STATUS EPILEPTICUS IN THE GENERAL ICU

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Seizures account for about 5% of general ICU admissions in the US.[1] Many risk factors emerged from the population-based study in Richmond VA.[2] SE lasting longer than 60 minutes carried a mortality of 32%; compared with 2.7% for a shorter duration. SE caused by anoxia was associated with 70% mortality in adults but less than 10% in children. The commonest cause of SE in adults was stroke, followed by withdrawal from antiseizure agents; cryptogenic SE; and that related to alcohol withdrawal, anoxia, and metabolic disorders. Systemic infection was the commonest cause of childhood SE, followed by congenital anomalies, anoxia, metabolic problems, antiseizure drug withdrawal, CNS infections, and trauma. Clusters of seizures in patients with intractable partial epilepsy appears to place these patients at increased risk for SE.[3] Other patients who may be at risk for SE, in whom either underlying disease or treatment may render recognition of difficult, include patients with severe head trauma.

Mitchell notes that four groups represent most treated episodes of SE in children: atypical febrile seizures presenting as SE; acute conditions including meningitis, encephalitis, trauma, tumors, and stroke; idiopathic or remote symptomatic epilepsy; and degenerative or progressive neurologic conditions.[4] Intoxication and recreational drug withdrawal are relatively uncommon causes of SE in children relative to adults. Lacroix reported that over a 10-year period in a PICU, SE accounted for 1.6% of all admissions. Fifty-one percent of cases of SE were in children less than 2 years of age, and the mortality rate for all cases of SE was 6% while in the ICU and 9% at one year.[5] The most common etiologies of SE in this study were underlying epilepsy (32%), atypical febrile convulsion (13.6%), purulent meningitis (13%), and encephalitis (13%). Other specified causes included intoxication, tumor, recent anoxic encephalopathy, systemic hypertensive crisis, and acute or chronic metabolic abnormalities (1.3-5%). The average length of ICU stay was 3.1 +/- 3.6 days. Cat-scratch disease has emerged as an important cause of SE in children.

Recent guidelines for SE treatment are available but are too lengthy to summarize here.[6,7] Pentobarbital and thiopental are usually reserved for refractory SE. While these drugs are effective in large enough doses, side effects may limit their utility[8] and are occasionally fatal.[9] However, they are important when other modalities fail. Propofol is effective in refractory SE, but has not been directly compared with other compounds.[10] It may offer a lower risk of ventilatory depression and more rapid awakening when the drug is discontinued. One study suggested a dosage range of 1 – 15 mg/kg/hr.[11] Early fears of a possible proconvulsant effect appear to be unfounded, although withdrawal convulsions may occur if the drug is abruptly terminated. The appropriate role of propofol in pediatric SE remains to be determined.

We reviewed our experience with propofol and midazolam in refractory SE, and discovered that there was a considerable difference in mortality for patients with APACHE II scores ≥ 20 (17% mortality with midazolam vs. 56% for propofol).[12] For this reason, we have returned to midazolam as our initial agent for refractory SE. Mayer's group recently reported on their experience with midazolam.[13]

Ketamine, an NMDA antagonist, is emerging as a potentially useful agent for refractory SE.[14,15] A loading dose of 2 mg/kg, followed by an infusion of 10 – 50 μg/kg/min appears to be appropriate, although the available data are limited.

Intravenous valproate has been reported in cases and small series.[1617] The appropriate dose for SE probably varies with the type of SE being treated. Venkataraman and Wheless reported that a 20 – 30 mg/kg loading dose could be safely administered at 3 – 6 mg/kg/min, and yielded serum concentrations between 64-204.1 ug/ml (mean 132.6).[18] One report describes hypotension associated with a 30 mg/kg loading dose.[19] Evidence suggesting its value continues to accrue.[20]

Topiramate may also be a valuable agent, primarily for withdrawing patients from intravenous agents. Up to 1600 mg/day via an enteral tube has been used.[21] Although no intravenous form is available, the next generation of this drug should be available parenterally. Levetiracetam may also be useful, and experience is rapidly accumulating.[22,23, 24,25] Lacosamide is also in use.[26,27,28]

Many other agents have been used successfully,[29] such as inhalational anesthetics[30] and lidocaine.[31] The critical care consultant should be familiar with these, but in my view, it is more important to be able to use a few potent agents quickly and understand them thoroughly than to pick a different drug every time one encounters refractory SE.

As in therapy of adults, the primary concerns in management of SE in children are provision of cardiorespiratory support while achieving rapid control of motor and electrical seizure activity. In the hospital setting, initial pharmacotherapy includes a benzodiazepine for rapid control (lorazepam 0.1 mg/kg IV or PR midazolam 0.05-0.34 mg/kg IV or PR, or diazepam 0.1-0.5 mg/kg IV or PR) followed by a long-acting agent such as phenytoin (20 mg/kg IV), fosphenytoin (20 mg/kg phenytoin equivalents IV), or phenobarbital (10-20 mg/kg IV).[32,33,34]

Management of SE in children usually begins before the admission to the ICU. Many prehospital caregivers now have protocols for administration of benzodiazepines in the field as a means of early initiation of therapy. Dieckmann studied rectal vs. IV diazepam in the prehospital setting for treatment of SE, and found both routes to be effective.[35] No child who received rectal diazepam in this study required endotracheal intubation before arrival in the emergency department, while 2 of 15 who received IV drug required intubation. Convulsions recurred in 60% of children who received IV diazepam, as compared to only 30.8% of those who received rectal drug. Alldredge et al found that prehospital therapy was associated with SE of significantly shorter duration (32 minutes vs. 60 minutes) and less likelihood of recurrent seizures in the emergency department (58% vs. 85%).[36] There were no significant differences between groups in the percentage of SE episodes that required endotracheal intubation or ICU admission, and route of diazepam administration (rectal vs. intravenous) was not significantly associated with SE duration, recurrent seizures in the ED, on subsequent in-hospital management.[37] Lorazepam had fewer side effects than diazepam, and either benzodiazepine was superior to placebo with respect to seizure control and need for ICU admission.

Lorazepam has been compared with diazepam for the acute treatment of seizures and SE in children presenting to the emergency setting.[38] Both drugs stopped convulsions within 20 - 60 seconds in all responders, however more patients who received diazepam required repeated doses (31%) for seizure control compared to 3% of those receiving lorazepam. Eight of 53 patients receiving diazepam required ICU admission because of respiratory depression, while only one patient receiving lorazepam showed respiratory depression and none required ICU admission, possibly due to the lack of need for repeated doses.

Midazolam infusion is gaining acceptance for the treatment of refractory SE in children.[39, 40, 41] Parent and Lowenstein reported achieving a burst-suppression pattern on EEG followed by generalized slowing with infusion rates of 0.3-11 μg/kg/minute in a 26 month boy with seizures after head trauma.[42] Rivera *et al* studied the use of midazolam infusion prospectively in 24 children with SE who were unresponsive to 3 IV doses of 0.3 mg/kg of diazepam, 20 mg/kg of phenytoin, and 20 mg/kg of phenobarbital.[43] Seizures were controlled in all patients after beginning midazolam infusion. The mean effective dose was 2.3 μg/kg/min (range 1-18). There were no clinically significant cardiorespiratory changes attributable to the use of midazolam in their study; of particular interest is that in this group of patients, none required endotracheal intubation or mechanical ventilation. Drug was weaned by 1 μg/kg/min every 15 minutes after a 12-hour period free of relapsing episodes of seizure. Midazolam appears associated with a lower mortality in pediatric SE than other agents, although it is more expensive.[44, 45]

Most reviews of SE in children refer to the use of pentobarbital therapy for treatment of refractory SE. While this approach has frequently been used, it should be recognized that few studies of its use in children have been published.[46] Kinoshita *et al* recently reported experience with a small series of children who achieved a burst-suppression pattern on EEG with dosages of 1.0-3.0 mg/kg/hr.[47] They recommended attempting to taper pentobarbital after 12 hours of sustained burst-suppression to minimize the known attendant risks of hypotension and pneumonia. A recent report suggested electroconvulsive therapy as potentially useful for children with NCSE,[48] but reports of NCSE produced by this treatment,[49] and the theoretical concern that ECT would promote rather than disrupt synchrony, argue against its use in the absence of a clinical trial. However, more emerging cases may change that balance.[50]

Recently, several investigators have reported that central nervous system or systemic autoimmune disorders may cause SE; in some cases, these diseases are paraneoplastic, but in others, they are cryptogenic. Since these patients have usually been described in case reports or small series, the contribution of these disorders to the epidemiology of SE is difficult to assess, but they appear to represent a substantial portion of cases previously termed infectious (since the patients often have a syndrome qualifying as an encephalitis) or cryptogenic. Table 4 lists some of the proven or probably associations of these disorders with SE, but in many cases the connection is suspected based on neuroimaging studies, spinal fluid analysis, or response to immunosuppressive treatments, without demonstrating a specific disease. This list will undoubtedly become much longer in the next few years.

Table. Autoimmune diseases associated with SE

Anti-NMDA receptor limbic encephalitis
Other anti-glutamate receptor limbic encephalitides
Other anti-neuronal antibody syndromes with limbic encephalitis
Paraneoplastic limbic encephalitis without a demonstrable antibody
Limbic encephalitis following various systemic viral infections
Limbic encephalitis following various vaccines
Limbic encephalitis associated with drug hypersensitivity reactions
Hashimoto's encephalopathy (autoimmune thyroid encephalopathy)
Systemic lupus erythematosus

The recognition of these associations, and the apparently beneficial response of some patients to various immunosuppressive treatments, leads me to conclude that diagnostic studies for patients with SE need to include consideration of these conditions. How extensive such a workup should be is not clear at this time. This also leads to consideration of immunosuppressive treatments, including corticosteroids, intravenous immunoglobulin or plasma exchange, cyclophosphamide, and calcineurin antagonists or other drugs usually employed to prevent transplant rejection. These treatments are rarely specific for a particular autoimmune syndrome, however, and the risks they pose regarding systemic infection must be considered.

As with most other areas of neurology, hypothermia is under investigation.[51] So is the ketogenic diet in adults.[52]

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