A patient with end-stage liver disease for semi-elective surgery

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A 52-year-old male presents to your anesthesia preoperative clinic to be evaluated for upcoming surgery. He is scheduled to have an open low anterior resection for newly diagnosed rectal cancer. The patient has a history of chronic hepatitis C with liver cirrhosis and is currently being worked up to be placed on a liver transplant waiting list. His disease has been complicated by portal hypertension, ascites, intermittent mild encephalopathy and one episode of spontaneous bacterial peritonitis. He had a transjugular intrahepatic portosystemic shunt (TIPS) placed 3 months ago. As part of his transplant workup, a CT scan of his abdomen and a routine colonoscopy revealed a large rectal mass which led to his diagnosis of rectal cancer. A note from his surgeon states that treating his rectal cancer is the last step to him being listed for a liver transplant, and the procedure is required for treatment. His last Model for End-Stage Liver Disease (MELD) score documented was 15.

1. What common problems are associated with end-stage liver disease?
2. What is a MELD score and how is it calculated?
3. What does the MELD score predict?
4. What else do you want to know about this patient?
5. Would you proceed with an elective surgery in a patient with end-stage liver disease?

You interview the patient and obtain his remaining medical history. The patient is obese with a body mass index of 38. He lives a sedentary lifestyle but can care for himself. He has a history of hypertension for which he no longer requires medication, mild chronic obstructive pulmonary disease, and smokes one pack of cigarettes a day for the last 35 years (35 pack years). He has grade 1 esophageal varices. He has had a few episodes of hepatic encephalopathy in the past year requiring hospital admission. He has only had surgery once as a child for a tonsillectomy, and recently had anesthesia for TIPS placement as well as an esophagogastroduodenoscopy and colonoscopy that were uneventful. On physical exam, he is a Mallampati class 2, his heart is regular with no murmur and his lungs are clear bilaterally. His abdomen is full and tympanitic with suspected ascites. Vitals are as follows: T: 97.9, BP: 92/53, P:63, RR: 16, SpO2: 95% on room air. His only medications are a multivitamin, albuterol inhaler PRN, furosemide and lactulose daily

6. What labs would you like to order preoperatively?
7. Does this patient warrant any kind of cardiac workup based on his history and physical exam?

Also noted in his chart is a recent resting transthoracic echocardiogram (TTE) performed during his workup for liver transplant that is read as the following: ejection fraction of 50-55%, no wall motion abnormalities, no valvular disease, a estimated right ventricular systolic pressure of 41mmHg, and mild right to left shunting suggested by agitated saline test.

8. What is the normal cardiovascular pathophysiology of end-stage liver disease?
9. What is your opinion of this patient's resting TTE?

10. What disease states can we screen for with a resting TTE in patients with end-stage liver disease?
11. Would you send the patient for any other testing based on his TTE?

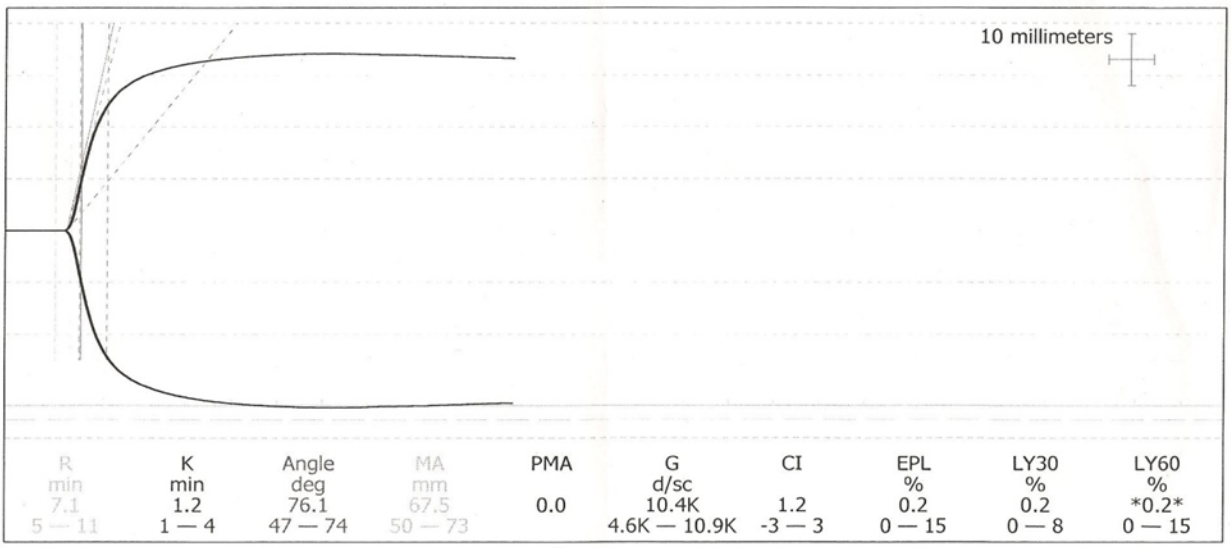
Based on the patient's abnormal resting TTE, you decide to send the patient for a stress test to further evaluate his cardiac function.

12. What are the different types of stress tests available to evaluate patients?
13. What type of stress test would you request for this patient and why?

It is now the day of surgery and you are chosen as the patient's anesthesiologist. You see that the preoperative labs you ordered this morning are as follows: Na: 131 mmol/L, K: 3.5 mmol/L, Cl: 100 mmol/L, carbon dioxide: 22 mmol/L, BUN: 20 mg/dL, Cr: 1.0 mg/dL, Total bilirubin 2.1 mg/dL, albumin 2.7 g/dL, AST 35 U/L, ALT 39 U/L, WBC: 4.3 K/uL, Hgb: 9.7 g/dL, Hct: 29%, Platelets 87 K/uL, INR 2.1.

14. What is the significance of this patient's elevated INR and low platelets?
15. Would you treat the patient with either platelets or FFP preoperatively in an attempt to correct these abnormalities?
16. What other tests can you order to evaluate this patient's overall coagulation status?

You obtain a thromboelastogram (TEG) prior to proceeding with the procedure which is pictured below.



17. What is a TEG and how is it evaluated?
18. How can the INR be 2.1 but the R time be normal?
19. Would you consider an epidural in this patient if his overall coagulation status is normal?

You proceed to the operating room and decide against doing an epidural. Your nurse anesthetist asks you what your anesthetic plan is.

20. What kind of induction would you perform for this patient?
21. What monitors would you use?
22. What kind of intravenous access would you want?

23. What blood products would you order if any?

The case proceeds uneventfully with minimal bleeding and the patient is extubated and brought to the PACU. The surgical team asks you and the acute pain team to follow the patient and make recommendations postoperatively for pain management.

24. What are the physiologic and pharmacologic concerns with drug metabolism in a patient with end-stage liver disease?

Discussion

Patients with end-stage liver disease can be very challenging to manage during the perioperative period. It is well documented that patients with advanced liver disease are at increased risk for perioperative morbidity and mortality (1,2). Specifically, patients with acute viral and alcoholic hepatitis have poor outcomes, and elective surgery remains contraindicated (1,3). Cirrhosis was once thought of as a contraindication to elective surgery as well, but procedures are now being performed more frequently on patients with chronic liver disease than in the past. This shift in practice is influenced by improvements in our understanding of their disease and in their perioperative care. In order to perform anesthesia safely on these patients, it is important to understand how best to evaluate them, and the various aspects of their disease which play a role in the perioperative period.

An anesthesiologist must be able to evaluate how severe a patient's liver disease is prior to taking them to the operating room. Scoring systems used to evaluate liver disease are the same systems used to decide allocation of organs on the liver transplant waiting list. Prior to 2002, the Child-Turcotte-Pugh (CTP) score was used and calculated based on five variables: encephalopathy, ascites, bilirubin, albumin and prothrombin time (5). Scores ranged from 3 to 15 and placed a patient into classes A, B or C, with a higher score or letter designating increased severity of disease. In 2000, the Model for End Stage Liver Disease (MELD) was developed. Similar to the CTP score, it is a clinical scoring system used to predict the severity of liver disease. It was originally shown to predict mortality within three months after placement of a transjugular intrahepatic portosystemic shunt (TIPS) (6). It has now been shown to be predictive of other sequelae, such as postoperative morbidity and mortality as well as risk of gastrointestinal bleed (1). In 2002, MELD was adopted by the United Network for Organ Sharing (UNOS) to more appropriately allocate livers to patients in need. Since its adoption, there has been a significant reduction in mortality while on the waiting list compared to the previously used CTP score (5,7). In January of 2016, the MELD score was replaced by the MELD-Na Score to include serum sodium as a factor in the calculation of the MELD score. This is the current score used by UNOS (https://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/). Hyponatremia is common in patients with cirrhosis and the severity of hyponatremia correlates with the severity of cirrhosis. Serum sodium reflects the vasodilatory state in cirrhosis and predicts waitlist mortality independent of the MELD score. There is a linear increase in mortality of 5% for each mmol decrease in sodium between 125 and 140 mmol/L (8,9). Traditional MELD scores are calculated using three variables: serum creatinine, serum bilirubin and international normalized ratio (INR). The score ranges from 6 to a maximum of 40. It is calculated using the following equation:

MELD= 3.78[Ln serum bilirubin (mg/dL)] + 11.2[Ln INR] + 9.57[Ln serum creatinine (mg/dL)] + 6.43

MELD-Na scores adds serum sodium in mmol/L to the calculation:

MELD-Na = MELD + 1.32 *(137-Na)-[0.033*MELD*(137-Na)]; if Na <125, set to 125 and if >137, set to 137

Any value less than one is given a value of one, and any patient who has been dialyzed twice in the past seven days is given a maximum serum creatinine of 4 mg/dl (5).

In certain situations, patients can have a MELD score that is not indicative of the severity of their liver disease. For example, patients are given MELD exception points for disease states such as

hepatopulmonary syndrome, portopulmonary hypertension or hepatocellular carcinoma where the benefit of early liver transplantation significantly outweighs the risk of waiting until their liver disease progresses. A patient on dialysis or taking warfarin will also have a MELD score not representing the severity of their liver disease secondary to falsely elevated creatinine or INR. Although the MELD score is not perfect, it remains the best option we currently have to select and prioritize patients awaiting liver transplantation.

Advanced liver disease has unique hemodynamic consequences which may present a number of physiologic changes that are of concern to the anesthesiologist. The majority of patients with advanced cirrhosis will develop a hyperdynamic circulation, primarily the result of progressive vasodilation. Classically, these patients will present with a reduction in their systemic vascular resistance and an increase in their cardiac output (10). The reduction in systemic vascular resistance may progress to the point of high output heart failure. In addition, there is a decreased response to vasoconstricting drugs such as phenylephrine. Larger doses of vasopressors are typically required to obtain an effect similar to a patient without liver disease (1). The degree of these hyperdynamic changes correlates with the severity of portal hypertension (11). Much of the pathophysiology of why these physiologic changes occur is very complex and still not completely understood. The main substrate resulting in this vasodilatory state is increased levels of nitric oxide (12). There are several other compounds that have also been shown to play a role such as prostacyclin, endothelium-derived hyperpolarizing factor, carbon monoxide, endocannabinoids, adrenomedullin, tumor necrosis factor alpha and hydrogen sulfide (12). The physiologic changes resulting from these compounds have a significant impact on multiple organ systems, especially the cardiac and pulmonary systems.

It is well known that there is a cardiomyopathy associated with liver disease but its physiology and incidence remain misunderstood by many medical professionals. The term “cirrhotic cardiomyopathy” has been used to describe this type of cardiomyopathy which is completely independent of coronary artery disease (13). It is defined as an intrinsic myocardial abnormality seen in patients with cirrhosis that results in a decreased ventricular response to stress (13). The vasodilatory state of cirrhosis decreases stress on the heart and can mask evidence of cardiomyopathy. This underlying cardiomyopathy may be revealed during periods of increased stress such as surgery, sepsis, or increased preload from a TIPS and can lead to significant heart failure. The pathology of this disease is complex but includes a diminished beta-adrenergic receptor signal transduction, cardiomyocyte cellular plasma membrane dysfunction, and increased levels of cardiodepressant substances (13).

Significant pulmonary physiologic changes also occur in cirrhosis. Hepatopulmonary syndrome and portopulmonary hypertension are two common and potentially severe consequences of cirrhosis. Hepatopulmonary syndrome is defined as hypoxemia in a patient with portal hypertension as a result of pulmonary capillary dilation, resulting in intrapulmonary shunting (1). Many believe the pulmonary capillary dilation occurs from a similar mechanism as the peripheral vascular dilation that occurs in cirrhosis, but much of its pathophysiology is still incompletely understood. It has been estimated to be present in up to 30% of patients with advanced liver disease (1). Diagnosis can be made by the presence of portal hypertension, a PaO_2 <80 mmHg on room air in the sitting position, and with evidence of intrapulmonary shunting, excluding other causes of hypoxemia (1). It may be difficult to diagnose as hypoxemia from other causes is a common finding in advanced liver disease. The classic presentation for a patient with hepatopulmonary syndrome is a patient with platypnea and orthodeoxia (15). Platypnea is dyspnea that is induced by moving a patient into an upright position and relieved with recumbency. Orthodeoxia is worsening of hypoxia when placed in an upright position. These two symptoms occur as a result of pulmonary capillary dilation that is mostly located in the bases of the lungs. Shifting a patient

to an upright position will make the bases of the lungs the dependent portions and therefore result in significantly more shunting. The only definitive treatment of this disease is liver transplantation (15). Prior to transplant, supportive treatment is necessary including supplemental oxygen.

Portopulmonary hypertension is a rare but potentially life-threatening disease in patients with portal hypertension. It is defined as pulmonary hypertension with a mean pulmonary artery pressure >25 mmHg and a pulmonary capillary wedge pressure <15 mmHg in the presence of portal hypertension (16). It has been estimated that up to 6% of patients with portal hypertension will develop this disease (1). If left untreated, 50% of these patients will die within the first year of diagnosis (1). It can present with a wide array of symptoms, with the most common being fatigue and dyspnea, but can range from being asymptomatic to overt right heart failure (16). It is usually screened for on a resting transthoracic echocardiogram which can estimate the systolic pulmonary artery pressure, and then confirmed with a right heart catheterization. Significant portopulmonary hypertension should be evaluated and treated by a pulmonologist familiar with the disease prior to liver transplantation or any elective surgery.

The preoperative workup of a patient with chronic liver disease is controversial, and there are no standardized recommendations. Not only do we need to consider that the patient has liver disease but also recognize the multisystem derangements present. Our case describes a patient with advanced liver disease who is being worked up to be placed on a liver transplant waiting list. According to the 2007 American College of Cardiology/ American Heart Association Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery, this patient would not warrant any further cardiac workup (19). An update was made to these guidelines in 2012 pertaining to liver and kidney transplant candidates recognizing them as being a higher risk cohort (26). The update recommends noninvasive testing if 1-2 risk factors are present and if it will change your management, regardless of functional capacity (26). Therefore, a patient already being evaluated for a liver transplant will likely have had some type of cardiac workup done, with the amount of testing being institution specific.

Typically all patients will have had a resting transthoracic echocardiogram (TTE) and if not, a significant argument can be made for one. A TTE can evaluate not only for cardiac disease and function but also can screen for signs of hepatopulmonary syndrome and portopulmonary hypertension. An agitated saline test can reveal signs of intrapulmonary shunting consistent with hepatopulmonary syndrome; however, this is not diagnostic without hypoxia. An estimation of the systolic pulmonary artery pressure can also be obtained by visualizing the tricuspid regurgitation jet with continuous-wave doppler (17). The right ventricular systolic pressure can be estimated with the use of doppler echocardiography and applying the simplified Bernoulli equation (17). Assuming the pulmonic valve is normal, the right ventricular systolic pressure is equal to the systolic pulmonary artery pressure (17).

The systolic pulmonary artery pressure measurement obtained on TTE is only an estimate and there are many factors which may alter it. Since most TTEs are performed by technicians, the test is only as good as the quality of the images. Suboptimal images or inexperienced technicians can alter the estimate of the systolic pulmonary artery pressure significantly (17). The tricuspid jet must be measured at end expiration in order to be accurate (17). The angle of the tricuspid regurgitation jet and continuous wave doppler beam must be parallel (17). Also of concern is that this method estimates systolic pulmonary artery pressure and traditionally mean pulmonary artery pressure is used to diagnose portopulmonary hypertension. The complete echo exam should be examined for other signs that may suggest pulmonary hypertension, such as decreased right ventricular function or abnormal flow patterns. It is important to realize this is only a screening test and any elevation concerning to the practitioner should be confirmed with a right heart catheterization.

Cirrhotic cardiomyopathy can also be suggested on a resting TTE. It is often picked up as a diminished contractile state and ejection fraction (13). Importantly, a normal ejection fraction in a patient without liver disease may be abnormal in a patient with significant liver disease. If the patient is significantly vasodilated, the heart should appear hyperdynamic with an increased contractile state and increased ejection fraction on TTE. An ejection fraction that was initially 75% but has fallen to 55% as a patient's liver disease has progressed is abnormal and somewhat concerning, but would appear normal if unaware of the patient's liver disease.

Many institutions will perform stress tests on patients being worked up for liver transplantation. A stress test not only screens for coronary artery disease but also can evaluate for cirrhotic cardiomyopathy. Typically when ordering a stress test, the decision of what kind of stress test to be performed is left up to the practitioner who is performing it. There are two main types of stress tests: the exercise stress test and the pharmacologic stress test. Of the pharmacologic stress tests, there are four common agents used: dobutamine, adenosine, dipyridamole (Persantine) and regadenoson (Lexiscan) (18). Each has their own unique advantages and disadvantages. Dobutamine is a beta-1 agonist that stimulates the heart to beat faster and increases contractility, therefore simulating increased stress on the heart (18). The big disadvantage of dobutamine is that it can easily cause arrhythmias and needs to be titrated carefully (18). It also has weak beta-2 activity which may result in worsening of vasodilation in a patient who likely is already significantly vasodilated (18). Adenosine acts by increasing cGMP production and indirectly causes coronary vasodilation, resulting in steal from areas of stenosis that should already be maximally vasodilated (18). Diverting flow away from areas with significant coronary lesions should cause ischemia. Dipyridamole and regadenoson are both derivatives of adenosine. Dipyridamole also increases cGMP production and acts indirectly to cause coronary vasodilation (18). Adenosine and dipyridamole can both exacerbate reactive airway disease and have led to the use of regadenoson (18). Regadenoson acts directly at A2A receptors to cause coronary vasodilation and is safe to use in patients with reactive airway disease (18).

Once the decision has been made to order a stress test, it is important to be aware of what type of stress test will be performed. The 2007 ACC/AHA Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery recommend exercise stress testing as first line for the evaluation of coronary artery disease in selected patients (19). The problem with this recommendation is that most patients with advanced liver disease have poor functional capacity at baseline and will not be able to exercise appropriately for the test to be adequate. If a patient cannot exercise, the next step is to decide which pharmacologic test is most appropriate. This has been a controversial topic that has yielded no definitive evidence to support one test over another. The argument made by most anesthesiologists who participate in liver transplants as well as transplant surgeons has been that dobutamine stress tests are superior in patients with advanced liver disease. This is because dobutamine stress tests do not rely on coronary vasodilation to produce ischemia. The vasodilatory state seen in advanced cirrhosis has been shown to affect multiple vascular beds including the coronary arteries (20). This state of vasodilatation should render vasodilators ineffective at inducing the necessary increase in coronary blood flow to induce ischemia (20). There is no good evidence comparing dobutamine versus adenosine type stress tests in this patient cohort. There is a substantial amount of evidence supporting the effectiveness of dobutamine stress tests in this population, with expert opinion being that it is an effective screening tool for coronary artery disease with good negative predictive value but a poor positive predictive value (21). At the University of Wisconsin, we prefer dobutamine stress testing as our pharmacologic stress test of choice based on these two points: the fact that dobutamine stress tests have been validated more than any other pharmacologic stress test to be an effective screening tool for

coronary artery disease and that in theory coronary vasodilators should be ineffective at inducing coronary ischemia in patients who are already vasodilated (20,21).

The coagulopathy that develops from liver disease is complex and tends to be misunderstood by many medical professionals. The notion that "all patients with advanced liver disease lack procoagulant factors produced by the liver" is true, but this does not necessarily put them at risk for significant bleeding. It is better to think of this coagulopathy not as a lack of pro-coagulant factors but as imbalanced hemostasis. Kang and Audu describe the five phases of hemostasis and how each is affected by liver disease. They make it clear that it is not only the lack of procoagulant factors that causes this coagulopathy, but also the lack of inhibitors of these procoagulant factors, regulatory proteins, and proteases involved in promoting and inhibiting fibrinolysis (22). The theory of "rebalanced hemostasis" has now been supported by most medical experts in this field. This theory states that the coagulation system of patients with liver disease is in a rebalanced state due to alterations in procoagulants, prolysins, and their inhibitors (1, 22). All forms of coagulopathy may therefore develop including bleeding, thrombosis, or disseminated intravascular coagulation depending on the net balance between these factors.

Evaluation of coagulation status in a patient with liver disease is difficult. Many patients have severe laboratory abnormalities, including prolonged prothrombin time (PT), activated partial thromboplastin time (aPTT) and INR. Other less common tests used to monitor coagulation status that can also be abnormal are the thrombin time (TT), retiplase time (RT), activated clotting time (ACT) and bleeding time. Although they all measure a different aspect of coagulation, one thing all these tests have in common is that they are only a measure of the procoagulant aspect of coagulation. None of these tests reflect the true hemostatic status of patients with advanced liver disease and are poor screening tools for bleeding risk (1,22).

Thromboelastography (TEG) is another option which measures the efficiency of blood coagulation. Kang and Audu also describe this test in detail. TEG continuously measures the shear elasticity of fibrins formed in fresh whole blood (22). The speed of clot formation and clot strength is typically measured and graphed by a computer. There are four values representing clot formation which can be obtained from this test. The reaction time (R) represents the time until blood begins to initiate clot. The clot formation time (K) value is the time from clot initiation to 20 mm amplitude on the graph and represents speed of clot formation. The R and K times correlate with aPTT and are typically prolonged when one lacks procoagulant factors or when drugs inhibiting these factors are given (22). The alpha angle is the tangent of the curve as the clot reaches the K value and is a measure of the rate of clot formation. The maximum amplitude (MA) is the widest displacement of the graph and represents overall clot strength. MA has been shown to correlate with platelet quality and function as well as fibrinogen. One can also look at the amplitude 60 minutes after the MA occurs and calculate a fibrinolysis index. If the fibrinolysis index is less than 85%, one can assume fibrinolysis is occurring.

TEG has some advantages over the previously mentioned tests of coagulation. It takes a short amount of time to run, with initial results in less than 10 minutes. It also gives an overall picture of the true coagulation status. This can be advantageous in a patient with advanced liver disease who may have significant alterations in other tests of coagulation. An elevated INR alone may indicate a deficiency in procoagulant factors required for the extrinsic and common pathways, but a TEG may show a normal R time, as the balance of procoagulants and anticoagulants may be normal. TEG has been shown to be useful for monitoring coagulation status in liver transplantation (1) but has not been recommended by any major groups to aid in diagnosing coagulation problems or guide transfusion practices. We are not

recommending the use of TEG in routine practice but merely suggest it as another option to evaluate coagulation status in this select patient population.

Drug metabolism in patients with advanced liver disease is a concern in the entire perioperative period. The liver plays a key role in pharmacokinetics of a majority of drugs that are given intraoperatively and to treat pain postoperatively. The primary concern when giving a drug is its hepatic clearance. The three main properties affecting hepatic clearance include: hepatic blood flow, the intrinsic properties of a drug that allow it to be extracted by the liver, and fraction of unbound drug available for extraction (1,23). Hepatic blood flow is significantly decreased in patients with advanced liver disease and even further decreased with an abdominal surgical procedure and general anesthesia. The intrinsic properties of a drug are defined by predefined hepatic extraction ratios that represent all pathological aspects involved in hepatic metabolism (1). Drugs that are highly extracted from the liver remain dependent mostly on hepatic blood flow and are less affected by protein binding (1). Drugs with lower extraction from the liver are significantly affected by protein binding and less so by liver blood flow (1). The fraction of unbound drug is determined by protein binding and is the form of drug that can diffuse across plasma membranes and signifies activity. To date, there have not been any good estimates of hepatic clearance or pharmacokinetic changes for specific drugs (1). Volume of distribution tends to be increased for many drugs, especially hydrophilic medications which can require a larger loading dose to obtain a desired effect, but lower maintenance doses because of decreased hepatic clearance (1). There is also evidence that pharmacodynamic effects which are incompletely understood play a role in the increased sedative effects of certain medications (1,24).

While the exact magnitude of response to a given drug may be unpredictable in a patient with cirrhosis, the type of response is in fact predictable. In order to safely care for patients with liver disease we should be aware of the hepatic extraction ratios and protein binding of commonly given drugs in the perioperative period. It is routine practice for many anesthesiologists to give benzodiazepines preoperatively prior to going to the operating room. Most benzodiazepines, such as midazolam and diazepam, are highly protein bound with low hepatic extraction and therefore can have an increase in their potency and duration of action (1). Many experts recommend significantly decreasing doses of midazolam or diazepam preoperatively and titrating doses carefully. Alprazolam has low protein binding and low hepatic extraction and is even more affected by hepatic clearance than drugs with higher protein binding (1). Succinylcholine metabolism can be prolonged by decreased levels of pseudocholinesterase, but this is usually clinically insignificant (18). Aminosteroid nondepolarizing neuromuscular blockers such as pancuronium, rocuronium and vecuronium all tend to have a prolonged duration in advanced liver disease (18). All have an increased volume of distribution and some degree of biliary excretion (18). They therefore will typically need an increased initial dose to achieve desired effect and decreased maintenance doses. The benzylisoquinolones atracurium and cisatracurium are metabolized by ester hydrolysis and Hoffmann degradation. Liver disease tends to not alter their pharmacokinetics and therefore many experts consider these as the neuromuscular blockers of choice if indicated.

Opioid pharmacokinetics can be difficult to predict but are dependent on the severity of liver disease in the patient. Mild liver disease tends not to alter many opioids, but severe liver disease will prolong the duration of nearly all of them. Longer acting opioids such as morphine and hydromorphone have increased sedative effects and can have prolonged duration of action in severe liver disease (1). Fentanyl, sufentanil and alfentanil are all highly protein bound and rapidly redistribute to tissue (1). When hepatic clearance is decreased, these medications can be significantly prolonged as they redistribute and have a higher free fraction of drug than usual. Remifentanil is metabolized by plasma

esterases and is the only narcotic unaffected by liver disease. Furthermore, amide-based local anesthetics are primarily metabolized by the liver. In individuals with liver injury or decreased liver function, metabolic activity is impaired leading to higher local anesthetic blood concentrations and to potential for local anesthetic toxicity.

Halothane is no longer used in the United States and should not be used in patients with liver disease. A mechanism thought to contribute to halothane-induced hepatotoxicity was the metabolism of the agent to trifluoroacetyl chloride. Both isoflurane and desflurane undergo similar metabolism but produce significantly lower trifluoroacetyl chloride and are thought to be safe in patients with liver disease. Sevoflurane produces no trifluoroacetyl chloride. Additionally, all volatile anesthetics reduce hepatic blood flow (27), which can further decrease liver function. At 1 MAC, isoflurane and sevoflurane have minimal impact in hepatic blood flow. Desflurane, however, can decrease hepatic blood flow by 30% at 1 MAC (28,29). Furthermore, some patients with cirrhosis may be at increased risk for neurotoxicity associated with nitrous oxide exposure (30,31).

In the postoperative period, pain control can be an issue in these patients as well. The same issues pertain to intravenous medications postoperatively as they do intraoperatively. Of more concern is the transition to oral medications. When given orally, drugs highly metabolized by the liver typically have significant first pass effect resulting in a low bioavailability. In cirrhosis, patients typically have portosystemic shunts from significant portal hypertension which can significantly reduce the first pass effect and increase bioavailability (1,25). Studies have evaluated drugs with high liver extraction and estimated bioavailability as high as 12 times normal (25). Practitioners caring for these patients postoperatively need to be aware of the properties of oral medications they are giving to patients with liver disease.

Neuraxial anesthesia is a controversial option for postoperative pain management in patients with end-stage liver disease. Thoracic epidural catheters are advantageous as they decrease administration of opioids which are affected by the adverse pharmacokinetic and pharmacodynamic changes in advanced liver disease. The main disadvantage, however, is a higher risk of epidural hematoma in a patient with thrombocytopenia, platelet dysfunction and coagulopathy. The majority of literature recommends against performing epidurals in patients with end-stage liver disease as hemostasis is unpredictable. Trzebicki et al. looked at the use of thoracic epidurals in liver transplant recipients over a 10 year period and showed a decreased time to extubation and better pain control without complications (1,32). This study suggests the procedure is safe but used strict selection criteria of an INR< 1.5, aPTT < 45 and platelets > 70 (1,32). The American Society of Regional Anesthesia (ASRA) guidelines recommend that insertion, manipulation or removal of neuraxial catheters not occur until the INR is < 1.5 while the European Society of Anaesthesiology recommends an INR < 1.4. The patient presented in this case has an INR of 2.0 and a normal TEG, suggesting a significant decrease in production of procoagulant factors but a normal hemostasis profile. Even with a normal TEG, very few experts would be willing to place an epidural believing that the risk outweighs the benefit. Surgery and intraoperative fluid shifts can quickly change this to an unbalanced hemostasis profile promoting bleeding. Currently there is not enough evidence to suggest routine use of epidurals in this patient population and one should evaluate for their use on an individual basis.

Suggested Reading:

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