**Zeitschrift:** Acta Tropica
**Herausgeber:** Schweizerisches Tropeninstitut (Basel)
**Band:** 37 (1980)
**Heft:** 3

**Artikel:** Low serum folate among persons taking Fansidar (pyrimethamine plus sulfadoxine) for prophylaxis of malaria

**Autor:** Stürchler, D. / Holzer, B.

**DOI:** https://doi.org/10.5169/seals-312655

Acta Tropica 37, 243–248 (1980)

Swiss Tropical Institute, Basel, Switzerland

# Low serum folate among persons taking Fansidar (pyrimethamine plus sulfadoxine) for prophylaxis of malaria

D. STÜRCHLER, B. HOLZER

## Introduction

By blocking the enzyme dihydrofolate-reductase, *pyrimethamine* may lead to folate deficiency and megaloblastic anaemia (Myatt et al., 1953; Waxman and Herbert, 1969). This effect is observed with doses of 25 to 50 mg *daily*, used for the *treatment* of some parasitic diseases; however, it does not occur with the same dose applied *weekly*, for *prevention* of malaria (Weniger, 1979), except when cotrimoxazole is administered simultaneously to pyrimethamine prophylaxis (Ansdell et al., 1976).

Sulfonamides such as *sulfadoxine* interfere with the synthesis of folate precursors, probably by competitive inhibition of the enzyme dihydropteroate-synthetase (Ferone, 1977; Goldstein, 1977). Haematological side effects of sulfonamides in therapeutic doses are haemolytic anaemias and bone marrow depression (Weinstein, 1975).

Both components are combined in the preparations of *Maloprim* (pyrimethamine plus dapsone) and of *Fansidar* (pyrimethamine 25 mg plus sulfadoxine 500 mg in one tablet). *Fansidar* is actually being widely recommended for *prophylaxis* of malaria, usually as 1 tablet per week, mainly for endemic areas with falciparum infections resistant to 4-amino-quinoleins (Peters, 1977). Both drug combinations are, furthermore, used for *treatment* of various conditions, and a case of megaloblastosis and pancytopenia due to *Maloprim* has been reported recently (Hughes and Gatus, 1979).

We wanted to investigate possible influences of *Fansidar* on serum folate concentrations with persons returning from tropical countries and using *Fansidar* for the prophylaxis of malaria.

### Patients and methods

Of the persons having consulted at the medical department of the Swiss Tropical Institute for examination after a stay abroad, the following groups were selected prospectively: (a) all persons indicating use of *Fansidar* for prophylaxis of malaria: the *"Fansidar-group"* (= F-group), (b) all

Correspondence: Dr. Dieter Stürchler, Swiss Tropical Institute, Socinstrasse 57, CH-4051 Basel

Table 1. Patients and laboratory results

| | F-group | NF-group |
|---|---|---|
| No. of persons | 81 | 99 |
| % males | 49 | 61 |
| Mean age in years (range) | 32 (21–61) | 37 (12–69) |
| Length of sojourn: % >8 weeks | 73 | 73 |
| Home return: % ≤6 weeks | 79 | 74 |
| Type of chemoprophylaxis | Fansidar: 81 | none: 56<br>chloroquine: 27<br>pyrimethamine alone: 16 |
| Mean hematocrite | 44 | 44 |
| Mean no. of WBC/mm³ (±SD) | 6239 (±2016) | 6716 (±1929) |
| % non-segmented neutrophils (±SD) | 5.8 (±6.2) | 5.6 (±4.5) |
| % segmented neutrophils (±SD) | 51.5 (±9.7) | 52.8 (±10.0) |
| No. with *Giardia lamblia* | 8 | 9 |

persons indicating diarrhoea within 2 weeks of consultation, but *not* taking *Fansidar*, (c) a sample of those without acute gastrointestinal troubles and not taking *Fansidar*. Later analyses showed, that diarrhoea did not influence serum folate concentrations, therefore, persons from groups (b) and (c) were summarised as *"Non-Fansidar-group"* (= NF-group). Pregnant and lactating women were excluded. Further characteristics of persons in the F- and NF-groups are presented in Table 1. The *history* was taken by means of a standard questionnaire prepared for international medicine (Stürchler, 1979). All persons had a complete *physical* examination.

In addition to standard *laboratory* investigations, *serum folate concentrations* were determined with radioimmunoassay, using kits produced by Diagnostic products corporation, 12306 exposition boulevard, Los Angeles, Ca. 90064. The assay uses the competitive binding of liberated serum folate and of $^{125}$I labeled folic acid to lactoglobulin (Heilmann and Bönninghoff, 1976). According to the manufacturer of the kit, normal values for adults from industrialised countries are above 6.8 nMol/L. *Statistical analysis* was done by t-test.

## Results

*Clinical and haematological findings: Physical* examination was non-contributary except for a 34-year-old male Swiss employee with whom clinical and electromyographical evidence of sensory *polyneuropathy* was found. The patient had taken *Fansidar* during 3 months (total dose approximating 12 tablets) for a trip to Southeast Asia. He presented with burning pains at hand and feet. At that time serum folate concentration was 5.3 nMol/L. *Fansidar* was discontinued, and the clinical, electromyographical and biochemical alterations normalised within 2 months (serum folate 10.4 nMol/L). As shown in Table 1, *hematocrite, white blood count* and *differentiation* were normal in both groups, but the number of leucocytes was lower in the F-group than in the NF-group (difference not significant). The frequency of intestinal *parasites* was comparable in both groups; no case of strongyloidiasis was found.

Table 2. Results of serum folate concentration studies

| | F-group | NF-group |
|---|---|---|
| Mean folate concentrations nMol/L ± SD | | |
| Overall | 8.2 (±3.3) | 12.7 (±7.7) |
| Males | 8.0 (±2.9) | 11.4 (±4.4) |
| Females | 8.5 (±3.7) | 15.0 (±10.7) |
| No. with folate concentration <6.8 nMol/L | | |
| Overall | 31 | 16 |
| Males | 13 | 8 |
| No. with folate concentration <4.0 nMol/L | | |
| Overall | 5 | 1 |
| Males | 1 | – |

*Serum folate concentrations* (Table 2): *Mean* folate concentration was above 6.8 nMol/L in both groups. However, it was significantly lower ($p < 0.001$) in the F-group than in the NF-group. The same significant differences were observed for *both sexes* within both groups; values for men were lower in both groups than for women. *Folate deficiency*, i.e. values below 6.8 nMol/L, was found with 47 persons (26.1%). Of these, nearly twice as many were from F-group than from NF-group ($p < 0.05$); 21 were males and 26 were females (difference not significant). Very low folate concentrations, i.e. below 4.0 nMol/L, occurred with 6 persons (3.3%). Of these, 4 were females, and all 4 were from the F-group ($p < 0.05$). 95% of all persons were between 20–49 years old, and within these *age* limits no effect of age on folate concentrations was observed. However, the 4 patients 60 years old or above had a mean serum folate concentration of 6.7 nMol/L.

In Fig. 1 the *total dose* of *Fansidar* and corresponding serum folate concentrations are plotted. Folate is low before the 10th dose already, i.e. before the 10th week of intake (8.1 ± 3.5 nMol/L). Thereon it remains at low level, also when taken for more than 30 weeks (8.4 ± 3.5 nMol/L). The mean folate concentration of 14 persons who took *pyrimethamine alone* during more than 30 weeks is also shown on Fig. 1; their folate value (13.9 ± 9.0 nMol/L) is significantly higher ($p < 0.05$) than the corresponding value of the F-group.

In Fig. 2 is shown how the mean serum folate concentration behaved during the time between *home leave* and *first consultation.* In the F-group, mean folate concentration was low, whether the 1st consultation was within less than 2 weeks after home leave (8.1 ± 3.1 nMol/L), within 2–6 weeks (7.8 ± 3.3 nMol/L) or more than 6 weeks after it (9.0 ± 3.7 nMol/L). For all three intervals of time, the corresponding values in the NF-group (12.6 ± 7.1, 11.6 ± 5.6 and 14.6 ± 10.4 nMol/L, respectively) were significantly higher ($p < 0.001$, $< 0.01$ and $< 0.01$, respectively). Chemoprophylaxis had been discontinued by the patients by the end of the 6th week.

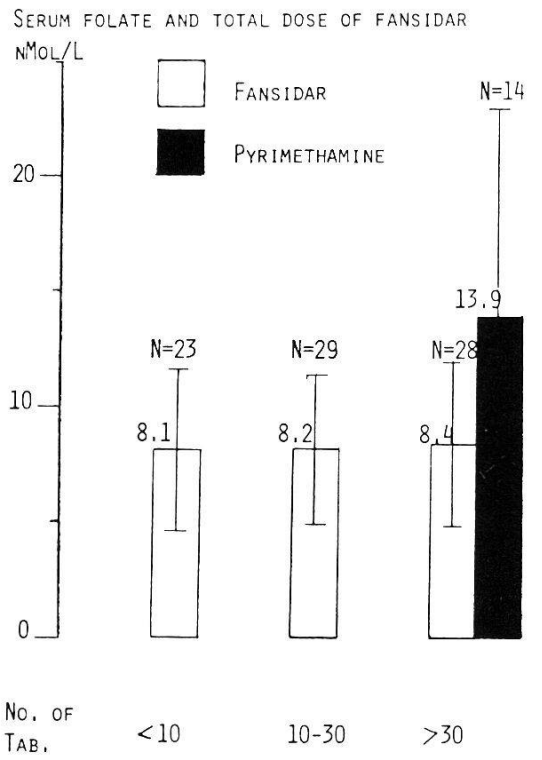


Fig. 1

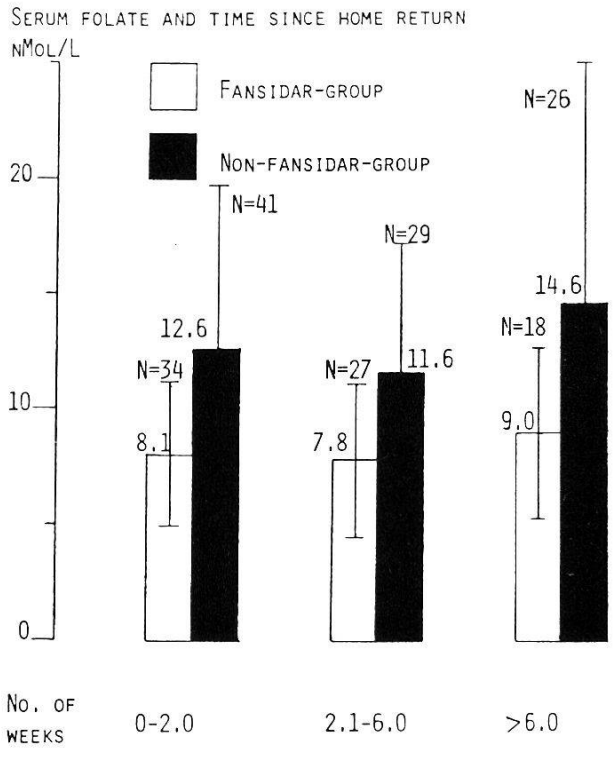


Fig. 2

## Discussion

The metabolism of folates in man (Rosenberg et al., 1971; Herbert, 1973; Thien et al., 1977) involves (a) dietary uptake; (b) absorption, hereby polyglutamates are hydrolysed to monoglutamates; (c) transport bound to proteins, and delivery to cells; (d) intracellular metabolisation and storing, mainly within erythrocytes; and (e) excretion. This complex metabolism is vulnerable, and folate deficiency due to alcoholism, pregnancy, dietary restriction with elderly people and due to drugs such as antiepileptics, contraceptives and antifolates is not uncommon in industrialised countries (Huser, 1975; Heilmann, 1977, 1979). In addition, among persons living in tropical environments, the tropical enteropathy syndrome (Fleischer, 1976), intestinal parasites such as *Giardia lamblia* and *Strongyloides stercoralis* (Cook, 1974) and nutritional deficiencies at any age may lead to folate depletion. The first sign of dietary folate deprivation is a lowering of serum folate, and only 3 months later erythrocyte folate will fall (Herbert, 1962).

The returners from tropical countries did not show signs of folate deficiency, and their mean serum folate concentrations were comparable with a standard of about 9 nMol/L for industrialised countries (Heilmann and Bönninghoff, 1976). The studied population seems to have consumed a balanced diet and was not affected by intestinal parasites in such a way as leading to malabsorption of folates. However, the study showed a significant antifolate effect of *Fansidar* among males and females alike. Fig. 1 produces evidence,

that this antifolate effect is due to the sulfonamide component of *Fansidar* and not due to its pyrimethamine part. The antifolate effect of *Fansidar* appeared before the 10th dose and was persistent over many weeks; it led to latent folate deficiency among 31 (38%) of 81 persons taking the drug for prevention of malaria. The higher sensitivity of some persons to *Fansidar* might be explained by a genetically determined low rate of metabolisation of *sulfadoxine.* Such a phenomenon has been shown to exist with the acetylation of *sulfalene* (Williams, 1978).

*Radioimmunoassay* is a reliable and sensitive technique for the determination of serum folate concentrations (Heilmann and Bönninghoff, 1976). According to the manufacturer of the commercial diagnostic kit, sensitivity is approximately 0.2 nMol/L within the diagnostically important range. The precise biochemical mechanisms of the antifolate effect of *Fansidar* could not be elucidated. We speculate about 2 possibilities: (a) influence on more than one of the enzymes involved in the intracellular folate metabolism in man, or, (b) interference with the absorption, transport and/or cellular uptake of folates. Effects of the second type have been demonstrated for methotrexate, trimethoprim and for other drugs (Waxman et al., 1970; Caspary, 1975).

We could confirm previous findings (Muto et al., 1970; Pearlman et al., 1977) of a tendency to a low white blood count under *Fansidar.* In addition, we report a case of Fansidar-induced polyneuropathy, which might have originated (a) from direct drug toxicity or (b) indirectly, by folate deficiency, which is a known cause of peripheral nerve lesions (Grand et al., 1965; Botez et al., 1978).

From our study we derive the following *conclusions:*

1. Fansidar should not be used for malaria prophylaxis when there is clinical suspicion of folate deficiency, i.e. with alcoholics, persons more than 60 years old, pregnant and lactating women, persons with chronic intestinal diseases or following treatment which affects folate metabolism, *unless* folate is substituted. Substitution of folates seems not to interfere with the suppressive effect of Fansidar (Tong et al., 1970).
2. It would be safe to discontinue Fansidar after 6 to 12 months of continuous use, in order to avoid haematological and/or neurological side effects, *unless* there are clinical and haematological examinations at regular intervals.
3. There seems to exist a group of persons particularly sensitive to get folate depleted by Fansidar; this Fansidar effect might be genetically determined.

Ansdell V. E. et al.: Megaloblastic anemia associated with combined pyrimethamine and cotrimoxazol administration. Lancet *1976*/II, 1257.

Blackwell E. A. et al.: Acute pancytopenia due to megaloblastic arrest in association with cotrimoxazole. Med. J. Aust. *1978*/II, 38–41.

Botez M. I. et al.: Polyneuropathy and folate metabolism. Arch. Neurol. *88*, 581–584 (1978).

Caspary W. F.: Die Beeinflussung der Resorptionsleistungen der Darmmucosa durch Pharmaka. Arzneimittel-Forsch. (Drug. Res.) *25*, 489–498 (1975).

Cook G. C.: Malabsorption in Africa. Trans. roy. Soc. trop. Med. Hyg. *68*, 419–435 (1974).
Ferone R.: Folate metabolism in malaria. Bull. WHO *55*, 291–298 (1977).
Fleischer N. K. F.: Folsäureabsorption bei tropischer Enteropathie. Med. Klin. *71*, 1273–1276 (1976).
Goldstein F. W.: Mécanismes de résistance aux sulfamides et au triméthoprime. Bull. Inst. Pasteur *75*, 109–140 (1977).
Grant H. C. et al.: Folate deficiency and neurological disease. Lancet *1965*/II, 763–767.
Heilmann E.: Folsäuremangel. Dtsch. med. Wschr. *102*, 1818–1819 (1977).
Heilmann E.: Vitamin-$B_{12}$- und Folsäure-Mangel. Fortschr. Med. *97*, 849–851 (1979).
Heilmann E., Bönninghoff E.: Folsäurebestimmungen im Serum und in den Erythrozyten mittels einer kompetitiven Proteinbindungsmethode mit 125-Jod-Markierung. Schweiz. med. Wschr. *106*, 1821–1823 (1976).
Herbert V.: Experimental nutritional folate deficiency in man. Trans. Ass. Amer. Phycns *75*, 307–320 (1962).
Herbert V.: Metabolism of folic acid in man. J. infect. Dis. *128*, suppl., S601–606 (1973).
Hughes A., Gatus A.: Severe megaloblastic anaemia caused by Maloprim. J. trop. Med. Hyg. *82*, 120–121 (1979).
Huser H. J.: Häufige und seltene Formen von Vitamin-B12- und Folsäuremangelanämien. Schweiz. med. Wschr. *105*, 1823–1829 (1975).
Muto T. et al.: Malaria in Laos. II. Peripheral leucocyte counts during long-term administration of combined folic inhibitors (Pyrimethamine with Sulformethoxine or Sulfamonomethoxine). Jap. J. exp. Med. *41*, 459–470 (1971).
Myatt A. V. et al.: Studies in human malaria. XXXIII. The toxicity of Pyrimethamine (Daraprim) in man. Amer. J. trop. Med. Hyg. *2*, 788–794 (1953).
Pearlman E. J. et al.: Chemosuppressive field trials in Thailand. III. The suppression of *Plasmodium falciparum* and *Plasmodium vivax* parasitemias by a Sulfadoxine Pyrimethamine combination. Amer. J. trop. Med. Hyg. *26*, 1108–1115 (1977).
Peters W.: Current concepts in parasitology. Malaria. New Engl. J. Med. *297*, 1261–1264 (1977).
Rosenberg I. H. et al.: The digestion and absorption of dietary folates. Gastroenterology *60*, 445–463 (1971).
Stürchler D.: Die Bedeutung der Tropenkrankheiten in der Schweiz. Bull. eidg. Gesundh.-Amt *47*, 637–642 (1979).
Thien K. R. et al.: Serum folates in man. J. clin. Path. *30*, 438–448 (1977).
Tong M. J. et al.: Supplemental folates in the therapy of *Plasmodium falciparum* malaria. J. Amer. med. Ass. *214*, 2330–2333 (1970).
Waxman S., Herbert V.: Mechanism of Pyrimethamine-induced megaloblastosis in human bone marrow. New Engl. J. Med. *280*, 1316–1319 (1969).
Waxman S. et al.: Drugs, toxins and dietary amino acids affecting vitamin B12 and folic acid absorption and utilisation. Amer. J. Med. *48*, 599–605 (1970).
Weinstein L., in: L. S. Goodman, A. Gilman (eds.): The pharmacological basis of therapeutics, p. 1113–1129. McMillan, New York 1975.
Weniger H.: Review of side effects and toxicity of Pyrimethamine. WHO unpubl. doc. WHO/MAL/79.907 1–22 (1979).
Williams R. L. et al.: The influence of acetylator phenotype on the response to Sulfalene in individuals with Chloroquine-resistant Falciparum malaria. Amer. J. trop. Med. Hyg. *27*, 226–231 (1978).