Intrahepatic cholestasis and cutaneous bullae associated with glibenclamide therapy

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Summary
Intrahepatic cholestasis and cutaneous bullae associated with glibenclamide therapy are described in a 61-year-old diabetic patient who presented with hypoglycaemic coma. These features have not previously been reported as side effects of glibenclamide therapy, but intrahepatic cholestasis may occur with chlorpropamide, a similar sulphonylurea agent. The mechanism of this cholestasis is not clear at present.

Introduction
Glibenclamide, a potent oral hypoglycaemic drug (Aumüller et al., 1966), has been considered to have fewer adverse effects than chlorpropamide which is an equivalent sulphonylurea agent. A diabetic patient presenting with hypoglycaemia is described who had reversible intrahepatic cholestasis and cutaneous bullae which appeared to have been induced by a 10 mg dose of glibenclamide.

Case history
A 61-year-old man with a 17-month history of maturity-onset diabetes mellitus, retinopathy and mild proteinuria was admitted unconscious with a blood glucose of less than 1·5 mmol/l. He had been treated with glibenclamide, initially 5 mg daily, and increased to 10 mg daily 5 months before admission. His other regular medication was digoxin 0·25 mg, frusemide 80 mg and Slow-K 1800 mg daily given for left ventricular failure due to ischaemic heart disease. He became gradually unwell with loss of appetite and drowsiness 3 weeks before admission. On admission he was in grade III coma without any localizing signs. There were 2 clear, colourless bullae 3 cm in diameter on the sole of the right foot and the right upper thigh. There was no evidence of inflammation around the bullae. He was also noted to be slightly jaundiced.

On investigation, he had a haemoglobin of 13·5 g/dl, white blood cell count 10 × 10⁹/l without eosinophilia, urea 7·3 mmol/l, creatinine 130 mmol/l, creatinine clearance 29 ml/min and urine protein 0·78 g/24 hr. His initial liver function tests showed bilirubin 55 µmol/l, aspartate aminotransaminase 115 u./l, alanine aminotransaminase 146 u./l, alkaline phosphatase 2420 u./l and albumin 35 g/l. Hepatitis B surface antigen and hepatitis A antibody were negative. Antinuclear factor, rheumatoid factor, smooth muscle antibody and antimitochondrial antibody were negative. Intraoperative cholangiogram and ultrasound scan of the liver and gall-bladder showed no evidence of extra-hepatic biliary obstruction. Liver biopsy performed 11 days after admission was normal when examined by light microscopy and electronmicroscopy using routine stains. No barbiturate was found in the serum on admission and urinary screen for porphyrins was negative.

He rapidly recovered consciousness with intravenous dextrose and 1 mg glucagon intramuscularly. Bilirubin, aspartate and alanine amino-transaminases returned to normal levels by the fourth day and alkaline phosphatase was normal after the thirty-seventh day. Both bullae gradually dried up over one month. Digoxin, frusemide and Slow-K were continued without any adverse effect. His diabetes was controlled by diet alone and he remains well on follow-up 3 months later.

Discussion
Glibenclamide is a potent and long-acting sulphonylurea drug which is relatively free of adverse effects. By contrast, its predecessor chlorpropamide has a number of adverse effects including intrahepatic cholestasis in 0·5% of patients (Reichel et al., 1960). Known adverse effects of these 2 drugs are listed in Table 1. Glibenclamide has been reported to cause transient skin rashes and slight
Table 1. Known adverse effects of chlorpropamide and glibenclamide

<table>
<thead>
<tr>
<th>Chlorpropamide</th>
<th>Glibenclamide</th>
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<tbody>
<tr>
<td><strong>Dermatological adverse effects</strong> (1)</td>
<td>Hypoglycaemia (10, 11)</td>
</tr>
<tr>
<td>Stevens-Johnson syndrome</td>
<td>Transient skin rashes (12)</td>
</tr>
<tr>
<td>Exfoliative dermatitis</td>
<td>Transient elevated aspartate and alanine aminotransaminases (12, 13)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Minor gastrointestinal disturbances (13)</td>
</tr>
<tr>
<td>Photodermatitis</td>
<td>Generalized hypersensitivity visceral arteritis (14)</td>
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<tr>
<td>Erythema nodosum</td>
<td>Nocturia (15)</td>
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<tr>
<td>Papular and purpuric rashes</td>
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<tr>
<td>Alopecia areata</td>
<td></td>
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<tr>
<td>Generalized pruritus</td>
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</table>

**Haematological adverse effects** (1)

- Aplastic anaemia
- Agranulocytosis
- Pancytopenia
- Leucopenia
- Thrombocytopenia
- Red cell aplasia (2)
- Immune haemolytic anaemia

**Hepatic adverse effects** (1)

- Cholestasis
- Hepatitis
- Granulomatus hepatitis (3)

**Miscellaneous adverse effects** (1)

- Hypoglycaemia
- Alcoholic flushing
- Diarrhoea
- Inappropriate secretion of antidiuretic hormone (4)
- Neonatal hypoglycaemia in infant of diabetic mother (5)
- Pulmonary eosinophilia (6)
- Possible increased incidence of myocardial infarction (7, 8)
- Anaphylaxis (9)

1. Harris, 1971
2. Recker and Hynes, 1969
3. Powell and Howells, 1966
4. Weissman, Shenkman and Gregerman, 1971
6. Bell, 1964
7. Boyle et al., 1972
8. Hadden, Montgomery and Weaver, 1972
9. Ravid, Rubinstein and Cabili, 1971
10. Gottesburen et al., 1970
11. Sillence and Court, 1975,
13. Burns, 1969
14. Clarke et al., 1974
15. Shaw, Bloom, and Bulpitt, 1977

Elevation of aspartate and alanine aminotransaminases which are reversible without alteration to dosage (Burns, 1969; O’Sullivan and Cashman, 1970). It is also known to cause minor gastrointestinal disturbances (Burns, 1969), hypoglycaemia (Sillence and Court, 1975), which can be fatal especially in the elderly (Gottesburen et al., 1970) and nocturia (Shaw, Bloom and Bulpitt, 1977). In one patient glibenclamide therapy was associated with a severe generalized hypersensitivity reaction resulting in fatal toxic erythema, cholestasis, eosinophilia and renal failure (Clarke et al., 1974). Post-mortem revealed a necrotizing angitis with associated granulomatous changes in the spleen and kidneys.

The combination of reversible intrahepatic cholestasis and cutaneous bullae due to glibenclamide has not previously been recorded. In this patient the probable diagnosis of drug-induced intrahepatic cholestasis was determined by exclusion of extrahepatic biliary obstruction, viral hepatitis and primary liver disease. The cholestasis cleared within 5 weeks of glibenclamide withdrawal, whilst other drug therapy was continued. It was felt that rechallenge with glibenclamide might carry a risk and was therefore unethical, especially as the patient did not require an oral hypoglycaemic drug to control his diabetes mellitus.

The two cutaneous bullae resembled those occasionally produced by barbiturate poisoning or seen in porphyria cutanea tarda. However, both these diagnoses were excluded and as no further bullae have appeared they too were probably an adverse reaction to glibenclamide therapy.

The mechanism of glibenclamide-induced intrahepatic cholestasis and cutaneous bullae is uncertain, although a hypersensitivity reaction in association
with toxic erythema and cholestasis was reported in a fatal case (Clarke et al., 1974). It has been suggested that a hypersensitivity reaction would account for chlorpropamide-induced intrahepatic cholestasis (Friedman, 1962). However, there was no firm evidence to support a hypersensitivity reaction in the present patient who had been on a standard dose of glibenclamide for 17 months before these 2 adverse effects developed.

In conclusion, attention should be drawn to the possibility of transient reversible intrahepatic cholestasis and cutaneous bullae induced by glibenclamide in a diabetic patient who presented with hypoglycaemic coma. All these adverse effects disappeared after the withdrawal of glibenclamide.

References
Bell, R.J.M. (1964) Pulmonary infiltration with eosinophils caused by chlorpropamide. Lancet, i, 1249.
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