The Oral Ammonium Tolerance Test as Aid in the Investigation of Suspected Esophago-Gastric Varices

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SINCE the introduction of surgical procedures which effectively reduce portal hypertension, it has become even more important to establish or rule out the presence of esophageal varices when they are clinically suspected.

Routine barium swallow examinations fail to demonstrate esophago-gastric varices in a considerable number of patients subsequently shown to have them, as pointed out by Conn *et al.*[4] and this technic is liable to error in interpretation. Esophagoscopy is considered to be more reliable by these authors and by Adson [1] and by Friedberg *et al.*[7]

Palmer [10] has described remarkable and rapid fluctuations that occur in the size of esophageal varices; moreover, in 35 of 133 of his patients in whom he has seen varices at one examination, he failed to do so on another occasion. Splenoportography is held by some to be the most accurate method of demonstrating esophageal varices although cases have been reported [6] where a single splenoportogram failed to demonstrate varices, although they were proved to be present a short time afterwards.

An effective screening or confirmatory test for the presence of portal-systemic shunting and, therefore most probably of esophago-gastric varices, would be of obvious value in the diagnosis of the patient who is suspected of having varices by clinical course or by x-ray examination.

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A preliminary report of one of the author's experience with the oral ammonium tolerance tests has been presented elsewhere; [9] with the continued use of this simple and inexpensive test, it has shown itself to be a reliable indicator of the presence or absence of portal-systemic shunting and, by assumption, the presence or absence of esophago-gastric varices. It is the purpose of this report to summarize the experience in the use of this test in the investigation of more than 90 patients. The value and limitations of the oral ammonium tolerance test are illustrated by reference to the case histories of selected patients in whom the test has been particularly valuable.

The observations which form the basis of this test began in 1932 when Van Caulaert and DeViller [12] observed that there was an increase in the concentration of ammonia in peripheral venous blood following the ingestion of ammonium chloride in patients with cirrhosis but not in normal subjects or in those suffering from acute obstructive jaundice or hepatitis. Kirk [8] made essentially similar observations and agreed that the most probable explanation for this finding in patients with cirrhosis was that some of the blood coming from the intestine was shunted around the liver directly into the blood entering the right atrium. Conn [2] showed a rapid rise in peripheral arterial and venous blood after cirrhotic patients swallowed 3 Gm. or less of ammonium chloride; the peak readings

occurred in 45 minutes, and the reading from arterial blood was higher than the venous sample. He did note, however, that those patients with clinical evidence of portal hypertension—splenomegaly, ascites and abnormal collateral veins on the abdominal wall—showed an even higher peak in the peripheral arterial or venous blood than cirrhotic patients in whom these clinical features were absent. However, he concluded that he could show no statistical relationship between an abnormal ammonium tolerance curve and the presence of esophageal varices demonstrated by x-ray or esophagoscopy.

Stahl [11] showed that in cirrhotic patients with no evidence of portal-systemic collateral circulation, the peripheral venous ammonia concentration might or might not increase after oral ammonium chloride and showed that the right heart or peripheral arterial blood invariably showed a rise under these circumstances. He has emphasized the role of the metabolism of ammonia by peripheral tissues in explaining this discrepancy.

White *et al.*,[13] using a technic of simultaneous sampling from hepatic and peripheral veins showed that in well compensated cirrhotics, the rise in ammonia concentration in peripheral venous blood must be due to portal-systemic shunting and not to a failure of urea synthesis.

In this study we have attempted to relate the shape of the ammonium tolerance curve to the degree of portal-systemic shunting and to the state of hepatic compensation.

Method

The patients were denied all food for at least six hours and generally 12 hours before the initial sample of peripheral venous blood was withdrawn. The dose of ammonium citrate then given by mouth was 10 Gm. unless the initial blood ammonia level was above 120γ% when only 5 Gm. was given. In either case, the ammonium citrate was dissolved in approximately 250 ml. of water or orange juice.

Thereafter, peripheral vein blood samples were withdrawn 30, 60, 120, and 240 minutes after the ammonium citrate had been swallowed. The concentration of ammonia in each sample was determined immediately after the blood was withdrawn by a modification of Conway's mico-diffusion technic.

The patients undergoing this test were divided into four groups on that basis of clinical, biochemical, radiological, and endoscopic findings. Biopsy or postmortem findings were also used in their categorizations, if these were available.

Group I included normal healthy volunteers and patients in whom it was possible to exclude all hepatic disease with confidence.

Group II consists of patients considered

TABLE 1. *Ammonia Concentrations (in γ%) in Peripheral Venous Blood*

	Initial Sample		½-hr. Sample		1-hr. Sample		2-hr. sample		4-hr. Sample	
	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean
Group I 26 cases	27–70	52	29–89	60	22–80	57	20–72	55	30–56	45
Group II 21 cases	21–89	56	38–132	76	35–120	81	41–96	68	53–80	70
Group III 30 cases	34–153	78	63–321	184	61–391	195	58–376	148	54–126	84
Group IV 15 cases	45–132	81	96–285	191	200–327	266	110–420	266	87–249	169

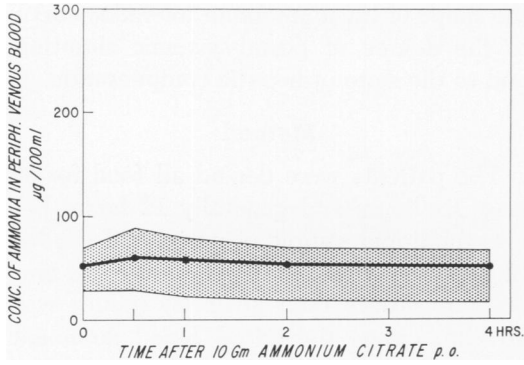

FIG. 1. Group I. (26 Cases) Patients *without* disease of the liver or portal circulation.

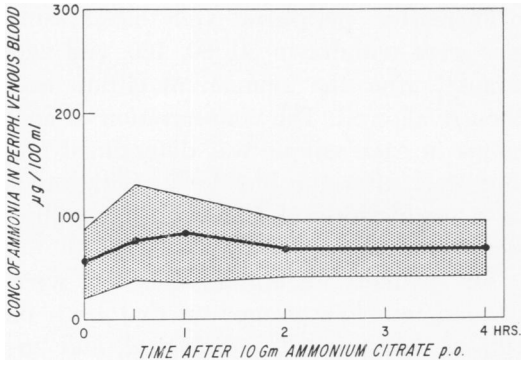

FIG. 2. Group II. (21 Cases) Patients *with* compensated cirrhosis but *without* demonstrable portal-systemic shunting.

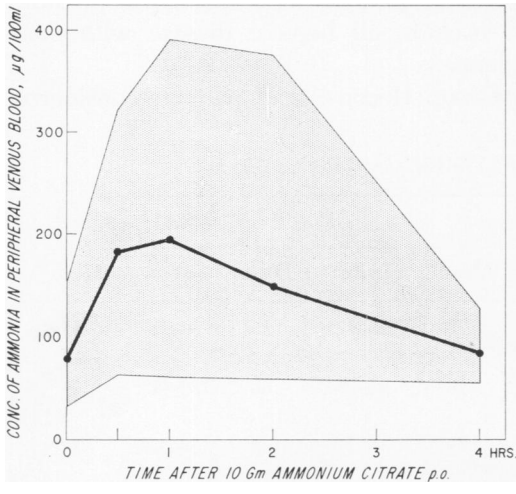

FIG. 3. Group III. (30 Cases) Patients with *both* compensated cirrhosis and portal-systemic shunting.

to have well-compensated cirrhosis with no evidence of esophageal varices or other porto-systemic shunting judged by clinical, radiological or endoscopic criteria.

Group III is similar to Group II except that all the patients had demonstrable esophageal varices shown at the time of operation or by splenoportography, barium swallow, or endoscopy.

Group IV consists of patients whose liver function was so poor as to be classified as decompensated. Criteria for this classification included grossly abnormal liver function tests, clinical jaundice, ascites, defects in the blood clotting mechanisms, and episodes of coma or pre-coma. This group included those known to have portal-systemic collateral circulation, as well as those in whom this had not been demonstrated.

Results

The results are summarized in Table 1.

In Figures 1 to 4 are graphed the arithmetic mean of and the range of concentrations of ammonia found in the peripheral venous blood before and up to four hours after the ingestion of 5 to 10 Gm. of ammonium citrate in each of the four groups of patients.

It can be seen that there is some overlapping of the range of readings obtained in each of the four groups of patients. This is hardly surprising in view of the obvious difficulties of exactly categorizing individual patients. However, when the arithmetic means of readings of these various groups are considered, it is evident that the patients without liver disease and those with well-compensated liver disease and no evidence of portal-systemic collaterals show essentially similar curves with little or no hyperammoniemia in response to the provocative dose of ammonium salts.

These are in sharp contrast to the mean curve of the patients with well-compensated liver disease, but with evidence of having portal-systemic collateral circulation. This Group (III) shows a sharp rise in periph-

eral venous blood ammonia concentration reaching a maximum 30 to 60 minutes after the oral administration of ammonium citrate. Thereafter, there is a rapid decrease with a return of the mean concentration to normal limits after four hours.

The patients with decompensated liver disease (Group IV) showed a similar increase in peripheral ammonia to the previous group. However, in contrast to Group III the majority of determinations remained as high, if not higher after two hours. In addition, it was uncommon for the four-hour reading to be within the normal range (40–70 γ %). The existence of decompensation made it difficult to separate the factors of shunting from intrinsic defects in urea synthesis by this technic.

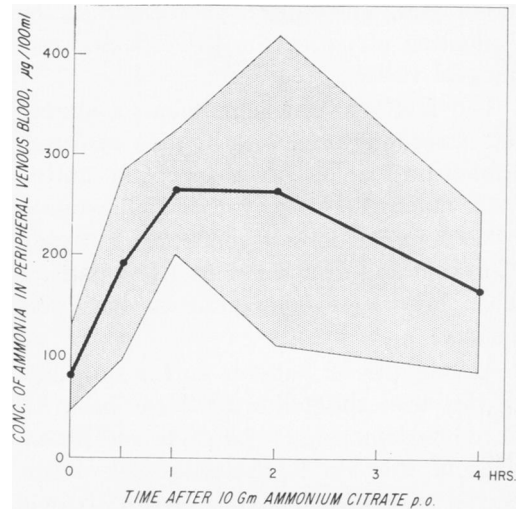

FIG. 4. Group IV. (15 Cases) Patients with advanced and decompensated cirrhosis with or without portal-systemic collaterals.

Discussion

The data presented here from the investigation of 92 patients with and without cirrhotic liver disease and with and without portal-systemic collateral circulation, shows the clinical value of this simple test.

Using the technic described above, it is not possible to distinguish normal subjects from those with well-compensated liver disease without portal-systemic shunting. No doubt if simultaneous peripheral arterial and venous sampling had been carried out, a distinction might have been apparent as was indicated in the studies of Conn [2] and of Stahl.[11] Both these authors showed a rise in peripheral arterial ammonia levels in all cirrhotic patients. On the other hand, some of the value of this test would have been lost had only peripheral arterial sampling been used, since these same workers were unable to determine the presence or absence of portal-systemic shunts in patients with well-compensated hepatic disease. With peripheral venous sampling, there is a sharp contrast in the pattern of the curves of patients with and without esophageal varices.

The group of patients with decompensated liver disease, the majority of whom also had esophageal varices, show initially a similar pattern of peripheral venous ammonia concentrations similar to those with well-compensated liver disease with portal-systemic shunting. However, the failure of the blood ammonia to fall rapidly after the first hour is in contrast to those with well-compensated disease and no doubt reflects a diminished ability of the liver to synthesize urea from the ammonia presented to it. In similar patients, White [13] has demonstrated this by means of simultaneous sampling of hepatic and peripheral veins, showing that in the presence of a poorly functioning liver, the hepatic venous ammonia concentration exceeds the peripheral venous level after the ingestion of ammonium chloride. With a well-compensated liver, but demonstrable portal-systemic shunting, the hepatic vein concentration is lower than the peripheral venous ammonia concentration.

In the opinion of the authors, this test has been a very sensitive index of the presence of portal-systemic shunting and should take its place alongside other chemical,

radiological, and endoscopic technics in the evaluation of patients with suspected esophogeal varices.

The fact that the ammonium tolerance test is not interfered with by the concurrent administration of broad-spectrum antibiotics widens the scope for its application.

No complications beyond transient mild confusion and drowsiness in a few patients with hepatic decompensation have occurred.

Among the 92 patients so far subjected to this test, the following have been selected to demonstrate the value and limitations of this aid to the diagnosis of suspected esophageal-gastric varices. It will be seen that the ammonium tolerance test is frequently more accurate in defining the presence or absence of esophageal varices than are radiological or endoscopic investigations.

Case Reports

Case 1. I. G., a 61-year-old woman, entered this hospital in June, 1961 with a history of five previous episodes of upper gastro-intestinal bleeding. For nine years she had been known to have cirrhosis of undetermined etiology. During previous admissions, she had four barium swallows and one esophagoscopy, which failed to demonstrate varices or any other source of bleeding.

On admission, she had been vomiting blood for two and a half days. Spider angiomata and palmar erythema were present. The lower margin of the right lobe of her liver was palpable two fingerbreaths below the costal margin, but the spleen was not palpable. There were moderate abnormalities in standard tests of liver function.

Emergency esophagoscopy showed large bleeding varices in the lower third of the esophagus. Following this, a Sengstaken tube was placed for two days and all bleeding controlled. Later, a barium swallow demonstrated varices for the first time. At the time of operation two weeks after admission, her portal pressure was 41 cm. of water and this was reduced to 16 cm. after a portacaval shunt was constructed. On reviewing her record it was noted that almost two years before this an ammonium tolerance test had been done and peripheral venous ammonia levels recorded as follows: initial 78 γ %, one half hour—175, 1 hour—142, 2 hours—77.

Comment. This illustrates the value of this test in indicating the presence of portal-systemic shunting (and therefore presumably esophageal varices) at a time when x-ray and endoscopic examinations were negative.

Case 2. H. O'K. was a 58-year-old woman who was admitted to this hospital on March 1, 1961 for the investigation of the source of persistent melena and secondary anemia for which a subtotal gastrectomy had been carried out at another hospital. This operation had neither controlled the melena nor demonstrated a source of the bleeding. The spleen was not palpable but there was evidence of "hypersplenism" in the form of mild leucopenia and thrombocytopenia. Liver function tests were within normal range except for a bromsulfapthalein retention of ten per cent and needle biopsy of the liver showed normal histology. There were no abnormalities demonstrated by either upper gastro-intestinal series or by esophagoscopy. An ammonium tolerance test showed the following levels of venous blood ammonia: fasting 77 γ %, one half hour—258, one hour—164, two hours—111, four hours—77. The melena ceased and the patient was discharged with a presumptive diagnosis of portal hypertension and possible esophageal varices.

During the subsequent year she had several minor episodes of gastro-intestinal bleeding and was re-admitted for further study. Splenoportography demonstrated an extrahepatic block in the portal vein with collateral vein channels coursing in the fundus of the stomach and lower esophagus. Splenectomy and spleno-renal shunt were performed. Splenic vein pressure was 33 cm. of saline and fell to 22 after the shunt. Convalescence was uneventful and there have been no further episodes of melena.

Comment. The ammonium tolerance test gave biochemical evidence of portal-systemic shunting secondary to extra-hepatic block at a time when both esophagoscopy and radiological examination of the esophagus showed no evidence of esophageal varices.

Case 3. A. M. was a 31-year-old man who was referred to this hospital after esophageal varices had been described on x-ray examination. Studies had been initiated because of hematemesis, anorexia and weight loss over a five month period. On physical examination, no abnormalities were observed. Liver function tests were all within

normal limits. An upper gastro-intestinal series confirmed the presence of large esophageal varices in the lower third of the esophagus. Ammonium tolerance test however, seemed incompatible with this diagnosis since there was no rise in the peripheral venous blood ammonia at any time following a provacative dose of 10 Gm. of ammonium citrate. The diagnostic confusion was clarified at operation when left thoraco-abdominal exploration revealed an infiltrating carcinoma of the upper stomach with finger-like extensions of tumor beneath the mucosa of the lower esophagus.

Comment. Although submucosal extensions of tumor presented a radiological picture indistinguishable from esophageal varices, the ammonium tolerance test reflected the true situation of a normal portal circulation with portal-systemic shunting.

Case 4. C. J. was a 75-year-old man who was referred to this hospital when x-ray examination following a massive hematemesis showed large gastric and esophageal varices. Except for a bromsulfapthalein retention of ten per cent, liver function tests were normal. An ammonium tolerance test showed the following values: fasting 68 γ %, one half hour—252, one hour—359, two hours—210 and four hours—110. Splenoportogram demonstrated a block in the portal vein just beyond the junction of the superior mesenteric and splenic veins, and a spleno-renal shunt was carried out. Liver biopsy showed normal histology and architecture.

Comment. This case again illustrates the biochemical pattern seen with extensive portal-systemic shunting despite the presence of normal liver function and histology.

Case 5. R. C. was a 61-year-old man who was admitted to the hospital shortly after he had vomited "large amounts" of blood and clots. Four days prior to entry he described an episode of epigastric pain with nausea, vomiting and retching which lasted several hours. On admission, gastric aspirate showed gross blood. There were no stigmata or liver disease and liver function tests were normal. An emergency gastro-intestinal series was unsatisfactory because it was impossible to determine whether demonstrable filling defects in the lower esophagus represented varices or blood clots. A repeat examination on the following day showed "large wormy filling defects in the lower esophagus consistent with varices"; a hiatus hernia was present and a prepyloric ulcer was suspected. An ammonium tolerance test showed no significant

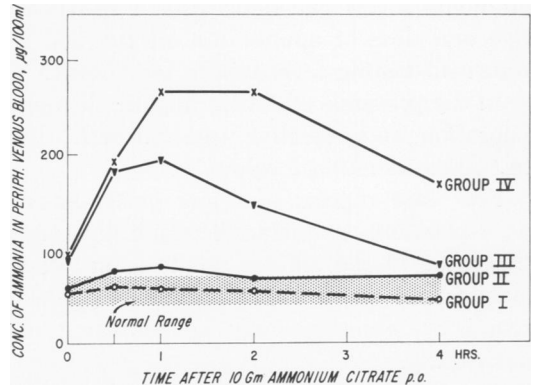

FIG. 5. Comparison of the mean levels of ammonium tolerance in the groups of patients categorized and studied.

rise in venous blood ammonia subsequent to the oral administration of 10 Gm. of ammonium citrate. Six days after admission, he again began vomiting bile-stained material which became grossly bloody. At exploration, a jagged laceration of the mucosa of the cardio-esophageal junction was found to be the source of bleeding and was sutured.

Comment. This case of the Mallory-Weiss syndrome illustrates the diagnostic problems posed in esoteric causes of upper gastro-intestinal hemorrhage and emphasizes the value of the ammonium tolerance test in ruling out esophageal varices.

Summary and Conclusions

An ammonium tolerance test is described in which peripheral venous blood ammonia levels are determined over a four-hour period subsequent to the oral administration of five to ten Gm. of ammonium citrate.

Ninety two patients have been studied in this fashion and categorized in four groups: I—normal; II—compensated liver disease without esophageal varices; III—compenated liver disease with esophageal varices; IV—decompensated liver disease with and without varices. Patterns of ammonium tolerance are described for each category.

In patients without hepatic decompensation, the test reflects the presence of portal-systemic shunting by a sharp rise in venous

ammonia levels one hour after a provocative oral dose of ammonium citrate, and a return to fasting level within four hours.

In the presence of severe hepatic decompensation, and defective urea synthesis, the test loses its clinical value.

Five case reports of upper gastro-intestinal bleeding are included which illustrate the value of the ammonium tolerance test in instances where radiologic or esophagoscopic examinations may be confusing or misleading.

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