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Purposeful repurposing: unexpected but not necessarily unwelcome effects of dexmedetomidine

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Severe liver disease doesn't only affect the way the liver functions but can also cause more systemic problems. Patients in liver failure, whether from alcohol-related, viral-related, or drug-induced liver damage, will often also present with multiple-organ damage and failure. This includes damage to the brain (encephalopathy), kidneys (hepatorenal syndrome) and lungs (hepatopulmonary syndrome[HPS]). Up to 47% of patients with severe chronic liver disease may have HPS, and these patients have a bad overall prognosis with few specific treatments available to help them (1). More acute liver injury also often goes hand-in-hand with signs of pulmonary damage, with patients having reduced lung function that can develop into full-blown respiratory distress syndrome (ARDS). The clinical features of pulmonary failure are mirrored on a cellular level with damage to (and death of) alveolar epithelial cells, as well as signs of inflammation with increased numbers of infiltrating immune cells and damage to the endothelial lining of small blood vessels. What causes all these cellular changes and damage isn't really clear, and this makes it hard to determine what might be a good treatment strategy to help lungs heal or prevent the damage from occurring in the first place.

In this issue of *Critical Care Medicine*, Cui *et al* (2) hypothesized that increased levels of bilirubin, which can be present in patients with either acute or chronic liver failure, damage alveolar epithelial cells, and that this damage can be ameliorated using a commonly-used intensive care unit (ICU) drug, dexmedetomidine (DEX). DEX is an alpha-2 adrenergic agonist with a good safety profile that is used primarily for patient sedation in many ICUs. Recent studies have suggested that using DEX can reduce the need to use other types of sedation (3), and may reduce the length of time that patients are on mechanical ventilation in the ICU (3). The mechanisms of DEX action to reduce ventilation days are poorly identified or understood, but DEX is thought to have antioxidant properties in addition to sedation, although little research has been done to really examine whether this potentially beneficial characteristic plays a role in the function of the drug in patients.

In this current study the authors tested the effects of DEX in an *in vitro* model, using a cell line derived from alveolar epithelial cells, and also *in vivo* using a model of acute

hyperbilirubinemia induced by common bile duct ligation (CBDL) in rats. *In vitro*, the investigators confirm that bilirubin increases alveolar epithelial cell death and reduces cell proliferation in a concentration-dependent manner. These effects are reduced in DEX-treated cells, and DEX-driven protection seems to be mediated partly through its alpha-adrenergic agonist properties. DEX also seems to directly affect cell survival by reducing the activation of certain apoptosis signaling pathways in bilirubin-treated alveolar epithelial cells. Apoptosis is a form of programmed cell death that can result from damage to mitochondria and release of reactive oxygen species (ROS) that are detrimental to cells (4). Reducing apoptosis and ROS formation may represent antioxidant actions of DEX separate from its main alpha-adrenergic agonist functions. However, this would need to be confirmed experimentally and this wasn't investigated in this particular study.

More interestingly for clinicians, data in this current study also demonstrate protective effects of DEX *in vivo* in the rat model of CBDL. This is an established experimental surgical model to induce hyperbilirubinemia (5), and the authors confirm what others have shown that bilirubin levels are highest at about 7 days after surgery and then start to decline, although the levels are still comparatively high at 21 days. In this current study, investigators gave one group of rats intraperitoneal injections of DEX every day for 7 days after CBDL and then looked to see if markers of lung damage were reduced compared to rats that underwent CBDL without DEX treatment. They found that DEX-treated rats had less lung edema, suggesting protection of the endothelial lining of small blood vessels in the lung, improved lung function and decreased evidence of apoptosis/cell death of lung epithelial cells when assessed by immunofluorescence staining of lung sections.

So this is great, right? Well, potentially yes. But before we start prescribing DEX to all those patients in liver failure in the ICU there are a few things that need to be considered. The first major issue is that DEX is relatively contraindicated in patients with severe liver failure. This is primarily because it is bound to albumin and is metabolized in the liver (6), meaning the half-life of the drug is increased in patients with liver dysfunction. This may, or may not, be a problem in patients and the pharmacokinetics are potentially mitigated by some experimental evidence (again in rats subjected to CBDL) to suggest DEX may also be hepatoprotective (7). A second pause-for-thought is that this current study is small (only 4 rats were in each experimental group) and of course studies in rats don't necessarily mean that similar findings would be seen in patients. CBDL causes acute hyperbilirubinemia, which may mimic some forms of liver damage but not the spectrum of subacute, chronic or acute-on-chronic disease that is seen in many patients. DEX may not have protective effects in the lung if bilirubinemia is already established, or if HPS or other forms of lung dysfunction are present. A third important factor is based on understanding the differences in the mode of administration of DEX in this study compared to in ICU patients. Rats in this study were given bolus doses of DEX intraperitoneally, but ICU patients are given a continuous infusion of DEX intravenously. The rats would therefore probably have initially higher serum concentrations of DEX that reduce over time, and these fluctuations of DEX concentration would not be apparent in patients. It may be that higher levels of DEX are needed to achieve pulmonary cell protection, and the concern would be that these higher doses could lead to adverse effects in patients. The level of sedation induced by increased

DEX dosing may also be prohibitive in patients with liver dysfunction who are also being clinically assessed for encephalopathy.

So, while the current study of DEX doesn't mean an immediately available new treatment for patients experiencing lung dysfunction secondary to their liver failure, it may herald future research to more definitively identify which properties and actions of DEX are important in cell and organ protection. Once we understand how and why the damage occurs we can direct therapy accordingly, and it remains to be seen whether DEX could be an important new weapon in the ICU physician's arsenal against sequelae of hepatic failure. Indeed, one of the best types of 'new' treatment for a difficult to treat disease or condition is where the drug is not in fact new but just being used for a new purpose. In this regard the study in this issue of *Critical Care Medicine* opens the door to further investigation of DEX and other similar drugs to see if their previously unidentified effects can in fact be helpful to patients.

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