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Letter to the Editor

To Assess Whether Tenapanor is Actually Beneficial in Hepatic Encephalopathy, Appropriately Designed Studies are Needed

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Letter to the Editor

We read with interest the article by Yea *et al*. on the efficacy of tenapanor (50 or 100 mg/day) in hepatic encephalopathy (HE) in five patients with decompensated liver cirrhosis, in which the endpoints of bowel movement frequency, improvement in HE symptoms, and safety were examined [1]. Four patients showed improvements in bowel frequency, stool consistency, and the severity of HE. In 3 patients, HE recurred after discontinuation of treatment [1]. It was concluded that tenapanor can alleviate HE with high safety and compliance [1]. The article is promising, but some points require further discussion.

The first point is that the diagnostic criteria used to diagnose HE in the 5 patients presented were not clearly specified [1]. HE is typically diagnosed clinically in patients with liver cirrhosis or portosystemic shunts using the West-Haven Criteria (WHC) to classify changes in mental status and asterixis [2]. The most important diagnostic elements include gastrointestinal bleeding, gastrointestinal infections, cognitive deficits, and the exclusion of alternative neurological disorders [2].

The second point is that the authors applied the HESA criteria instead of the WHC criteria [1]. However, the disadvantages of the HESA criteria are that their application is time-consuming and difficult, that they require special training, that they are not widely used compared to the WHC, that they lack comprehensive validation, that they are less sensitive in cases of extreme severity, and that they remain subjective, as they rely on clinical judgment and leave room for observer variability [3].

The third point is that no alternative explanations for disturbances of consciousness, cognitive deficits, and abnormal behavior were provided [1]. To rule out alternative cerebral disorders that could explain the clinical presentation of the five patients, such as stroke, hemorrhage, infectious or immunological encephalitis, PRES, or ADEM, it is crucial that contrast-enhanced cerebral MRI and MRA had been performed in all five patients. Since HE can also be associated with seizures [4], it would also have been necessary to record an electroencephalogram for each of the five patients.

The fourth point is that the study design (case series) is unsuitable for assessing the efficacy of tenapanor in HE. To confirm or rule out a positive effect of tenapanor in HE, a randomized controlled trial (RCT) would have been necessary [5]. RCTs are considered the “gold standard” for demonstrating the efficacy of drugs, as they minimize bias through randomized assignment and controlled comparisons [5].

The fifth point is that comorbidities and concomitant medications were not reported for any of the five patients [1]. To assess whether concomitant medications could have influenced the effect of Tenapanor, it is crucial to know whether the included patients suffered only from cirrhosis or also from other diseases and which medications they were taking regularly.

The sixth point is that serum ammonia levels were not reported for any of the five patients [1]. Since hyperammonemia is a key feature of liver dysfunction and all five patients suffered from cirrhosis, it is crucial to know the serum ammonia concentrations.

Finally, hepatic encephalopathy is frequently associated with tremor (asterixis), yet no tremor was reported in any of the patients [1].

Overall, appropriately designed studies are necessary before it can be claimed that tenapanor alleviates hepatic encephalopathy.

Declarations

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