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ularly in settings where liver transplantation is not available. As stated in our review, since the evidence base for care is very limited, the use of most therapies is based on opinion. Although the use of lactulose may be beneficial in some patients with cirrhosis and low-grade encephalopathy, its role in critically ill patients with acute liver failure is not established. Its use may be deleterious because patients with acute liver failure frequently have ileus that may be worsened, particularly if oral fluid intake is inadequate. There are no clinical data to suggest a prolongation of survival, and we and others do not recommend the use of lactulose for the great majority of patients.¹

Dhaliwal and Singh bring up autoimmune hepatitis and specific infections as causes of acute liver failure; space considerations prevented us from an exhaustive discussion of all of these in our review. Severe liver involvement may be seen in some systemic infections, and in such cases the early administration of targeted antimicrobial medication is central to effective management. Autoimmune processes may be important in the pathogenesis of liver injury in acute liver failure due to a number of causes, including new presentations of autoimmune hepatitis²;

however, this cause of acute liver failure is very uncommon, and clinical management may be challenging.³ Although some patients may have a response to immunosuppressive therapy, a key issue is that inappropriately prolonged therapy in an attempt to achieve medical control of disease may preclude successful and definitive transplantation, owing to the development of treatment-related sepsis and other complications.⁴

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Increased Phenylephrine Plasma Levels with Administration of Acetaminophen

TO THE EDITOR: Over-the-counter combinations containing acetaminophen and phenylephrine for the treatment of the common cold and influenza are widespread after the substitution of phenylephrine for pseudoephedrine. This substitution has been allowed in the United States and elsewhere without any additional safety or efficacy studies, since phenylephrine has been called “generally recognized as safe and effective” at oral doses of 10 mg on the assumption that the pharmacokinetic behavior of one drug is not altered by another, despite a lack of supporting data.¹⁻³

Three randomized, open-label, crossover studies in healthy volunteers were undertaken as part of the development of a new-fixed dose combination containing acetaminophen, ibuprofen,

and phenylephrine. The results showed an unexpected pharmacokinetic interaction among the three drugs: the administration of phenylephrine (at a dose of 10 mg) in combination with acetaminophen (1000 mg) and ibuprofen (300 mg), as compared with the administration of 10 mg of phenylephrine alone, resulted in nearly a quadrupling in the maximal plasma concentration (3220 pg per milliliter vs. 874 pg per milliliter) and a doubling in the area under the curve (2220 pg per milliliter per hour vs. 1020 pg per milliliter per hour) (Fig. 1). Ibuprofen was subsequently shown not to contribute to this increase. Halving the dose of phenylephrine that was combined with acetaminophen to 5 mg produced a plasma concentration–time curve similar to that for 10 mg of phenylephrine administered alone.

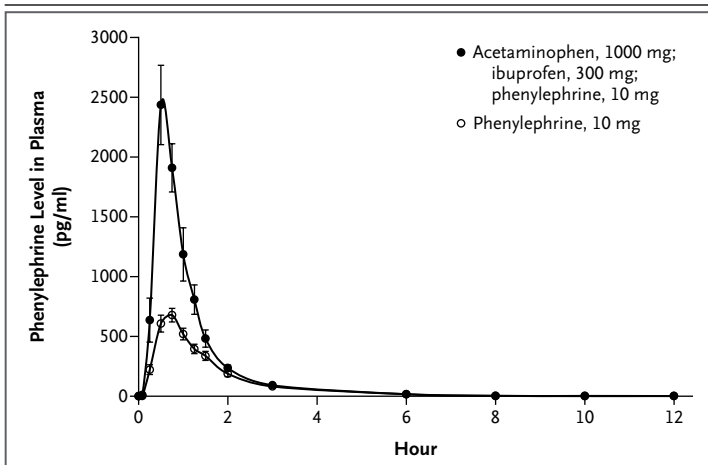


Figure 1. Pharmacokinetic Interaction for Phenylephrine, Acetaminophen, and Ibuprofen.

Shown are the mean plasma levels of phenylephrine after the single administration to healthy human volunteers of a combination of 1000 mg of acetaminophen, 300 mg of ibuprofen, and 10 mg of phenylephrine (black circles), as compared with 10 mg of phenylephrine alone (white circles). The I bars indicate standard errors.

These findings have implications from both regulatory and safety perspectives. First, it is clear that many approvals for the addition of phenylephrine to any number of analgesic agents were based on assumptions that were incorrect for acetaminophen. Second, the plasma exposure of phenylephrine combined with acetaminophen (measured as the area under the curve) is doubled, increasing exposure beyond levels that were previously deemed to be safe and effective

and increasing the potential risk of adverse events.

Since phenylephrine is metabolized by sulfation in the intestinal wall, it seems likely that acetaminophen interferes with this process and increases the level of phenylephrine with respect to bioavailability.⁴ If so, other drugs may also interact with phenylephrine, including ascorbic acid. Multiple variants of acetaminophen combined with phenylephrine are now available on worldwide markets. Is further investigation required?

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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Speech in an Orally Intubated Patient

TO THE EDITOR: We report the successful use of an electrolarynx in an orally intubated 59-year-old man who was receiving mechanical ventilation. The device enabled him to produce intelligible speech (Fig. 1). A video-assisted bilobectomy of the right lung for adenocarcinoma had been performed at another hospital, and the procedure was complicated by the development of a bronchopleural fistula. Because of this complication, there was a need for continued mechanical ventilation. His family informed us that the patient was frustrated by his inability to talk. He consented to the plan to use the electrolarynx,

and to his surprise — and ours — the device immediately returned the gift of speech to him, without the passage of air through the vocal cords. In response to the question “Were you able to sleep this evening?” he replied, “I slept reasonably well.” (See video, in Dutch, with English translation, available with the full text of this article at NEJM.org.) Nurses were able to place the device after just 2 minutes of instruction, and the usefulness of the device in other intubated patients has been confirmed.

The electrolarynx, which is known for its use after laryngectomy, is an oscillating device that



A video showing the patient speaking with use of an electrolarynx is available at NEJM.org