ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 1978, p. 636-638
0066-4804/78/0014-0636$02.00/0

Vol. 14, No. 4
Printed in U.S.A.

Artifactual Depression of Serum Glutamic Oxaloacetic Transaminase by Metronidazole

J. PETER RISSING,* CHERYL NEWMAN, AND WILLIAM L. MOORE, JR.

Veterans Administration Hospital and Department of Medicine, Medical College of Georgia, Augusta, Georgia 30904

Received for publication 24 April 1978

Eighteen patients developed abnormally low serum glutamic oxaloacetic transaminase values during metronidazole therapy. Metronidazole absorbs at 340 nm, simulating reduced nicotinamide adenine dinucleotide, which is the final colorimetric product of the serum glutamic oxaloacetic transaminase assay.

Metronidazole is undergoing clinical trials in the treatment of anaerobic infections in the United States. In vitro studies suggest excellent activity against many clinical anaerobic pathogens (4). *Bacteroides fragilis* is rapidly killed by metronidazole in vitro (11). Clinical studies suggest that metronidazole is useful in serious anaerobic infections (7, 8, 10, 13-15).

We report a potentially confusing factitious depression of the serum glutamic oxaloacetic transaminase (SGOT) in patients treated with metronidazole.

Patient selection. Eighteen consecutive patients were identified as infected by the isolation of one or more pathogenic anaerobic organisms in appropriate cultures of surgical specimens, translaryngeal sputum collections, paracentesis fluid, or wound cultures. Written informed consent was obtained from all patients.

Treatment. Nine patients received parenteral metronidazole at approximately 30 mg/kg per day; 13 patients received oral metronidazole in similar doses. Five patients received both formulations. Doses were calculated to obtain serum levels of 15 μg/ml. In 14 of 15 studied patients, plasma metronidazole levels approximated or exceeded this (metronidazole levels courtesy of G. D. Searle Laboratories by high-pressure liquid chromatography, method of A. A. Schwartz).

Monitoring. All patients were monitored for potential adverse effects by daily examination, frequent multiphasic screening tests, complete blood counts, and urinalysis. Routine monitoring of serum enzymes was done in a Technicon SMA-12/60. Additional SGOT determinations were performed on the Technicon SMAC system. Normal SGOT values are 7 to 40 and 7 to 41 IU, respectively.

All 18 patients developed abnormally low SGOTs; in 16 of 18 patients the SGOT fell to zero (Table 1). Onset of this abnormality was typically abrupt, although several patients had a gradual downward trend. With cessation of metronidazole the SGOT values returned promptly to pretreatment levels or to levels consistent with the patient's disease in all cases studied. An elevated SGOT prior to metronidazole therapy was not protective; six patients with an initially elevated SGOT were found to have abnormally low levels during therapy.

Other serum enzyme measurements, including lactic dehydrogenase and alkaline phosphatase, and bilirubin remained normal or consistent with the patients' known diseases. One patient had multiple abdominal abscesses from an anastomatic breakdown after total gastrectomy. Prior to treatment his bilirubin, alkaline phosphatase, and SGOT were all elevated. During metronidazole therapy the SGOT decreased progressively, reaching a nadir of 0 IU. Twelve hours after cessation of metronidazole the SGOT rebounded to 264 IU, entirely compatible with his illness.

SGOT levels are determined by a two-step enzymatic reaction. The unknown quantity of glutamic oxaloacetic transaminase (GOT) in serum catalyzes the reaction of alpha-ketoglutamic acid to oxaloacetic acid and glutamic acid. Oxaloacetic acid then reacts with reduced nicotinamide adenine dinucleotide (NADH) in the presence of malate dehydrogenase to form malate and NAD. NADH absorbs at 340 nm; NAD does not. The reaction is monitored at 340 nm; high levels of GOT are associated with decreased amounts of NADH and decreased absorbance at 340. Therefore, the SGOT scale is inverted such that low levels of SGOT are associated with high absorbency at 340 nm.

Metronidazole has an extinction coefficient of approximately 320 nm, but 65% of this activity remains at 340 nm (L. Hunt, personal communication). It was postulated that therapeutic levels of metronidazole interfered with the se-

rum assay by nonspecific absorption, simulating that of NADH. Preliminary experiments disclosed that " spiking" normal human sera with metronidazole generated low SGOT readings. Five paired sera from patients receiving metronidazole were tested by Technicon's SMA-12/60 and SMAC systems. The SMAC system differs from the SMA-12/60 by using the patient's own sera as a blank. Absorbance is then compared to the blank. This system obviates nonspecific spectrophotometric absorption and more closely resembles a kinetic enzyme analysis. Comparison confirmed that the observed abnormality is artifactually induced by the method of measurement (Table 2).

Serum glutamic pyruvate transaminase results were also obtained in selected patients by using the SMAC system and were normal where studied; none were done on the SMA-12 system.

Factitious depression of absorption of NADH at 340 nm in the presence of metronidazole has been documented previously (5). The effect was attenuated by using a 2-mm light path instead of the more conventional 10-mm light path. Both Technicon instruments use a rather long 15-mm light path, which would probably augment any nonspecific absorption.

Singh et al. studied the in vitro effect of 45 commonly used drugs on the 12 automated tests of the Technicon SMA 12/60 (12). Only eight had effects at clinical concentrations. Most artifactual abnormalities of the SGOT are elevations, although depressions have been noted with psychotropics: fluspirilene (1), trifluoperazine (2), and clothiapine (9); and also with pindolol (9), progestogen (6), pyridoxine deficiency (3), and hemodialysis (16).

These factitious results should not be dismissed. One managing physician erroneously interpreted the cause of death as "total hepatic failure" in his patient because of these laboratory data. Several other physicians were confused and responded by ordering more SGOT determinations. Hepatic abscesses and peritoneal infections are commonly caused by anaerobic organisms, frequently by *B. fragilis*. Whereas diminution of parameters thought to assess obstructive biliary disease (bilirubin and alkaline phosphatase) are normally followed in these patients, the diminution of the SGOT is frequently used as ancillary evidence of improvement. Failure to appreciate the significance of these findings could allow the physician a false sense of security.

TABLE 1. *SGOT values in metronidazole-treated patients*

Patient no.	SGOT (IU)		
	Pretherapy	During therapy[a]	Post-therapy
1	21	0 (10)	9
2	19	0 (5)	17
3	263	0	NA[b]
4	80	0	264
5	4	0 (5)	NA
6	122	0 (2)	NA
7	15	0 (2)	24
8	23	0	27
9	14	0	21
10	135	5	30
11	30	0 (9)	43
12	24	0	NA
13	19	0	27
14	24	0	NA
15	38	6	38
16	63	0	16
17	NA	0	15
18	80	0	22

[a] Results presented are nadirs; numbers in parentheses denote number of observations. Results during therapy differ from those both pre- and post-therapy. $P < 0.002$ and $P < 0.02$, respectively (Student's independent t test).

[b] NA, Not available.

TABLE 2. *SGOT values of paired sera from patients receiving metronidazole*

Patient no.	SGOT by SMA-12 (IU)	SGOT by SMAC[a] (IU)
12	0	38
13	3	33
14	0	17
15	12	39
16	4	18

[a] $P < 0.005$ (Student's dependent t test).

This investigation was supported in part by a grant from the G. D. Searle Co.

The technical assitance of T. Buxton and W. Moore III and the secretarial assistance of Brenda Vaughn are gratefully acknowledged.

LITERATURE CITED

1. **Bankier, R. G.** 1973. A comparison of fluspirilene and trifluoperazine in the treatment of acute schizophrenic psychosis. J. Clin. Pharmacol. **13**:44–47.
2. **Bankier, R. G., and F. A. L. Mathewson.** 1972. A clinical study of mesoridazine and trifluoperazine in relapsed schizophrenic patients. Dis. Nerv. Syst. **33**:529–534.
3. **Baysal, A., B. A. Johnson, and H. Linkswiler.** 1966. Vitamin B6 depletion in man: blood vitamin B6, plasma pyridoxal-phosphate serum cholesterol, serum transaminases and urinary vitamin B6 and 4-pyridoxic acid. J. Nutr. **89**:19–23.
4. **Chow, A. W., V. Patten, and L. B. Guze.** 1975. Susceptibility of anaerobic bacteria to metronidazole: relative resistance of non-spore-forming gram-positive baccilli. J. Infect. Dis. **131**:182–185.
5. **Coombs, G. H., and B. R. Rabin.** 1974. Flagyl and reduced nicotinamide adenine dinucleotide. FEBS Lett. **42**:105–107.

6. **Eckstein, P., M. Whitby, K. Fotherby, et al.** 1972. Clinical and laboratory findings in a trial of Norgestrel, a low-dose progestogen-only contraceptive. Br. Med. J. **3**:195–200.
7. **Ingham, H. R., G. E. Rich, J. B. Selkon, et al.** 1975. Treatment with metronidazole of three patients with serious infections due to *Bacteroides fragilis*. J. Antimicrob. Chemother. **1**:235–242.
8. **Ingham, H. R., J. B. Selkon, S. C. So., et al.** 1975. Brain abscess. Br. Med J. **4**:39–40.
9. **Jadin-Starodoubsky, A., P. A. Delwaide, and C. Penders.** 1973. Psychotropic drug interferences with clinical chemistry determination, p. 299. *In* G. Seist (ed.), Reference values in human chemistry. S. Karger Basel.
10. **Mitre, R. J., and E. B. Rotheram, Jr.** 1974. Anaerobic septicemia from thrombophlebitis of the internal jugular vein (successful treatment with metronidazole). J. Am. Med. Assoc. **230**:1168–1169.
11. **Nastro, L. J., and S. M. Finegold.** 1972. Bactericidal activity of five antimicrobial agents against *Bacteroides fragilis*. J. Infect. Dis. **126**:104–107.
12. **Singh, H. P., M. A. Herbert, and M. H. Gault.** 1972. Effect of some drugs on clinical laboratory values as determined by the Technicon SMA 12/60. Clin. Chem. **18**:137–144.
13. **Study Group.** 1974. Metronidazole in the prevention and treatment of bacteroides infections in gynecological patients. Lancet **ii**:1540–1543.
14. **Study Group.** 1975. An evaluation of metronidazole in the prophylaxis and treatment of anaerobic infections in surgical patients. J. Antimicrob. Chemother. **1**: 393–401.
15. **Tally, F. P., V. L. Sutter, and S. M. Finegold.** 1975. Treatment of anaerobic infections with metronidazole. Antimicrob. Agents Chemother. **7**:672–675.
16. **Wolf, P. L., D. Williams, and N. Coplon.** 1972. Low aspartate transaminase activity in serum of patients undergoing chronic hemodialysis. Clin. Chem. **18**: 569–570.