Oral Ammonia Tolerance Test in Patients with Portal Hypertension

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KOYAMA, K., OWADA, Y., IMAOKA Y. and SATO, T. Oral Ammonia Tolerance Test in Patients with Portal Hypertension. Tohoku J. exp. Med., 1981, 135 (1), 93-101 — Eighty patients with portal hypertension due to various hepatic diseases were subjected to the oral ammonia tolerance test (OATT). Blood samples were collected before and at 30-min intervals after the administration of ammonium chloride (50 mg/kg). The ammonia levels, and the OATT curve patterns and \( \Delta \text{NH}_3-\text{N} \) values were determined and it was investigated whether there are correlations between these values and various other parameters of hepatic function. The results of OATT correlated with the plasma disappearance rate of indocyanine green and the molar ratio of branched chain amino acids to aromatic amino acids. Our findings suggest that the OATT may reflect the degree of hepatic parenchymal disorders rather than the hepatic circulatory abnormalities and that they may represent a valuable aid in the differential diagnosis of hepatic diseases and in determining the operative indication.

oral ammonia tolerance test; ammonia metabolism; portal hypertension; hepatic failure

Ammonia is thought to be an important factor in the manifestation of hepatic failure, and has been investigated in patients with hepatic disorders, especially hepatoencephalopathy in portasystemic shunt (McDermott 1957; Conn 1969). The increased ammonia level in the blood of patients with hepatic diseases is thought to be ascribable to the sum of ammonia derived via two routes, decrease in ammonia metabolism and the inability of ammonia to enter the metabolic cycle due to the existence of an intra- and/or extrahepatic shunt. It is difficult to determine which of these routes represents the major contributor to the increased ammonia level in the blood of the patients with hepatic disease.

In this report, the results of the oral ammonia tolerance test (OATT) in patients with portal hypertension are described.

Patients and Methods

Eighty patients with portal hypertension were treated in our department, of these cases 58 had liver cirrhosis, 17 idiopathic portal hypertension with hepatic fibrosis and 5 extrahepatic portal obstruction. Four gastric cancer patients without hepatic abnormalities served as the controls. Before inception of this study, voluntary informed consent was obtained from all participating patients.

Received for publication, November 28, 1980.
Ammonium chloride (50 mg/kg) was administered orally before breakfast and the patients were monitored electroencephalographically. Blood samples were obtained from the femoral artery before, and 30, 60, 90 and 120 min after the administration. The ammonia concentration values, determined by the modified method of Okuda and Fujii (Okuda and Fujii 1966) were plotted and the shape of the resulting curves and the totals of individual values were analyzed and compared with the results of various hepatic function tests and histological findings of the liver.

**RESULTS**

**OATT Curves**

These could roughly be classified into Type I through Type IV. In Type I, the blood ammonia level remained within the normal range throughout the 120-min post-loading period. In Type II, the blood ammonia level increased after the administration of ammonium chloride and returned to the pre-administration level within 120 min. In Type III, the ammonia level rose after the administration and decreased gradually, however, at the end of the 120-min observation period, it remained above the pre-administration value. In Type IV, the post-administration level of blood ammonia remained elevated and manifested no decrease with elapsing time.

\( \Sigma \text{NH}_3-N \)

In each patient the blood ammonia concentration was summed of all blood samples obtained from the OATT and this sum was designated the \( \Sigma \text{NH}_3-N \) value.

![Fig. 1. Correlation between \( \Sigma \text{NH}_3-N \) and pattern of oral ammonia tolerance test (OATT).](image-url)
In Type I, with one exception, the $\Sigma$NH$_3$-N values were below 500 $\mu$g/100 ml, in Type II they ranged from 300 $\mu$g/100 ml to 1,100 $\mu$g/100 ml, in Type III they ranged from 500 $\mu$g/100 ml to 1,500 $\mu$g/100 ml, in Type IV they were from 700 $\mu$g/100 ml to 2,200 $\mu$g/100 ml (Fig. 1).

Correlation between $\Sigma$NH$_3$-N values and liver function tests

There was a significant correlation between $\Sigma$NH$_3$-N and plasma disappearance rate of indocyanine green (ICGk) values (correlation coefficient, 0.62, Fig. 2) and between $\Sigma$NH$_3$-N values and the ratio of branched chain amino acids (BCAA) to aromatic amino acids (AAA) in the blood (correlation coefficient, 0.72, Fig. 3). On the other hand, there was no obvious correlation between the $\Sigma$NH$_3$-N values and GOT, GPT, serum protein concentration, albumin, $\gamma$-globulin, prothrombin time,
thrombotest values, or the glucose tolerance test pattern. The value of $\Sigma NH_3-N$ was also independent of portal pressure and wedged hepatic venous pressure.

**OATT patterns in various hepatic diseases**

The 4 control patients and 1 of the 5 patients with extrahepatic portal obstruction manifested the Type I pattern. The 4 remaining extrahepatic portal obstruction patients showed the Type II pattern, as did 12 of the 17 idiopathic portal hypertension with hepatic fibrosis and 12 of the 58 liver cirrhosis patients. Type III comprised 5 hepatic fibrosis and 20 liver cirrhosis patients and only patients with liver cirrhosis manifested Type IV (Fig. 4).

### Fig. 4. Patterns of oral ammonia tolerance test in the cases of portal hypertension with various liver diseases. Control patterns are obtained from the cases of early gastric cancer without liver disease. Abbreviations in the illustration are as follows: EHPO, extrahepatic portal obstruction; IPH, idiopathic portal hypertension (portal hypertension due to hepatic fibrosis of unknown cause); LC, liver cirrhosis.

$\Sigma NH_3-N$ values in various hepatic diseases

The $\Sigma NH_3-N$ values of the controls did not exceed 500 $\mu g/100$ ml with the exception of 2 patients of idiopathic portal hypertention with hepatic fibrosis, only liver cirrhosis patients manifested levels above 1,000 $\mu g/100$ ml (Fig. 5). However, as similar numbers of liver cirrhosis patients manifested levels above and below 1,000 $\mu g/100$ ml, above 1,000 $\mu g/100$ ml in 26 cases and below 1,000 $\mu g/100$ ml in 32, the $\Sigma NH_3-N$ value alone does not represent a sufficient parameter for the differential diagnosis of liver cirrhosis.

To elucidate whether there is the difference in liver cirrhosis between a group with $\Sigma NH_3-N$ values above 1,000 $\mu g/100$ ml and that with $\Sigma NH_3-N$ values below 1,000 $\mu g/100$ ml, we compared the results of liver function tests in our patients. As shown in Fig. 6, there was a significant difference with respect to the ICGk value ($p<0.025$) and the molar ratio of BCAA to AAA ($p<0.005$) between the two groups. On the other hand, the wedged hepatic venous pressure, the serum albumin concentration and the prothrombin time were similar.
Five patients with different hepatic diseases were subjected to repeated OATT. The type of OATT curve and the $\Sigma NH_3-N$ value were similar upon every test, confirming the reproducibility of the OATT. Comparison of the OATT before and after esophageal transection showed no significant changes.

Reproducibility of OATT and changes after esophageal transection

Five patients with different hepatic diseases were subjected to repeated OATT. The type of OATT curve and the $\Sigma NH_3-N$ value were similar upon every test, confirming the reproducibility of the OATT. Comparison of the OATT before and after esophageal transection showed no significant changes.
after esophageal transection for varices revealed a slight decrease in the $\Sigma$NH$_3$-N value, whereas, there was no change in the pre- and postoperative types of the OATT curve (Fig. 7). This finding indicates that devascularization of the collateral circulation had only a slight effect on the OATT.

### OATT as an indicator for surgery

The possibility of using the $\Sigma$NH$_3$-N value as an indicator for esophageal variceal surgery in patients with liver cirrhosis was investigated. The $\Sigma$NH$_3$-N values of patients in whom, according to conventional parameters such as the level

![Image](https://via.placeholder.com/150)

**Fig. 7.** Patterns and $\Sigma$NH$_3$-N of the oral ammonia tolerance test in the same case before and after esophageal transection. •—•, before transection; o—o, after transection.

![Image](https://via.placeholder.com/150)

**Fig. 8.** Operative indication and $\Sigma$NH$_3$-N. ET, esophageal transection; SP-DV, splenectomy with gastric devascularization.
of ICGk, serum albumin and ascites, esophageal transection alone was deemed advisable, were higher than in those who were thought to be able to tolerate transection and splenectomy with devascularization. Four of 6 patients who, because their liver disorders were severe, were thought to be inoperable, manifested $\Sigma$NH$_3$-N values above 2,000 $\mu$g/100 ml (Fig. 8).

**Side effects of OATT**

In 6 of 80 patients (7.5%) with hepatic disorders, the oral administration of ammonium chloride induced vomiting, and this could be prevented by admixing it with a glucose solution. In patients monitored electroencephalographically, no abnormalities were noted with the exception of 3 patients who showed a transient abnormal pattern reminiscent of a triphasic wave. However, these patients required no special treatment and the normal, pre-administration pattern was re-established within a few hours.

**DISCUSSION**

Hepatic failure on hepatoencephalopathy in patients with hepatic disorders has been attributed partly to an increase in their blood ammonia levels (McDermott 1957; Conn 1969). According to ammonia loading studies, the results of OATT are correlated with the degree of esophageal varices and portal hypertension (Egense 1960; Conn and Conn 1967), suggesting that the increase in the ammonia levels is due to the intra- and extrahepatic shunts. On the other hand, some reports suggested that OATT results reflect the degree of hepatoparenchymal disorders, as the OATT values differed in cases of compensatory and decompensatory liver cirrhosis (McDermott and Huston 1963). Takamura et al. (1980) who administered $^{13}$N ammonia transrectally to patients with liver cirrhosis reported that it passes through the liver and, in the presence of a portasystemic shunt, accumulates in the heart, lungs and brain. In addition, based on their comparative study of the time-sequential level of $^{13}$N ammonia metabolites in the blood and the 15-min retention of ICG, these workers suggested that the blood ammonia level not only reflects an abnormality in the ammonia metabolism, but also the development of a portasystemic shunt.

The present study, in which we subjected patients with portal hypertension to OATT, revealed that the test was useful in the diagnosis of the degree of the hepatic disorder and suggesting the histological changes of the liver. The determination of blood ammonia level alone was not so informing. For example, there was no remarkable difference in the blood ammonia level between patients with liver cirrhosis and fibrosis. On the other hand, many patients with these diseases manifested OATT curves of different types and different $\Sigma$NH$_3$-N values. In addition, while the $\Sigma$NH$_3$-N value did not correlate with the result of standard liver function tests, there was a correlation with the ICGk value and the molar ratio of BCAA to AAA. The former is thought to be an important indicator of hepatic parenchymal functions and of hepatic circulation, especially in patients with
portasystemic shunt (Reemtsma et al. 1960; Teranaka and Schenk 1977), and the molar ratio of BCAA to AAA reflects the degree of the existing hepatic parenchymal disorder (Morgan et al. 1978). The correlation of the $\Sigma$NH$_3$-N values with these parameters suggests that the OATT reflects the degree of the hepatic parenchymal disorder and/or that of the circulatory abnormality. Although it is difficult to determine which of these has the greater influence on the OATT, based on the following considerations, we would suggest that the former does. Patients with extrahepatic portal obstruction in whom portography confirmed the existence of a high hepatofugal collateral circulation, manifested OATT curves of Type I or II and low $\Sigma$NH$_3$-N values. On the other hand, patients with liver cirrhosis had Type III or IV OATT curves and high $\Sigma$NH$_3$-N values, even if the collateral circulation was not remarkable. Furthermore the results of OATT before and after esophageal transection showed only a slight postoperative decrease in the $\Sigma$NH$_3$-N values and no change in the type of OATT curve. These findings suggest that the collateral circulation exerts only a slight effect on the outcome of the OATT. Based on these considerations, we would propose that the OATT results are primarily reflective of the hepatic parenchymal disorder.

As the OATT is easily carried out and, unlike the $^{13}$N ammonia method, does not require special instruments, it is of clinical value. Our study showed the OATT is reproducible, therefore, pre- and postoperative data can be assessed with confidence. Furthermore, the results of OATT are in good agreement with other parameters conventionally used as indicators for surgical treatment and in cases of $\Sigma$NH$_3$-N values above 1,500 $\mu$g/100 ml, major surgical insult should be avoided.

On the other hand, the application of the OATT presents some disadvantages. This method requires the administration of a large amount of ammonia. Therefore, in patients with blood ammonia levels exceeding 300 $\mu$g/100 ml, or in patients with a history of hepatoencephalopathy, special caution is required and electroencephalographic monitoring is advisable. Some of our patients vomited the administered ammonia, however, this problem could be circumvented by giving the required dosage in a glucose solution. In the case of vomiting, the $\Sigma$NH$_3$-N value obtained should be disregarded and only the pattern of the OATT curve should be taken into consideration.

References


