

Diazoxide treatment for insulinoma: a national UK survey

GV Gill, O Rauf, IA MacFarlane

Summary

A survey of UK patients receiving the drug diazoxide, revealed 40 patients with insulinoma on this treatment. Mean age (\pm SD) was 67 ± 18 years, and 74% were female. Duration of treatment was 7 ± 6 years (range 1–22). Most (55%) patients were treated with diazoxide because of tumour non-localisation (including failed previous surgery). Metastatic disease (20%) and poor surgical risk (10%) were other indications. Side-effects (notably fluid retention and hirsutism) were common (47%) but not troublesome. Treatment was highly effective – 59% were symptom free and 38% had only occasional symptoms. Only one patient had frequent hypoglycaemia despite treatment. We conclude that diazoxide is effective in the management of insulinoma. Side-effects are common but not problematic. Treatment should be considered for all patients not cured by surgery, or unsuitable for surgical treatment.

Keywords: insulinoma, hypoglycaemia, diazoxide

Insulin-secreting tumours of the pancreatic beta cell ('insulinomas') cause problematic hypoglycaemia, and surgical removal is the ideal therapeutic management.¹ Sometimes, however, this treatment option is not possible. Tumour localisation may be extremely difficult, and pancreatic resection may fail to resolve symptoms. Also, some patients are old and debilitated at presentation, and may not be good candidates for major surgery. In such instances, medical treatment with the drug diazoxide is usually tried. Though known for many years to be a potentially effective option² there is no recent information as to how widely the drug is used, its effectiveness and side-effects. We therefore decided to perform a national survey of diazoxide usage for insulinoma in the UK.

Patients and methods

In the UK, diazoxide is not freely prescribable. It is manufactured for treatment only on a 'named patient' basis. When a physician requests the drug, it is supplied by the manufacturers (Allen and Hanburys Ltd) to a local pharmacy for a specific, named, patient. The manufacturers hold a list of all UK patients currently receiving diazoxide, and with their help and co-operation, we sent a confidential questionnaire to doctors who had requested

diazoxide for a patient who was still receiving the drug. We requested details of age and sex, underlying diagnosis, reason for medical treatment, duration of treatment, dosage and side-effects, and effectiveness of treatment.

As many patients receive diazoxide because of failure of insulinoma localisation, for the purposes of this study we defined 'insulinoma' biochemically, ie, laboratory-proven hypoglycaemia (plasma glucose < 2.2 mmol/l) associated with inappropriately raised plasma insulin concentrations (the actual level depended on local assay characteristics, but was usually over 10 mU/l).

Results

A total of 127 questionnaires were sent to all physicians listed as having patients currently supplied with diazoxide in the UK. A repeat mailing was sent and eventually 47 (37%) were returned. One cause of the low return may have been that the original physician had changed or moved without informing the manufacturers of the drug. Although this introduced the possibility of selection bias, it did tend to identify patients on long-term diazoxide therapy, which was our purpose. Of the 47 patient details returned, 40 were being treated for insulinoma, and seven for other conditions (two for nesidioblastosis, two for severe reactive hypoglycaemia and three for undiagnosed hypoglycaemia). The following results refer only to the patients being treated for insulinoma.

Of the 40 insulinoma patients, 17/23 (74%) were female (in the rest sex was not disclosed), and mean age ($n=37$) was 67 ± 18 years. Ages ranged from 21–93 years, and 21 (57%) patients were over 70 years. Duration of treatment ($n=37$) was 7 ± 6 years (range 1–22) and 11 (30%) had been taking diazoxide for over 10 years. Indications for diazoxide treatment are shown in table 1. In most cases (55%) this was due to tumour non-localisation (including failed surgery), with metastatic disease and poor surgical risk being other important reasons.

Mean diazoxide dose was 267 ± 138 mg/day (range 100–600). The commonest dosage used was 100 mg tid (36%). Drug side-effects were recorded in 17/36 (47%), and are detailed in table 2. Fluid retention was the commonest, with hirsutism next. In all cases, however, adverse effects were mild and did not require cessation of treatment, or dose adjustment. Diuretics were used in addition to diazoxide in 20/36 (55%) patients.

Department of
Medicine, Walton
Hospital, Rice Lane,
Liverpool L9 1AE,
UK

GV Gill
O Rauf
IA MacFarlane

Accepted 29 January 1997

Table 1 Indications for diazoxide treatment in 40 patients with insulinoma

Indication	Number (%)
Tumour non-localisation*	22 (55)
Metastatic disease	8 (20)
Unfit for surgery	4 (10)
Failed surgery	3 (7)
Refused surgery	3 (7)

*This indication includes patients surgically treated, but with continuing hypoglycaemia

Table 2 Diazoxide side-effects in 17 out of 36 patients with insulinoma (four respondents did not answer the question on side-effects, hence $n=36$ here)

Side-effect	Number (%)
Fluid retention	11
Hirsutism	4
Hypotension	1
Rash	1
Headache	1
Nausea	1
Weight gain	1

Information on the effectiveness of treatment was available from 39 questionnaires (in one case the question was not answered). In 23 (59%) patients, freedom from symptoms resulted, and there was occasional hypoglycaemia in 15 (38%). Frequent persistent symptoms on treatment occurred in only one patient.

Discussion

In this study, we identified 40 patients on long-term diazoxide treatment for insulinoma. The group was in general elderly (mean age 67 years) with a female predominance (74%). Treatment was prolonged, with a mean duration of seven years, and almost one-third had been on treatment for over 10 years. Most (55%) patients were taking diazoxide because of tumour non-localisation (see table 1). Though side-effects (table 2) were frequent (47%), especially fluid retention and hirsutism, supervising physicians did not consider them serious, and they have probably been exaggerated in the past. Diuretics (usually thiazides) were used in 55%, both to combat fluid retention and to give a possible 'adjunctive' hyperglycaemic effect. Treatment was judged to be highly effective in all but one case. Symptoms were either abolished, or rendered infrequent, once patients had been titrated to the optimal individual dose. The responding physicians were clearly very positive about diazoxide treatment.

As mentioned, diazoxide has been used for insulinoma for over 30 years.¹⁻³ It counteracts

Summary points

- though surgical removal is the best treatment for insulinoma, medical treatment with diazoxide is a valid and effective alternative
- indications include failed previous surgery, failure of tumour localisation, metastatic disease, and patient debility
- side-effects of diazoxide are common (eg, hirsutism and fluid retention) but are mild and not generally problematic

hypoglycaemia probably by effects on beta-cell potassium channels.⁴ Stefanini *et al*² reviewed 28 early reports of diazoxide usage in insulinoma covering 88 patients. The duration of treatment was generally short (maximum five years, and in many cases only a few months). 'Good results' (not accurately defined) were reported in 55% of patients. Side-effects were similar to those we have noted, but again were not troublesome. The authors of this report considered diazoxide effective, but 'not extremely satisfactory'.

Twelve years later Goode *et al*⁵ reported on diazoxide treatment in 18 patients with insulinoma, seen at one centre over a 17-year period. In 16 patients, however, treatment was for two years or less (and often a few weeks or months prior to surgery). Fourteen patients (78%) had a 'good' or 'fair' response to treatment. It is of interest, however, that all of the four longer-term patients (1-11 years) responded (three 'good', one 'fair'). Side-effects were once more noted to be common, but not troublesome.

Since these surveys, however, localisation procedures and surgical management of insulinoma have considerably improved. Diagnostic techniques have also advanced, and it is likely that nowadays more patients with insulinoma are being identified, and successfully treated surgically. Our survey is therefore important as it pertains to current patients who are not eligible for surgery, or in whom surgery has failed.

Although our study may be open to selection bias, we have identified a relatively large number of patients with insulinoma well-controlled on diazoxide therapy. We conclude that this drug is an effective treatment in the management of insulinoma, particularly in those with tumour non-localisation (including failed surgery), metastatic disease and those unfit for surgery. Side-effects are common, but not problematic, and most patients show excellent symptomatic response. Diazoxide treatment for insulinoma should be more widely considered, and the drug should be more easily available in the UK.

We are grateful to Allen and Hanburys Ltd, and all the physicians caring for the patients.

1 Fajans SS, Floyd JC. Diagnosis and medical management of insulinomas. *Annu Rev Med* 1979; 30: 313-29.
 2 Stefanini P, Carboni M, Patrassi N, Bernardinis GD, Negro P. Problems of the management of insulinomas. Review of 132 cases treated with medical measures. *Acta Diabet Lat* 1974; 11: 71-7.
 3 Graber AL, Porte D, Williams RH. Clinical use of diazoxide and studies of the mechanism of its hyperglycaemic effects in man. *Ann NY Acad Sci* 1968; 150: 303-8.

4 Flatt PR, Shieber O, Szecowka J, Berggren PO. New perspectives on the action of sulphonylureas and hyperglycaemic sulphonamides on the pancreatic beta-cell. *Diabete Metab* 1994; 20: 157-62.
 5 Goode PN, Farndon JR, Anderson J, Johnston IDA, Morte JA. Diazoxide in the management of patients with insulinoma. *World J Surg* 1986; 10: 586-92.