Psoriasis, alcohol, and liver disease

The relations between psoriasis, consumption of alcohol, and liver disease are usually discussed in textbooks in the context of methotrexate hepatotoxicity but have never been studied in a large number of subjects.¹ The aim of this study was to assess the prevalence of psoriasis according to alcohol consumption and the presence of liver disease.

Patients, methods, and results

For each of 1987 subjects admitted between November 1981 and November 1983 the presence or the absence of psoriasis was noted whatever the medical diagnosis and whatever the alcohol consumption. In cases of clinical doubt the advice of a dermatologist was obtained. No patient was treated with methotrexate. For each patient the quantity of alcohol drunk daily during the past five years was noted. Of the 639 subjects who drank more than 50 g (mean 120 g) a day, 370 underwent percutaneous liver biopsy. Drinkers were therefore divided into four groups—namely, those without liver disease (normal result of liver biopsy, $n=47$); those with non-cirrhotic alcoholic liver disease (histologically proved steatosis, fibrosis, or acute alcoholic hepatitis, $n=228$); those with alcoholic cirrhosis ($n=258$), comprising those with histologically proved cirrhosis ($n=97$) and those with clinically obvious cirrhosis ($n=161$); and those without clinically obvious cirrhosis who did not undergo liver biopsy ($n=106$).

The table shows the prevalence of psoriasis according to alcohol consumption and liver disease. Ten of the 1348 non-drinkers (0.7%) had psoriasis compared with 34 of the 639 drinkers (5.3%) ($p<0.001$). The estimated relative risk of psoriasis associated with an alcohol consumption of over 50 g a day was 7.5 (95% confidence interval 3.5-16.4). Among non-drinkers there was no difference in the prevalence of psoriasis between subjects with and without liver disease. When the drinkers were divided into groups on the basis of the severity of their liver disease the prevalence of psoriasis was similar in all four groups. We found no significant difference between drinkers with and without psoriasis in the following variables: age, sex, mean daily alcohol intake, duration of alcoholism, serum glucose concentration, mean red cell volume, serum total bilirubin concentration, serum γ -glutamyl transpeptidase activity, serum cholesterol concentration, and serum triglyceride concentration.

Prevalence of psoriasis according to consumption of alcohol and liver disease

	Total No of subjects	No of subjects with psoriasis	Prevalence of psoriasis (%)
Alcohol consumption ≤ 50 g/day	1348	10	0.7
No liver disease	1072	6	0.6
Non-alcoholic liver disease	276	4	1.4
Alcohol consumption > 50 g/day	639	34	5.3
Normal liver	47	2	4.3
Steatosis, fibrosis, or acute alcoholic hepatitis	228	13	5.7
Cirrhosis	258	14	5.4
No biopsy	106	5	4.7
Total	1987	44	2.2

*Significantly greater than prevalence of psoriasis in patients drinking less than 50 g alcohol/day with and without liver disease ($p<0.001$).

Comment

This study shows that psoriasis is more common among subjects who drink over 50 g alcohol a day and that it is not related to liver disease. The highly significant relation between alcohol consumption and psoriasis is not synonymous with a causative relation; whether alcohol enhances the onset of psoriasis or psoriasis enhances the onset of alcoholism is not known. Prospective studies of abstinence in subjects with psoriasis and studies of the sequence of development of psoriasis and alcoholism might give a clue to the role of alcohol in psoriasis.

The relation between alcohol and psoriasis might explain some of the biochemical abnormalities observed in patients with psoriasis such as hyperlipidaemia,² folate deficiency,³ hyperuricaemia,⁴ and overproduction of free radicals.⁵ Abnormalities of lipid metabolism may result in abnormal keratinisation and have been incriminated in the pathogenesis of psoriasis. In this study the absence of a difference in blood lipid concentrations in drinkers with and without psoriasis militates against this hypothesis.

This study did not show any relation between psoriasis and liver disease, the prevalence of psoriasis being the same whatever the histological appearance of the liver. Among non-drinkers the prevalence was not significantly different between subjects with (1.4%) and

without (0.6%) liver disease, but, given the number of subjects with non-alcoholic liver disease ($n=276$), a small difference (type II error) cannot be definitely excluded.

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- 1 Delaney TJ, Leppard B. Alcohol intake and psoriasis. *Acta Derm Venereol* 1974; 54:237-8.
- 2 Benton JM, Brown PE, Church RE. Serum cholesterol in psoriasis. *Lancet* 1963;i:583-4.
- 3 Touraine R, Revuz J, Zittoun J, Jarret J, Tulliez M. Study of folate in psoriasis: blood levels, intestinal absorption and cutaneous loss. *Br J Dermatol* 1973;89: 335-41.
- 4 Graciansky P, Larregue M, Martinet C. Hyperurémie et psoriasis. *Annales de Dermatologie et de Syphiligraphie* 1976;103:591-2.
- 5 Zadrozny BA, Adolf EV, Schevchenko VP. Free radical in the skin of patients with psoriasis and their relationship to oxidative and reductive processes. *Vestn Dermatol Venerol* 1973;47:25-8.

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Hyperosmolar non-ketotic diabetes mellitus associated with metolazone

Metolazone is a sulphonamide diuretic related to quinethazone and chlorthalidone, differing chemically from other thiazide diuretics because of a heterocyclic ring structure. Thiazides impair glucose tolerance and induce hyperglycaemia, as well as producing hypokalaemia, hyperuricaemia, and hypomagnesaemia and altering lipid metabolism. Metolazone has not previously been associated with the hyperosmolar non-ketotic diabetic syndrome. A recent review has, however, highlighted the propensity of other thiazides to cause this.¹

Case report

A 64 year old woman was admitted with heavy glycosuria, nausea, and vomiting. She had suffered from general malaise for six weeks and excessive thirst and polyuria for one week. She had a 14 year history of hypertension treated with metolazone 10 mg and sustained release metoprolol 200 mg daily. She was also taking fluphenazine hydrochloride 500 μ g, nortriptyline hydrochloride 10 mg (Motival), and flurazepam for mild depression and insomnia. She had no history of diabetes, nor did her family.

On admission she was moderately obese, clinically dehydrated, and obtunded but did not smell ketotic. She did not have fever, evidence of infection, or neurological signs. Blood pressure remained around 150/90 mm Hg. Her haemoglobin concentration was 16.6 g/dl, white cell count $15.5 \times 10^9/l$, platelet count $291 \times 10^9/l$, and packed cell volume 0.527. Serum electrolyte concentrations were sodium 120 mmol(mEq)/l, potassium 3.8 mmol(mEq)/l, chloride 81 mmol(mEq)/l, and bicarbonate 20 mmol(mEq)/l, urea 22.5 mmol/l (135 mg/100 ml) and glucose 58.8 mmol/l (1060 mg/100 ml). Calculated serum osmolality (using the formula: osmolality = $2 \times (\text{sodium} + \text{potassium concentration}) + \text{urea} + \text{glucose}$) was 328.9 mmol(mOsm)/l. Analysis of urine showed glucose + + + + and Acetest + +.

She was managed by careful rehydration and a continuous insulin infusion. Prophylactic heparin was also given in view of the liability to thrombosis. Metolazone was stopped by metoprolol continued. Her clinical state improved rapidly, and she was biochemically normal after 48 hours. She was discharged taking sustained release metoprolol 200 mg and a twice daily combination of neutral insulin (Neusulin) and insulin zinc suspension (Neulente) (total dose 54 units). Subsequently, insulin was withdrawn; hyperglycaemia did not recur, and she remained well.

Comment

Our patient had severe hyperglycaemia with little change in serum

bicarbonate concentration, which indicated a non-ketoacidotic coma. We believe this to have been due to metolazone.

Controversy over the use of thiazide diuretics in hypertension continues because of their adverse metabolic effects. Consequently, the use of this group of drugs for hypertension may diminish. The use of metolazone, however, may increase in refractory oedema or sodium retention (due to congestive heart failure, hepatic cirrhosis, and renal disease) as a loop diuretic has a synergistic effect when given with a thiazide.²

β Adrenergic blocking drugs have been associated with carbohydrate intolerance—and propranolol particularly with recurrent non-ketotic hyperosmolar diabetic coma³—but in our patient metoprolol was continued without ill effect. Fonesca and Phear found that β adrenergic blockers are not of great importance in the pathogenesis of the hyperosmolar non-ketotic state.¹ Few reports of disturbance of carbohydrate metabolism with metolazone exist, and the Committee on Safety of Medicines (personal communication) has only one report each of diabetes mellitus, abnormality of electrolyte concentrations, and glycosuria. Metolazone has, however, been shown to influence diabetic control adversely.⁴ The mechanism of this adverse reaction is not known and is common to all diuretic benzothiadiazines, including some without diuretic activity such as diazoxide. It may entail both a decrease in the secretion of insulin and an extrapancreatic effect on the liver.⁵

This case emphasises that despite its different chemical structure metolazone, like chlorthalidone, may be associated with the hyperosmolar non-ketotic diabetic syndrome. Clinicians using this drug in refractory sodium retention should be alert to this possibility as well as that of massive natriuresis, so that early detection may prevent the development of coma with its attendant high mortality.

- 1 Fonesca V, Phear DN. Hyperosmolar non-ketotic diabetic syndrome precipitated by treatment with diuretics. *Br Med J* 1982;284:36-7.
- 2 Ostler JR, Epstein M, Smoller S. Combined therapy with thiazide-type and loop diuretic agents for resistant sodium retention. *Ann Intern Med* 1983;99:405-6.
- 3 Podolsky S. A possible role of propranolol in recurrent non-ketotic hyperosmolar diabetic coma. *Diabetes* 1970;19:398.
- 4 Walsh CH, O'Sullivan DJ. A study of the effect of metolazone on carbohydrate metabolism in diabetic subjects. *Journal of the Irish Medical Association* 1974;67:223-6.
- 5 Wales JK, Krees SV, Grant AM, Viktora JK, Wolff FW. Structure activity relationships of benzothiadiazine compounds as hyperglycaemia agents. *J Pharmacol Exp Ther* 1968;164:421-32.

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Pituitary apoplexy after combined test of anterior pituitary function

Evidence of infarction or haemorrhage of pituitary adenomas is a common histological finding. Clinically important pituitary apoplexy, a syndrome characterised by headache, vomiting, cranial nerve palsies, decreased consciousness, and occasionally death, is much less common.^{1,2} We report the occurrence of pituitary apoplexy after a combined test of anterior pituitary function.

Case report

A 39 year old, previously healthy woman presented to her general practitioner in June 1984 with a history of three months' galactorrhoea and six months' secondary amenorrhoea after stopping an oral contraceptive in December 1983. She had no history of menstrual irregularity and had had two normal pregnancies, 10 and 14 years previously. She had been taking an oral contraceptive continuously for four years until December 1983. Serum prolactin concentration was raised at 1959 mU/l (normal range < 350 mU/l), and a plain skull x ray film showed ballooning and erosion of the pituitary fossa. Bromocriptine 7.5 mg daily was started in June 1984, and she was referred to our endocrine clinic.

She was seen in August, when her serum prolactin concentration had fallen to 90 mU/l and she had just menstruated for the first time since December 1983. Bromocriptine was stopped, and in view of the enlargement of her pituitary fossa she was admitted for further assessment one month

later. Physical examination was unremarkable, blood pressure was 120/80 mm Hg, and the galactorrhoea had resolved. Visual fields were full by perimetry. Computed tomography with enhancement showed an enlarged pituitary fossa with erosion of the floor, dorsum sellae, and anterior clinoids, and the left sphenoid sinus was invaded by tumour. There was 9 mm suprasellar extension of a pituitary tumour.

A combined test of anterior pituitary function was carried out after an overnight fast. Insulin 0.15 U/kg, luteinising hormone releasing hormone 100 μ g, and thyrotrophin releasing hormone 200 μ g were injected intravenously. By 30 minutes she was clinically and biochemically hypoglycaemic (blood glucose concentration 1.3 mmol/l (23 mg/100 ml)) (table).

Results of combined test of pituitary function

Time (min)	Glucose (mmol/l)	Growth hormone (mU/l)	Cortisol (nmol/l)	Luteinising hormone (U/l)	Thyroid stimulating hormone (mU/l)	Follicle stimulating hormone (U/l)	Oestradiol E ₂ (pmol/l)
0	4.5	1	250	4	4.2	2	410
30	1.3	1	260	8	7.5		
45	1.3	1					
60	2.4	2	390	7	8.8		
90	2.8	1	420				
120	3.5	< 1	470				

Basal prolactin concentration 595 mU/l (normal < 350 mU/l); thyroxine 88 nmol/l (6.8 μ g/100 ml) (normal 75-160 nmol/l; 5.8-12.4 μ g/100 ml); and free thyroxine 11.6 pmol/l (0.9 ng/100 ml) (normal 9-23 pmol/l; 0.7-1.8 ng/100 ml).

Conversion: SI to traditional units—Glucose: 1 mmol/l $\approx$ 18 mg/100 ml. Cortisol: 1 nmol/l $\approx$ 36.3 ng/100 ml. Oestradiol: 1 pmol/l $\approx$ 0.29 pg/ml.

At 40 minutes she began to complain of frontal headache, which persisted after spontaneous restoration of normoglycaemia at 120 minutes (blood glucose concentration 3.5 mmol/l (63 mg/100 ml)). Her headache worsened. By the third day she had developed blurred vision and a partial left third nerve palsy. Computed tomography showed a low density area within the pituitary tumour indicating infarction. Her visual acuity suddenly deteriorated and bilateral third nerve palsies developed, the left pupil becoming fixed and dilated. Urgent craniotomy was carried out, and a haemorrhagic and necrotic pituitary tumour was found to be raising and compressing both optic nerves. Decompression was performed. She recovered completely with full restitution of neurological function and was discharged 10 days later. Histological examination of the tumour showed extensive infarction with resulting necrosis and areas of free haemorrhage. Tissue not affected by these vascular changes had the appearance of a chromophobe adenoma.

Comment

The development of pituitary apoplexy during a test of anterior pituitary function raised the possibility that the test was causally related to the illness. Bernstein *et al* reported a similar case, in which neurological signs developed after a combined test of pituitary function; urgent surgical intervention showed necrosis of a pituitary tumour.³

Of the three drugs used in the test, thyrotrophin releasing hormone would seem to be the one most likely to have an aetiological role. Cimino *et al* described transient amaurosis after 200 μ g thyrotrophin releasing hormone in a man with a pituitary tumour,⁴ and Drury *et al* also reported amaurosis and headache after injection of thyrotrophin releasing hormone.⁵ In one of their cases surgical evidence of pituitary apoplexy was found. How thyrotrophin releasing hormone produces this clinical picture is not clear.

The risk of pituitary apoplexy after tests of pituitary function is extremely low, but the condition should be borne in mind because of its potentially fatal outcome.

- 1 Nakai S, Fukushima T, Feramoto A, Sono K. Pituitary apoplexy: its incidence and clinical significance. *J Neurosurg* 1981;55:187-9.
- 2 Mohr G, Hardy J. Hemorrhage, necrosis and apoplexy in pituitary adenomas. *Surg Neurol* 1982;18:181-9.
- 3 Bernstein M, Hegete RA, Gentili F, *et al*. Pituitary apoplexy associated with a triple bolus test. *J Neurosurg* 1984;61:586-90.
- 4 Cimino A, Corsini R, Radceli E, *et al*. Transient amaurosis in patient with pituitary macro adenoma after intravenous gonadotropin and thyrotrophin releasing hormones. *Lancet* 1981;ii:95.
- 5 Drury PL, Belchetz PE, McDonald WI, *et al*. Transient amaurosis and headache after thyrotrophin releasing hormone. *Lancet* 1982;ii:218-9.

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