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Studies of the Source and Significance of Blood Ammonia IV. Early Ammonia Peaks after Ingestion of Ammonium Salts

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In the course of studies of ammonia absorption from the gastrointestinal tract in cirrhosis it was noted that the highest arterial ammonia levels were achieved shortly after oral ingestion of ammonium chloride. Peak values usually occurred within 15 min of administration. The rapid appearance time of the zenith was surprising in view of previous studies of ammonia tolerance, which had suggested that the peak blood ammonia level, determined on either arterial or venous blood, occurred between 30 and 60 min after ingestion(1–3). Several laboratories, ours included, have used the 45-min blood ammonia level as the peak value in performing ammonia tolerance tests(4–6). We have previously presented data associating impaired ammonia tolerance with portal–systemic shunting(5), esophageal varices(7) and patent portacaval anastomoses(8) using the 45-min arterial ammonia level.

The present investigation was undertaken to determine the nature of the arterial ammonia tolerance curve in normal subjects and cirrhotic patients. In addition, it was planned to compare the peak arterial ammonia levels, whenever they occurred, with the 45-min level in assessing the presence or absence of esophageal varices in the cirrhotic patients so studied.

METHODS AND MATERIALS

Ammonia tolerance tests (ATT) were performed by administering 20 mg NH_4Cl per pound body weight as noncoated tablets with a maximal dose of 3.0 g for patients weighing more than 150 lbs. All tests were carried out in the

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morning after an 8- to 12-hr fast. Arterial blood specimens were obtained through an indwelling Cournand needle before and at 15-min intervals after the administration of NH_4Cl. Blood ammonia levels were measured using the Seligson–Hirahara method(9). The magnitude of ammonia intolerance was defined as the increment in blood ammonia levels, i.e., the area under the curve of the ammonia tolerance values above the baseline level, was calculated by computer and expressed in microgram-minutes per 100 ml.

Twenty normal volunteer subjects (13 men and 7 women) with an average age of 32 years were studied. In addition 50 male patients with biopsy-proved cirrhosis who had been admitted to the West Haven Veterans Administration Hospital were studied. Nineteen of these patients had had portacaval anastomoses (PCA) which had been proved to be patent in 16 and were presumed to be patent in the others. Esophagoscopy had been performed to determine the presence or absence of esophageal varices with either the Eder–Hufford or the Olympus fiberoptic esophagoscope within 10 days of the ammonia tolerance test in the cirrhotic patients.

RESULTS

Normal subjects. The mean curve of arterial ammonia levels is shown in Fig. 1. There was a small, transient increment in ammonia concentration which peaked at 15 min and returned to fasting levels by 30 min. The pattern was similar for the men and women although the absolute levels were lower for the women, who were an average of 13 years younger than the men. In nine of the 20 subjects there was no significant increase ($> 20\ \mu g/100$ ml) above the baseline level. In

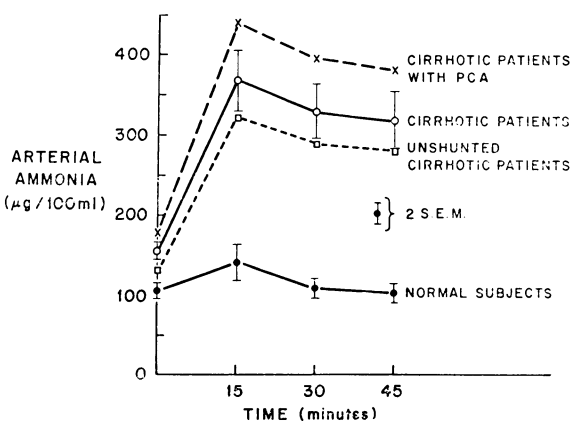

FIG. 1. Ammonia tolerance tests (mean ± 2 SEM). Normal subjects showed a small increment in ammonia concentration at 15 min which rapidly returned to baseline levels. In cirrhotic patients there was an enormous increase in ammonia level at 15 min followed by a slow decrease. Cirrhotic patients with PCA exhibited a more abnormal pattern than unshunted cirrhotic patients, but qualitatively the pattern was the same.

nine patients (81%) the peak ammonia level occurred at 15 min and in two (19%) at 30 min (Fig. 2).

Cirrhotic patients. The mean ammonia tolerance curve in the cirrhotic patients differed from that of normal subjects in several ways (Fig. 1). The mean fasting arterial ammonia level was significantly greater in the cirrhotic group ($P < 0.001$) than in the normal group. The fasting ammonia concentration was significantly higher in the subgroup of cirrhotic patients with PCA than in those without (178 ± 6 vs 141 ± 7 μg/100 ml, $P < 0.01$).

In one of the cirrhotic patients there was no rise in ammonia concentration after ammonium chloride. In 36 of the remainder (72%) the peak ammonia level occurred at 15 min (Fig. 2). Peak levels were observed in six (21%) and seven (14%) at 30 and 45 min, respectively. This distribution was not significantly different from that observed in normal subjects. The patterns were similar in the cirrhotic patients with and without PCA (Fig. 2).

The magnitude of ammonia intolerance was significantly greater for the cirrhotic patients than for normal subjects ($P < 0.001$) (Table 1). Ammonia intolerance was significantly greater for the cirrhotic patients with shunts than those without ($P < 0.01$) (Table 1).

Diagnostic accuracy of peak ATT levels. Using the empiric criteria previously derived(6) that ammonia tolerance levels greater than 250 μg/100 ml were diagnostic of esophageal varices, the diagnostic accuracy for each ammonia tolerance level, i.e., 15, 30 and 45 min, was assessed using the endoscopic findings as proof of the presence or absence of esophageal varices. The 15-min value was correct

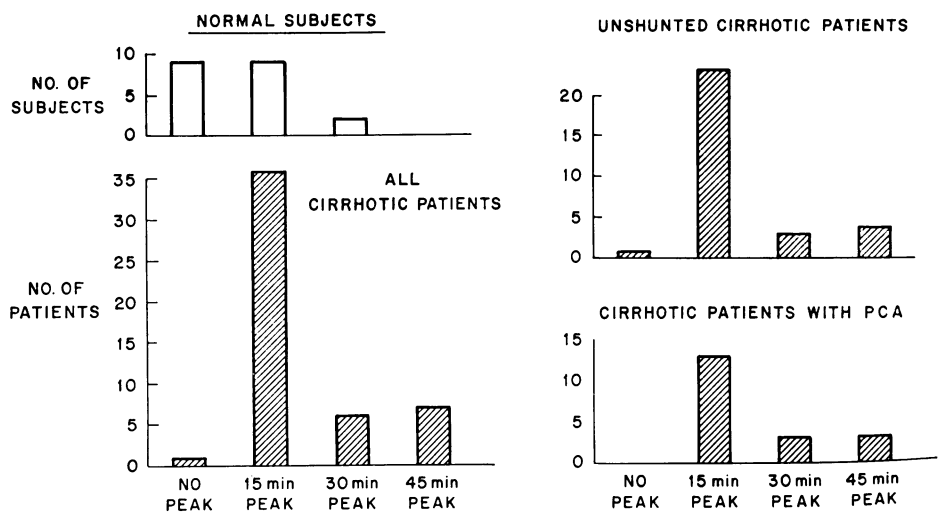

FIG. 2. Distribution of time of peak ammonia concentration after NH_4Cl administration. In approximately half of the normal subjects no increment in arterial ammonia level occurred. Peak ammonia concentration occurred 15 min after ingestion in most of the others. In the cirrhotic group about three-fourths of the patients exhibited peaks at 15 min. The patterns were similar whether or not the patients had portacaval anastomosis.

in 17 of 31 patients (55%), the 30-min value in 19 (61%) and the 45-min level in 19 (61%). These differences are not significant statistically. Previous studies in a much larger series of patients have shown the ATT to be of greater diagnostic accuracy than the present series suggests(7).

Applying the same criteria, i.e., ammonia tolerance levels >250 μg/100 ml are diagnostic of esophageal varices, the pre-45-min peak levels were compared with the 45-min values in the 31 cirrhotic patients. In four of these patients the peak level occurred at 45 min. In 23 of the patients the diagnostic implication was the same for the 45-min and pre-45-min peak. In four, however, the earlier peak which occurred at 15 min was >250 μg/100 ml, i.e., indicative of varices, while the 45-min value was <250 μg/100 ml, indicating that no varices were present. In three of these four instances the 45-min value was in accord with the endoscopic diagnosis, while the earlier peak did not concur. Thus, the early peak did not appear to enhance the diagnostic accuracy of the ATT.

It is not possible to evaluate in the same manner the accuracy of the ATT in assessing the patency of PCA since this determination is not based on the absolute blood ammonia concentration but, rather on the increment above preshunt levels.

Diagnostic accuracy of increments in ammonia intolerance. All eight patients with esophageal varices had increments in blood ammonia levels of >5000 microgram-minutes NH_4N/100 ml, while 13 of the 23 patients (57%) without esophageal varices had similar values. Based on such a criterion the diagnosis of varices, or their absence, would have been made correctly in 21 of the 31 patients (68%). This value is slightly, but not significantly, greater than the peak or 45-min levels in assessing the presence or absence of varices.

DISCUSSION

These studies demonstrate that peak arterial ammonia levels usually occur 15 min after an oral load of NH_4Cl—earlier than had been previously thought. There are several possible explanations for the difference. First, very few investigators have measured blood ammonia levels prior to 30 min after ingestion. In the studies of White *et al.*(1), Egense(2) and Castell(5), who reported ammonia levels at both 30 and 60 min, two-thirds of their patients had had higher am-

TABLE 1

MAGNITUDE OF AMMONIA INTOLERANCE

Group	Number	Ammonia Intolerance mean ± SEM microgram-minutes NH_3N per 100 ml	Statistical significance *P* value
Control	20	558 ± 206	< 0.001
Cirrhosis	50	7016 ± 523	
Unshunted cirrhosis	31	5946 ± 678	< 0.01
Cirrhosis with PCA	19	8762 ± 658	

monia levels at 30 than at 60 min. We and others assumed, perhaps naively, that the average patient would have achieved peak levels at 45 min. In retrospect, it is equally possible, and in view of our present data, probable, that the highest levels had occurred prior to the 30-min determination in many of their patients. In fact, the slope of the decrease in blood ammonia concentration during the 30–60-min period in these three studies is similar to that which we observed during the 30–45-min period (Fig. 3). Second, the uptake of ammonia by the peripheral tissues(10,11) may be greater just after an ammonia load, but the capacity of skeletal muscle to remove ammonia may rapidly decrease, resulting in a later venous than arterial peak. The data of Stahl *et al.*(4), who measured simultaneous arterial and venous ammonia levels, showed that the greatest increment in arterial ammonia concentration occurs by 15 min while the greatest venous increment occurs between 15 and 45 min levels. This phenomenon would tend to result in earlier arterial peaks, as we observed, and later venous peaks as reported by most other observers who used venous determinations. Third, different ammonium salts may play a role. We used NH_4Cl while other investigators administered similar amounts of ammonium ion as citrate or acetate. Although all of these salts are highly soluble, it is conceivable that NH_4Cl is more rapidly absorbed. Finally, each of the authors used different techniques for measuring blood ammonia, although it is unlikely that methodologic differences would create so systematic an artifact.

Although use of these prompt peak values does not alter appreciably the diagnostic accuracy of the ammonia tolerance test in estimating the degree of portal–systemic shunting or in assessing the presence of esophageal varices, it has several important implications. First, absorption of ammonia from the intestinal tract is far faster than had been believed. We have noted, for example, that peak portal venous ammonia levels often occur within 5–10 min after the ingestion of the

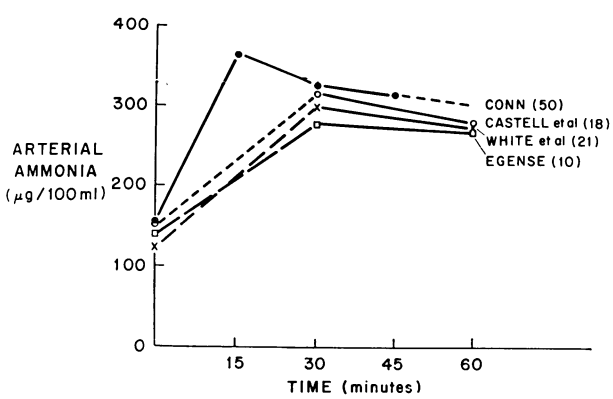

FIG. 3. Ammonia intolerance values in cirrhosis. The mean curves of ammonia tolerance tests by different investigators are depicted. The slope of the curves is similar for all four curves from 30 to 60 min after the ingestion of NH_4Cl. The broken portions of the curves indicate the previously presumed ammonia tolerance curves. In retrospect, it is more likely that additional earlier ammonia values would have shown curves more like those that we observed (top curve).

ammonia load, and that peak arterial ammonia concentrations occasionally occur at that time (unpublished observations). Investigators who fail to take into account this rapid ammonia absorption may miss much pertinent information. Second, the early peak in arterial ammonia concentration appears to be critical in assessing ammonia metabolism in heterozygotic relatives of patients with ornithine transcarbamylase deficiency. Preliminary observations have suggested that asymptomatic carriers of this inherited defect may be identified by impaired ammonia tolerance, which is most evident within 15 min of ingesting ammonium chloride(12). This abnormality may be minimal or absent on more delayed sampling.

SUMMARY

Previous studies of ammonia tolerance have suggested that arterial ammonia levels peak 30–60 min after the oral administration of ammonium salts. The performance of ammonia tolerance tests (ATT) in 20 normal subjects and 50 cirrhotic patients demonstrates that the highest arterial ammonia levels usually occur within 15 min of administration. Approximately half of normal subjects show no rise in arterial ammonia concentration; 80% of the remainder exhibit peak levels within 15 min. Virtually all cirrhotic patients, with or without portacaval anastomosis, show a considerable increment in ammonia levels which occurs promptly in three-fourths. Although the diagnostic assessment of portal–systemic shunting is not improved by using prompt peak levels, recognition of the rapid absorption of ammonia from the upper gastrointestinal tract may be important in understanding nitrogen metabolism in normal and pathologic states.

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