Brit. J. Psychiat. (1983), **142,** 388–390

Abnormal Metabolite in Alcoholic Subjects

STEWART WOLF, MICHAEL E. FELVER, MARK D. ALTSCHULE, NICHOLAS T. WERTHESSEN, ROBERT GERNER and RICHARD L. VEECH

Summary: 2,3-butanediol appears in the blood of some alcoholics following ethanol ingestion. Whether it be a genetic trait or a phenomenon of induction remains to be determined. It may be associated in some way with depression.

Higher alcohols including 2,3-butanediol have been identified in the blood of the patients with hepatic coma and severe uremia, as well as in alcoholics suffering from lactic acidosis (Thölen *et al,* 1961; Thölen *et al,* 1962a, 1962b, 1962c; Soling *et al,* 1964 and Mamer *et al,* 1978). Apart from these situations of severe metabolic derangements, 2,3-butanediol was reported over 25 years ago in the blood of physically healthy individuals suffering from manic-depressive psychosis (Dawson *et al,* 1956a and 1956b).

The chemical measurements in these studies were performed by an old analytical technique. Altschule *et al* (1977), using gas chromatography (GLC) reported the presence of 1,3-butanediol in the blood of a patient who had displayed violent behaviour following alcohol consumption. The present study used a new and highly sensitive GLC method for measuring higher alcohols in blood, with confirmation by mass spectrometry (see Felver *et al,* 1980; Veech *et al,* 1981). One hundred and thirteen unselected alcoholic patients (27 females and 86 males) ranging in age from 15 to 79 years admitted during a period of nearly 16 months between 11/29/78 to 3/12/80 to an alcohol detoxification center in Bethlehem, Pennsylvania, had their blood ethanol and diols measured. Their serum was separated, frozen and stored at minus 70°C and then sent blind to the Intramural Laboratory of Metabolism of the National Institute of Alcohol Abuse and Alcoholism. From 26 of the subjects subsequent blood specimens were obtained 18 hours later and analyzed in the same fashion. Fifty-four non-alcoholic healthy subjects (15 females and 39 males) between 27 and 81 years of age including 7 non-alcoholic diabetics (3 females and 4 males) between 46 and 72 years of age served as controls.

Analysis

Ethanol concentration of whole serum was determined by a modification of the method of Baker (Baker *et al,* 1969) using a 6-ft. porapak QS column operated at 125°C. The carrier gas was helium. At a flow rate of 30 ml/min ethanol eluted at 4.1 minutes free from interfering peaks.

2,3-butanediol, 1,3-butanediol and 1,2-propanediol were measured in deproteinized sera using a 6-ft. column packed with Porapak PS coated with 3 per cent Carbowax 20 M. Serum proteins were removed by precipitation with 0.5 M perchloric acid. The clear, protein-free supernatant was neutralized with KOH in order to remove perchlorate ion and to eliminate artifactual peaks often encountered in acidified extracts. 2,4-pentanediol (Aldrich Chemical Co., Milwaukee, WI) was arbitrarily chosen as the internal standard and was added to the serum extracts immediately prior to analysis. At 150°C, with a helium flow rate of 15 ml/min, 1,3-butanediol, and the internal standard were eluted at 5.2, 9.8 and 10.8 min, respectively.

The recovery of both isomers of butanediol and 1,2-propanediol from serum was 99 per cent as determined by standard addition of the diols (Aldrich) to serum from control subjects before deproteinization. The identifications of 2,3-butanediol and 1,2-propanediol in serum samples from alcoholic patients was confirmed by mass spectrometry. The detection limit of this method for the diols is 1 nanogram (11 picomoles).

Results

Ethanol in concentration ranging from 3 to 96 mM was found in the serum of 78 of the 113 alcoholics but in none of the 54 controls.

2,3-butanediol was found in concentrations ranging from 0.01 to 0.841 mM in the serum of 79 of the 113 alcoholics tested at the time of admission. In ten cases there was no alcohol present, but 2,3-butanediol up to 0.059 mM, while nine had ethanol in concentrations as high as 85 mM, but no detectable 2,3-butanediol. Eighteen hours after admission neither alcohol nor butanediol were present.

1,3-butanediol was never found but propanediol was detected. Unfortunately, because many of the specimens were collected in vacutainers lined with a plasticizer that apparently contained traces of 1,2-propanediol, the significance of the propanediol must remain in doubt.

The clinical diagnoses made entirely independently included alcoholic hepatitis or cirrhosis of the liver in 29 cases; diabetes mellitus in eight and Korsakoff's syndrome in six. There was no correlation between the presence or severity of these conditions and the presence or absence of butanediol in the blood. Nor did butanediol correlate with the age of the patient, severity or duration of the alcoholism, or the type of alcoholic beverage said to be consumed. Indeed, the groups with and without 2,3-butanediol in their blood although discordant as to numbers, were well matched on age and sex and clinical data.

A diagnosis of mental depression had been recorded on the hospital charts of a fifth of the 113 alcoholic subjects. The serum of all but two contained measurable concentration of ethanol ranging from 4 to 70 mM. 2,3-butanediol in concentration ranging from 0.013 to 0.14 mM was found in the serum of all but one of them.

Manic-depressives

Blood sera from 17 manic depressive patients under the care of one of us (R.G.) were tested for 1,2 propanediol, and 2,3 butanediol. In every case the measurements of 2,3 butanediol were less than 0.01 mM.

One 51-year-old alcoholic man with a positive family history of alcoholism was repeatedly studied by one of us (R.L.V.) over a period of 10 years. The patient's uncontrolled drinking began at age 18, marked by episodes of continuous intoxication lasting from five days to 13 weeks and occurring twice to four times a year. During the intervals he drank no alcohol but often used marijuana, cocaine and amphetamines. During the past six years he also displayed profound mood swings typical of manic depressive psychosis. Elevated levels of 1,2 propanediol and 2,3 butanediol were not found during his sober intervals, but after a few days of drinking, 2,3 butanediol concentration reached as high as 0.140 mM, with 1,2 propanediol at 0.057 mM.

Discussion

The reduction of acetoin to 2,3-butanediol is a well-known pathway of microbial metabolism and has also been shown to occur *in vivo* (Dawson and Hullin, 1954). Acetoin has been produced *in vivo* following acetaldehyde ingestion (Stotz *et al*, 1944). Recently Veech and collaborators demonstrated the production of 2,3-butanediol in germ-free rats during the metabolism of ethanol. Moreover, they demonstrated acetoin production by the brain and 2,3-butanediol formation from acetoin by the liver (Veech *et al*, 1981). The clinical significance of the presence of 2,3-butanediol in the blood of alcoholics remains to be determined. The absence of 2,3-butanediol in a segment of the population of alcoholics (12 per cent) despite high serum concentrations of ethanol suggests the possibility of a genetic basis for the high alcohol (Rutstein and Veech, 1978). The suggestive association of the presence of 2,3-butanediol in alcoholics with an independently made diagnosis of depression is intriguing but inconclusive. It does, however, suggest the need for a thorough study of the relationship of 2,3-butanediol to brain function in alcoholic subjects.

Acknowledgement

Supported by Contract N00014 78 C 0233, U.S. Navy Office of Naval Research.

References

Altschule, M. D., Werthessen, N. T. & Miller, S. A. (1977) High levels of endogenous 1,3-butanediol in the blood of a man after ethanol ingestion. *Journal of Toxicology and Environmental Health*, 3, 755–758.

Baker, R. N., Abantz, A. L. & Zack, J. F. Jr. (1969) Simultaneous determination of low alcohols acetone and acetaldehyde in blood by gas chromatography. *Journal of Chromatographic Science*, **7**, 312–14.

Dawson, J., Hullin, R. P. & Crockett, B. M. (1956a) Metabolic variations in manic-depressive psychosis. *Journal of Mental Science*, **102**, 168–77.

—— —— & Pool, A. (1956b) Variations in the blood levels of acetoin and butane-2-3-diol in normal individuals and mental patients. *Journal of Mental Science*, **102**, 168–71.

—— —— (1954) Metabolism of acetoin—the function and utilization of acetoin and butane 2,3 diol in decerebrated cat. *Biochemical Journal*, **57**, 177–80.

Felver, M. E., Lakshmanan, M. R., Wolf, S. & Veech, R. L. (1980) The presence of 2,3-butanediol in the blood of chronic alcoholics admitted to an alcohol treatment center. Alcohol and Aldehyde Metabolizing Systems. IV. Thurman, R.G., (ed.) *Advances in Experimental Medicine and Biology*, **132**, 229–35.

Mammer, O. A., Montgomery, J. A., Tjoa, S. S., Crawhall, J. C. & Feldkamp, C. S. (1978) Profiles in altered metabolism. I. The organic acids accumulating in acute non-diabetic ketoacidosis associated with alcoholism. *Biomedical Mass Spectrometry*, **5**, 287–90.

Rutstein, D. D. & Veech, R. L. (1978) Genetics and addiction to alcohol. *New England Journal of Medicine*, **298**, 1140–41.

Soling, H. D., Kohlhaw, G., Schnermann, J., Holzer, H. & Creutzfeldt, W. (1964) Zur Bedeutung des Acetoins fur die Pathogenese des Coma Hepaticum. *Deutsch Medizinische Wochenschrift*, **89**, 457–63.

Stotz, E., Westerfeld, W. W. & Berg, R. L. (1944) The metabolism of acetaldehyde with acetoin formation. *Journal Biological Chemistry*, **154**, 41–50.

Thölen, H., Bigler, F. & Staub, H. (1961) Zur Pathogenese des Urämiesyndroms. I Mitt: Der Gehalt von Acetoin und 2,3-Butylenglykol im Blut urämischer Patienten. *Pathological Microbiology*, **24**, 262–92.

—— —— HEUSLER, A., STOUFFACHER, W., STAUB, H. (1962a) Zur Pathogenese des Urämiesyndroms. Brentztraubensaure, Acetoin Leberkrank-berten. *Experientia,* **18,** 454–5.

—— —— (1962b) Pathogenetische Beziehungen Zivischen uramischem und hepatischem Koma. *Deutsch Medizinische Wochenschrift,* **87,** 1188–92.

—— —— HEUSLER, A. & STAUB, H. (1962c) Therapie des Leberkomas mit Coenzym A, α-Liponsaure, und Diphosphopyridinnukleotid. *Deutsch Medizinische Wochenschrift,* **87,** 457–63.

VEECH, R. L., FELVER, M. E., LAKSHAMNAN, M. R., HUANG, M. T. & WOLF, S. (1981) Control of a secondary pathway of ethanol metabolism by differences in redox state. In *Current Topics in Cellular Regulation* (ed. Bernard L. Horecker). Volume 18, New York: Academic Press, 151–179.

Stewart Wolf, M.D., *Director, Totts Gap Medical Research Laboratories, Box 1262, Bangor, PA 18013, U.S.A.*

Michael E. Felver, *Research Associate, Laboratory of Metabolism, N.I.A.A.A., 12501 Washington Avenue, Rockville, MD 20852, U.S.A.*

Mark D. Altschule, M.D., *Francis A. Countway Library of Medicine, 10 Shattuck Street, Boston, MA 02115, U.S.A.*

Nicholas T. Werthessen, Ph.D., *Bioscientist, Office of Naval Research, Department of the Navy, 495 Summer Street, Boston, MA 00210, U.S.A.*

Robert Gerner, M.D., *Associate Professor of Psychiatry, UCLA School of Medicine, Los Angeles, CA 90024, U.S.A.*

Richard L. Veech, M.D., *Chief, Laboratory of Metabolism, N.I.A.A.A., 12501 Washington Avenue, Rockville, MD 20852, U.S.A.*

(Received 3 August; revised 2 November 1982)