Liver-Function Tests in Patients Receiving Iproniazid

LOUIS ZETZEL, M.D.,* HERMAN KAPLAN, M.D.,† and KARL T. DUSSIK, M.D.‡

THE RECENT AND EXTENSIVE USE of iproniazid in a variety of clinical conditions has focused attention not only on its usefulness but on certain undesirable associated reactions. A clinical picture and laboratory findings indistinguishable from viral hepatitis have been seen in some patients during iproniazid administration.[1-8] The best statistics presently available indicate a case incidence of 1:4000 and are based on incomplete reports of hepatitis among an estimated number of 400,000 patients receiving this drug.[9] The mortality rate is more firmly established and in practically all series is 15–20 per cent of those involved with hepatitis.

The protocols of those patients succumbing to iproniazid hepatitis fail to reveal any early clue to the subsequent and rapid clinical deterioration. It was felt that the serial determination of appropriate laboratory tests might indicate such a degree of liver damage that the drug could be omitted before serious disease had become established. Shay and Sun had suggested that abnormalities in serum glutamic oxalacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT), might offer the earliest evidence of iproniazid liver toxicity.[10]

MATERIAL AND METHOD

To this end a group of 34 patients in a large general psychiatric hospital was studied for approximately three months while they were receiving iproniazid.§ Thirty patients had already been re-

From the Gastrointestinal Clinic and the Medical Service, Beth Israel Hospital, the Department of Medicine, Harvard Medical School, and the Metropolitan State Hospital, Boston, Mass.

*Assistant Clinical Professor of Medicine, Harvard Medical School; Chief, Gastrointestinal Clinic, Beth Israel Hospital. †Research fellow in medicine, Harvard Medical School; assistant resident in gastroenterology, Beth Israel Hospital; United States Public Health Service trainee. ‡Clinical instructor in psychiatry, Tufts University Medical School; senior psychiatrist, Metropolitan State Hospital.

§The iproniazid used in this study was the trademarked brand, Marsilid (Roche Laboratories).

ceiving iproniazid for varying periods of time when the first liver-function tests were obtained. The remaining 4 were observed during a double-blind study, so that liver-function determinations were made during a period of placebo as well as subsequent iproniazid administration. All patients were observed clinically and serial determinations of the serum bilirubin,[11] thymol turbidity,[12] and serum glutamic pyruvic transaminase[13] were made every 7 to 10 days.

RESULTS

All patients had normal serum bilirubin levels throughout the period of observation. In 2 of the 4 patients who received a placebo before iproniazid, all three tests of liver function remained normal throughout the period of observation, and there was no clinical evidence of liver disease. The thymol turbidity reaction was abnormal in the remaining 2 patients in this group even before iproniazid was started, and it remained essentially unchanged during the subsequent period of iproniazid administration. In these same two patients, however, the SGPT, which had remained normal during the period of the placebo administration, was found to be elevated for the first time after 50 and 55 days, respectively, of iproniazid administration (Table 1). In no instance was there any associated clinical evidence of liver disease, nor did any develop subsequently. The SGPT levels were normal when re-examined some nine months later, in spite of continued iproniazid administration.

In the group of 30 patients who had been receiving iproniazid for periods ranging from 10 to 172 days before the first observations were made of liver function, 22 showed neither clinical nor laboratory evidence of hepatic dysfunction throughout the period of study. Four patients had a persistently elevated thymol turbidity test at the very first determination (Table 2). In four other patients in this group there was a distinct rise in SGPT levels after preliminary observations during the preceding 3–12 weeks were normal (Table 3). These were isolated findings and were not associated with or followed by any clinical or other laboratory evidence of liver disease.

DISCUSSION

The elevated thymol turbidity tests in the 6 patients cannot properly be attributed to iproniazid, since these findings were present at the very first determination, in 2 patients even during the period

TABLE 1. Abnormal Liver-Function Tests in Controlled Patients

Name	Age	Sex	Diagnosis	Average daily dose iproniazid	Date		Bilirubin (mg./100 cc.)	Thymol turbidity (units)	SGPT (units)
A. S.	52	F	Manic-depressive reaction	50 mg.	During placebo administration	3-20-58	0.4	10.0	17
						4- 1-58	0.4	11.8	3
						4-10-58	0.4	6.7	3
						4-22-58	0.1	11.1	3
					During iproniazid administration	5- 6-58	0.3	13.1	8
						5-22-58	0.8	7.9	8
						6- 3-58	0.3	9.2	25
						6-24-58	0.3	9.6	47
						4-14-59	..	11.5	25
R. H.	70	F	Manic-depressive reaction	150 mg.	During placebo administration	3-25-58	0.5	0.7	17
						4- 1-58	0.4	14.0	8
						4-10-58	0.3	11.5	8
						4-22-58	0.1	12.6	3
					During iproniazid administration	5- 8-58	0.3	8.8	2
						5-22-58	0.3	8.2	3
						6- 3-58	0.2	10.4	3
						6-12-58	0.2	9.6	15
						6-26-58	0.6	7.2	47
						4-14-59		7.9	14

TABLE 2. Abnormal Thymol Turbidity Test in Patients Receiving Iproniazid Without Previous Control Studies

Name	Age	Sex	Diagnosis	Duration of iproniazid administration before first liver-function tests	Average daily dose iproniazid (mg.)	Date	Bilirubin (mg./100 cc.)	Thymol turbidity (units)	SGPT (units)
F. A.	41	F	Schizophrenia	73 days	150	4-17-58	1.8	6.2	2
						4-29-58	0.7	7.5	3
						5- 8-58	0.5	7.9	18
						5-20-58	0.4	10.6	6
						5-29-58	0.3	5.0	2
						6-10-58	0.6	7.9	3
						6-19-58	0.6	6.6	3
						4-23-59	.	7.2	14
L. S.	71	F	Schizophrenia	110 days	50–100	3-25-58	0.5	0.2	10
						4- 1-58	0.5	10.0	8
						4-15-58	0.6	8.9	8
						4-22-58	0.2	9.6	22
						5- 6-58	0.4	9.6	6
						5-22-58	0.6	8.8	10
						6- 3-58	0.5	10.6	11
						6-12-58	0.3	7.7	11
						6-24-58	0.4	6.2	15
						4-23-59	..	6.6	274
						5- 4-59	..	7.5	75
P. C.	67	F	Paranoid state	98 days	50–100	3-25-58	0.5	0.4	17
						4- 1-58	0.5	9.2	3
						4-10-58	0.4	6.9	12
						4-22-58	0.3	9.6	20
						5-16-58	0.2	13.8	8
						5-22-58	0.3	13.6	11
						6- 3-58	0.4	15.3	8
						6-12-58	0.1	11.3	11
						6-24-58	0.5	11.1	33
						4-23-59	..	5.6	14
B. G.	68	F	Psychoneurosis	22 days	100	5-22-58	0.2	8.9	3
						6- 3-58	0.3	6.9	2
						6-12-58	0.5	8.6	6
						6-24-58	0.6	7.9	18
						4-23-59	..	13.1	36

TABLE 3. Abnormal SGPT Levels in Patients Receiving Iproniazid Without Previous Control Studies

Name	Age	Sex	Diagnosis	Duration of iproniazid administration before first liver-function tests	Average daily dose iproniazid (mg.)	Date	Bilirubin (mg./100 cc.)	Thymol turbidity (units)	SGPT (units)
B. P.	61	F	Involutional psychosis	17 days	50	5- 6-58	0.6	5.5	22
						5-22-58	0.6	3.6	8
						6- 3-58	0.8	3.9	13
						6-12-58	0.4	4.6	106
						6-24-58	0.5	2.8	4
						4-14-59	..	3.6	16
R. L.	74	F	Senile psychosis	10 days	100	3-25-58	0.9	0.2	13
						4- 1-58	0.8	5.0	3
						4-10-58	0.8	2.5	3
						4-22-58	1.2	3.6	2
						5-22-58	0.1	5.3	3
						6- 3-58	0.2	5.3	3
						6-12-58	0.9	3.7	3
						6-24-58	1.0	3.9	140
						4-14-59	1.2	6.6	6
G. V.	69	M	Manic-depressive psychosis	172 days	50	5-29-58	0.4	3.9	2
						6-13-58	0.7	4.1	11
						6-24-58	0.3	5.0	66
						4-22-59	..	5.0	6
J. F.	55	F	Depressive reaction	44 days	100	5-22-58	0.4	2.2	10
						6- 3-58	0.1	2.5	8
						6-13-58	0.2	4.4	26
						6-24-58	0.4	3.0	43

of placebo administration. These results may be explained in the light of findings by Kline that in 85 per cent of several thousand patients in a large mental hospital one in four routine liver-function tests were outside the normal range even before any drug therapy had been instituted.[9]

The development of a significant rise in SGPT levels in 6 of 34 patients after a preliminary period of normal observations is more readily associated with iproniazid administration. Whether the elevated SGPT is actually due to iproniazid or to some nonspecific abnormality of the liver as a reflection of nutritional deficiencies or other vague aberrations in mental patients cannot be determined. Of importance is the fact that these SGPT abnormalities, whatever their cause, were not associated with or followed by any clinical or other laboratory evidence of liver disease, in spite of continued administration of iproniazid.

Pare and Sandler have recently described levels of SGOT above 28 units in 9 of 29 patients receiving iproniazid and advised discontinuance of the drug if the level rose above 40 units.[14] In our studies SGPT levels were determined because of their more specific relation to liver disease and as a more sensitive reflection of acute hepatitis.[15] Only levels above 40 were considered abnormal. Our own findings bear out the skepticism of others as to the value of any liver-function test as a warning sign of impending disaster.[10]

CONCLUSIONS

Elevations in SGPT may occur in mentally sick patients receiving iproniazid, but they do not foreshadow the inevitable development of liver disease in spite of continued administration of the drug.

REFERENCES

1. O'Connor, J. B., Howlett, K. S., Jr., and Wagner, R. R. Side effects accompanying use of iproniazid. *Am. Rev. Tubere. 68:*270, 1953.
2. Zetzel, L., and Kaplan, H. Liver damage concurrent with iproniazid administration. *New England J. Med. 258:*1209, 1958.
3. DeVerteuil, R. L., and Lehmann, H. E. Therapeutic trial of iproniazid (Marsilid) in depressed and apathetic patients. *Canad. M.A.J. 78:*131, 1958.
4. Rosenblatt, M. B. Iproniazid (Marsilid) hepatitis. *New York J. Med. 58:*3680, 1958.
5. Kahn, M., and Perez, V. Jaundice associated with the administration of iproniazid. *Am. J. Med. 25:*898, 1958.
6. Frantz, A. G. Fatal jaundice associated with iproniazid (Marsilid) therapy (Report of a case). *J.A.M.A. 167:*987, 1958.

7. SMARR, E. R., WOLF, H., and PRESSMAN, M. D. Experiences with Marsilid with report of one death. *Am. J. Psychiat. 114*:1115, 1958.
8. POPPER, H. Pathological findings in jaundice associated with iproniazid therapy. *J.A.M.A. 168*:2235, 1958.
9. MATTIA, V. D., *et al.* Discussion: Is Marsilid a dangerous drug? *Dis. Nerv. System 19*:548, 1958.
10. SHAY, H., and SUN, D. C. H. Massive necrosis of the liver following iproniazid. *Ann. Int. Med. 49*:1246, 1958.
11. MALLOY, H. T., and EVELYN, K. A. Determination of bilirubin with photoelectric Colorimeter. *J. Biol. Chem. 119*:481, 1937.
12. REINHOLD, J. G. In SIMMONS, J. S., and GANTZKOW, C. J. (Eds.): *Medical and Public Health Laboratory Methods.* Philadelphia, Lea, 1955.
13. REITMAN, S., and FRANKEL, S. A colorimetric method for the determination of serum glutamic oxalacetic and serum pyruvic transaminases. *Am. J. Clin. Path. 28*:56, 1957.
14. PARE, C. M. B., and SANDLER, M. Acute hepatic necrosis following iproniazid therapy. *Lancet 7067*:282, 1959.
15. WROBLEWSKI, F., and LADUE, J. S. Serum glutamic pyruvic transaminase (SGP-T) in hepatic disease: A preliminary report. *Ann. Int. Med. 45*:801, 1956.