Chemical can reproduce complications for some patients

May 1 2009

Medical science took a giant leap forward with the development of techniques that, at least temporarily, perform the function of vital organs. These processes, including the use of the heart-lung machine and renal dialysis, require the blood to be circulated through tubing outside the body and are hence known as extracorporeal circulation (EC) and have provided critical life support for millions of patients. Yet EC is not without its own risks. Among them are unique morbidities such as depressed cardiac output, abnormal heart rhythm, and swelling of the major organs. Studies have been conducted for decades to determine how these effects can be reduced and eliminated.

In a new study conducted by a Johns Hopkins team, the researchers examined whether a solvent used in the production of intravenous (IV) bags and EC circuits could play a role. Their results indicate that 1) the solvent cyclohexanone (CHX) can leach into IV and EC fluids, and 2) CHX administered in controlled doses in an animal model replicates the cardiovascular and lung morbidities that are seen in patients during and after EC treatment. The study sheds new light on the potential causes of EC-related disorders.

The study was conducted by Caitlin S. Thompson-Torgerson and Lakshmi Santhanam, Department of Biomedical Engineering; Hunter C. Champion, Department of Medicine (Division of Cardiology); Z. Leah Harris, Department of Anesthesiology and Critical Care Medicine; and Artin A. Shoukas, Departments of Biomedical Engineering, Anesthesiology and Critical Care Medicine, and Physiology, The Johns

Hopkins University School of Medicine, Baltimore, MD. The study, entitled Cyclohexanone Contamination From Extracorporeal Circuits Impairs Cardiovascular Function, is published in the online edition of the *American Journal of Physiology—Heart and Circulatory Physiology*.

The Study

Cyclohexanone (CHX) is an organic solvent widely used in the production of polyvinyl chloride (PVC) medical devices, including IV fluid bags and EC circuits. CHX can migrate from PVC tubing and connections into fluids that come in contact with PVC. CHX can leach from PVC bags and IV tubing into intravenous fluids in sufficient concentrations to be detected in neonatal urine samples. Therefore, it is possible that patients on EC support are at risk for CHX exposure, given that their full blood volumes circulate continuously through CHX-treated tubing and are frequently augmented with IV fluids.

While the toxicity of PVC and CHX has been previously documented in animal models, no studies have made comparisons to clinical intravenous CHX exposure. Accordingly, the researchers developed a series of experiments to establish current values for CHX contamination in crystalloid fluid from IV bags and EC circuits, and to test the hypothesis that a clinically observed dose of CHX could reproduce the vital organ dysfunction that can accompany EC support/treatment.

Methodology

To quantify the degree of CHX contamination of fluids, researchers from Johns Hopkins Medical Institutions collected saline samples from IV bags and other commercially available bags, bypass circuits, ECMO circuits and dialysis circuits. CHX levels were measured using gas chromotography-mass spectrometry (GCMS). These results were used to

determine a clinically relevant intravenous dose of CHX. A dose of CHX was then calculated and given intravenously to adult male rats. Saline stored in and administered from glass bottles was given to a control group. Dosing calculations were designed so that they approximated a conservative adult EC patient exposure to CHX, including the abrupt nature of the exposure that EC patients undergo when they are connect to circuit tubing.

There were three protocols used in the study:

Protocol 1 was designed to measure several aspects cardiovascular function. Animals were anesthetized, tracheotomized, ventilated using a rodent ventilator, and then instrumented so that the researchers could measure cardiac output, heart rate, stroke volume, blood pressure, and heart contractile function. Measurements were made at baseline and again 60 minutes after infusion of CHX or saline.

Protocol 2 was designed to measure cardiovascular autonomic function, including how well the nervous system was able to maintain blood pressure in the face of a challenge. After the animals were anesthetized and instrumented to measure blood pressure, both carotid arteries were occluded (obstructed), which stimulates a reflex called the baroreflex that controls blood pressure. After this baseline assessment of reflex function, CHX or saline was infused and allowed to circulate for 30-40 minutes, followed by another round of occlusions. A subsequent identical infusion was given and allowed to circulate for an additional 30-40 minutes, followed by a final round of occlusions.

Protocol 3 was designed to measure edema formation, or the volume of water that has been retained in major organs of the body. After the animals were anesthetized, each rat received an infusion of either CHX or saline, which was allowed to circulate through the body for 2 hours. After 2 hours, the animal was euthanized, and the liver, kidneys, lungs,

and skin were harvested, weighed, dried at 100°C, and weighed again to quantify the fluid content in each organ at the time of death. Results In protocol 1, all baseline values were similar between saline and CHX groups. In the 60 minutes following saline infusion, none of the variables changed significantly from baseline. The CHX infusion, however, induced significant adverse changes in all cardiovascular variables. Both stroke volume and heart rates values were significantly depressed after one hour of CHX, resulting in a significant decline in cardiac output in the CHX rats. Stroke volume, in turn, was depressed because the inherent contractile ability of the heart was significantly reduced. CHX exposure also resulted in high blood pressure in the lung vessels, a dangerous condition known as pulmonary hypertension.

In protocol 2, prior to infusions, both saline and CHX groups exhibited similar significant baroreflex pressor responses to carotid occlusion. After both 1st and 2nd saline infusions, the pressor response in the control group did not differ significantly from baseline. However, in the CHX group, the pressor response was blunted after the first infusion and was undetectable after the 2nd CHX infusion. There are a myriad of neurological complications that develop in patients who undergo EC support. The relative contributions of the underlying disease vs. the treatment are often difficult to discern. Moreover, the potential contribution of CHX to the evolution of these complications has not been investigated.

In protocol 3, the wet/dry ratio of organ weights served as an index of tissue fluid retention and, thus, edema formation. The ratios for all individual organs within each treatment group were pooled to create an overall index of edema formation. The pooled ratio for the CHX group was significantly higher than the saline group.

Conclusions

According to Dr. Thompson-Torgerson, lead author on the paper, and Dr. Shoukas, the senior researcher on the study, "The data from this study provide a current estimate of CHX contamination in most commercially available IV bags and EC circuits. The data allowed us to determine a clinically relevant CHX exposure. A similar level of exposure in animals resulted in cardiovascular morbidities analogous to those observed following clinical EC treatment. This supports our hypothesis that CHX may contribute to EC-related cardiovascular insufficiency. However, we would never tell patients to decline EC treatment if they need it. On the contrary, EC technologies are life-saving medical advances, and the benefits of EC therapy still far outweigh the risks of the associated morbidities. If a patient and doctor have decided that EC treatment is the best course, then stick to that plan. As scientists, we are simply trying to understand how the side effects are triggered and what the best method will be to mitigate, and ultimately remedy, these morbidities. "

Source: American Physiological Society (news : web)

Citation: Chemical can reproduce complications for some patients (2009, May 1) retrieved 19 April 2024 from https://medicalxpress.com/news/2009-05-chemical-complications-patients.html

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