

Folate levels in patients with ulcerative colitis receiving sulphasalazine

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Summary

The question of folate deficiency in patients receiving sulphasalazine is still controversial. A random sample of patients with ulcerative colitis receiving sulphasalazine were studied to determine the clinical significance of the inhibition of folic acid absorption by the drug. No significant lowering of folate levels could be determined.

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Patients and methods

A random selection of 24 outpatients with ulcerative colitis who had been receiving sulphasalazine for at least 1 year was made. Those on vitamin supplements were excluded. No other patient variables were controlled for, but a control group of 10 staff members was included.

The following measurements were carried out: vitamin B₁₂, serum folate and red-cell folate levels (by radio-assay) and white blood cell count (Coulter), reticulocyte count, and erythrocyte sedimentation rate (Westergren).

Results

No patient receiving sulphasalazine had red-cell folate or serum folate levels outside the normal range for the assay used (serum folate 1,7 - 15,5 ng/ml and red-cell folate 210 - 280 ng/ml).

The mean values for red-cell folate levels in sulphasalazine users (346,8 ng/ml) and controls (334,4 ng/ml) were not significantly different, neither were serum folate levels in the two groups (4,8 mg/ml v. 4,56 mg/ml). In neither group were vitamin B₁₂ levels below the normal range (220 - 270 pg/ml). There was no indication of haemolysis due to sulphasalazine; all reticulocyte counts measured were within the normal range (10 - 100 x 10⁹/l) with a mean of 55,3 x 10⁹/l in patients on the drug.

There were no significant differences in mean haemoglobin levels and mean cell volume in controls (14,7 g/dl and 92,4 fl) and patients on the drug (13,7 g/dl and 89,3 fl).

To determine whether dosage had an effect on folate levels, as stated by Longstreth and Green,¹ two groups were compared, one group on high dosage (≥ 2 g/d) and one on low dosage (< 2 g/d). Again there was no significant difference between the two groups as regards red-cell folate levels; the mean level in the high-dose group was 325,5 ng/ml against 346,2 in the low-dose group.

Discussion

The mode of action of sulphasalazine is still unknown. It has certain properties of an antifolate drug in that it is a competitive inhibitor of folate transport by the intestine.² *In vitro* studies have shown it to be a folate antagonist in lymphocytes,³ as these cells predominate in the inflammatory reaction in inflammatory bowel disease this possibly explains the immunosuppressive effects noted by Holm and Perlman.⁴

The clinical significance of the inhibition of folate absorption is variably reported in the literature. Franklin and Rosenberg⁵ found that 63% (49 of 78) of their patients had low serum folate levels. This was supported by Andersson *et al.*⁶ who found low serum folate levels in 25% of patients with ulcerative colitis who were taking sulphasalazine. Swinson *et al.*⁷ found only a 2,5% (2 out of 80 patients) incidence of anaemia associated with low serum folate or red-cell folate levels, although another 10% had low red-cell folate levels. Longstreth and Green¹ found that maintenance doses rarely caused clinically significant folate deficiency, although subclinical tissue depletion, as documented by low mean red blood-cell folate levels, occurred as a dose-related effect in patients receiving more than 2 g daily. Goldberg⁸ recently stressed the benefit of folic acid supplementation in patients with ulcerative colitis receiving the drug. Halsted *et al.*⁹ felt that folate malabsorption and deficiency are predictable in most patients taking sulphasalazine.

Conclusion

In the patients studied, there was no significant lowering of folate levels at any dosage.

Possible explanations for the difference in published findings are:

1. In some studies patients with Crohn's colitis were included.⁵ Subclinical jejunal disease may be an additional cause of decreased folate absorption.
2. The newer radio-assay procedures for determining levels of folate and vitamin B₁₂ are more accurate than previously used microbiological assay techniques. The microbiological assay which utilized bacteria was subject to errors from factors which could influence growth rate, such as the presence of antibiotics (possible role of sulphapyridine, a breakdown product of sulphasalazine) and antimetabolites in the sample.

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