The effect of disulfiram on the urinary excretion of catecholamine metabolites in alcoholic males

A. H. ROBINS, J. L. BARRON

Summary

The urinary excretion of vanillylmandelic acid (VMA), homovanillic acid (HVA) and total metanephrines (TMNs) was studied in a group of White male alcoholic patients under three experimental conditions — on admission and prior to treatment, after 7 days of administration of a placebo, and after 9 days of administration of disulfiram 400 mg/d. Disulfiram caused a significant decrease in VMA levels compared with the pretreatment ($P<0,01$) and placebo ($P<0,05$) levels. The output of HVA and TMNs was unchanged. It is suggested that disulfiram may produce false-negative results in cases of suspected phaeochromocytoma if VMA levels only are assayed. TMNs would appear to be the measurement of choice in such a situation.

S Afr Med J 1983; **63:** 41-42.

Departments of Clinical Pharmacology and Chemical Pathology, University of Cape Town and Groote Schuur Hospital, Cape Town
A. H. ROBINS, M.D., D.P.M., M.R.C. PSYCH.
J. L. BARRON, M.SC., M.B. CH.B., F.F.PATH.

Date received: 16 September 1982.

Disulfiram inhibits aldehyde dehydrogenase;[1] it is this mechanism which accounts for the alcohol-disulfiram reaction and forms the basis for its use in the treatment of alcoholism. In addition, disulfiram inhibits dopamine-ß-hydroxylase (DBH) through a copper-chelating action.[2] Since DBH catalyses the conversion of dopamine to noradrenaline, we decided to investigate the urinary excretion of catecholamine metabolites in a group of recently admitted alcoholic patients before and after the administration of disulfiram.

Patients and methods

Ten White male alcoholics aged between 22 and 52 years (median age 33,5 years) were studied. They had been admitted to the William Slater Hospital, Cape Town, and had all given informed consent. The project was approved by the Ethical Review Committee of the Faculty of Medicine, University of Cape Town. None of the patients showed clinical evidence of alcohol withdrawal and there were no obvious physical abnormalities on examination.

Twenty-four hour urine specimens were collected in containers containing 10 ml of concentrated hydrochloric acid on the following three occasions: (*i*) on admission to hospital and before treatment (pretreatment phase); (*ii*) after 7 days of placebo administration (placebo phase); and (*iii*) after 9 days of treatment with disulfiram (400 mg/d) (disulfiram phase).

The samples from each subject were assayed in the same batch for vanillylmandelic acid (VMA) by the method of Pisano *et al.*,[3]

TABLE I. URINARY VMA, HVA AND TMN EXCRETION

Patient No.	VMA (μmol/mol creatinine) Pretreatment	VMA Placebo	VMA Disulfiram	HVA (μmol/mmol creatinine) Pretreatment	HVA Placebo	HVA Disulfiram	TMNs* (μmol/mmol creatinine) Pretreatment	TMNs* Placebo	TMNs* Disulfiram
1	1,57	1,31	0,57	1,23	1,16	1,19	0,09	0,22	0,11
2	1,77	1,28	0,52	1,72	1,92	0,19	0,04	0,19	0,05
3	1,46	1,64	1,04	2,05	2,18	3,21	0,33	0,24	0,26
4	1,68	1,58	0,63	3,73	3,47	5,02	0,16	0,13	0,11
5	2,08	1,66	0,32	4,50	3,75	5,35	0,14	0,14	0,20
6	1,12	0,36	0,00	2,30	1,07	3,62	0,13	0,20	0,27
7	1,89	1,42	0,16	5,50	2,60	2,10			
8	1,08	1,20	0,69	4,60	8,40	6,90			
9	2,12	1,68	1,14	2,38	13,70	8,10			
10	1,94	1,34	0,53	5,00	3,00	3,50			
	Significance: disulfiram v. pretreatment — $P < 0,01$; disulfiram v. placebo — $P < 0,05$			**NS**			**NS**		

* This represents metanephrine and normetanephrine.

homovanillic acid (HVA) by the specific colorimetric method described by Barron and Peak,[4] and total metanephrines (TMNs) by the method of Pisano.[5] This latter assay was performed on 6 patients.

Results of the assays were expressed in micromoles per millimole of creatinine. Non-parametric statistics were applied in the form of Friedman's two-way analysis of variance.

Results

There were no significant differences in the HVA or TMN levels (Table I) under the three experimental conditions. However, there was a significant decrease in VMA excretion after the disulfiram phase when compared with the pretreatment phase ($P<0,01$) and with the placebo phase ($P<0,05$) (Table I).

Discussion

This study on male alcoholic patients has shown that the administration of disulfiram (400 mg/d) for 9 days significantly depressed urinary excretion of VMA. This finding is in agreement with studies on normal volunteers[6,7] and it probably reflects the reduced oxidative catabolism of the aldehyde metabolites of noradrenaline and adrenaline to VMA on account of aldehyde dehydrogenase (ADH) inhibition.

The unchanged urinary HVA excretion after disulfiram is not consistent with either of two previous studies on the effects of disulfiram. One of these[7] showed a significant rise in urinary HVA, while in the other[8] there was found to be a reduction in cerebrospinal fluid HVA. The unchanged HVA excretion in our subjects may possibly represent the net effect of increased dopamine concentrations (low DBH activity) and reduced oxidative catabolism (low ADH activity).

Urinary TMN levels were also unaffected by disulfiram administration in our patients. This observation is difficult to explain, especially as one would have expected low concentrations of noradrenaline and adrenaline as a result of DBH inhibition. It must be emphasized, however, that the specific effect of disulfiram on noradrenaline *in vivo* is still not established with certainty. Studies in which noradrenaline concentrations have been measured in human subjects after disulfiram administration have produced conflicting results.[7,9]

The most striking conclusion of this study is the marked reduction in urinary VMA excretion after disulfiram treatment, with no change in urinary TMNs. If VMA estimation were to be used as the sole measurement in the laboratory diagnosis of phaeochromocytoma, disulfiram might produce false-negative results. From our data, however, it would appear that TMN assay is probably the screening test of choice in disulfiram-treated patients with suspected phaeochromocytoma. Furthermore, there would be no need to discontinue the drug prior to investigation. In any case, determination of TMN levels has been reported to be a more reliable indicator of a phaeochromocytoma than VMA.[10]

This project was funded by the South African Medical Research Council and the University of Cape Town Research Fund. We are grateful to Dr Iain S. Fraser and the nursing staff of the William Slater Hospital for their co-operation.

REFERENCES

1. Kjeldgaard NO. Inhibition of aldehyde oxidase from liver by tetraethylthiuramdisulphide (Antabuse). *Acta Pharmacol Toxicol (Copenh)* 1949; **5**: 397-403.
2. Goldstein M, Anagnoste B, Lauber E, McKereghan MR. Inhibition of dopamine-ß-hydroxylase by disulfiram. *Life Sci* 1964; **3**: 763-767.
3. Pisano JJ, Crout JR, Abraham D. Determination of 3-methoxy-4-hydroxymandelic acid in urine. *Clin Chim Acta* 1962; **7**: 285-291.
4. Barron JL, Peak BR. Simplified colorimetry of homovanillic acid. *Clin Chem* 1980; **26**: 527.
5. Pisano JJ. A simple analysis for normetanephrine and metanephrine. *Clin Chim Acta* 1960; **5**: 406-414.
6. Vesell ES, Passananti GT, Lee CH. Impairment of drug metabolism by disulfiram in man. *Clin Pharmacol Ther* 1971; **21**: 785-792.
7. Rogers WK, Benowitz NL, Wilson KM, Abbott JA. Effect of disulfiram on adrenergic function. *Clin Pharmacol Ther* 1979; **25**: 469-477.
8. Major LF, Ballenger JC, Goodwin FK, Brown GL. Cerebrospinal fluid homovanillic acid in male alcoholics: effects of disulfiram. *Biol Psychiatry* 1977; **12**: 635-642.
9. Lake CR, Major LF, Ziegler MG, Kopin IJ. Increased sympathetic nervous system activity in alcoholic patients treated with disulfiram. *Am J Psychiatry* 1977; **134**: 1411-1414.
10. Juan D. Pheochromocytoma: clinical manifestation and diagnostic tests. *Urology* 1981; **17**: 1-12.