Leucopenia Associated with Trimethoprim-Sulphamethoxazole after Renal Transplantation

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Summary

Four patients who had received cadaveric renal allografts developed a profound and sustained leucopenia in association with a trimethoprim-sulphamethoxazole preparation. Ten other cadaveric renal allograft recipients received identical chemotherapy with no adverse effects. Statistical analysis showed that the association of leucopenia and trimethoprim-sulphamethoxazole therapy was dependent on the time after the transplantation procedure and was not related to the dosage of immunosuppressive chemotherapy or renal function.

Introduction

Trimethoprim (2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine) acts as an antimetabolite by competitively inhibiting the enzyme dihydrofolate reductase and blocking the conversion of dihydrofolic acid to tetrahydrofolic acid; this results in inhibition of purine synthesis since tetrahydrofolic acid is the normal carrier of one carbon atom moieties in purine synthesis (Hitchings and Burchall, 1965), and Ghilchik *et al.* (1970) demonstrated immunosuppressive activity with this agent. However, the bacterial enzyme dihydrofolate reductase is at least 10,000 times more sensitive to trimethoprim than the mammalian enzyme (Hitchings, 1969), and it is this feature which qualifies it for use as an antibacterial chemotherapeutic agent. Furthermore, when trimethoprim is used in combination with a sulphonamide, such as sulphamethoxazole, there is pronounced synergism with conversion of the bacteriostatic actions of the individual drugs to bacteriocidal activity (Bushby and Hitchings, 1968).

Trimethoprim-sulphamethoxazole is bacteriocidal to most Gram-negative bacilli found in infected urine with the notable exception of *Pseudomonas aeruginosa*, and clinical trials have shown that this drug regimen is superior to either ampicillin or a sulphonamide alone in the treatment of urinary tract infections (Reeves *et al.*, 1969). However, there have been a number of case reports (Evans and Tell, 1969; McCarthy, 1969; Mohan, 1969; Paulley, 1970) of an association between the use of trimethoprim-sulphamethoxazole and a neutropenia or thrombocytopenia. Renal transplant recipients on immunosuppressive therapy with azathioprine and corticosteroids are particularly at risk from leucopenia, and we have therefore reviewed the incidence of leucopenia in patients who have received a cadaveric transplant in this unit over the past three years, with particular reference to whether they were treated with trimethoprim-sulphamethoxazole.

Patients and Methods

Patients Receiving Trimethoprim-Sulphamethoxazole.—Fourteen patients received 18 courses of the drug combination for bacteriologically proved urinary tract infections and the dosage, irrespective of body weight and renal function, was trimethoprim 320 mg and sulphamethoxazole 1·6 g daily for 10 days. Each patient was allocated an identification number at the time of transplantation, as shown in Tables I, II, and III. The same code has been used in a previous publication (Pletka *et al.*, 1969).

TABLE I—*Clinical Details of Patients with a Leucopenia and Receiving Trimethoprim-Sulphamethoxazole*

No.	Days after Transplantation	Creatinine Clearance (ml/min)	Azathioprine (mg/day)	Onset of Leucopenia	Duration of Leucopenia (Days)
95	22	65	175	13	7
107	56	36	125	2	40
116	41	60	175	2	14
129	36	70	175	2	30

TABLE II—*Clinical Details of Patients Receiving Trimethoprim-Sulphamethoxazole without a Leucopenia*

No.	Days after Transplantation	Creatinine Clearance (ml/min)	Azathioprine (mg/day)
54	1,170	80	175
71	900	85	175
	1,080	85	175
	1,140	85	175
86	810	80	175
95	57	65	175
100	240	65	150
	600	65	150
101	630	85	240
112	44	8	75
113	120	75	200
	180	60	200
114	360	60	100
122	48	50	125

TABLE III—*Comparison of Patients Receiving Trimethoprim-Sulphamethoxazole*

	Trimethoprim-Sulphamethoxazole		*t*	P
	Effect	No Effect		
Days after transplantation	38·7 ± 14·0*	527 ± 430*	2·22	0·05—0·02
Creatinine clearance (ml/min)	57·5 ± 15·5*	67·7 ± 20·7*	0·91	0·4—0·3
Azathioprine (mg/day)	160 ± 25*	163·6 ± 42·0*	0·05	0·9

*Mean and 2 S.D.

Patients Not Receiving Trimethoprim-Sulphamethoxazole.—Sixty patients received 70 renal transplants between January 1968 and December 1970. All patients had 15 to 20 mg of prednisolone daily and azathioprine 3·0 mg/kg body weight when the creatinine clearance was greater than 20 ml/min and reduced to 1·5 mg/kg body weight if the creatinine clearance was less than 20 ml/min. At the time of a clinically recognized rejection episode the dosage of azathioprine was doubled for five days and the presnisolone dosage was increased to 200 mg daily; the latter dosage was reduced stepwise every five days until the maintenance therapy was achieved after 35 days.

Laboratory Investigations.—Renal function was determined by serial 24-hour creatinine clearances; plasma and urinary creatinine were measured by an automated technique (Chasson *et al.*, 1961). Total white blood count and differential white blood count were determined by routine laboratory techniques. A leucopenia was arbitrarily defined as a total peripheral white blood cell count of under 2,500/mm³ on two consecutive days and the duration of the leucopenia was the length of time until the white blood cell count was consistently greater than 3,000/mm³.

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All patients with a leucopenia received tetrahydrofolic acid 6 mg intramuscularly daily for three days.

Results

Four patients developed a leucopenia after the administration of trimethoprim-sulphamethoxazole (Table I); in three the leucopenia occurred within two days of the onset of chemotherapy. Despite immediate cessation of the drug and the administration of tetrahydrofolic acid the leucopenia persisted for a mean time period of 23 days. Furthermore, one patient (No. 129) died of a *Ps. aeruginosa* septicaemia 30 days after the onset of the leucopenia. These four patients had received a renal transplant less than 60 days previously and all had adequate creatinine clearances (Table I); two (Nos. 95 and 116) had begun rejection immunosuppressive therapy 10 and 11 days previously.

Ten patients received 14 courses of trimethoprim-sulphamethoxazole for urinary tract infections without any alteration in the white blood cell count. The clinical details are shown in days. Statistical analysis of the clinical data of the two groups of Table II. Seven of the patients had been transplanted for over 120 patients who had received chemotherapy (Table III) showed a significant difference in the time period after the transplant procedure. Indeed, four of the seven patients who received trimethoprim-sulphamethoxazole during the first 60 days after renal transplantation showed a profound leucopenia. However, there were no significant differences between either the creatinine clearance or azathioprine dosage in the two groups of patients.

Sixty patients received 70 renal transplants during the three years under study; 14 had a leucopenia of less than 2,500 cells/mm³ and their clinical details are shown in Table IV. Four (Nos. 105, 110, 122, and 123) had recently been treated for a rejection episode within 14 days of the onset of the leucopenia. The duration of the leucopenia was significantly less in this group of patients than in those developing a leucopenia associated with trimethoprim-sulphamethoxazole (Table V). There were, however, differences in both creatinine clearance and azathioprine dosage in the two groups of patients; those with a leucopenia and not receiving trimethoprim-sulphamethoxazole had lower creatinine clearances and significantly lower daily azathioprine therapy.

TABLE IV—*Clinical Details of Patients with a Leucopenia and Not Receiving Trimethoprim-Sulphamethoxazole*

No.	Days after Transplantation	Creatinine Clearance (ml/min)	Azathioprine (mg/day)	Duration of Leucopenia (Days)
105	9	0·9	75	9
106	49	55	100	8
108	44	30	50	4
109	44	40	125	4
110	49	29	100	8
121	31	5	100	13
122	35	33	100	6
123	57	35	200	14
130	56	30	75	3
133	160	40	150	27
139	41	85	150	12
140	34	95	150	12
143	47	50	125	5
146	31	45	150	10

TABLE V—*Comparison of Patients with Leucopenia*

	Trimethoprim-Sulphamethoxazole (Effect)	No Trimethoprim-Sulphamethoxazole	*t*	P
Days after transplantation	38·7 ± 14*	49·1 ± 34*	0·58	0·6
Creatinine clearance (ml/min)	57·5 ± 15·5*	40·9 ± 25·6*	1·22	0·2
Azathioprine (mg/day)	160 ± 25*	117·8 ± 39*	2·10	0·05
Duration of leucopenia (days)	22·75 ± 15*	9·6 ± 6·1*	2·71	0·02—0·01

*Mean and S.D

Discussion

Azathioprine is an antimetabolite drug which is converted in vivo by the liver (Mitchell *et al.*, 1970) to mercaptopurine and other metabolites; mercaptopurine blocks the conversion of inosinic acid to adenylic acid and so inhibits adenine synthesis.

A well-recognized side effect is bone marrow depression of white blood cell precursors, but a daily dosage of 3 mg/kg body weight is usually both safe and active as an immunosuppressive agent. However, this dosage is often associated with a leucopenia if the patients have a creatinine clearance of less than 20ml/min (Mowbray *et al.*, 1965), and an azathioprine dosage of 1·5 mg/kg body weight under such circumstances is usually both safe and effective. The patients with a transient leucopenia while not receiving trimethoprim-sulphamethoxazole had lower creatinine clearances than the patients receiving trimethoprim-sulphamethoxazole though it was only less than 20 ml/min in two subjects (Table IV) and the azathioprine dosage was 1·5 mg/kg body weight. However, 12 of the 14 patients had higher creatinine clearances though the values were lower than the other two groups of subjects, and caution must therefore be exercised rather than adhering to a fixed drug regimen.

Three of the four patients who developed a leucopenia in association with trimethoprim-sulphamethoxazole did so within two days of administration of the preparation. The white blood cell count had shown no evidence of a leucopenia previously and the close time relationship suggests that the association was not fortuitous. There are at least two possible explanations; all the patients with a leucopenia in the presence or absence of trimethoprim-sulphamethoxazole had received a renal transplant less than 60 days previously, had been maintained for several months by either peritoneal dialysis or haemodialysis, and may have been deficient in folic acid. However, all patients were given large doses of parenteral tetrahydrofolic acid and the leucopenia persisted for a considerable time period in those patients who had received trimethoprim-sulphamethoxazole.

A second possibility could be that an unidentified plasma constituent, present in chronic renal failure, potentiated the antimetabolic effect of trimethoprim-sulphamethoxazole and that it was slowly excreted or degraded after a successful renal transplantation procedure. It is unlikely that trimethoprim interfered with the renal excretion of intermediary metabolite of azathioprine, since the adverse effects occurred only for the first 60 days after transplantation and there was no significant difference in the creatinine clearances of the two groups of patients receiving trimethoprim-sulphamethoxazole. There was no evidence that the leucopenia was the result of an idiosyncrasy to sulphamethoxazole. No patient developed skin reactions or fever and one (No. 95) received two courses of trimethoprim-sulphamethoxazole; the first treatment was associated with a leucopenia (Table I) and the second course, 35 days later (Table II) was uneventful.

Though no cause has been found for the profound leucopenia in association with the trimethoprim-sulphamethoxazole preparation, extreme caution should be exercised if it is prescribed during the first 60 days after a cadaveric transplant irrespective of renal function.

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Mental Health Aspects of Shoplifting*

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Summary

A ten-year follow-up of 886 shoplifters showed clear differences between women and men. Men tended to have previous convictions and to steal books (unknown in women). Of the 532 women nearly one third were foreign-born, and this group comprised 46% of offenders aged 17-30. The peak age among British women was 51-60.

First offenders accounted for 80% of the women, and their reconviction rate was 11%; among those with any kind of previous conviction the rate was 50%. The rate of admission to hospital for women shoplifters is three times higher than average.

Introduction

Attitudes to shoplifting, perhaps more than to any other crime, are stereotyped. Psychiatrists often stress that some respectable and usually middle-aged women shoplift for neurotic reasons with minimal motive of gain. This view is well accepted by magistrates, especially women magistrates, who can easily identify with these unfortunate women. On the other hand, shop managers and detectives draw attention to the large amount of casual shoplifting for simple gain by girls and women who are not maladjusted in any way. Both attitudes are correct, but recognition of one should not conceal the existence of the other. The problem is to place offenders along the continuum from casually dishonest to pathological and to throw light on the distribution. With this object in mind we studied the records of certain groups of offenders.

Firstly, with the help of local probation officers, we recorded brief details of all the 763 women dealt with by two magistrates' courts in the West End of London in a period of three months; 316 (41%) were shoplifters. Our main concern, however, was with the part mental ill health plays in shoplifting, so, secondly, we studied the subsequent 10-year history of 532 women convicted of shoplifting in 1959 (Gibbens and Prince, 1962), about whom probation officers supplied detailed information, and the subsequent history of 234 male shoplifters convicted in 1959, about whom less detailed information was obtained. Thirdly, we have followed up for 10 years 202 women shoplifters and 50 women convicted of other types of theft admitted in 1959 to Holloway prison on remand or sentence, and interviewed at that time by Dr. Phyllis Epps, then a medical officer at the prison Information on subsequent convictions in the 10-year follow-up periods was obtained from the Criminal Records Office and on any admission to a psychiatric unit from the Department of Health and Social Security. The latter, however, refers only to the five years 1964-9. Whenever there was a record of a period of probation or admission to a hospital we wrote for a report or case notes.

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Results

COURT SAMPLE

Of the 316 women shoplifters appearing in West End of London magistrates' courts in a period of three months 60% were foreign girls mostly aged 17 to 25. They included 22 au pair girls and 51 students most of whom were foreign. They had little money to spend but many were apparently healthy, normally honest girls from stable, educated families—yet they compared notes about where to shoplift.

WOMEN CONVICTED IN 1959

Of the 532 women studied in 1959 525 were traced. The reconviction rate among them was 20%—similar to that of a group of cases convicted in the same courts in 1949. For the purposes of analysis four groups (A, B, C, and D) have been distinguished and are shown in relation to age in 1959 in Table I. In round figures 70% had not been convicted before or reconvicted after 1959 (group A); 10% were first offenders in 1959 who were reconvicted (group B); 10% had one or more convictions before 1959 but none since (group C); and 10% had had conviction both before and after 1959. Of the 80% who were first offenders, therefore, 11% were reconvicted; and of the 20% who had had one or more previous convictions of any kind 50% were reconvicted.

The distribution in Table I is fairly even but it includes rather different groups. Even in 1959 29% of the women were foreign born, mainly from Europe and Asia. They comprised 46% of the group aged 17-30. They were not all au pair girls or students, and a quarter had been in England for over five years. Ten per cent. were reconvicted. Among those born in the British Isles the peak age was 51-60. The most interesting figure in Table I is that out of 80 first offenders in their 50s as many as 22% were subsequently reconvicted.

In 1959 the detailed schedule of social and medical information (kindly filled in by probation officers in addition to their ordinary duties) was incomplete in some 42% of the 532 women offenders. However, among the 58%—that is, 304 women—in whom information was complete there had been a good deal of physical and mental ill health. Some 17% of those fully investigated (10% of the total 532) had been in hospital with a major physical illness (in half the cases in the last year); a further 10%