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Seizure and It's Management in Various Clinical Conditions - beyond Controversy

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Abstract

Seizures are the second most common neurological complications in critically ill patients in ICU. For new onset seizures in critically ill patients the internist should consider more specific etiologies & therapeutic interventions which should be cost effective & time bound.

A more selective strategy for acute management of seizure in different medical disease patients should be implemented by understanding the pharmacokinetic & pharmacodynamics of drugs in different disease milieu. Patients in ICU having discrete symptomatic seizure or even status epilepticus at times require multidisciplinary approach to treat the underlying preexisting or undiagnosed disease entity as well as its short & long term complications. It is essential to elevate the expertise of both internists & neurologists in area of seizure evaluation & treatment so as to effectively treat it within the context of that particular disease. The advent of newer Antiepileptic drugs with better Kinetic profile & safety at time helps to treat these seriously ill patients with so much co-morbid conditions more efficaciously.

Introduction

An epileptic seizure may be defined as a discrete spontaneous alteration in behavior or a subjective occurring due to an abnormal hypersynchronous excessive discharge of a collection of neurons within the brain. Although seizures may complicate a variety of chronic medical illnesses,

seizures are seen most commonly in patients who are critically ill. Such seizures are often provoked situation-related seizures and occur in patients who do not have epilepsy (defined as recurrent unprovoked seizures). These provoked seizures are also referred to as acute symptomatic seizures. The proper evaluation of acute symptomatic seizures is critical in guiding management, optimizing neurologic outcome, and often avoiding unnecessary long-term treatment with inappropriate and sometimes toxic therapy with anticonvulsant medications.

Acute symptomatic seizures occur in close temporal relationship to a systemic or neurological insult, and occur as an indirect or direct consequence of this insult **(Table 1)**.

Seizures are categorized into generalized and focal (or partial) types depending on whether they arise deep within thalamocortical circuits, or whether they arise from a specific site (or focus) within the brain, respectively. A partial seizure may evolve into a tonic-clonic convulsion, a process referred to as secondary generalization. Most tonic-clonic convulsions occurring in adults happen as a result of this secondary generalization from an abnormal focus. The management of acute symptomatic seizures involves stabilization of the patient, short-term use of appropriate anticonvulsant drugs such as benzo-diazepines and phenytoin, and correction of the underlying cause or causes. If these underlying factors can be corrected, then long-term use of anticonvulsant medication is usually not indicated.

Seizure in Patients with Cardiovascular Disease

Several anticonvulsants have potential cardiovascular side effects and should be used with caution in patients with known cardiac disease. Phenytoin has the potential to cause hypotension and cardiac arrhythmias, primarily in the setting of rapid, intravenous (IV) infusion. In patients with known heart disease, infusions of phenytoin should not exceed 25 mg/min, rather than the usual recommended maximum rate of 50 mg/min. Symptoms of hypotension, bradyarrhythmias, and transient chest pain can be reversed by slowing or discontinuing the infusion. Some of the cardiovascular side effects are caused by the propylene glycol solvent used in IV phenytoin preparations. The prodrugfosphenytoin(which does not contain propylene glycol) should be the form of choice in patients with significant cardiac disease. IV infusions with phenytoin should be accompanied by continuous electrocardiogram (EKG) and blood pressure (BP) monitoring in all patients. Carbamazepine is a well-documented pro-arrhythmic agent and should be avoided in patients with cardiac disease. It has been shown to exacerbate known conduction abnormalities, as well as causing de novo arrhythmias in elderly patients. Bradyarrhythmias, Stokes-Adams attacks, aggravation of sick sinus syndrome, or atrioventricular block with resultant congestive heart failure have all been described. Phenobarbital carries a significant risk of hypotension with IV loading. Rapid dosing should be avoided in patients with limited cardiac reserve.

Recommendations

Although fosphenytoin may be used with caution when rapid loading is required, IV valproic acid carries less risk of arrhythmia or hypotension.

When rapid loading is not required, current information indicates that newer agents such as topiramate or lamotrigine or levetiracatem can be initiated safely in this population.

Seizure in Patients with Hepatic Disease

Hepatic disease will change the biotransformation and disposition of most of the commonly used anticonvulsants. Decreased hepatic blood flow and compromised hepatocyte function will alter drug metabolism. Alterations in serum protein levels will alter protein binding and levels of circulating free drug. Direct hepatotoxic effects of anticonvulsants are rare, although more common with valproic acid than any other. Phenytoin protein binding correlates with serum albumin and total bilirubin levels, therefore, low albumin and bilirubin levels in combination with decreased biotransformation can result in high concentration of circulating drug, with a large unbound fraction. Careful monitoring of free phenytoin levels (target range, 1-2 mg/L) will help to avoid intoxication. Valproic acid is generally contraindicated in the setting of hepatic failure because of direct hepatotoxicity and risks of fulminant hepatic failure. Hyperammonemia may also be enhanced by valproate, particularly when it is used in combination with other anticonvulsants. The drug should be used with extreme caution in patients with compromised hepatic function and is best avoided, especially if other anticonvulsants may be used concurrently. Phenobarbital is subject to fewer kinetic alterations with liver dysfunction than is phenytoin or valproate.

Recommendations

When acute therapeutic levels must be achieved, phenobarbital may be used, with careful monitoring of serum levels. Benzodiazepines may also be used acutely. Oxazepam, a short-acting benzodiazepine, may have less potential problems because of its limited oxidative metabolism and may be preferred to diazepams or lorazepam. Gabapentin and levetiracetam have profiles that uniquely suit them for use in this setting. Neither these drugs have significant hepatic metabolism, nor is significantly protein-bound, and both are excreted renally. Both would be useful when rapid loading is not required.

Seizure in Patients with Renal Disease

Renal dysfunction will increase circulating levels of most anticonvulsants and their metabolites. In addition, uremia can significantly alter protein binding characteristics, with resultant increases in free drug fractions. Phenytoin has decreased protein binding in uremic patients. Free drug fractions can increase from 10% to 30% of total, without changes in total measured serum levels.Phenobarbital has significant accumulation in uremic patients, as elimination depends primarily on renal function.Valproic acid has decreased protein binding in uremic patients, correlating with the degree of renal dysfunction. As it is primarily excreted by the liver, little is accumulated in renal failure. An increased incidence of valproate-induced pancreatitis has been described in patients with advanced renal failure. As with all patients receiving this drug, serum amylase should be measured if abdominal pain or excessive nausea occurs. Newer anticonvulsants, lamotrigine, topiramate, tiagabine, levetiracetam, and zonisamide are all completely or partially excreted renally. All may be expected to have accumulation and prolonged half-lives with renal failure.

Recommendations

Valproate, carbamazepine, and oxcarbazepine have the least potential for toxicity in renal failure. Patients on valproate should be monitored for pancreatitis via serum amylase. Free phenytoin levels should be monitored when used in uremic patients. Gabapentin, levetiracetam, and phenobarbital carry

risks of significant accumulation with renal dysfunction. Topiramate should be used with caution in patients with renal dysfunction. Its action as a weak carbonic anhydrase inhibitor increases the risk of renal calculi. Zonisamide has been associated with a similar risk of calculi, especially in patients with a history of prior stones.

Seizures in Alcoholic Patients

The term alcohol-related seizures (ARS) has been adopted in recognition of the multifactorial origin of seizures in the setting of acute and chronic alcoholism. A variety of etiologies for seizures related to alcohol exist, the most frequent being the partial or absolute withdrawal of alcohol following a period of heavy use. In addition, seizures may be caused by acute head trauma or alcohol-related toxic-metabolic disorders,like Hypoglycemia, Hyponatremia, Hypomagnesemia&Hypocalcemia, CNS infections, Subdural hematoma, CVA & cerebral atrophy and non-compliance with AED.Factors associated with early withdrawal that may contribute to seizures include metabolic disorders such as alkalosis, hypomagnesemia and hypoglycemia.

Recommendations

Patients should also receive 100 mg of thiamine, particularly if receiving 5% dextrose and normal saline, to prevent Wernicke-Korsakoff syndrome. The addition of multivitamins and 2 g of magnesium to the first liter of intravenous fluids is probably warranted in chronic alcoholics.

Numerous pharmaceutical agents have been used to treat seizures related to alcohol. The ideal agent should have properties that effectively manage all aspects of the spectrum of acute alcohol withdrawal syndrome. Treatment is directed at terminating current seizure activity while simultaneously preventing recurrent episodes. Lorazepam is an ideal agent to use because it has minimal depressant effects on respiration and circulation, has a shorter half-life than diazepam, and has no active metabolites. Because lorazepam is distributed in tissue less rapidly and less extensively than is diazepam, its ability to control seizures is prolonged. Phenytoin has also been shown to be ineffective in preventing recurrent seizures. Patients with ARSs without coexisting structural abnormalities or preexisting epilepsy do not require long term anticonvulsant therapy.

Seizures in Dyselectrolemias

In critically ill patients, the finding of an electrolyte imbalance in the setting of new-onset seizure activity should not preclude a search for other potential causes of seizures.

Sodium Imbalance

Abnormalities of serum sodium typically produce central, rather than peripheral, neurological manifestations. Because the brain has considerable ability to adapt to changes in serum osmolality, the propensity of hyponatremia or hypernatremia to produce neurologic symptoms typically depends on the rapidity with which the serum sodium abnormality develops. In the setting of hyponatremia, neurological symptoms, including seizures, usually manifest when serum sodium has fallen quickly below 120 mmol/L. Shivering, myoclonic jerks, and periodic decorticate posturing can be misinterpreted as seizure activity in ICU patients. Carbamazepine and oxcarbazepine are anticonvulsants that can also cause hyponatremic seizures. Serum sodium levels should be measured in epileptics on these anticonvulsants if "break-through" seizures occur. Seizures in a patient with hyponatremia should be managed in the same manner as with any

other patient with a new-onset seizure. Treatment of the hyponatremia is usually dependent on removing the factors producing the hyponatremia. One word of caution, central pontinemyelinolysis (osmotic demyelination syndrome) may occur if hyponatremia is corrected too rapidly, particularly if the hyponatremia has been chronic.

Magnesium Imbalance

Hypomagnesemia is conventionally defined as serum levels of magnesium less than 1.2 meq/L. In hypomagnesemia auditory and tactile stimuli can precipitate neurologic symptoms and seizures. Among hospitalized patients, the incidence of hypomagnesemia is as high as 10%. For rapid replacement, IV Magnesium sulfate is the agent of choice and is ideally delivered using infusion pump. In the adult, an initial dose of 4 g Magnesium sulfate is given at the rate not exceeding 1 g/min. If convulsions persist, another 2 g of magnesium sulfate can be given after 15 min. During magnesium administration, urine output should be carefully monitored.

Potassium Imbalance

Hypokalemia and hyperkalemia rarely affect the CNS. Although hypokalemia may occasionally be associated with seizures, this usually reflects coexisting undetected hypomagnesemia. Hypokalemia refractory to potassium repletion is often the consequence of decreased magnesium tissue stores and is not correctable until the magnesium deficit is addressed.

Calcium Imbalance

Symptomatic hypocalcemia is correlated with serum-ionized calcium concentrations (true hypocalcemia). Ionized serum calcium is related to serum protein concentration and pH. In severehypocalcemia associated with seizures, the treatment should include IV calcium chloride or calcium gluconate in addition to IV anticonvulsants. Management of symptomatic hypocalcemia can be treated with slow IV bolus of 15 ml of 10% calcium gluconate solution followed by a slow IV infusion (10 ml/h) of 10% calcium gluconate solution.

Medication-Associated Seizures (Iatrogenic Seizures)

Medication-associated seizures are an uncommon but important complication of medical therapy. Most of the drug induced seizures are typically brief generalised tonic-clonic convulsions as a result of intrinsic epileptogenicity of medication or as an indirect effect **(Table 2)**. Clinicians of all disciplines will care for patients at risk for this dramatic medication toxicity. A working knowledge of the high risk medications will enable clinicians to choose safer medicines for patients at risk of seizures.

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Table 1: Causes of Seizure in Critically Ill Patients

• Cerebrovascular disease Thombosis Embolism Hemorrhage Vasculitis • Cerebral infection Meningitis Encephalitis Abscess • Hypoxic-ischaemic encephalopathy • Hypotensive syndromes (shock, Stokes-Adams attacks, vasodepressor syncope) • Hypertensive encephalopathy • Autoimmune encephalitis • Eclampsia • Fever or Hyperpyrexia • Metabolic Hypoglycemia Hyponatremia/hypernatremia Hypocalcemia	Metabolic (*cont.*) Hypomagnesemia Alkalosis • Organ Failure Hepatic failure Renal failure • Endocrine Hypothyroidism Thyrotoxicosis • Vitamin deficiency (e.g., pyridoxine deficiency) • Drugs- Therapeutic (e.g., penicillins, imepenem, isoniazid, phenothiazines, meperidine, theophylline, cyclosporine, etc.) • Alcohol withdrawal • Sedative drug withdrawal • Environmental toxins (e.g., lead, mercury, arsenic, strychnine, thallium) • Idiopathic

Table 2: Iatrogenic Drugs in Therapeutic use

Moderate Risk	Intermediate Risk	Low Risk
Chlorpromazine	Theophylline	Flouroquinolones
Clozapine	Isoniazid	Antiviral drugs
Maprotiline	□-Lactam antibiotics	□-blockers
Clomipramine	Cyclic antidepressants (except clomipramine and maprotiline)	Local anesthetics (Lidocaine)
Bupropion	Antipsychotic agents (except chlorpromazine and clozapine)	SSRIs
Meperidine	Contract agents	MAO inhibitors
Flumazenil	Tramadol	