. Pathologic respiratory pattern
10. Stable period of 6 - 12 hours

F. Lacunar infarction

1. 20% of all infarctions
2. Risk factors are those with small vessel disease (i.e. diabetes, hypertension)
3. Areas most highly affected include:
   a. Basal ganglia
   b. Pons
   c. Thalamus
4. These infarcts are subcortical, so rarely have cognitive deficits

G. Transient ischemic attack (TIA)

1. Focal symptoms: usually weakness or numbness
2. Usually not: dizziness, syncope or altered mental status
3. Lasting < 24 hours
4. Majority last 10 - 15 minutes
5. 20% have a stroke within one month
6. 50% have a stroke within five years

H. Differential diagnosis of TIA

1. Partial seizure
2. Presyncope, syncope
3. Episodic vertigo (vestibular disease)
4. Intracranial mass
5. Migraine

I. Risk factors for stroke
   1. Same as atherosclerotic vascular disease
      a. Hypertension
      b. Heart disease
      c. Elevated cholesterol
      d. Diabetes
      e. Cigarette smoking

J. Clinical assessment
   1. ABCs
   2. Altered mental status protocol
   3. Glucose check, not D50W
   4. Level of consciousness
   5. AVPU
   6. Glasgow coma scale

K. Neurological exam
   1. Eye: pupillary reflex, gaze preference
   2. Facial weakness, distinguish from peripheral causes by ability to wrinkle forehead. Bell's palsy cannot, stroke can
   3. Motor
   4. Sensory: light touch, pain
   5. Cerebellar testing: finger to nose, gait
   6. Deep tendon reflexes, Babinski

L. While assessing the patient keep in mind
   1. 10-20% of strokes has brain stem compression
   2. 5% of strokes have an acute seizure

M. Ancillary tests
   1. CBC
   2. Chemistry
   3. PT/PTT
   4. EKG
   5. CT scan
IV. HEMORRHAGIC STROKES

A. Epidemiology

1. 15% of all strokes
2. 2/3 intracerebral
3. 1/3 subarachnoid
4. 30 day mortality rate is 50%
5. Usually occur during working hours
6. Headache is a symptom in only 50% of patients
7. 85% of SAH patients have headache

B. Pathophysiology of cerebral hemorrhage

1. Strong correlation with hypertension
2. Usually in the middle cerebral artery distribution
3. 2/3 is in the basal ganglia
4. Microaneurysm which is susceptible to changes in blood pressure (cocaine)

C. Pathophysiology of subarachnoid hemorrhage

1. 3/4 occur in the Circle of Willis-Berry Aneurysm
2. Most occur before age 50
3. Aneurysm, AVM

D. Clinical assessment

1. ABCs
2. Altered mental status: unconsciousness
3. Respiratory pattern
   a. Cheyne-Stokes respirations may indicate a large ICH
   b. Deep irregular respirations may indicate a putamen hemorrhage
   c. Normal respirations may be seen in a cerebellar hemorrhage
4. Pupils
   a. Pin point pupils may indicate a pontine hemorrhage
   b. Dilated pupils may indicate a putamen hemorrhage
   c. Gaze preference to the side of the lesion
5. Neurologic exam
   a. Similar to findings for ischemic stroke
   b. Directed exam
   c. Include consciousness assessment, can change rapidly
E. Ancillary tests

1. Same as ischemic strokes
2. EKG: increased sympathetic outflow causes increased dysrhythmias
3. PT/PTT for coagulopathy

F. CT scan

1. 95% of ICH can be seen on CT
2. Will miss the very small and those in the 5-9 day window
3. 90% of SAH can be seen on CT
4. LP on all negative CT scans for SAH

G. SAH CT scan findings

1. High density hemorrhage injury
2. Interhemispheric fissure
3. Third ventricle
4. Ambient cistern
5. Sylvian fissure

V. TREATMENT OF HEMORRHAGIC STROKE

A. Introduction

1. If intubation is necessary, remember ICP. Pre-treat with lidocaine
2. Lower hypertensive blood pressure to a diastolic of 100-110
3. Nitroprusside, Labetalol, Esmolol and Nicardapine
4. Head of the bed to 45 degrees
5. Hyperventilation should only be used if a neurosurgeon is going to perform a definitive procedure within hours of the initiation. Hyperventilate to a CO2 of 25-30 mmHg.
6. Diuretic: mannitol 20% solution 0.25g-1.0g per Kg
7. Steroids generally not used in hemorrhagic stroke
8. Phenytoin at the discretion of the neurosurgeon
9. Nimodipine useful in SAH

B. Nimodipine

1. Ca channel blocker
2. Greater effect on cerebral arteries: lipophilic
3. Decreases neurological deficits in SAH
4. Used in SAH Hunt and Hess Grades I-III
5. Most common adverse reaction is decreased BP
6. 60mg PO every 4 hours

C. Treatment: surgery

1. Usually not helpful in ICH
2. Used in large ICH to prevent herniation or hydrocephalus
3. Recommended in SAH: timing is controversial
4. Recommended in cerebellar hemorrhage

VI. TREATMENT OF ISCHEMIC STROKE

A. Treatment: Hypertension

1. Because of impaired cerebral autoregulation treatment of hypertension is controversial
2. Treatment should be begun if the patient is a candidate for thrombolytic therapy or shows signs of:
   a. Hypertensive encephalopathy
   b. Aortic dissection
   c. Severe hypertension
   d. Myocardial infarction

B. Treatment: Anti-coagulation

1. Prevent thrombus propagation and further embolization
2. Proven in cardiac arrhythmia
3. Useful in TIA to decrease the number of recurrent ischemic events
4. Unfractionated heparin
   a. International Stroke Trial: 2 doses (5,000 and 12,500 IU SQ BID), 19,435 subjects, no improvement in outcome at 6 months, significantly more intracerebral bleeds (especially the 12,500 IU group)
   b. Risk of bleed in large stroke reported as high as 14%
5. Low-molecular weight heparin
   a. Kay et al (using Nadroparin) found in 306 subjects that both 4100 IU SQ daily and 4100 IU SQ BID, given within 48 hours of the onset of symptoms, were effective in improving outcomes at 6 months compared to placebo. There was no difference among the three groups in regards to death or bleeding related complications
   b. TOAST trial found in 1281 subjects, that Org 10172 given within 24 hours of the onset of symptoms, lead to improved outcomes at 7 days but similar outcomes at 3 months when compared to placebo
C. Treatment: Anti-platelet agents

1. Cyclooxygenase: thromboxaneA2; platelet aggregation
2. Aspirin inhibits Cyclooxygenase for the life of the cell
3. Aspirin decreases the stroke risk by 20% when taken prior to symptom onset
4. International Stroke Trial when combined with the Chinese Acute Stroke Trial shows a decrease in 10 deaths or recurrent strokes per 1000 at 2-3 weeks when aspirin (300 mg) was given within 48 hours

D. Thrombolytic agents for stroke

1. Streptokinase and urokinase trials
   a. All trials terminated by safety committees for exceeding acceptable parameters for bleeding or mortality
   b. MAST-I
      i. Controlled, randomized, open-label, 622 patients
      ii. Streptokinase (1.5 million units), ASA (300 mg), both or neither
      iii. 6 hour window for enrollment
      iv. Outcome was 10 day mortality which was excessive in the streptokinase and streptokinase and ASA treatment groups.
   c. MAST-E
      i. Double-blind, randomized, controlled, 310 patients
      ii. Streptokinase (1.5 million units) or placebo
      iii. 6 hour window for enrollment
      iv. 10 day mortality was 34% in the streptokinase group and 18% for the placebo group (p=0.002)
      v. Hemorrhagic transformation of ischemic infarcts was the primary cause of mortality.
   d. ASK
      i. Double-blind, randomized, controlled, 340 patients
      ii. Streptokinase (1.5 million units) or placebo
      iii. 4 hour window for enrollment
      iv. Excessive deaths occurred in the group that received streptokinase after 3 hours

2. TPA clinical trials
   a. ECASS
      i. 6 hour window for enrollment, median time 4.3 hours
      ii. TPA dose was 1.1 mg/kg
      iii. 620 patients enrolled, 109 were later excluded for protocol violations because of major infarction or primary hemorrhage on CT scan when the data was reviewed.
iv. In the "intention to treat" group (all 620), there was no significant benefit of TPA at 90 days.

v. In the "target" group (minus the 109), there was a significant improvement at 90 days in the Rankin scale (disability scale).

vi. There was a higher incidence of intracerebral hemorrhage in the TPA group, but no difference in the 30 day mortality using either analysis (target orientation to treat).

vii. Because of the difference between the analyses the authors concluded that the use of TPA in an unselected stroke patient population was not recommended.

viii. Post-hoc analysis showed that though there was an increased risk of death in the treatment group overall outcome was improved.

ix. ECASS II is under way with half of the rate of large ischemic lesions and parenchymal hematomas as ECASS I.

b. NINDS

i. 3 hour window for enrollment, many within 90 minutes

ii. TPA dose was 0.9 mg/kg

iii. 624 patients enrolled

iv. Part 1: No significant improvement in 24 hours though secondary analysis showed a significant improvement in the median NIHSS (42 point scale of specific neurological deficits) at 24 hours.

v. Part 2: Significant improvement in outcome at 3 months overall and in each of the four components; NIHSS, Barthel Index (activities of daily living), Modified Rankin Scale (comparison to pre stroke function) and Glasgow Outcome Scale (level of independent living).

vi. Increased bleeding was found in the TPA group, but 3 month mortality was no different.

vii. The overall conclusion was those treated with TPA were 30% more likely to have little or no disability at 3 months. Follow up has shown this to continue to 6 months and 1 year. Ischemic stroke lesion size, as measured on CT, was reduced in the TPA treated group.

c. ECASS II

i. TPA vs. placebo within 6 hours of symptom onset.

ii. 0.9 mg/kg, maximum 90 mg.

iii. End point: minimal or no disability at 3 months.

iv. Unexpectedly high placebo response rendering the efficacy evaluation inconclusive.

v. Mortality was half that of ECASS I, and there was no difference in mortality between the TPA and placebo groups.
vi. Conclusion: Safety confirmed compared to placebo. Efficacy for 0-6 hour window not proven. There was a trend toward significance in the 20% of patients treated in the 3 hour window, but the n was insufficient.

d. ATLANTIS
i. TPA vs. placebo within 5 hours of symptom onset
ii. 0.9 mg/kg, maximum 90 mg.
iii. Enrollment discontinued because interim analysis showed no significant improvement in outcome and projected that a significant difference would not be reached with the additional 500 patients scheduled to be enrolled

E. Guidelines for "brain attack" protocol

1. EMS, emergency physician, EM nurse and consultant (Neurology and Radiology) education is the major factor in implementation and meeting the time goals
2. A team approach to the rapid assessment, diagnosis and ancillary test availability (CT scan) is essential
3. CT available 24 hours a day and within 20 minutes of request with prompt, reliable reading
4. TPA stored in the ED

F. Time goals

1. Door to emergency physician - 10 minutes
2. Door to CT - 25 minutes
3. Door to CT reading - 45 minutes
4. Door to TPA - 60 minutes
5. Door to ICU bed - 2 to 3 hours

G. TPA protocols

1. Administered within 3 hours from the onset of symptoms, not arrival in ED
2. Head CT
3. 0.9 mg/Kg to a maximum of 90 mg
4. 10% bolus over 1-2 min
5. 90% infusion over 1 hour
6. Facilities to handle bleeding complications
7. Patients who receive TPA should not receive anti-platelet or anti-coagulant therapy for 24 hours.

H. TPA eligibility

1. Age 18 or older
2. Diagnosis of ischemic stroke with measurable neurological deficits
3. Time of symptom onset to drug administration less than 3 hours

I. TPA exclusion criteria

1. Similar to cardiac TPA
   a. Head injury within 3 months
   b. Surgery within 2 weeks
   c. GI or GU bleeding within 3 weeks
2. Currently on anti-coagulants
3. Platelet count <100,000
4. Improving symptoms
5. Post treatment blood pressure >185/110
6. Isolated or mild neurological deficits
7. Blood glucose <50 or >400 mg/dl
8. Recent myocardial infarction
9. Seizure related to the stroke
10. Clinical presentation suggestive of subarachnoid hemorrhage

VII. CONCLUSION

A. Stroke is treatable
B. Time is neurons
C. TPA and other therapeutic modalities all have "time to administration" as an important factor
D. “Brain Attack” protocols and a "stroke team" are essential to the treatment of stroke patients

Seizures

I. EDUCATIONAL OBJECTIVES

A. Describe the epidemiology of acute seizures
B. Define the principles of diagnosis and management of acute seizures in the emergency department (ED)
C. Determine the utility of new acute seizure therapies in improving patient outcomes
D. Discuss current guidelines, issues, and unanswered clinical questions
II. SEIZURE DISORDERS: EPIDEMIOLOGY AND SOCIETAL COSTS

A. 6/1000 prevalence; 2.5 million in US
B. 147,000 newly diagnosed seizure patients/year
C. 28% of patients with epilepsy visit an ED annually
D. 82,000 hospitalizations/year
E. $3.6 billion annual cost
F. 15% ($558 million) direct costs

III. ACUTE SYMPTOMATIC SEIZURES: EPIDEMIOLOGY

A. CVD, trauma, infection, AED withdrawal account for 60% of cases
B. Toxic, metabolic: 15% of cases

IV. STATUS EPILEPTICUS (SE): EPIDEMIOLOGY

A. 50,000 -150,000 cases annually
B. 50 cases per 100,000 population
C. Infants and elderly: greatest risk
D. 20% of patients with epilepsy will have SE by age 5
E. Etiology: 1/3 acute insult; 1/3 chronic epilepsy; 1/3 new onset

V. SEIZURE OUTCOMES

A. Injury/death: 15%
B. Head contusions/lacerations common
C. Mortality
   1. 1.2% of all seizures
   2. 3% to 26% in SE
   3. 10 times higher in adults (vs children)
   4. Highest with hypoxic or ischemic insult
VI. SE DURATION AND MORTALITY

A. SE > 60 min: 10-fold greater 30-day mortality (32% vs 2.7%)

B. Worse outcome associated with longer duration, refractory to 1st drug

VII. SEIZURE CLASSIFICATION

A. Status Epilepticus: definition

1. Needed for epidemiologic and clinical trials
2. Historical definitions
   a. Two seizures within 30 min without a lucid interval
   b. One seizure >30 min duration
3. More recent definitions more aggressive
   a. Two seizures over any interval without a lucid interval
   b. One seizure of >10 min duration

B. Status Epilepticus: classification

1. Generalized convulsive SE:
   a. Primarily and secondarily generalized
   b. Overt: GTC (Generalized Tonic Clonic) or major motor SE
      subtle: myoclonic SE, "electrical" SE
2. Nonconvulsive SE: epileptic twilight state
   a. Complex partial SE
   b. Absence SE: spike-wave stupor
3. Simple partial SE
   a. No impairment of consciousness

C. Refractory Status Epilepticus

1. Lack of response to first-line drugs: benzos, phenytoin, phenobarbital
2. 2000 - 6000 cases yearly in USA
3. 6% - 9% of all SE cases, suggests progressive CNS disorder
4. 20-30% mortality

VIII. SEIZURE MECHANISMS

A. Abnormal discharge by a few unstable neurons

B. Propagation by recruitment of normal neurons
C. Failure of normal inhibitory neurotransmitters (GABA)

D. Enhancement of excitatory neurotransmitters (glutamate, aspartate, acetylcholine)

E. Interference with normal metabolic processes
   1. Glucose, $O_2$ metabolism
   2. Na+, Ca++, K+, Cl- ion shifts

IX. CEREBRAL CHANGES IN SE

A. CNS injury independent of systemic effects

B. Neuronal injury due to repetitive firing and excessive metabolic needs

C. CNS injury will occur even if systemic disturbances are treated (fever, hypertension, motor activity)

D. Early in SE, BP and CBF (Cerebral Blood Flow) are increased

E. Late in SE, BP and CBF are decreased

X. SYSTEMIC CHANGES IN SE

A. BP: early hypertension, followed by hypotension

B. Fever: 49% have temperature $>$100.5°F

C. Lactic acidosis: 30% will reach blood pH $<$7.00

D. Hypercarbia: 84% will have increased pCO$_2$

E. Catechols: levels within 30 min

F. Leukocytosis without bands

G. CSF pleocytosis: 2%-18% have $>$5 PMNs

XI. POST-ICTAL PHYSICAL FINDINGS

A. Focal findings
   1. Anisocoria, Todd's paralysis
2. Plantar response, hyperreflexia
3. Evidence of trauma (e.g., tongue lacerations)

B. Altered mental status should improve within 20-30 min

XII. LABORATORY TESTING

A. Basic metabolic tests
   1. 2.4% of seizures due to chemistry derangements
   2. Full workup with comorbidity, age extremes

B. AED (Anti Epileptic Drug) levels

C. Toxicologic and ETOH screens (when indicated)

D. Accu-Chek, pulse oximetry, rhythm strip, pregnancy test

XIII. LUMBAR PUNCTURE (LP)

A. ACEP/AAN/AANS/ASN Neuroimaging Guidelines
   1. Recent trauma or anticoagulation
   2. Fever, cancer, AIDS
   3. New focal deficit, persistent AMS
   4. Persistent headache history

B. ACEP/AAN/AANS/ASN Practice Option
   1. Emergent neuroimaging considered
      a. First-time seizure patients
         I. Older than 40 y
         II. Partial-onset seizure
      b. Prior history of seizures
         i. New seizure pattern or type
         ii. Prolonged postictal confusion
         ii. Worsening mental status

XIV. COMPUTED TOMOGRAPHY (CT)

A. Abnormal CT most likely
   1. Abnormal neurologic exam after recovery
   2. Malignancy history
B. Abnormal CT less likely
   1. Alcohol-related seizure
C. Focal seizure alone does not increase likelihood of positive CT
D. Initial CT should be non-contrast

XV. MAGNETIC RESONANCE IMAGING (MRI)
   A. Intractable epilepsy: 25% positive CT, 50% positive MRI
   B. May not be appropriate in ED due to off-site location
   C. After a negative non-contrast CT in the ED

XVI. EMERGENT ELECTROENCEPHALOGRAM (EEG)
   A. ACEP Clinical Policy: Acute Seizures (Non-SE)
      1. Detailed evaluation for prolonged AMS
      2. Directed workup for uncomplicated, self-limited seizures
      3. Follow-up care with primary care MD
      4. Review driving precautions

XVII. PHARMACOTHERAPY OF ACUTE SEIZURES
   A. Benzodiazepines
      1. GABA inhibition of repetitive neuronal firing
      2. 79% control of SE in 47 studies
      3. Lorazepam vs diazepam
         a. Adult SE
            i. Comparable efficacy in seizure termination
         b. Pediatric seizures
      4. Lorazepam may be more effective
         a. Intubation more common with diazepam in SE (73% vs 27%)
      5. Emulsified Diazepam (Diastat)
      6. Diazepam emulsified injection
         a. Less local irritation than diazepam
         b. Seizure termination in 5 to 7 min
         c. No significant respiratory depression
         d. PR dose: 0.25 to 0.5 mg/kg
B. Phenytoin

1. Overview
   a. Stabilizes membrane Na+ channels
   b. Regulates Ca++ channels
   c. Effective in generalized seizures and SE
   d. Seizure termination in 40% to 80% of patients
   e. 18 mg/kg loading dose results in therapeutic (10 /mL) levels up to 24 h
   f. Constant infusion preferred over slow IVP use

2. Oral Phenytoin Loading Regimens
   a. 18 mg/kg oral load
      64% achieve level of 10 mg/mL by 8 h
      i. Mean phenytoin level does not exceed 10 mg/mL until after 4 h
   b. Delayed absorption may relate to large loading dose or phenytoin preparation
   c. Delay in achieving therapeutic level did not result in seizure recurrence in 8 h

3. High-Dose Phenytoin Therapy
   a. Initial Rx for GCSE
      i. Maximal benzodiazepine dose
      ii. 20 mg/kg phenytoin load
   b. Additional half load of phenytoin
      Give 10 mg/kg for a total 30 mg/kg dose
   c. Phenytoin level may exceed 10 to 20 mg/kg
   d. Higher therapeutic levels may be required in refractory SE

C. Fosphenytoin (Cerebyx): Phosphate-Ester Prodrug

1. Water soluble prodrug
2. Complete conversion in vivo to phenytoin
   a. Therapeutic free phenytoin levels within 2.7 minutes (IV)
3. Conversion comparable in all demographic groups and all disease states
4. Available for rapid IV infusion (up to 150 mg PE/min in SE)
5. Available for IM use
6. Dosing is equivalent to phenytoin dosing
7. Limited need for monitoring
8. Drug level testing: 2h after IV, 4h after IM
9. Perioral and perineal paresthesias and pruritus, not an allergic reaction
D. Barbiturates

1. Phenobarbital
   a. Barbiturate crosses blood-brain barrier slowly
   b. Long half life (21-42 h)
   c. Enhances GABA inhibition
   d. Infuse at 100 mg/min up to 10 mg/kg
   e. Monitor for
      i. Respiratory depression
      ii. Hypotension
   f. Good drug for SE treatment
   g. Third-line therapy for refractory GCSE
   h. Stops seizure motor activity and suppresses EEG burst patterns
   i. Loading dose: 5 mg/kg infused at 25 mg/min
   j. Maintenance infusion: 2.5 mg/kg/h
   k. Intubation, ventilatory support, hemodynamic and EEG monitoring required

E. Other Agents

1. Lidocaine
   a. Membrane stabilizing effect at Na+/K+ pump
   b. Reduces neuronal excitability
   c. Possible role in refractory GCSE
   d. Use only as third-line agent
   e. Load at 1.5 mg to 3 mg/kg

2. Propofol
   a. Third-line agent, after benzodiazepines, phenytoin, phenobarbital
   b. Anesthetic agent; GABA mechanism
   c. Provides burst suppression
   d. Loading dose: 2 mg/kg
   e. Requires continuous infusion
   f. EEG monitoring required
   g. Hypotension, respiratory depression, acidosis

3. IV Valproic Acid (Depacon)
   a. IV valproate now available
   b. Restores valproate level quickly
   c. French study tested IV valproate in SE
      i. GCSE and partial SE
      ii. 19/23 patients (83%) controlled in 20 minutes
      iii. EEG control achieved
4. Not indicated for SE in USA

XVIII. PRIMARY CAUSES OF DRUG-INDUCED SEIZURES

A. Cocaine

1. Consider multiple etiologies (inhalation, body stuffing)
2. Indirect CNS causes: ischemia, hemorrhage, vasculitis
3. Diagnostic work-up low yield with brief seizures, rapid return to normal CNS status
4. Treatment: benzodiazepines
5. Avoid beta blockers

B. Isoniazid (INH)

1. Inhibits pyridoxine kinase
   a. Enzyme that forms pyridoxal phosphate
   b. Cofactor in GABA formation
2. Administer pyridoxine on gram for gram basis
   a. Unknown overdoses, give 5 g IVP, repeat q 5 h X 6
   b. Acidosis & refractory seizures improved with pyridoxine
3. Rx: GABA agonists (benzodiazepines, barbiturates)

C. Theophylline

1. Seizures common in chronic ingestions
2. Treat with benzodiazepines, barbiturates
3. Phenytoin probably not effective
4. Enhance elimination
   a. Multiple doses of activated charcoal
   b. Hemodialysis or hemoperfusion

D. Cyclic Antidepressants

1. Seizure (39%) and coma (61%) common in TCA deaths
2. Seizures more likely when QRS > 100 msec
3. Rx: benzodiazepines
   a. Consider pentobarbital or propofol in refractory SE
   b. Phenytoin, physostigmine, NaHCO3 of limited value

E. Alcohol Withdrawal Seizures

1. Epidemiology
   a. 61% occur within 24 hours of last drink
   b. Peak incidence by 12 hours of last drink
c. Generalized seizures common, 60% recur
d. 44% Of GCSE cases due to alcohol
e. Prolonged post-ictal state, but good outcome in alcohol-withdrawal SE

2. Diagnosis and treatment
   a. Baseline chemistries to evaluate specific etiologies
   b. CT for head trauma, deteriorating mental status, or focal neurologic finding
   c. EEG required excluding idiopathic seizures (if not performed previously)
d. IV D5NS, thiamine, K, Mg, lorazepam
e. Avoid progression of disease to DTs

3. Phenytoin use
   a. Phenytoin not effective in preventing seizure recurrence within 6 hours
   b. Decision to load with phenytoin multifactorial
      i. Not preferred for simple, uncomplicated seizures
      ii. Must be considered in seizures refractory to optimal benzodiazepine therapy
      iii. May be advisable without knowledge of patient's medical and seizure history

XIX. SEIZURE TREATMENT IN ACUTE STROKE

A. Stroke patients who present with seizure merit anticonvulsant therapy

B. High-risk patients may benefit from seizure prophylaxis

   1. Elderly
   2. Large hemorrhage
   3. Anterior hemispheric location

XX. EPIDEMIOLOGY OF POST-TRAUMATIC SEIZURES

A. Adult high-risk criteria: 20% incidence

   1. Glasgow Coma Scale < 10
   2. Intracranial hemorrhage
   3. Penetrating injury or depressed skull fracture

B. Pediatric high-risk criteria: 39% incidence

   1. Loss of consciousness
   2. Glasgow Coma score 3 to 8
   3. Abnormal CT scan
C. Phenytoin in post-traumatic seizures

1. One-year, placebo controlled trial in severe TBI
   a. Phenytoin associated with fewer seizures within 7 d vs placebo (3.6% vs 14.2%)
   b. Late-onset seizure rate similar in both groups (28% and 21%) at 1 and 2
2. Mortality rates similar (24% and 21%) by 2nd year
3. Absence of late effect not due to mortality, low phenytoin levels, or treatment crossover

XXI. PREGNANCY AND SEIZURES

A. Overview

1. Changes in seizure frequency and free AED levels may occur
2. Status epilepticus rare; mortality with SE
3. Fetal monitoring necessary
4. Evaluate for eclampsia (seizure in association with pre-eclampsia)

B. Magnesium sulfate for prevention of eclampsia

1. Smooth muscle relaxant
2. Superior to phenytoin for prevention of eclampsia
3. Lower risk of recurrence versus diazepam and phenytoin
4. Lower risk of recurrent convulsions versus diazepam and phenytoin

XXII. PEDIATRIC SEIZURES

A. Epidemiology

1. Immature CNS
   a. More prone to seizures
   b. More resistant to consequences
2. 2% to 5% of children experience a febrile seizure
3. 1% of children have an afebrile seizure by age 14
   a. Highest afebrile seizure incidence before age 3
4. 0.4 to 0.8% of children develop epilepsy by age 11
5. SE most common in children younger than 1 year old

B. Etiologies

1. Meningitis
   a. Seizures in 23% of meningitis cases
b. AMS, complex seizures, or meningitis signs uniformly present
   c. Simple seizure rarely the sole manifestation
   d. HBig makes this etiology rare
2. Hyponatremia
   a. Cause of long-duration seizures and SE
   b. Infants < 6 months old without an obvious etiology
   c. Temperature < 36.5° C
3. Cocaine
   a. Consider in infants with new onset seizures

C. Pediatric SE epidemiology

1. Age
   a. Mean 3.2 years
   b. Median 1 year
   c. 61% by age 3
2. Etiology: age dependent
   a. 25% febrile SE
   b. Acute causes more common in children < 1 year (75%)
   c. Epilepsy, fever, and CNS infection most common

D. Pediatric Seizure Outcomes

1. Outcome
   a. Based on CNS status prior to SE
   b. Normal CNS prior to seizure: 64% remain intact
2. Mortality
   a. 3% to 6%
   b. Most often in children with an acute neurologic insult or chronic CNS condition

E. Febrile Seizure Definition

1. Seizure accompanied by fever
2. No CNS infection
3. Age 6 months to 5 years
4. Simple: <15 minute duration, none within 24 h
5. Complex:
   a. Focal
   b. >15 minute duration
   c. Occurring in a flurry

F. Simple Febrile Seizures: Management

1. LP: consider based on age
XXIII. CVA and Seizures

1. Laboratory studies: not routinely necessary
   a. Directed lab testing beneficial
   b. CBC, blood culture may help in evaluating fever

2. EEG, neuroimaging: not recommended

3. Treat hyperpyrexia and infection

4. Do not start chronic seizure medications

G. Pediatric Seizure Management: No IV Access

1. Benzodiazepines: IM or rectal use
2. Phenytoin: can be given interosseous
3. Fosphenytoin: IM use
4. Phenobarbital: caution with IM use
   a. Prepared with same toxic diluents as phenytoin

H. Pediatric Seizure Prognosis: Afebrile Seizures

1. Seizure recurrence 42%; most within 2 years
2. Greater recurrence risk with a remote symptomatic first seizure
   (prior CNS insult)
3. Status epilepticus
   a. 17% recurrence of SE; most (88%) with neurologic abnormality

I. Pediatric Seizure Prognosis: Febrile Seizures

1. 1% epilepsy rate by 7 years in low-risk patterns
2. Risk increases with family seizure history, prior CNS insult,
   complex febrile seizure
3. SE: higher risk with abnormal baseline CNS status

XXIII. SEIZURES IN THE ELDERLY

A. Greatest seizure frequency and incidence at ages <1 y and >60

B. Nonconvulsive SE may present as new onset AMS

C. Increased risk for drug-drug and/or drug/disease state interactions
   1. Increased drug utilization
   2. Increased frequency of comorbid medical conditions

D. New Onset Seizures in the elderly
1. New-Onset Seizures: Recurrence risk
   a. 51% recurrence risk after first unprovoked seizure
   b. 75% recurrence rate within 2 years of a first seizure
   c. Nearly 20% will seize again within 24 h
   d. Predictors of recurrence risk
      i. Seizure etiology (partial and remote > risk)
      ii. EEG findings
      iii. SE does not increase recurrence risk in idiopathic seizures

XXIV. REFRACTORY SE MANAGEMENT

A. Goal of treatment: achieve an EEG with burst-suppression pattern

B. Pentobarbital: 5 mg/kg, load at 25 mg/min

C. Propofol: 2 mg/kg load, 7 to 10 mg/kg/h maintenance

D. Lorazepam and midazolam IV

E. Chloral hydrate, lidocaine, valproate

F. Inhalation anesthetics less useful

G. Neuromuscular blockade not an anticonvulsant

XXV. PSYCHOCGENIC SEIZURES

A. Etiology: functional

B. Conversion disorder vs. malingering

C. Normal EEG

D. Seen in up to 20% of patients with epilepsy

E. Neurogenic seizures also occur in up to 58% of psychogenic seizure patients

F. Characteristics of psychogenic seizures

   1. Asynchronous movements
   2. Forward pelvic thrusts
   3. Voluntary eye deviation
   4. Retained consciousness
   5. Absence of post-ictal period
XXVI. EPILEPSY FOUNDATION OF AMERICA SE TREATMENT PROTOCOL

A. EFA: Drug Recommendations

1. Adequate dosing of each drug
2. Benzodiazepines, phenytoin, phenobarbital
3. Benzodiazepine for active seizures (>50% will respond)
4. High-dose phenytoin (up to 30 mg/kg)
5. Blinded, placebo-controlled, comparative trial

XXVII. VETERANS ADMINISTRATION (VA) TRIAL OF SE

A. 5-year double-blind study in 16 VA and 4 university hospitals

B. N = 581 patients in GCSE or subtle SE randomized to

1. Phenytoin, 18 mg/kg
2. Diazepam, 0.15 mg/kg, then phenytoin, 18 mg/kg
3. Phenobarbital, 15 mg/kg
4. Lorazepam, 0.1 mg/kg

C. Outcome: no clinical & electrical seizures 20 to 60 min after onset of infusion

D. Lorazepam superior to phenytoin alone, all others equal in SE

E. All equally poor in refractory SE

XXVIII. PREHOSPITAL CARE OF SEIZURES

A. SE in children improved with EMS care (diazepam)

1. Reduced seizure duration (32 vs 60 min)
2. Reduced seizure recurrence (58% vs 85%)

B. Similar data lacking for adults

C. Early EMS intervention may affect outcome for prehospital SE

D. Prehospital management issues

1. ALS care required
   a. Neurologic compromise
b. Abnormal vital signs
c. Serious comorbidity
2. Low-risk criteria based on EMS GCS not reliable
3. Backboard and collar not needed for seizures
   a. Spinal fractures extremely rare (0 of 1656 seizures)
   b. Non-spinal fractures rare (3 of 1656 seizures; 0.2%)

E. Prehospital drug therapies

1. Rectal diazepam
   a. Effective in children, reduced respiratory depression
   b. Similar seizure termination and recurrence rates as IV diazepam
2. IM midazolam
   a. Useful when no IV access available, effective in 80% of seizures
   b. Seizure termination only slightly longer than IV (116 sec vs 34 sec)
3. Pre-Hospital Trial of Status Epilepticus (PHTSE): diazepam vs lorazepam vs placebo

XXIX. RESEARCH HORIZONS IN ACUTE SEIZURES

A. Better epidemiologic data specific to ED seizure patients

B. Optimal prehospital protocols

C. Optimal ED protocols

D. Specific drugs, dosages, sequences for optimal outcomes

XXX. CONCLUSIONS: EMERGENCY MANAGEMENT OF SEIZURES

A. Seizures and SE are medical emergencies

B. Optimal outcome depends on early interventions

C. Appropriate drugs

D. Dosing based on mg/kg requirements

E. Knowledge of new drugs and protocols will allow for advances in seizure care and patient outcomes
XXXI. RECOMMENDATIONS: EMERGENCY MANAGEMENT OF SEIZURES

A. Be aggressive with this neurologic emergency

B. Develop a specific plan for treatment of SE

C. Educate providers of healthcare regarding optimal treatment strategies

D. Conduct research to improve EMS and ED care
CVA AND SEIZURES

PEARLS

CVA

1. 50% of TIAs go on to CVAs in five years.

2. Gaze is TOWARD the affected side in intracerebral lesions and AWAY from the affected side in brain stem abnormalities.

3. Cerebellar hematomas require immediate neurosurgical evaluation.

4. Pontine hemorrhages result in pinpoint pupils.

5. Anterior cerebral artery infarct produces weakness in the contralateral leg more than arms and face.

6. Middle cerebral artery infarct (the most common infarct) produces weakness in the contralateral arm and face more than the leg.

7. TIAs last less than 24 hours.

8. The easiest way to lower the intracranial pressure is to put the head on the bed at 45 degrees.

9. TPA must be administered within 3 hours of the ONSET of symptoms when treating an ischemic stroke.

10. The dose for TPA for ischemic stroke (0.9 mg/kg, max 90 mg) is different from that used to treat a myocardial infarction.

Seizures

1. SE mortality exceeds 30% when seizures occur for longer than 60 minutes.

2. SE occurs when there is a seizure of greater than 10 minutes duration or two seizures without a lucid interval.

3. CNS neuron injury can occur even if the systemic effects of seizures (fever, motor activity, hypertension) are controlled.

4. Mental status changes should begin to resolve within 20-30 minutes of a seizure. Failure of the mental status changes to begin to resolve within
this time period suggests subtle SE.

5. Subtle SE is electrical SE without the associated motor activity. It is a late manifestation of prolonged SE and is associated with a high mortality.

6. Subtle SE can only be diagnosed by EEG monitoring. EEG monitoring should be considered with prolonged altered mental status, after neuromuscular paralysis, and with pentobarbital coma or general anesthesia.

7. All first line therapies for seizures are about 80% effective when used quickly in appropriate doses (based on mg/kg dosing).

8. Seizures caused by INH overdoses must be treated with pyridoxine in order for control to be achieved by standard seizure therapies.

9. Alcohol withdrawal seizures are best controlled and prevented with lorazepam.

10. Seizures associated with eclampsia are best treated and prevented with magnesium sulfate.

11. Greater than 50% of psychogenic seizure patients will have at least one neurogenic seizure, such that therapy should only be withheld if the diagnosis of psychogenic seizures is confirmed clinically.

12. When IV access is not available, rectal diazepam, IM midazolam and IM fosphenytoin all can be used to control seizures.
SUGGESTED READINGS


OTHER REFERENCES


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