treatment with chloroquine.¹⁻³ Our analysis suggests that there is also a high risk of severe cutaneous adverse reactions when Fansidar is used as monophylaxis.

Reactions to Fansidar

Seventy eight reactions in 52 Swedish travellers occurring between 1978 and the end of June 1985 were considered by the Swedish Adverse Drug Reactions Advisory Committee to have had a probable or possible causal relation with Fansidar. During the same period roughly 1.2 million tablets were sold in Sweden. All 52 travellers used Fansidar as monophylaxis, and only four took any other drugs. All except three took one tablet weekly. Four travellers had previously experienced adverse reactions to sulphonamides. Only three went to chloroquine resistant areas in Africa.

Skin reactions were reported in 24 travellers after a median of 13 days (range 1-45 days). Seven patients experienced severe cutaneous adverse reactions (table).

Characteristics of seven Swedish travellers with severe cutaneous adverse reactions associated with Fansidar prophylaxis

Age (years)	Sex	Dose (tablets/week)	Diagnosis	Time to reaction (days)	Concomitant drugs	Outcome
50	F	1	EM	15	No	Recovered
48	F	1	SJS	21	No	Recovered
68	F	1	SJS	7	No	Recovered
41	M	1	SJS	7	No	Recovered
24	F	1	SJS	13	Levothyroxine	Recovered
31	M	1	TEN	23	No	Died
39	M	1	TEN	18	No	Died

EM=Erythema multiforme; SJS=Stevens-Johnson syndrome; TEN=toxic epidermal necrolysis (Lyell's syndrome).

Three cases of photosensitivity and 14 of exanthema were reported. None of the travellers who suffered cutaneous reactions had previously experienced adverse reactions to sulphonamides. Liver reactions occurred in 15 travellers (12 women), developing after a median of 52 days (range 16-91 days). Five had increased liver enzyme activities alone, while the others were also icteric. One of the eight travellers with respiratory symptoms (seven men) complained of dyspnoea and one had pleuritis, while the remaining six also suffered pulmonary infiltrations and fever. Symptoms occurred 1-30 days after treatment was started.

Two men developed severe generalised vasculitis. One became ill with fever, orchitis, jaundice, cutaneous vasculitis, and gastrointestinal bleeding after two weeks. The other developed cutaneous vasculitis and rapidly progressive nephritis after three weeks. Severe megaloblastic anaemia was noted in one traveller after six weeks, one traveller experienced reversible hyperaesthesia, and one reported itching.

Comment

The true risk of adverse reactions is difficult to estimate. The duration of prophylaxis varies and many tablets are never used and some are prescribed for self treatment. In addition, many adverse reactions are never reported.⁴ Despite these difficulties, however, a rough estimate can be made.

The intended duration of Fansidar prophylaxis was stated for 30 of the 52 travellers. Assuming that they were representative of all users and taking into account the package sizes, the average number of tablets taken by each traveller was 17, giving an estimated number of around 70 000 users. Fatal reactions were thus reported for one in 35 000 and severe cutaneous adverse reactions for one in 10 000. These figures are well in accordance with the estimated risks in American travellers taking Fansidar in combination with chloroquine.² Thus our data do not support the theory that an interaction with chloroquine might increase the frequency and severity of adverse reactions to Fansidar.³

In South America and South East Asia the risk of contracting *Plasmodium falciparum* malaria is smaller than that in Africa and resistance to Fansidar is more common. Fansidar should therefore generally not be recommended for prophylaxis outside areas with chloroquine resistance in Africa.

All the severe cutaneous adverse reactions and the two cases of generalised vasculitis developed within less than one month of treatment. Fansidar therefore cannot be unequivocally recommended for short term prophylaxis, but it might be justified for non-immune subjects who have been taking Fansidar for some time and live in areas of Africa with a high risk of chloroquine resistant *P. falciparum* to continue using it.

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Department of Infectious Diseases of the Karolinska Institute, Roslagstulls Hospital, Box 5651, S-114 89 Stockholm, Sweden

URBAN HELLGREN, MD, registrar
LARS ROMBO, MD, consultant physician
BJARNE BERG, nurse

Department of Infectious Diseases, Akademiska Sjukhuset, Uppsala University, S-751 85 Uppsala, Sweden

JOHAN CARLSON, MD, senior registrar

Swedish Adverse Drug Reactions Advisory Committee, Department of Drugs, National Board of Health and Welfare, S-751 25 Uppsala, Sweden
BENG-ERIK WIHOLM, MD, PhD associate professor

Correspondence to: Dr Hellgren.

Immune haemolytic anaemia induced by glibenclamide in selective IgA deficiency

Glibenclamide is a widely prescribed and well tolerated oral antidiabetic drug. We report a case of immune haemolytic anaemia associated with glibenclamide treatment in a patient with selective IgA deficiency.

Case report

A 48 year old mentally retarded man with mild diabetes was given glibenclamide for two months. He had been taking zuclopenthixol for several years. During treatment with glibenclamide he became jaundiced and increasingly fatigued. Anaemia and a raised bilirubin concentration led to admission to hospital.

On examination he had icteric scleras but no fever, hepatosplenomegaly, or lymphadenopathy. Haemoglobin concentration was 85 g/l and red cell count $2.67 \times 10^{12}/l$ with 58% reticulocytes. Erythrocyte sedimentation rate was 108 mm in the first hour, serum bilirubin concentration 59 $\mu\text{mol}/l$, lactate dehydrogenase activity 696 IU/l, haptoglobin concentration $<0.25 \text{ mg}/l$, and ferritin concentration 113 $\mu\text{g}/l$. A peripheral blood smear showed polychromasia, spherocytosis, anisocytosis, and some nucleated red blood cells. The white cell morphology was normal except for 16% eosinophils. A bone marrow specimen showed erythroid hyperplasia. A Paul-Bunnell test and a complement fixation test for mycoplasma antibodies gave negative results and cold agglutinins were not found. A direct Coombs test gave strongly positive results with anti-IgG and weakly positive results with anti-C₃ and anti-C₄. Serum IgG concentration was 8.9 g/l, IgM 1.7 g/l, C₃ 0.75 g/l, C₄ 0.24 g/l, and IgE $<5 \times 10^3 \text{ U}/l$. IgA could not be shown in the serum ($<0.006 \text{ g}/l$). Tests for antinuclear and rheumatoid factors gave negative results.

After one week in hospital the patient's haemoglobin concentration had fallen to 78 g/l, and he received three units of blood. As this resulted in only a temporary increase in haemoglobin concentration glibenclamide was stopped. A few days later the blood variables began to improve, and on follow up examination five weeks later haemoglobin concentration was 132 g/l, erythrocyte sedimentation rate 24 mm in the first hour, and red cell count $4.62 \times 10^{12}/l$ with 23% reticulocytes. His diabetes was well controlled by diet alone.

His serum did not agglutinate normal red cells *in vitro*, and no agglutination occurred when glibenclamide at various concentrations was added to the serum. Six months later, a Coombs test with anti-IgG still gave strongly positive results, but negative results were obtained with anti-C₃ and anti-C₄. There was no haemolysis.

Comment

The rapid and complete recovery when glibenclamide was stopped strongly suggests that this drug caused the immune haemolytic anaemia. The neuroleptic treatment was continued, and the patient had not received any other drugs before admission. Although a wide variety of drugs may induce haemolysis,¹ sulphonylureas have seldom been found responsible.^{2,3} The Committee on Safety of Medicines and the manufacturer have not received any reports of a possible association between glibenclamide and haemolytic anaemia (personal communication). Logue *et al* described

immune haemolytic anaemia in a patient treated with chlorpropamide; in vitro testing showed cross reactivity with glibenclamide and related compounds. Immune haemolysis in vivo caused by glibenclamide, however, does not seem to have been reported before. The mechanism of haemolysis was compatible with the cephaline type, as a Coombs test gave a positive result with both anti-IgG and anti-C₃ and anti-C₄. This result is caused by a non-specific binding of serum proteins, including IgG and complement, to a damaged or altered erythrocyte surface. The antiglobulin test may give a positive result for many months, as was seen in our patient.

Selective IgA deficiency is the most common form of dysgammaglobulinaemia and is, for unknown reasons, often associated with immunological disorders.⁴ Whether the IgA deficiency and the drug induced haemolytic anaemia in our patient were connected was uncertain.

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Medical Department B, University of Bergen, Haukeland Hospital, Bergen, Norway

O B NATAAS, MD, consultant
I NESTHUS, MD, consultant

Correspondence to: Dr Nataas.

Lyme disease presenting as recurrent acute meningitis

The neurological manifestations of Lyme disease have been increasingly recognised in Britain,^{1,2} Muhlemann and Wright identifying 21 cases with such symptoms last year in the United Kingdom and Irish Republic.³ The usual neurological manifestations are fluctuating symptoms of meningoencephalitis with superimposed cranial or peripheral radiculopathy, but although these features are often intermittent, the duration of meningitic symptoms is more like that of chronic meningitis.⁴

We report on a patient with Lyme disease who presented with recurrent acute meningitis and no history of tick bite, cutaneous eruptions, or other systemic symptoms.

Case report

A 55 year old man was admitted in October 1984 with a history of feeling unwell and occipital headaches for two days. He was feverish, and clinical examination showed only slight stiffness of the neck on extreme flexion.

Investigations showed a normal full blood count. Studies of cerebrospinal fluid showed a raised protein concentration (2.4 g/l), a glucose concentration of 5.3 mmol/l, and 240×10^9 leucocytes/l (100% lymphocytes); tests for the presence of bacteria, fungi, and viruses yielded negative results. He was treated with intravenous penicillin 16 megaunits daily for seven days and recovered completely within the next few days. Sixteen months later he was admitted with similar symptoms of short duration and slight stiffness of the neck. Cerebrospinal fluid studies showed a raised protein concentration (0.8 g/l), a glucose concentration of 5.8 mmol/l, and lymphocytes $< 1 \times 10^9$ /l; cultures yielded negative results. He recovered spontaneously within a few days without any specific treatment.

Seven months later he again presented with similar symptoms of one day's duration; examination showed a fever (38°C) with slight stiffness of the neck but no other physical abnormality. Cerebrospinal fluid contained 60×10^9 leucocytes/l (95% polymorphs); the protein concentration was 1.8 g/l and glucose concentration 4.2 mmol/l. Cultures for *Mycobacterium tuberculosis* and tests for fungi and viruses yielded negative results. A repeat examination of cerebrospinal fluid after seven days showed 196×10^9 leucocytes/l (100% lymphocytes), a protein concentration of 1.13 g/l, and a glucose concentration of 4.7 mmol/l. A computed tomogram of the brain showed no abnormality. Intravenous penicillin 16 megaunits daily was started on the second day of admission, and he made a complete recovery within the next 24 hours. Treatment was continued for two weeks, and he had no further complications. An indirect immunofluorescence test for antibodies to *Borrelia burgdorferi* yielded a positive result. Seven weeks after admission his serum IgG titre was 1/256 and IgM titre negative. A further sample of serum 10 days later had an IgG titre of 1/64 and a negative IgM titre.

Comment

Our patient had two symptom free periods of 16 and seven months, respectively, between three episodes of acute meningitis. Serological tests were done only during the last admission. Although we cannot exclude the possibility of reinfection, which is known to occur in Lyme disease,⁵ we believe that these episodes were recurrences. The first episode occurred after the patient had worked on a road in a deer forest. He had not done this before the second and third episodes, and the presenting symptoms were similar on each admission. The subsequent episodes are therefore unlikely to have been due to reinfection as he did not develop the more common dermatological and systemic symptoms before either of them. Inadequate treatment of the first episode is also unlikely because the intervals between attacks were too long.

Recurrent meningitis is often difficult to diagnose. The natural course of bacterial, fungal, and viral meningitis is well understood, but in some cases it may be exceptionally difficult to establish the source of infection. When only neurological symptoms are present a diagnosis of Lyme disease may not be obvious.²

Patients with recurrent episodes of aseptic meningitis should have serological tests for *B burgdorferi* even if there is no history of tick bite or cutaneous lesions; if Lyme disease is diagnosed early high dose intravenous penicillin can shorten the duration of meningitic symptoms.

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Wrexham Maelor Hospital, Wrexham, Clwyd LL13 7TD

G S PAL, MB, MRCP, medical registrar
J T BAKER, MSC, FRCP, consultant physician
P R D HUMPHREY, DM, MRCP, consultant neurologist (also at Walton Hospital, Liverpool)

Correspondence to: Dr Pal.

Bromocriptine induced impotence in Parkinson's disease

Increased sexual drive may be common in patients with Parkinson's disease receiving treatment with levodopa or dopamine agonists.¹ The incidence of a true "aphrodisiac" effect, however, is difficult to assess. Frankly hypersexual or deviant behaviour occurs rarely and is usually associated with an acute brain syndrome or history of hypersexuality.²

Though diminished libido is a common feature of Parkinson's disease,³ impotence related to dopaminergic treatment has not been reported. We describe four men with idiopathic Parkinson's disease with no history of sexual difficulty who spontaneously complained of impotence associated with dopamine agonist (bromocriptine) treatment.

Case reports

Case 1—A 59 year old man was receiving treatment with incremental doses of bromocriptine. After seven months, when the total daily dose was increased from 45 mg to 60 mg and good control of the parkinsonian symptoms had been gained, he became impotent. In spite of noticeably increased sexual urge he achieved erections only transiently and penetration was impossible. When the dose was reduced to 30 mg daily erectile function returned to normal, with worsening of the parkinsonian symptoms. Subsequent increases in the dose of bromocriptine invariably produced impotence. A combined regimen, however, of levodopa (Sinemet-Plus, one tablet three times daily) and bromocriptine (5 mg three times daily) resulted in good control of Parkinson's disease and normal sexual drive and erectile function.

Case 2—A 34 year old man was receiving incremental doses of bromocriptine. After four months (22.5 mg daily) he experienced inability to sustain erections. When the dose was reduced to 11.25 mg daily normal sexual function returned.