Excretion of 4-hydroxy-3 methoxy mandelic acid in cases of ulcerative colitis and diarrhoea of nervous origin

J. T. WRIGHT AND A. K. DAS

From the Department of Gastroenterology, The London Hospital

SUMMARY Urinary excretion of 4-hydroxy-3 methoxy mandelic acid (VMA) was used as an index of catecholamine activity in 59 cases of ulcerative colitis compared with 59 controls and 18 cases of diarrhoea of nervous origin. No significant differences were observed between cases and controls but the level of VMA excretion was raised in nervous diarrhoea.

The cause of ulcerative colitis is unknown, but relapses are commonly related to emotional trauma, and, since catecholamine excretion has often been used to measure the effect of emotional tension (Elmadjian, Hope, and Lamson, 1957; Byers, Friedman, Roseman, and Freed, 1962; Levi, 1963; von Euler, 1964; Hames, Lichtman, and McDonough, 1965; Nestel, Verghese, and Lovell, 1967), we have studied the excretion of 4 hydroxy-3 methoxy mandelic acid (VMA) in this disease.

METHOD

Thirty-five men and 24 women with ulcerative colitis were studied over a period of up to three-and-a-half years in some cases. The cases divided conveniently into two approximately equal age groups, 15 to 39 and 40 to 64 years. A control series matched for age and sex was also studied. Furthermore, during the course of this work similar observations were made on 18 patients with 'nervous' diarrhoea; the diagnosis in these cases was made largely by exclusion, there being no radiological or sigmoidoscopic abnormality and no evidence of infection, endocrine disorder, or malabsorption syndrome; on the other hand all cases had a positive history of nervous tension.

Most of the observations were made on urine samples passed on arrival at a morning gastroenterological clinic, although some 24-hour urine specimens were examined in the event of patients being admitted to hospital. The control series was drawn from patients with other gastroenterological disorders, mainly peptic ulcers, attending the same clinic. The object of this study was to determine whether colitis patients show differences in VMA excretion compared with patients suffering from other gut disorders in many of whom abnormal emotional tension may prevail. Results are expressed in mg/VMA per gram of creatinine.

Urine specimens were acidified to pH 1 as soon as possible after collection and VMA was measured by a modification of Pisano's method (Connellan and Godfrey, 1964). Creatinine was estimated by the method of Bonsnes and Taussky's (1945).

The orange colour of the urine in patients receiving salazopyrin did not appear to affect the results of either VMA or creatinine assays. Other drugs used, including steroids, ACTH, barbiturates, codeine, and phenothiazines, appeared to have no direct effect on results. Duplicate estimations showed a mean difference of only 4% between pairs.

RESULTS

Excretion rates for VMA ranged from 0.90 mg/g creatinine to 11.9 mg/g creatinine but in individuals on whom repeated observations were made variation was relatively slight (Fig. 1 and Table I).

FIG. 1. Urinary VMA/creatinine ratios in three patients with ulcerative colitis studied over a long period.

TABLE I

COEFFICIENT OF VARIATION IN VMA/CREATININE VALUES IN INDIVIDUAL PATIENTS

No. of Observations	No. of Patients	Coefficient of Variation (%)
9	1	26
8	1	43
7	1	31
6	1	35
5	3	32
4	8	41
3	13	23
2	14	24

TABLE II

MEAN URINE VMA/CREATININE RATIOS IN CONTROLS AND IN PATIENTS WITH ULCERATIVE COLITIS AND 'NERVOUS' DIARRHOEA

	Age Group (yr)			
	15 to 39		40 to 64	
	Male	Female	Male	Female
Controls	(15) ¹ 3.1 ± 0.30	(10) 3.4 ± 0.19	(20) 3.28 ± 0.31	(14) 4.0 ± 0.43
Ulcerative colitis	(18) 3.2 ± 0.39	(13) 4.4 ± 0.37	(17) 3.66 ± 0.39	(11) 5.1 ± 0.49
'Nervous' diarrhoea	0 ²	(4) 5.8 ± 1.5	(4) 4.5 ± 1.1	(10) 6.9 ± 0.81

¹Figures in parentheses show numbers of cases in subgroups
²Standard error of mean

Under the circumstances the mean VMA excretion for each group of patients has been compiled from the sum of the mean values for each patient. Table II compares mean VMA excretion rates in the various groups of patients studied. Mean VMA creatinine ratios are higher in women than in men and in both sexes higher in the older than in the younger age group. These differences are likely to be due to lower excretion of creatinine in women than men and in the elderly as compared with the young. Compared with the controls, the ratio is slightly higher in colitis patients and considerably higher in the nervous diarrhoea group.

The inequality of subgroups and other uncontrolled variables inherent in a pilot study of this sort prohibits formal statistical testing of the results but a trial series of analysis of variance was nevertheless performed (Table III). This shows that differences exist between the groups that are unlikely to be due to chance and that these are dependent on the diagnosis, age, and sex of the individual. It is unfortunately impossible to say what is the individual contribution of each of these factors except that the difference between the values for nervous diarrhoea and the controls is indeed likely to be due to the diagnostic difference between these groups.

TABLE III

SERIAL ANALYSIS OF VARIANCE

Source	df	Sum of the Squares	Variance	F	P
Groups	10	149.12	14.91	7.93	<0.01
Error	125	235.14	1.88		
Diagnosis	2	103.02	51.51	24.41	<0.01
Error	133	218.24	2.11		
Sex	1	55.09	55.09	22.39	<0.01
Error	134	329.17	2.46		
Age	1	18.58	18.58	6.81	≠ 0.01
Error	134	365.68	2.73		
Total	135	384.26			

Many of the colitis patients in this series were already under treatment when the study began and few have had serious relapses. Opportunities for making observations in individual patients in both active and quiescent phases have therefore been few, but in 14 out of 20 such cases VMA/creatinine ratios were slightly higher in relapse than in quiescence and in one there was no difference. In two of the remaining six cases the value observed during quiescence was more than double that during activity of the disease, but both values were based on single estimations.

DISCUSSION

Raised VMA excretion in 'nervous' diarrhoea may be only a concomitant feature indicating release of adrenaline from the adrenal medulla as a response to stress or it may indicate a direct neuro-humoral mechanism involving liberation of noradrenaline from sympathetic nerve endings.

Theoretically adrenergic activity in the smooth muscle of the gut is inhibitory, but, as many recent studies have shown that diarrhoeal states are often associated with such inhibition, the theory is quite compatible with the facts. This aspect of the problem might have been clarified by estimation of the catecholamines themselves or of the intermediate breakdown products, 3 methoxy-adrenaline and 3 methoxy-noradrenaline. The disadvantage of studying these substances is their great lability in excretion levels. By measuring VMA excretion, which, as von Euler (1964) observes, is a sluggish index of catecholamine activity, we hope to reduce variation in urine levels consequent upon the immediate stress of attendance at hospital.

We have been unable to show convincing differences in catecholamine activity of colitis patients compared with controls but the general trend of the results suggests that the subject justifies further study. Increased catecholamine excretion is of course not confined to a group of cases with 'nervous'

diarrhoea; several of the colitics in whom nervous stress was obvious also had high VMA excretion rates. However, further experience may show that a high VMA excretion rate is of some diagnostic value in cases of diarrhoea for which there is no obvious physical cause.

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