Local treatment for bacterial vaginosis

Bacterial vaginosis (non-specific vaginitis) is a mild but common condition. O'Dowd *et al* reported that organisms associated with vaginosis could be isolated from 37% of women who presented with vaginal symptoms.[1] The current treatment of choice is an oral nitroimidazole (metronidazole or tinidazole), given either as a single large dose or as a twice daily regimen for five to seven days. A problem with any treatment for vaginosis is the high rate of recurrence.[2]

This study compares the efficacy of metronidazole given as a single oral 2 g dose with that of local treatment in the form of chlorhexidine pessaries in curing vaginosis and preventing recurrence.

Patients, methods, and results

Premenopausal women attending the Praed Street Clinic, London, with vaginosis were entered into a randomised single blind study. One group was allocated to receive a single 2 g oral dose of metronidazole and the other to receive intravaginal chlorhexidine as a single pessary containing 150 mg active drug on two consecutive days. A diagnosis of vaginosis was based on finding three of the following: "clue" cells, an abnormal vaginal discharge, a positive amine test result, and a vaginal pH>4·5.[3] Cervical and vaginal samples were taken for culture of *Neisseria gonorrhoeae*, *Gardnerella vaginalis*, lactobacilli, and anaerobic cocci and curved rods. Quantitative bacterial cultures were done on vaginal washings.

Seventy nine women entered into the trial reattended for assessment at seven days. Forty three received chlorhexidine and 36 metronidazole. There was no significant difference in age, ethnic origin, parity, past history of sexually transmitted diseases, or forms of contraception between the two groups. Differences in results of treatment were analysed by χ^2 test.

Chlorhexidine and metronidazole had similar efficacy in reducing both symptoms and signs of vaginosis (table). Metronidazole eradicated vaginal colonisation by *G vaginalis* in more patients than did chlorhexidine, but this was the only significant difference between the two regimens. When *G vaginalis* persisted there was no difference between the treatment groups in the numbers of organisms found (mean 10^7 colony forming units/g vaginal exudate).

Of the 79 women assessed seven days after treatment, 63 (80%) returned at 28 days. Thirty four had been treated with chlorhexidine and 29 with metronidazole, of whom 26 and 20, respectively, had no discharge at seven days. Of these patients, 10 (38%) in the chlorhexidine group and 4 (20%) in the metronidazole group had a recurrence of vaginal discharge at 28 days. This difference was not significant (p=0·3).

With regard to signs of vaginosis (raised pH and presence of amines, clue cells, and abnormal discharge), 27 of the chlorhexidine group had two or fewer at seven days, as did 25 of the metronidazole group. By day 28, 13 (48%) of the 27 patients in the chlorhexidine group and 10 (40%) of the 25 in the metronidazole group had signs of recurrence (three or four findings positive). Again this difference was not significant (p=0·7), a finding matched by the colonisation rates of *G vaginalis* and anaerobes in the two groups.

Patients cured of bacterial vaginosis at seven days by chlorhexidine and metronidazole

	No negative at seven days/No positive at entry (%)		p Value for difference between groups
	Chlorhexidine	Metronidazole	
Symptom:			
Vaginal discharge	32/41 (78)	20/30 (67)	0·42
Signs:			
pH>4·5	24/42 (57)	22/35 (63)	0·78
Amines	30/42 (71)	29/36 (81)	0·50
"Clue" cells	34/43 (79)	26/36 (72)	0·65
Abnormal discharge	28/42 (67)	20/35 (57)	0·53
More than three signs	36/43 (84)	28/36 (78)	0·70
Culture:			
Anaerobes	20/37 (54)	20/31 (65)	0·53
Gardnerella vaginalis	8/39 (21)	15/32 (47)	0·03

Comment

Our results show that vaginal chlorhexidine is as effective as oral metronidazole in curing bacterial vaginosis and that recurrence rates with the two treatments are not significantly different. We find that in vitro chlorhexidine is active against both *G vaginalis* and relevant anaerobes such as *Bacteroides bivius*.

A striking feature in our series was that two thirds of the women had had one or more previous episodes of vaginosis. Recurrence is a major factor in the condition. This together with an association between recurrence and menstruation and sexual activity may suggest a role for treatment continued at key periods over more than one menstrual cycle, an approach for which local agents may be more suitable. More work needs to be done on the formulation of local antibacterial agents such as chlorhexidine for use in the vagina, but this study shows that such treatment may be effective in vaginosis.

This work was supported by ICI PLC.

1 O'Dowd TC, West RR, Ribeiro CD, Smail JE, Munro JA. Contribution of Gardnerella vaginalis to vaginitis in a general practice. *Br Med J* 1986;292:1640-2.
2 Blackwell A, Fox AR, Phillips I, Barlow D. Anaerobic vaginosis (non-specific vaginitis): clinical, microbiological, and therapeutic findings. *Lancet* 1983;ii:1379-81.
3 Eschenbach DA, Bekassy S, Blackwell A, *et al*. The diagnosis of bacterial vaginosis. In: Mardh P-A, Taylor-Robinson D, eds. *Bacterial vaginosis*. Stockholm: Almqvist and Wiksell International, 1984:260-1.

(Accepted 11 August 1987)

Departments of Medical Microbiology and Venereology, St Mary's Hospital Medical School, London W2 1PG

C A ISON, PHD, FIMLS, research assistant in medical microbiology
R F H TAYLOR, MB, MRCP, research registrar
C LINK, SRN, research nurse
P BUCKETT, BSC, medical laboratory scientific officer, department of medical microbiology
J R W HARRIS, MRCP, consultant in genitourinary medicine
C S F EASMON, MD, PHD, professor of medical microbiology

Correspondence to: Professor Easmon.

Treatment of post-kala-azar dermal leishmaniasis with sodium stibogluconate

Sodium stibogluconate is used to treat post-kala-azar dermal leishmaniasis, but a high rate of relapse and treatment failure has been reported.[1-3] We undertook this study to find the optimal regimen of treatment.

Patients, methods, and results

We studied 108 patients (56 male, 52 female; mean age 23·7 years, range 4-72); 100 patients definitely had post-kala-azar dermal leishmaniasis and had had no drug treatment for six months, and eight patients with morphological features of the disease (six with a doubtful history of kala-azar, two with no history) were also included. Total and differential white cell count, haemoglobin and serum protein concentrations, and serum alanine transaminase and aspartate transaminase activities were measured. Urine examination, chest radiography, electrocardiography, and skin smears to show the presence of parasites were performed. These tests were repeated every 20th day during drug treatment. A skin biopsy sample was taken in selected patients.

Patients were randomly allocated to three groups and given sodium stibogluconate intramuscularly daily for 120 days: group A, 10 mg/kg body weight; group B, 15 mg/kg; and group C, 20 mg/kg. Patients were assessed on day 120.[2] If the clinical response was slow in groups A and B the drug dose was changed to 20 mg/kg body weight; the course was prolonged until the lesions resolved. Patients were seen every month for 12 months after the end of treatment, and cure was assumed when there had been no relapse during follow up.

The doctor who examined the patients for response to treatment was blind to the drug dose being taken. Patients were asked to describe any toxic effects such as anorexia, rashes, muscle pain, hypersensitivity reactions, palpitation, and yellowness of the eye. Statistical analysis was by Fisher's exact test with Armitage's modification for two tailed tests.

The response started within 20 days in all three groups. The rate of cure was significantly greater with the 20 mg regimen at 20 days (p<0·001). The rate of cure was greater in group B (15 mg) than group A (10 mg), but not significantly so, at 120 days. Eighteen patients in group A and 12 in group B were not cured at 120 days, so their dose was increased to 20 mg/kg; all were cured after a further three months. Three patients required more than 120 days' treatment with the 20 mg dose; all were cured with further treatment, two with another 40 injections and one, with extensive lesions, with another 80 injections. Two patients in group C developed electrocardiographic changes, and the drug was stopped for 20 days; the changes resolved and the drug was restarted. One patient developed arthralgia with a plasma urate concentration of 0·49 mmol/l; this responded to allopurinol and indomethacin while the treatment was continued. All patients tolerated the longer course of treatment.

Comment

The cure rate in this series was significantly higher with the 20 mg regimen compared with the 10 mg and 15 mg regimens. In Singh's series the relapse rate was 91% after the fourth course of treatment.[1] Sen Gupta found that two thirds of the patients with nodular and erythematous disease and half of those with hypopigmented macules were completely cured, with a

noticeable improvement in about two thirds of the remainder. About one sixth of the total cases showed slight or no improvement.[4] These differences between their and our results were mainly due to an inadequate dose of the drug being given for an inadequate time. We found that nodular lesions responded quickly and depigmented macules very slowly. Our high dose and longer duration of treatment were based on the fact that sodium stibogluconate is quickly excreted in the urine and six hours after an intravenous injection blood concentrations have fallen to less than 1% of peak values. The danger of cumulative toxicity might be exaggerated.[5]

We thank Dr R S Jha, department of pathology; Mr R J Sharma, technician; and Mr C P Singh, who typed the manuscript. We received financial support from the United Nations Development Programme/World Bank/World Health Organisation special programme for research and training in tropical disease.

1 Singh RP. Observation on dermal leishmanoid in Bihar. *Indian J Dermatol* 1968;3:1-5.
2 Thakur CP. Epidemiological, clinical and therapeutic features of Bihar kala-azar (including post kala-azar dermal leishmaniasis). *Trans R Soc Trop Med Hyg* 1984;78:391-8.
3 Anonymous. The leishmaniasis. *WHO Tech Rep Ser* 1984;No 701.
4 Sen Gupta PC. Leishmaniasis. In: Baneerjea JC, Bhattacharya PB, eds. *A handbook of tropical diseases*. 6th ed. Calcutta: Academic Publishers, 1960:103-40.
5 Rees PH, Keating MI, Kager PA, Hockmeyer WR. Renal clearance of pentavalent antimony (sodium stibogluconate). *Lancet* 1980;ii:226-9.

(Accepted 11 June 1987)

Patna Medical College and Hospital, Patna, India
C P THAKUR, MD, MRCP, emeritus professor of medicine
K KUMAR, MB, MD, registrar, department of dermatology
P K SINHA, MB, MD, clinical assistant
B N MISHRA, MB, BS, clinical assistant
A K PANDEY, MB, MD, resident medical officer

Correspondence to: Dr C P Thakur, Fraser Road, Patna-800001, India.

The haemolytic uraemic syndrome and bone marrow transplantation

The haemolytic uraemic syndrome has been reported in seven patients[1-4] and thrombotic thrombocytopenic purpura in two[5] after allogeneic bone marrow transplantation. All these patients died; only one received specific treatment (plasma exchange) for these complications, but he died before the response could be evaluated.

We successfully controlled the haemolytic uraemic syndrome after allogeneic bone marrow transplantation by plasma exchange with fresh frozen plasma.

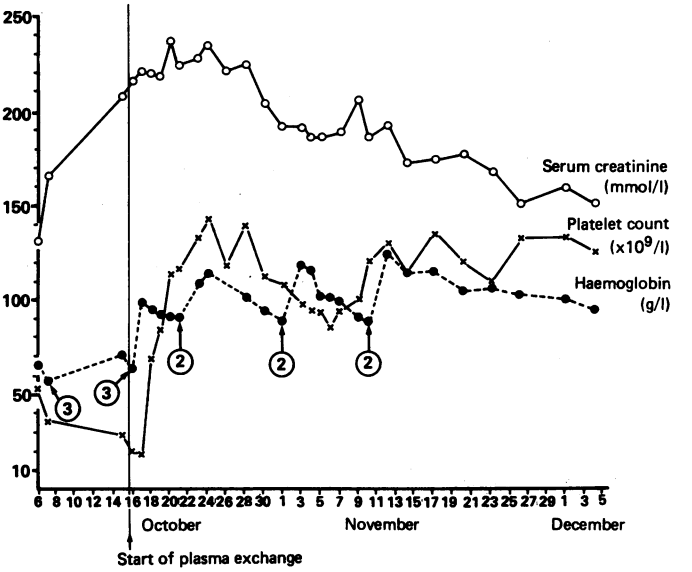
Case report

A 17 year old man received an allogeneic bone marrow transplant from an HLA compatible sibling in March 1986 for a T cell lymphoma while in third remission and after conditioning with total body irradiation and high dose cyclophosphamide. Prophylaxis against graft versus host disease consisted of intravenous cyclosporin 2·5 mg/kg twice daily until day 14 followed by oral cyclosporin 5 mg/kg twice daily until day 50. Thereafter the dose was reduced by 5% each week and the drug stopped at six months. He did not have antibodies to cytomegalovirus, and only blood products negative for cytomegalovirus were transfused. Full haematological recovery ensued, and there was no evidence of graft versus host disease or recurrence of the lymphoma.

In September he developed a normochromic normocytic anaemia (haemoglobin concentration 86 g/l) and thrombocytopenia (platelet count 114 × 10^9/l). There was mild red cell fragmentation, and intravascular haemolysis was confirmed by laboratory investigations. Cyclosporin was stopped.

In October he developed hypertension (blood pressure 165/110 mm Hg) with deteriorating renal function (blood urea concentration 18 mmol/l, plasma creatinine concentration 207 μmol/l, and creatinine clearance 16 ml/min). Results of a coagulation screen were normal, as were immunoglobulin and complement concentrations. Blood cultures and fungal and viral studies, including tests for cytomegalovirus, yielded negative results. A renal biopsy specimen showed changes compatible with the haemolytic uraemic syndrome. A trial of intravenous infusion of fresh frozen plasma was stopped because of an abrupt rise in blood pressure despite concomitant antihypertensive treatment. Plasma exchange was then begun, the haemoglobin concentration being 63 g/l, platelet count 20 × 10^9/l, and plasma creatinine concentration 215 mmol/l. Altogether 28 plasma exchanges with 2·5-3·0 litres of fresh frozen plasma were performed from October to December with concentrated red cell transfusions as required.

The frequency of exchanges was determined by his clinical state, haemoglobin concentration, and platelet count (figure). Clinically there was a dramatic response, with resolution of headache during the first exchange and a reduction in blood pressure from 160/100 mm Hg to 140/90 mm Hg at 24 hours; his malaise gradually improved and his blood pressure was stabilised with various drugs over the next two weeks. Although the serum creatinine concentration rose during the first week of plasma exchange, with continued treatment it gradually fell. Seven months after the last exchange he was clinically well with a normal haemoglobin concentration and platelet count and no evidence of haemolysis. Hypertension persisted but was controlled with oral hydralazine and metoprolol. Renal function had improved (blood urea concentration 7·2 mmol/l, plasma creatinine concentration 119 μmol/l, and creatinine clearance 42 ml/min).



Serum creatinine concentration, platelet count, and haemoglobin concentration in a patient receiving 28 plasma exchanges with fresh frozen plasma. Arrows indicate transfusions of red cell concentrate (2 or 3 units).

Comment

This patient is the tenth reported as having the haemolytic uraemic syndrome or thrombotic thrombocytopenic purpura complicating allogeneic bone marrow transplantation, but is the first to have responded to treatment with plasma exchange. The aetiology is unclear: cyclosporin toxicity, graft versus host disease, and cytomegalovirus infection have been suggested as causes. Of the patients reported on, six received cyclosporin as prophylaxis against graft versus host disease, five developed cytomegalovirus infection, and four developed graft versus host disease. Our patient showed no evidence of graft versus host disease or bacteriological, fungal, or viral infection. Although he was still receiving cyclosporin when he developed the haemolytic uraemic syndrome, his condition worsened after the drug was stopped. This suggests that the syndrome was an uncommon complication of allogeneic bone marrow transplantation; his response to plasma exchange indicates that this treatment should be considered early in such patients.

This patient was under the care of Dr A C Parker. We also thank Dr R Winney and Dr J Gillon for their advice, Dr M Cook for referring the patient to us, and Pat Stewart for typing the manuscript.

1 Gluckman E, Barrett AJ, Arcese W, Devergie A, Degoulet P. Bone marrow transplantation in severe aplastic anaemia: a survey of the European group for bone marrow transplantation. *Br J Haematol* 1981;49:165-73.
2 Powles RL, Clink HM, Spence D, *et al*. Cyclosporin A to prevent graft-versus-host disease in man after allogeneic bone marrow transplantation. *Lancet* 1980;i:327-9.
3 Shulman H, Striker G, Deeg HJ, Kennedy M, Storbe R, Thomas ED. Nephrotoxicity of cyclosporin A after allogeneic bone marrow transplantation. *N Engl J Med* 1981;305:1392-5.
4 Marshall RJ, Sweny P. Haemolytic uraemic syndrome in recipients of bone marrow transplants not treated with cyclosporin A. *Histopathology* 1986;10:953-62.
5 Atkinson K, Biggs JC, Hayes J, *et al*. Cyclosporin A associated nephrotoxicity in the first 100 days after allogeneic bone marrow transplantation: three distinct syndromes. *Br J Haematol* 1983;54:59-67.

(Accepted 20 July 1987)

Haematology Department, Royal Infirmary, Edinburgh EH3 9YW
J I O CRAIG, MB, MRCP, registrar
T SHEEHAN, MB, MRCP, senior registrar

Edinburgh and South East Scotland Regional Blood Transfusion Service, Edinburgh
K BELL, MB, CHB, registrar

Correspondence to: Dr Craig.