tion,⁴ and with a similar "intellectual content," were not preferred by the respondents, largely for aesthetic reasons. The greater convenience and economy of reprints cited by several of those who returned the questionnaire no doubt reflected a personal outlook not shared, I imagine, by most reprint providers—although I hope that most would support the solitary philatelist.

If the number of reprint requests reflects the interest generated, it seems an author ought to receive over 110 requests for a paper of above average interest. Most authors accept a moral responsibility to provide reprints and this must be balanced against the costs. Often these are wholly or partially derived from research funds, official sources, or the NHS. In any case, money has to be spent and if borne directly by the individual concerned, as in my case, almost certainly would be better spent on more worthwhile projects or persons.⁵

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(Accepted 26 January 1978)

Department of Infectious Diseases, Royal Free Hospital, Coppelts Wood Hospital, London N10 1JN

PHILIP D WELSBY, MRCP, senior registrar

Trial of aspirin during weaning patients with transient ischaemic attacks from anticoagulants

Treatment with anticoagulants reduces both the frequency of transient ischaemic attacks (TIAs) and the risk of cerebral infarction.^{1 2} One of its problems is recurrence of TIAs and cerebrovascular accidents during the three months after treatment is stopped.^{3 4} Recent work has suggested that, because of its effect on platelets, aspirin may reduce the frequency of strokes and TIAs.⁵ The present study explores the role of aspirin during withdrawal of anticoagulant treatment.

Methods and results

Eighteen patients who had been taking warfarin for at least a year because of TIAs were included. Twelve had had attacks in the carotid (10 hemisphere, two retinal) and six in the vertebrobasilar territory. Thirteen had undergone angiography showing appropriate vascular lesions. After explanation the patients were divided into two groups. Six in each group had had carotid and three vertebrobasilar TIAs. Warfarin was withdrawn from both groups but one group received aspirin, 300 mg twice daily, while the other received inert tablets of identical appearance. The patients were seen every two weeks for three months by a physician who was unaware to which group they belonged.

The attack rate while taking warfarin was 0.02 attacks per patient months (24 attacks in 981 patient months). Three patients had experienced attacks at a time when warfarin had been temporarily reduced. Only one patient had had an attack in the three months before the start of the study. In the three months after warfarin was stopped six patients experienced a total of eight TIAs, the TIA occurring in the same territory as the initial episode. If the three months before and after stopping warfarin are compared, there is a significant increase in the proportion of patients experiencing TIAs ($\chi^2 = 4.01$ $P < 0.05$). Warfarin was restarted within the study period in two of the patients who experienced a recurrence (one at four and the other at seven weeks). The attack rate calculated for the period off warfarin was 0.16 attacks per patient month (eight TIAs in 50.75 patient months). This represents an eightfold increase over the preceding three months on warfarin (0.02 attacks per patient month). There was no difference between the group receiving aspirin and that receiving placebo, three patients in each group having further episodes.

Discussion

The importance of TIAs lies in the increased risk of a stroke, which over five years is roughly one in three. Most TIAs are believed to be due to thromboembolism from carotid lesions. Endarterectomy and anticoagulant treatment are effective in reducing the frequency of

TIAs and the risk of strokes. Although anticoagulants are effective, there are difficulties in their use. Marshall and Reynolds³ showed that there was an increase in ischaemic events when anticoagulants were withdrawn. We confirmed this in the present study, the attack rate showing an eightfold increase.

There is currently considerable interest in the use of aspirin for treating TIAs through its inhibitory effect on platelet aggregation.⁵ On the basis of present information it was appropriate to see whether aspirin would protect patients against the increased risk of thromboembolic incidents during the period immediately after stopping warfarin treatment. The results showed no protective value from aspirin, 300 mg twice daily. This may not be entirely relevant to the general use of aspirin in patients with TIAs, since there may be a unique hypercoagulable state during withdrawal of anticoagulation. Nevertheless, we noted that in each case the TIAs that occurred on withdrawal were in the same territory as the patients' spontaneous episodes, which suggests that the pathophysiological mechanism was still the original one.

Thus, while the roles of surgery and anticoagulants are generally defined, that of aspirin is only now emerging. A more rational choice of treatment for TIAs may be possible when we can detect the presence, source, and nature of embolic material in individual patients better than at present.

We thank Dr R O McKeran for his help in following some of the patients during this study, Seaford Laboratories for a supply of placebo tablets, and Miss Beryl Laatz for maintaining the records of the trial.

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(Accepted 26 January 1978)

Institute of Neurology, National Hospital for Nervous Diseases, London WC1N 3BG

J JESTICO, MRCP, registrar

M J G HARRISON, DM, FRCP, consultant physician

JOHN MARSHALL, MD, FRCP, professor of neurology

Unusual case of skin discoloration

Cyanosis is recognised as a deep blue discoloration of the skin due to increased amounts of reduced haemoglobin in the blood stream. This is particularly evident in the exposed parts of the body such as the face and the fingers and toes. Sulphaemoglobinaemia and methaemoglobinaemia simulate this condition and are usually the effect of drug interference with the haemoglobin molecule. A metallic blue colour is a feature of the absorption of silver, which is particularly striking in its response to ultraviolet light. A somewhat similar colour is seen in cases of haemochromatosis.

We describe here a patient, dubbed "the blue lady", whose remarkable appearance remained a puzzle for many months.

Case report

A 51-year-old nurse had noticed that her lips, face, and trunk had developed a greyish-blue colour which seemed less definite on her fingers and toes. She was a garrulous woman with a long history of psychiatric ailments which had apparently followed poliomyelitis when young, since this had left her severely disabled in spite of numerous operations to correct the deformity of her right leg. The results of all routine tests of the cardiovascular, respiratory, and haematological systems were normal including the arterial blood gases. Spectrographic tests for methaemoglobinaemia and sulphaemoglobinaemia gave negative results. It was noted, however, that the blood had a brown tinge, whereas the plasma was pink. On precipitation of the protein, the supernatant fluid became clear. Scrutiny of many urine specimens showed that it was often dark yellow, though not concentrated. The pH was acid, but when made alkaline the urine changed to an intense purple-blue.

Specific inquiries regarding drugs which might contain a dye showed that she had been taking imipramine hydrochloride and diazepam for six years, but denied completely using gentian violet or methyl violet. Subsequently

she admitted that she swallowed large quantities of the laxative Dorbanex in the belief that she had severe constipation. Witnesses had noted yellow streaks around the mouth, which came from this drug. She was advised to stop taking Dorbanex and to rely on another laxative. This she agreed to do after many exhortations. Eventually, after some months, the blue colour of the skin faded and its normal colour was restored.

Discussion

After the initial negative findings, our investigations centred on the laxative Dorbanex. Its two constituents are (a) poloxamer 188, which is virtually unabsorbed from the gut and thus excreted in the faeces, and (b) danthron, which is a synthetic anthroquinone compound, allied chemically to cascara, senna, rhubarb, and aloes, with an action on the nerve endings of the myenteric plexus to stimulate the muscle of the intestine. Side effects are recognised as a temporary but harmless pink or red colouring of the urine with discoloration of the perianal skin and occasionally of the mucosa of the large intestine.

The interest in this case stems from the greyish-blue colour of the skin in contrast to the pink colour of the plasma. Possibly some interaction between the danthron component of the laxative and phenolphthalein, which she also took in excess, might account for the blue colour, although no colour change occurred on mixing the two in the laboratory. Subsequently, phenolphthalein was added to the urine of another patient taking Dorbanex. No colour change occurred at pH 7.4 or at 8.5. At pH 9.0 an orange colour appeared and above pH 9.4 this became an increasingly deeper red. It could not be established that there was a relation between Dorbanex and other drugs which were present in the blood as a result of treatment of the mental instability. Animal studies were deemed of no value. None the less, despite the obsessional use of a laxative, the rarity of the condition does suggest that a special relationship may have existed.

We thank Dr H E Lewis of Riker Laboratories; Dr J A Vale of the National Poisons Information Service; and Dr R D Stark of the Pharmaceutical Division, Imperial Chemical Industries Ltd.

(Accepted 20 January 1978)

Northern General Hospital, Sheffield S5

C S DARKE, MD, FRCP, consultant physician
R G COOPER, senior technician, chemical pathology

Symptomatic and objective effects of venesection on patients with intermittent claudication

There is no standard medical treatment for intermittent claudication. Reconstructive surgery is suitable only in a small proportion of patients and the results are not satisfactory. Blood flow may be increased by reducing whole blood viscosity.^{1 2} Beneficial effects have

been described in patients with ischaemic heart³ and brain disease after venesection, in both polycythaemic⁴ and in haematologically normal patients.⁵ Theoretical and epidemiological grounds suggest that blood flow and oxygen supply continue to improve as the haematocrit value falls well beneath normal limits. We wished to discover whether measurable benefit was observed after venesection among patients with severe calf claudication.

Patients, methods, and results

Nine patients who developed calf pain within a 200-yard (180 m) walk at their customary speed were selected (see table for details). They had no other clinical features of ischaemic disease. 500 ml of blood was withdrawn from these patients at fortnightly intervals on three occasions. Assessment was made before the first venesection and a fortnight after the final venesection. They indicated whether they experienced any change and were objectively assessed on the following criteria:

Claudication count—The subject "walked" up and down three 9-inch (22.5 cm) steps at a rate of one step per second. The "claudication count" was the time in seconds before the onset of calf pain.

Venous occlusion plethysmography—Arterial blood flow to the calf was measured both before and after two min of arterial occlusion, using mercury-in-rubber strain gauge plethysmography.

Ankle to arm systolic pressure index—This pressure ratio was measured before and immediately after a standard exercise (one step per second, as described above, for one minute). The time required for ankle pressures to return to a new resting value was also recorded.

The results are shown in the table.

Discussion

These preliminary data fail to indicate that it would be fruitful to extend the study. Moreover, there is no indication that venesection to a predetermined haemoglobin concentration would be a more promising approach. If we relate a benefit score derived from the observed changes to the haemoglobin concentration reached after venesection we fail to show any relation between benefit and haemoglobin concentration. There is convincing evidence that reducing raised haemoglobin concentrations in subjects without peripheral vascular disease improves blood flow. Nevertheless, the occlusive lesions in our patients are such that blood flow occurs through the collateral vessels. Under these circumstances a fall in haemoglobin concentration appears to have no consistent effect.

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(Accepted 26 January 1978)

Departments of Vascular Surgery and Haematology, St James's Hospital, Balham, and St George's Hospital, Tooting

T F FORD, FRCS, registrar

A BERENT, BSC, research physiologist, department of surgery

K SPEED, MB, BS, lecturer, department of haematology

M S ROSE, PHD, MRCPATH, consultant haematologist and senior lecturer

J A DORMANDY, FRCS, consultant surgeon

Case No	Age and sex	Hb		PCV		CT		Subjective change		MRF		PF		Systolic blood pressure ankle/brachial (mm Hg)		Recovery time (min and s)	
		Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
1	62 M	15.0	12.2	47	37	1.15	1.20	0	0	8.5	10			115/170	90/150	2	5
2	62 M	13.6	12.5	42	38	>4	>4	0	0	6	7			100/140	90/125	3	10
3	69 M	16.5	14.4	49	41	2.30	>5	0	+	6	5.5	9.3	4.3	110/130	110/	4	1
4	66 M	14.1	10.7	44	34	>5	>5	0	+	3.5	5.7	4.5	16.0	150/180	100/145	20	4.20
5	67 M	16.0	11.6	49	35	3.30	1.0	0	+	7.3	11.0	16.5	12.0	90/	75/145	6	6.30
6	59 F	14.9	12.7	45	39			0	0	6.3	8.5	10.4	17.8	80/	80/110	3.30	4
7	55 F	13.3		40		1.30	1.15	0	0	6.8	4.0	3.8	5.2	90/100	80/130	1	1.30
8	65 M	16.7	14.8	50.5	45	1.20	1.45	0	0	1.9	3.7	5.3	5.3	70/160	85/140	5.30	3
9	66 M	12.9	12.4	40	38	1.30	0.50	0	0	3.2	2.3	9.0	7.5	120/210	125/210	4	

CT = Claudication time. MRF = Mean resting blood flow. PF = Peak blood flow.