Management of agitation and convulsions in hepatic encephalopathy

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Hepatic encephalopathy represents a reversible decrease in neurological function caused by liver disease. Overall incidence of seizures in hepatic encephalopathy varies between 2% and 33%. Non-convulsive status epilepticus may be particularly common in these patients. Psychiatric disturbances manifest as agitation, personality change, delusions, etc. Aims of seizure management include treatment of basic disease, correction of precipitant factors, imaging of head, and choice of a pharmacologically safe agent. It is important to consider non-convulsive status epilepticus and rule it out by an EEG. Absolute data for safety profile of drugs in liver disease is still not clear, as changes of pharmacokinetics make choice of drugs difficult. Free drug concentrations may be higher, making plasma concentration monitoring essential in such circumstances. A single seizure may not require therapy. However, when started, antiepileptic drugs are usually discontinued early. Drugs with sedative effects are best avoided because of a risk of precipitating coma. Phenytoin and gabapentin are relatively preferred drugs; however, monitoring of drug levels is desirable. Management of agitation includes physical restraint and medication. Benzodiazepines are best avoided. Haloperidol is a safer choice in the presence of liver disease. Overall management of neuropsychiatric state aims at management of underlying pathology, the resolution of which leads to improvement in the clinical symptomatology. [Indian J Gastroenterol 2003;22(Suppl 2):S54-S58]

Key words: Anticonvulsant therapy, seizures

Management of neuropsychiatric disturbances in hepatic encephalopathy is difficult and challenging in view of the altered disposition and safety profile of various drugs. This review deals with problems and available options in managing patients with seizures and agitation in presence of hepatic encephalopathy.

Hepatic encephalopathy represents a reversible decrease in neurological function caused by liver disease. This neuropsychiatric state complicates all varieties of liver disease, occurring most notably in patients with portal hypertension.

Psychiatric manifestations of hepatic encephalopathy are variable. They range from an acute psychiatric state manifesting as a paranoid-schizophrenic state or hypomania in acute hepatic encephalopathy to intermittent confusional states for months or years, in the chronic form. The clinical features include agitation, changes in personality, delusions and restlessness. Patient may show anti-social behavior or disturbances in character. Violent behavior is also common.

Seizures in hepatic encephalopathy may represent a manifestation of the clinical syndrome itself or its attendant complications. The frequency of seizures varies from 2% to 33% in various studies. Adams and Foley reported convulsions in one-third of their patients, whereas among 83 patients reported by Plum and Posner, only one convulsed. In a retrospective analysis by Ficker et al., epileptiform abnormalities were observed in 15% of the electroencephalographic (EEG) recordings of patients with hepatic encephalopathy. Overall prognosis in the subgroup with seizures was poorer when compared to other patients. Focal, multifocal, or generalized convulsions can occur, usually late in the course. Common precipitants or causative factors associated with convulsions include hypoglycemia, and electrolyte and acid-base disturbances. Biochemical changes that can provoke seizure activity include abnormalities in cerebral glutamate levels, which is the principal excitatory neurotransmitter in the brain. Glutamate-mediated neurotransmission is altered in neurological disorders including epilepsy and ischemic brain damage, and increased extracellular concentration of glutamate has been documented with worsening encephalopathy in animal models of acute liver failure.

Cerebral edema is another major factor precipitating or potentiating seizures. This is frequently observed in patients with fulminant hepatic failure and has been observed in patients with advanced cirrhosis and encephalopathy. Non-convulsive and clinically subtle status epilepticus may be particularly common in these patients. However, it is a poorly recognized entity. Recognition of this phenomenon is important to prevent cerebral hypoxia and development of cerebral edema.

Frequency of subclinical seizure activity and role of prophylactic phenytoin therapy in patients with acute liver failure and encephalopathy have been recently studied. Subclinical seizure activity was recorded in 3 patients in the phenytoin-treated group and 10 patients in the control group. Postmortem cerebral edema was noted in
22% of the phenytoin-treated versus 70% of the untreated patients. The authors recommended EEG monitoring for subclinical seizure activity in all patients with grade III or IV encephalopathy and consideration for the use of prophylactic phenytoin therapy in such patients.

Management

The cornerstone of management of neuropsychiatric disturbances in hepatic encephalopathy includes the management of underlying liver dysfunction, its toxicemic state and attendant complications. This includes lowering of ammonia levels, and correction of precipitating factors like electrolyte disturbances, hypoxia and hypoglycemia.

Seizure management

Treatment of convulsions in presence of liver disease with or without encephalopathy is centered on managing the underlying liver disease and reducing blood ammonia levels. It is important to promptly recognize and manage seizures, in order to prevent anoxia and exacerbation of brain damage. It is prudent to rule out a structural lesion by performing imaging studies. A solitary seizure precipitated by a specific recognizable metabolic derangement may not require antiepileptic drug therapy. However, frequent assessment of metabolic factors is needed and where chances of recurrent convulsions is higher, appropriate antiepileptic drug (AED) therapy can be instituted. Recurrent seizures need AED therapy, which can be withdrawn once the underlying disease is controlled. Long-term therapy is not required unless preexisting cerebral damage is present. Drugs with sedative effects should be avoided because of tendency to precipitate coma. Antiepileptics may themselves induce further organ dysfunction, complicating or contradicting their further use. Non-convulsive status epilepticus should be strongly considered in appropriate setting and ruled out by an EEG.

Liver disease and anti-epileptic drugs

Data and guidelines for safety of drugs in presence of liver disease are still unclear. Alterations in pharmacokinetics and pharmacodynamics of drugs in presence of liver damage make choice of anticonvulsant, its dosage and monitoring difficult. As degree of debility and response to AED varies significantly among patients, specific rules cannot be inferred and practical guidelines can only be offered. Therefore it is advisable that clinical monitoring as well as drug level assessment are frequently done in such a setting.

Being the primary site of drug metabolism, hepatic insufficiency can significantly alter biotransformation and disposition of drugs. Hepatic blood inflow through the portal vein, hepatocellular mass and functional capacity determine the effects of liver disease on drug handling. Table 1 highlights some of the changes seen in major disease states.

At least five categories of liver disease affect drug disposition. These include (a) chronic liver disease, (b) acute hepatitis, (c) drug-induced hepatotoxicity, (d) cholestasis, and (e) hepatic infiltrative / neoplastic disease. Patients with hepatic failure may have normal serum albumin but low drug protein-binding ability, leading to higher free drug concentrations. In addition, medication must be classified not only by protein binding but also by the capacity of the liver to extract the drug as blood flows through it.

Two major categories of drugs can thus be recognized: (i) flow-limited and (ii) capacity-limited with high protein binding. Flow-limited drugs have higher extraction ratios as their metabolism is dependent on the amount of drug presented to the liver, which is proportional to blood flow. Most anticonvulsants are capacity-limited drugs, as their extraction ratios are low. Capacity-limited, binding-sensitive drugs like phenytoin, valproic acid, and carbamazepine are highly protein bound. Therefore, alteration in plasma protein concentration and binding characteristics can significantly alter hepatic clearance.

For drugs with low protein binding, clearance is less affected with changes in protein binding. Type and duration of liver disease alters intrinsic clearance. Therefore, the effects of changes in protein binding in capacity-limited, binding-sensitive drugs are complex. Increased free fraction in presence of low protein binding may eventually lead to a reduced total drug concentration when clearance is normal. Where clearance is lowered, drug concentrations may rise, causing toxic effects at lower than expected drug levels.

Because of various types of drugs and stages of liver disease, as well as interindividual variation, predicting changes in drug kinetics in patients with hepatic dysfunction remains a difficult problem. Choice of a specific antiepileptic drug in presence of significant liver disease is thus difficult and factors like drug metabolism, disposition, tendency to accumulate, and risk of sedation are extremely important considerations before choosing the drug.

Table 1: Pathophysiologic changes in various types of liver disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Hepatic blood flow</th>
<th>Hepatocyte function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>⤴</td>
<td>⤴</td>
</tr>
<tr>
<td>Moderate</td>
<td>⤵</td>
<td>⤴</td>
</tr>
<tr>
<td>Severe</td>
<td>⤵</td>
<td>⤵</td>
</tr>
<tr>
<td>Acute inflammatory disease</td>
<td>⤵</td>
<td>⤵</td>
</tr>
<tr>
<td>Viral hepatitis</td>
<td>⤵</td>
<td>⤵</td>
</tr>
<tr>
<td>Alcoholic hepatitis</td>
<td>⤵</td>
<td>⤵</td>
</tr>
</tbody>
</table>

1 Decreased; 2 unchanged; 3 increased; 4 depends on the severity of liver disease.
Table 2: Disposition of common antiepileptic drugs in liver disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Protein binding</th>
<th>Total plasma concentration</th>
<th>Plasma half life</th>
<th>Risk of intoxication</th>
<th>Dosage adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>↓</td>
<td>↓</td>
<td>-</td>
<td>Considerable</td>
<td>UN or slight ↓</td>
</tr>
<tr>
<td>Valproate</td>
<td>↓</td>
<td>↓</td>
<td>-</td>
<td>Considerable</td>
<td>UN or slight ↓</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Unknown</td>
<td>-</td>
<td>↑</td>
<td>Considerable</td>
<td>UN or slight ↓</td>
</tr>
<tr>
<td>Primidone</td>
<td>Unknown</td>
<td>-</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>↓</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Considerable</td>
<td>Unknown</td>
</tr>
<tr>
<td>Benzodiazepines*</td>
<td>↓</td>
<td></td>
<td>↑</td>
<td>High</td>
<td>Reduction</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Low</td>
<td>Unnecessary</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Unknown</td>
<td>Reduction</td>
</tr>
<tr>
<td>Felbamate</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>C/1</td>
<td>C/1</td>
</tr>
</tbody>
</table>

* Except oxazepam, which shows no evidence of altered disposition in various liver diseases; UN: unnecessary; ↓ decreased; ↑ increased; C/1: contraindicated

Phenytoin: It is a highly protein-bound drug (90%), binding chiefly to albumin. Elimination of this drug occurs chiefly through hepatic microsomal biotransformation with less than 5% excreted unchanged in urine. In hepatic insufficiency, presence of low albumin and/or reduced binding capacity may lead to higher drug levels. This is a relatively preferred drug in the management of convulsions in presence of liver dysfunction. Decreased biotransformation capacity in patients with liver disease results in accumulation of the drug and an increased potential for toxicity. Nonlinear kinetics and difficulty in estimating hepatic metabolic capacity limits the ability to predict dose adjustments.

Phenobarbital: It is 40%-60% plasma protein-bound and about 25% of the drug is excreted by renal mechanisms, the rest being metabolized in the liver. Cholestasis does not seem to alter serum levels significantly. It seems to be a potentially useful agent in the presence of liver disease. However, its prolonged half-life, increased sedation and likelihood for precipitating coma are the reasons for its avoidance in presence of encephalopathy especially with underlying cirrhosis. Frequent drug level monitoring is desired in patients who are on therapy with this drug.

Sodium valproate: This drug should be used with extreme caution in the presence of liver disease. Significant accumulation may occur as a result of increased half life. There is a risk of worsening liver function because of its potential for hepatotoxicity. The drug is thus best avoided.

Carbamazepine: The drug is highly protein bound (70%) and is biotransformed in liver by epoxidation and hydroxylation with active epoxide metabolite. It carries a risk of toxicity in presence of significant liver dysfunction. The potential for sedation is also not desirable. Frequent drug level monitoring is advisable.

Benzodiazepines: These are best avoided in presence of hepatic disease especially in encephalopathy because of the risk of precipitating coma. Liver disease can alter the metabolism of these drugs significantly. Of all benzodiazepines, oxazepam is least affected by liver derangement. Midazolam has the advantage of being short-acting but the risk of respiratory embarrassment and precipitating coma are significant.

Gabapentin: This drug is not metabolized, has a low protein binding, and most of the drug is excreted unchanged in the urine. It does not inhibit or induce hepatic enzymes. Thus, it is a highly promising drug for use in presence of liver disease because of its exclusive clearance through kidneys. However, lack of parenteral preparation is a major disadvantage. Current data, however, are not enough to recommend using this drug routinely in patients with liver disease.

Lamotrigine: This is metabolized predominantly by glucuronidation and eliminated renally. However definitive safety for its use in presence of liver disease is still not established. It is important that initiation, titration and dosing should be reduced by approximate 50% in patients with moderate hepatic impairment and 75% in patients with severe hepatic impairment.

Topiramate and vigabatrin demonstrate renal elimination and low protein binding. Although they seem promising, sufficient data regarding their use in presence of liver disease are not presently available.

Suggested guidelines for management of convulsions

(i) Detailed information on the duration, severity, type of liver dysfunction, and recent precipitants must be taken in every patient. History of fever, headache, neck pain, and focal deficits must be recorded, and detailed neurological examination should be performed. Previous history of seizures and type of drug(s) taken should be detailed.

(ii) The primary aim should be to treat underlying liver disease and encephalopathy.

(iii) CT scan, MRI, or EEG should be done as and when necessary, especially in a patient with recurrent focal seizures, focal deficit and worsening sensorium in spite of adequate treatment.

(iv) Phenytoin and gabapentin are relatively safe options for seizure control. Benzodiazepines and sodium valproate are best avoided in presence of hepatic disease.
(v) Drug dosage should be adjusted and reduced to avoid toxicity. Drug levels should be monitored frequently. In patients who are already on AED at the time hepatic disease sets in, dosage modification may become necessary depending on the liver function status; this requires frequent drug level monitoring.

(vi) Convulsive status epilepticus is a medical emergency. The most important factor in managing status in presence of hepatic encephalopathy is to recognize any immediately correctible biochemical factor and stop the perpetuation of seizure cascade. There are no guidelines published in literature for management of status in presence of hepatic encephalopathy. Since the benefits of aborting a status outweigh the risks associated with drug use, the usual protocol may have to be followed. Early status may be aborted by using a benzodiazepine, although at the expense of increasing obtundation and precipitating coma. Considering shorter half life and rapidity of action, midazolam seems a theoretically better choice. Lignocaine, which was previously used as a second-line drug for status epilepticus, could have a theoretically important role in presence of hepatic encephalopathy, as it does not produce sedation. However, the efficacy of bolus injection is short lived. It accumulates in presence of liver dysfunction and also requires cardiac monitoring. Paraformaldehyde might find a small role in early status where facilities of resuscitation are not available. For established status, phenytoin would be a safer option although lower doses are preferred for risks of accumulation. We use phenytoin at lower doses with frequent monitoring of drug levels. For refractory status, it is difficult to say which drug would be safer. Since anesthetic dosages are used, induction of coma is inevitable. Thiopental has the advantage of reducing intracranial tension but has strong pharmacokinetic disadvantages including satable kinetics, strong tendency to accumulate and prolonged recovery from coma.

(vii) Non-convulsive status epilepticus should be strongly considered in appropriate setting and excluded by an EEG. Subclinical seizure activity in a patient is suggested by persisting altered sensorium after last seizure, intermittent surges of hypertension, pupillary changes, and increasing intracranial pressure during monitoring.

It is thus obvious that many interacting factors contribute to a lower threshold of seizures in patients with hepatic encephalopathy. Not all patients have persistent or irreversible processes that lead to recurrent seizures or a need for maintenance AED therapy. Because AED contribute to the potential for drug interactions, side effects, and toxicities in situations already encountered with significant polypharmacy, the decision not to initiate such therapy can be even more important than selecting the best agent, best route of administration and best dose from the growing list of AED.

Management of agitation and other psychiatric manifestations

In general, there are three ways to manage violence, impending violence or agitation.11,23,22 These include: (1) verbal de-escalation, (2) medication, and (3) physical restraint. However, with gross organic dysfunction as in hepatic encephalopathy, the patient is less likely to respond to verbal interventions. Hence the physician has the options of restraint and emergency medication.

Indications for the use of physical restraints include: (a) control of violent behavior, unmanageable by medications or other interventions, and (b) marked agitation in a patient whose physical condition limits the use of antipsychotic medication.22 Physical restraints can also be used temporarily before the medication takes effect, if it is ineffective, or if the patient has contraindications to available psychotherapeutic measures. The mainstay of treatment of agitation in hepatic encephalopathy remains pharmacological.

Dopamine receptor antagonists22,23 are used to treat patients who are severely agitated. Haloperidol may be a good choice in presence of liver disease, as no convincing evidence indicates that non-phenothiazine dopamine receptor antagonists can produce hepatic side effects like cholestatic jaundice. However, the lowest possible dose should be used and a close monitoring is desired. Although metabolized in liver, its effectiveness in low doses and less marked effect on the level of consciousness and cognition make it a safer option. Haloperidol is relatively safe in seriously ill patients. The potency of intravenous doses is twice that of the oral doses. The starting doses should be 0.25 mg twice or thrice a day with further increments as required.

Parenterally administered droperidol21,22,24 is also used to treat acutely agitated and confused patients. It is more sedating, but has a faster onset of action and fewer extrapyramidal complications as compared to haloperidol. Newer drugs like clozapine and risperidone have been used in delirious states. However, there use in presence of liver disease is still not established.

ii) Although benzodiazepines21,23 are good drugs to control agitation, their use is relatively contraindicated in presence of liver disease. However, in special situations like alcohol withdrawal complicating the disease, oxazepam in low doses could be a relatively safe choice.

iii) β-blockers like propranolol22,23 and pindolol have also been used effectively to treat agitation in organic brain syndromes. However, specific use in presence of liver disease is not mentioned although propranolol has
been used in management of portal hypertension with benefit.

Thus, the mainstay of treatment remains the management of the underlying pathology, with the resolution of which the neuropsychiatric manifestations should also resolve.

References

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