Generalized Convulsive Status Epilepticus

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Generalized convulsive status epilepticus (GCSE) is the most common form of status epilepticus and affects about 14,000 people annually in the UK. It is a medical emergency and failure to recognize and treat it effectively results in major morbidity and mortality. It is traditionally defined as continuous seizure activity lasting 30 minutes or intermittent seizure activity lasting 30 minutes during which consciousness is not regained.

Clinical features: GCSE is usually diagnosed easily by observation alone and is characterized by unconsciousness, tonic-clonic muscle activity, tongue biting and urinary incontinence. However, as the duration of seizure activity increases, clinical signs of abnormal muscular activity may become subtle (e.g. restricted to minor twitching of the fingers or eyelids). There is seldom doubt about the diagnosis, but other conditions that should be considered include rigors due to sepsis, myoclonic jerking, generalized dystonia and pseudostatus epilepticus.

Aetiology: determining the aetiology of GCSE is of fundamental importance and may be divided into acute and chronic processes (Figure 1). In 50% of cases of GCSE presenting to non-specialized centres, status epilepticus is the first manifestation of epilepsy. The aetiology also affects the prognosis of GCSE.

Pathophysiology: two distinct phases with specific neurophysiological changes occur during the progression of GCSE. In phase I, the increased metabolic requirements of abnormally discharging neurons are adequately met. The increased cerebral activity results in a coupled increase in cerebral blood flow and an increase in autonomic activity. The latter results in tachycardia, hypertension and an increase in blood glucose levels. After about 30 minutes of seizure activity, the compensatory mechanisms that have maintained adequate cerebral perfusion begin to fail. This stage (phase II) is characterized by a failure of cerebral autoregulation, a rise in intracranial pressure, systemic hypotension, hypoglycaemia and a rise in systemic and intracranial lactate levels. When this occurs, cerebral oxygen requirements exceed supply and electromechanical dissociation occurs in which cerebral seizure activity may be accompanied by minimal visible muscular twitching.

The disruption of normal cerebral physiology is further compounded by many of the systemic derangements that are seen during GCSE. These include CNS pathology (cerebral anoxia, haemorrhage, oedema, hippocampal damage, cerebral venous thrombosis), respiratory system pathology (respiratory failure, pneumonia, pulmonary hypertension, pulmonary oedema, pulmonary embolus), cardiovascular system pathology (arrhythmias, hyper/hypotension, myocardial infarction, cardiac arrest), metabolic disorders (electrolyte imbalance, metabolic acidosis, hyperpyrexia, renal and hepatic failure, acute pancreatitis) and other complications (rhabdomyolysis, fractures, sepsis syndromes, disseminated intravascular coagulation).

Management

GCSE requires decisive and rapid treatment. The longer GCSE continues, the greater the likelihood of neuronal damage, systemic complications, unresponsiveness to treatment and the development of chronic epilepsy. The mortality of GCSE is also related to its duration. Management falls into three categories that need to be instituted simultaneously:

- emergency medical management
- identification and investigation of aetiological factors that have precipitated status epilepticus
- drug treatment of the seizures.

Emergency medical management

Monitoring of ECG, blood pressure and pulse oximetry should be started immediately. Generally, patients in GCSE require early tracheal intubation and mechanical ventilation to protect the airway from aspiration of gastric contents and to ensure adequate ventilation and oxygenation while seizures are being controlled. A rapid sequence induction of anaesthesia should be performed using thiopental (thiopentone) or propofol followed...
by suxamethonium. Before induction, intravenous access is often required to allow fluid resuscitation. The administration of fluids is often all that is needed to restore normotension, but patients who have experienced prolonged status epilepticus may also require inotropic therapy. Blood pressure should be maintained at normal or supranormal levels to ensure an adequate cerebral perfusion pressure. Following intubation, the use of long-acting non-depolarizing neuromuscular blocking drugs is seldom necessary and obscures the clinical manifestations of continuing seizure activity.

Blood should be taken for determination of electrolytes, full blood count, blood glucose, toxicology screen, liver function tests and arterial blood gas analysis. Patients with pre-existing epilepsy should have their anti-epileptic drug levels measured. A bedside test for glucose should be performed immediately and, if hypoglycaemia is present, 50% glucose, 50 ml, should be given. The theoretical danger of exacerbating cerebral ischaemia by an increased blood glucose level is outweighed by the correction of hypoglycaemia. If there is evidence of alcoholism or malnutrition, intravenous thiamine, 100 mg, should be given before administration of glucose to avoid precipitating Wernicke’s encephalopathy.

Metabolic acidosis is common during uncontrolled status epilepticus, but acid–base balance is usually restored with control of seizures and with adequate resuscitation. There is experimental evidence that acidosis in GCSE may be neuroprotective.

High temperatures may occur in status epilepticus due to the increased muscle activity and may exacerbate or prolong seizure activity. Where possible, normal body temperature should be maintained using surface cooling and antipyretic agents.

Identification and investigation of aetiological factors

A careful history often provides a clue to the aetiology of the status epilepticus (e.g. a known epileptic who has failed to take his medication, an alcoholic who has been on a binge, a patient with a previously diagnosed cerebral tumour). Similarly, a general and neurological examination of the patient often reveals a systemic or neurological cause of the seizures. Further investigations (e.g. CT, MRI, examination of CSF, blood cultures) may be required.

Drug treatment of seizures

Drug treatment of seizures must be instituted early and should proceed during resuscitation. All anti-epileptic drugs used in the treatment of status epilepticus are sedative and their effect on the conscious level of the patient needs to be monitored closely. There have been few well-conducted trials of the optimum treatment for GCSE, however, Figure 2 shows a widely used and accepted regimen.

Benzodiazepines act by enhancing γ-aminobutyric acid (GABA)-mediated inhibition in the CNS by increasing chloride conductance at the post-synaptic ligand-gated GABA_A receptor. Lorazepam, 0.1 mg/kg i.v., is the benzodiazepine of choice in GCSE. Although it is less lipophilic than diazepam, it terminates seizures as rapidly as the latter. Its main advantage is its long duration of action (over 12 hours) and it is often effective as the sole agent in terminating GCSE. In contrast, diazepam has a short duration of action due to rapid redistribution to body fat stores and is less effective than lorazepam.
Hydantoins (phenytoin and fosphenytoin): if seizures continue following administration of lorazepam, phenytoin, 20 mg/kg i.v., is the drug of choice as a second-line treatment. It acts by blocking neuronal sodium channels and inhibiting repetitive firing of neurons. The range of normal therapeutic plasma levels is 40–80 µg/litre.

Phenytoin should be given only via a large vein, because of its high alkalinity. It should be made up in saline and concurrent administration of other drugs should be avoided because of the risk of precipitation. The maximum rate of infusion is 50 mg/minute, but even lower rates carry the risk of hypotension and arrhythmias. Meticulous monitoring of ECG and blood pressure is mandatory.

Fosphenytoin is a recently introduced water-soluble prodrug of phenytoin and its dose is expressed in ‘phenytoin equivalence’ (75 mg of fosphenytoin is labelled ‘50 mg phenytoin equivalent’). Its main advantage over phenytoin is that it can be administered more rapidly. However, serious cardiovascular sequelae may occur and careful monitoring during and after administration is vital.

Phenobarbital (phenobarbitone): if seizures persist despite adequate plasma levels of phenytoin, phenobarbital (phenobarbitone), 10–20 mg/kg i.v., should be given. This barbiturate acts on a receptor site associated with GABA chloride channels. Its main side-effects include excessive sedation, respiratory depression and hypotension.

General anaesthesia: refractory status epilepticus that has not responded to hydantoin and/or phenobarbitone requires general anaesthesia using either thiopental (thiopentone) or propofol. This should be carried out in a specialist unit where the anaesthetic agents can be titrated against continuous EEG monitoring. Most authorities aim for a burst suppression pattern on EEG though evidence that outcome is improved is sparse. Optimum levels of phenytoin and phenobarbitone (phenobarbitone) should be maintained during this period. Patients are intermittently woken while being monitored for evidence of clinical or electroencephalographic seizures.

Prognosis

Adult GCSE carries an overall mortality of about 25%. Over 85% of those who die do so as a result of the aetiology of the status epilepticus; only about 2% of deaths are due to the GCSE itself. The aetiology also determines outcome; 90% of patients with status epilepticus secondary to drug withdrawal have a good outcome compared with only 30% of patients with status epilepticus due to stroke. Duration of seizures is also an important factor; GCSE lasting over 1 hour has a mortality of 35% while seizures lasting less than 30 minutes have a mortality of 3.7%.

FURTHER READING