Arthritis and primary biliary cirrhosis

Articular problems are more commonly associated with active chronic hepatitis, viral hepatitis, and haemochromatosis,¹ than with primary biliary "cirrhosis" (PBC; chronic, non-suppurative, destructive cholangitis).^{2,3} Of 12 patients with PBC seen in this hospital over the past three years, however, five had appreciable arthritic lesions and circulating rheumatoid factor. We wish to emphasise the frequency of this association by reporting details of these patients.

Case reports

Case 1—A woman aged 47 developed nodular, erosive peripheral arthritis, a pleural effusion, and pericarditis. A liver biopsy was performed 12 months later because of persistently raised concentrations of alkaline phosphatase in serum. The histological appearance of the specimen suggested primary biliary cirrhosis with lymphocytic infiltration of the portal tracts.

Case 2—This woman, aged 69, presented with symmetrical, peripheral, erosive arthritis without nodules, but with iritis and a raised concentration of serum alkaline phosphatase. The histological appearances of a liver biopsy specimen were compatible with PBC.

Case 3—For many years this 62-year-old woman had experienced episodes of symmetrical arthritis affecting knees and small joints. There were erosions of bone but no nodules. She then developed pruritus, steatorrhoea, hepatomegaly, and a raised concentration of alkaline phosphatase. A liver biopsy specimen confirmed the diagnosis of PBC.

Case 4—This woman, aged 54, had abnormal liver function test results and a palpable spleen. The histological appearances of a liver biopsy specimen showed probable PBC. Subsequently she developed a non-erosive, anodular arthritis of the hands and knees.

Case 5—A 49-year-old woman developed pruritus after cholecystectomy. An operative liver biopsy specimen showed the histological appearances of PBC. Jaundice, hypercholesterolaemia (maximum serum cholesterol concentration 24 mmol/l (927 mg/100 ml)), and hepatosplenomegaly developed, as did a non-erosive anodular arthritis affecting the hands, wrists, shoulders and one knee.

Comment

Arthralgia or rheumatoid arthritis are thought to occur only rarely in patients with PBC, although circulating rheumatoid factor may be detected in a quarter of such patients.⁴ Thus articular symptoms were recorded in four per cent of 47 patients in one series² and "rheumatoid arthritis" in five per cent of 100 patients in another.³

The severity of the arthritic symptoms of the five patients we described and the histological evidence for PBC varied, the two aspects being generally inversely related. Serological results were positive for rheumatoid factor in all patients (see table), and patients 1 and 2 fulfilled the American Rheumatism Association's criteria for "definite" rheumatoid arthritis. Patient 1 had severe systemic involvement compatible with rheumatoid disease, and articular erosions and nodules; lesser erosive changes were present in patients 2 and 3. Only patient 5 had hypercholesterolaemia, and although the joint fluid from this patient contained free cholesterol crystals, crystals from a needle synovial biopsy were too minute to identify. A similar biopsy finding was obtained from patient 4, in whose joint fluid no crystals were detected. The relation of crystals to joint symptoms is not clear.

There were periportal granulomatous changes in the liver biopsy specimens from patients 3 and 5, and that from patient 4 showed abnormal proliferating bile ductules. The specimens from patients 1 and 2, however, were only suggestive of PBC, their appearances being similar to those described in a series of patients having "autoimmune hepatitis" and circulating antimitochondrial antibodies but without overt liver disease.⁵ In patients 1 and 2 the greatly raised levels of

serum alkaline phosphatase and in patient 2 the detection of anti-mitochondrial antibody suggest the diagnosis of PBC.

We thank Dr B Creamer for permission to report details of two of the patients.

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(Accepted 14 April 1977)

St Thomas's Hospital, London SE1 7EH

D L CHILD, MB, MRCP, registrar (present address: Wusasa Hospital, Wusasa, PA Zaria, Kaduna State, Nigeria)

J A MATHEWS, MB, MRCP, consultant physician, department of rheumatology

R P H THOMPSON, DM, MRCP, consultant physician

Effect of disodium cromoglycate on virus-cell systems in vitro

The effect of disodium cromoglycate (DSCG) on virus-cell interactions has not been extensively investigated. We therefore studied the effects of DSCG on in-vitro cell cultures, in in-vitro and in-vivo antiviral test systems, and on virus neutralisation by serum antibodies.

Methods and results

We examined the in-vitro cellular toxicity of DSCG by four different methods: (1) morphological changes induced in a monolayer of HEP₂ cells incubated in tissue culture for not less than two days (human cell line); (2) inhibition of migration of guinea pig macrophages (primary mammalian); (3) morphological changes induced in chick embryo fibroblast cells (primary avian) in monolayer culture during three days' exposure to the compound; (4) alteration of ciliary activity of human bronchial tissue (human primary explant), measured on a highspeed camera.

For methods 1, 2, and 3 the cells were examined after exposure to different concentrations of DSCG (range 0.9-76 mmol/l (0.5 mg/ml)), but in each case the only dose showing toxicity was 9.76 mmol/l. Human ciliated tissue was not exposed to concentrations greater than 1.95 mmol/l (1 mg/ml). No toxic effects on ciliary frequency were observed. We also examined the effects of DSCG on virus-cell systems (see table). In the vaccinia, herpes, and polio systems, plaque assays were used to assess infectivity, while haemagglutination and haemadsorption was used to identify growth of virus for influenza and parainfluenza, and cytopathic effect for respiratory syncytial virus. DSCG was not found to have any activity in any of these systems up to the level at which toxicity in the cells was observed (9.76 mmol/l).

The effects of DSCG on viral antigen-antibody neutralisation reactions were studied in the following systems: human antiserum and influenza A/PR/8, herpes, and polio viruses; rabbit antiserum and influenza A/PR/8, parainfluenza (Sendai), vaccinia, and polio viruses; and ferret antiserum and influenza A/HK virus. We used the assay systems referred to above, but no measurable effect of DSCG on virus-neutralising titre of the serum anti-

Results of Rose-Waaler (sheep-cell agglutination) tests, x-ray appearances of joints, presence or absence of antimitochondrial antibody and antinuclear factor, and maximum serum alkaline phosphatase concentrations in five patients with primary biliary cirrhosis and arthritis

Patient no	Age (years) and sex	X-ray appearance	Serum alkaline phosphatase concentration (normal range 3-13 KAU)	AMA	ANF	Rose-Waaler test
1	47 F	Erosive	41	+	1/10	1/1024
2	69 F	Eroded ulnar styloid	26	+	1/50	1/64
3	62 F	Eroded ulnar styloid	110	+	1/50	1/32
4	54 F	Degenerative joint disease	105	+	+	1/32
5	49 F	Para-articular osteoporosis	42	+	1/50	1/256

AMA=antimitochondrial antibody; ANF=antinuclear factor

Virus-cell systems in which activity of DSCG was examined

Virus	Classification	Cell system
Pox virus	Vaccinia	CEF
Herpes virus	Herpes simplex	CEF
Picornavirus	Poliovirus 2	HEP ₂
Orthomyxovirus .. {	Influenza A/PR/8 (H ₂ N ₂)	CAM ₂
Paramyxovirus	Influenza A/Hongkong (H ₂ N ₂)	CEF/CAM
Metamorphovirus ..	Parainfluenza 1 (Sendai)	CEF/CAM
	Respiratory syncytial (RS)	HEP ₂

CEF = chick embryo fibroblast; CAM = chorioallantoic membrane.³

bodies was observed after incubation of the mixtures for one hour (concentration of DSCG up to 1.95 mmol/l).

In-vivo experiments in mice—These included intracerebral inoculation of a mouse-adapted strain of polio virus type 2 at various dilutions and the intranasal and contact infection of mice with influenza and parainfluenza viruses. The drug was administered by mouth, subcutaneously, intranasally, and by aerosol at various dose levels up to 500 mg/kg/day. No antiviral activity was observed, nor did it affect the symptoms of the infections in the mice.

Comment

These limited studies did not show that DSCG had antiviral activity. While the drug has been shown to be remarkably non-toxic in laboratory and clinical use, we found that the upper non-toxic concentration of DSCG in vitro was about 7.8 mmol/l (4 mg/ml). Above this point signs of toxicity were usually apparent.² In contrast, the most effective concentration used by Penttinen *et al*¹ in their in-vitro studies of inhibition of virus-induced cytopathic effects was 19.5 mmol/l (10 mg/ml). While their results are obviously interesting and of significance for further investigation into exacerbation of asthma associated with virus infections, the level of drug to be used and the methodology and design of future experiments is most important.

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(Accepted 6 April 1977)

Pharmaceutical Division, Fisons Ltd, Loughborough, Leicestershire LE11 0QY

D E E LOVEDAY, PHD, MRIC, systems officer

R B M WENHAM, BSC, head of scientific services, life sciences department

Serum sodium and osmolality during carbamazepine treatment in children

Carbamazepine is an anticonvulsant used in treating different epileptic disorders in all age groups. It has an antidiuretic activity similar to that of the antidiuretic hormone.¹⁻³ The risk of hyponatraemia and low plasma osmolality during carbamazepine treatment in adult patients is related to the dose and blood concentration of the drug. We present here our findings in paediatric patients in these respects.

Patients, methods, and results

Twenty-eight patients attending the paediatric clinic of Malmö General Hospital for control of epileptic disorders were reviewed. Their average age was 12 years (range 6-18), the average daily dose of carbamazepine 650 mg (range 100-1400), and the average duration of therapy 36 months (range 2-113). Eleven of the children were taking carbamazepine only and 17 carbamazepine in combination with other anticonvulsants. Eighteen children with an average age of 11 years (range 3-18) under treatment with other anticonvulsants only, mainly phenytoin, were reviewed for comparison.

A serum sample was taken from each patient and analysed for carbamazepine and electrolyte concentrations. Serum osmolality was measured by

means of the depression of freezing point technique. Carbamazepine concentration was measured by gas chromatography using cyheptamide as an internal standard.

The results are summarised in the table. The mean serum sodium concentration was 143 (141-146) mmol (mEq)/l in children on carbamazepine only, 142 (141-145) mmol (mEq)/l in children on carbamazepine together with other anticonvulsants, and 142 (140-145) mmol (mEq)/l in children treated with other antiepileptic drugs only. The corresponding figures for serum osmolality were 285 (279-294), 288 (281-297), and 286 (278-297) mmol (mOsm)/kg respectively. None of the patients had hyponatraemia and no lowering of the serum osmolality was registered. No correlation was found between the daily dose of carbamazepine and serum sodium.

Details of patients on carbamazepine

Case No	Age (years)	Sex	Carbamazepine treatment		Cpss (μmol/l)	Serum Sodium (mmol/l)	Serum osmolality (mmol/kg)	Other drugs
			Duration (months)	Daily dose (mg)				
1	12	M	30	1400	27	141	284	P
2	13	M	67	1200	32	142	284	P
3	10	F	11	1200	30	143	289	P
4	16	M	113	1000	27	145	284	P, E
5	12	M	8	900	23	142	297	P
6	18	M	48	800	27	141	287	P
7	8	F	48	800	16	141	287	P
8	16	F	42	800	35	142	288	P
9	7	F	52	800	24	144	294	P, N
10	15	M	91	800	25	143	296	P, E
11	16	M	21	600	27	142	284	E
12	6	M	18	600	36	143	281	P
13	11	M	20	600	18	142	293	P
14	15	M	2	600	28	146	288	—
15	11	M	42	600	41	144	279	—
16	9	M	45	600	42	143	284	—
17	8	F	11	500	27	143	285	P, D
18	8	M	84	500	20	143	288	P, D
19	12	F	12	500	38	143	291	—
20	12	F	24	500	31	141	282	—
21	14	M	22	400	29	141	281	—
22	11	M	35	400	31	143	284	—
23	11	M	2	400	24	143	286	—
24	10	M	3	400	16	142	292	P
25	9	M	13	400	34	142	294	—
26	7	F	15	400	32	144	287	—
27	17	M	42	200	31	144	283	—
28	16	F	50	100	14	143	286	—

Cpss = Carbamazepine steady-state concentration. P = Phenytoin. E = Ethosuximide. N = Nitrazepam. D = Diazepam.

Conversion: SI to traditional units—Cpss: 1 μmol/l ≈ 0.24 μg/ml. Serum sodium: 1 mmol/l = 1 mEq/l. Serum osmolality: 1 mmol/kg = 1 mOsm/kg.

Comment

The antidiuretic action of carbamazepine has been used in the treatment of diabetes insipidus.¹⁻³ Henry *et al*⁴ have shown that this action is not confined to patients with diabetes insipidus. A high daily dose of carbamazepine may induce hyponatraemia in adults with other diseases. Furthermore, elderly patients with cardiovascular disease may be particularly vulnerable.⁵ We did not find any significant abnormalities in serum sodium or serum osmolality in children treated with carbamazepine alone or in combination with other anticonvulsants for epileptic disorders. Apparently with the dose of carbamazepine commonly required to ensure good control of a convulsive disorder in children there is hardly any risk of hyponatraemia. Nevertheless, in children with symptoms such as confusion, weakness, or lethargy while on carbamazepine, hyponatraemia should be considered.

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(Accepted 14 April 1977)

Department of Paediatrics, University of Lund, General Hospital, S-214 01 Malmö, Sweden

I HELIN, MD, research fellow

K O NILSSON, MD, assistant professor

I BJERRE, MD, assistant professor

P VEGFORS, MD, consultant physician