ORIGINAL ARTICLE

Is it time to re-assess the role of gliclazide? Targeting insulin resistance in type 2 diabetes patients suboptimally controlled with insulin

N Brown

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Correspondence to:
Dr N Brown, Yardley
Green Medical Centre, 73
Yardley Green Road,
Birmingham B9 5PU, UK;
Neil.Brown@
EasternBirminghamPCT.
nhs.uk

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Background: Adult patients with type 2 diabetes controlled with insulin frequently require the addition of insulin sensitising drugs such as metformin and sometimes glitazones to achieve optimum glycaemic control. Five of a group of eight people with suboptimal diabetes control who were treated by the introduction of gliclazide are reported on. Three patients were excluded. One with type 1 diabetes and two others who had dietary or other therapeutic interventions coinciding with re-introduction gliclazide. Does the re-introduction of gliclazide effect a clinically significant improvement in glycaemic control in type 2 diabetes patients with suboptimal control taking combinations of short and long acting insulin plus metformin?

Method: Five adult patients with type 2 diabetes with suboptimal control using combinations of short and long acting insulin plus metformin who were adherent to their dietary regimen were treated by the addition of gliclazide at different doses. Two of the patients were taking pioglitazone in addition to metformin and insulin. Their glycaemic control was monitored over the following six months.

Results: All five showed significant improvement in glycaemic control after three months. Mean reduction in HbA1c was 1.4% (range 0.9% to 2.5%). Six months after the introduction of gliclazide four patients had HbA1c below base line figure and in two patients clinically significant improvement had been maintained.

Conclusion: A double blind randomised placebo control study is necessary to evaluate a possible role for gliclazide in type 2 diabetes patients who have suboptimal glycaemic control using combinations of short and long acting insulin plus metformin.

Effective management of patients with insulin resistant type 2 diabetes presents a challenging problem to clinicians. These patients frequently require insulin sensitising drugs such as metformin and glitazones in addition to substantial amounts of exogenous insulin. An inner city practice of 9000 people with a recognised diabetic population of 400 patients may have more than 50 patients with type 2 diabetes controlled with insulin. Many of them will not reach the optimum glycaemic control target (HbA1c below 7%) without the addition of metformin and in the most insulin resistant cases some diabetologists recommend the addition of glitazones although this combination is not currently licensed for use in the UK.

The British National Formulary¹ states that gliclazide reduces blood glucose by stimulating the pancreatic β cell to produce more insulin but that in long term administration it may have an extra-pancreatic effect.

This small retrospective study reports the effect on five patients with type 2 diabetes from of a group of eight patients with suboptimal glycaemic control using combinations of short and long acting insulin plus maximum tolerated metformin who were treated by the introduction of gliclazide. Two of the patients were extremely insulin resistant and were also taking pioglitazone on diabetes specialist advice.

Three of the original group of eight patients were excluded from analysis. One because she had type 1 diabetes and the other two because dietary intervention and other therapeutic changes coincided with introduction of gliclazide.

Tables 1 and 3 show details of patients included in the study. Results from the three patients excluded from the study are shown in tables 2 and 4.

METHOD

The five patients reported on were all female between 52 and 68 years of age, three white, one South Asian, and one Afro-Caribbean.

All had type 2 diabetes with suboptimal control using combinations of short and long acting insulin plus maximum tolerated doses of metformin.

All received regular diabetic follow up and were reasonably adherent to their dietary regimen and in each case at least three records of HbA1c* were available for the 12 months before the introduction of gliclazide.

None had significant deterioration in renal function that would interfere with the use of HbA1c as a measure of glycaemic control.

None received specific dietary intervention but all had routine encouragement to maintain healthy eating.

They were observed for six months during which time no adjustment to the dose of metformin was made.

In one patient (GH) the evening dose of insulin was reduced by four units after four weeks because of nocturnal hypoglycaemia.

One patient (CD) had a reduction in her total insulin dose from 260 units daily to 211 units daily after three months when she converted from a hybrid fixed mixture/basal bolus regimen to a full basal bolus regimen. She was taking Humalog mix 25–100 units twice daily plus Humalog 60 units at midday at the start of the study. After three months this

*HbA1c measurements were carried out using a DCCT aligned method (normal range 4.3% to 6.5%) at George Eliot Hospital, Nuneaton, UK using high performance liquid chromatography method. The machine type was HA 8160 supplied by A Menarini Diagnostics.

Table 1 Background medical history of patients included

	AB	CD	EF	GH	JK
Age (y)	52	53	64	57	68
Age at onset diabetes (y)	33	47	47	49	53
Duration diabetes (y)	19	6	17	9	16
Number of years taking insulin (y)	11	5	4	6	6
Family history of diabetes	yes	yes	no	no	yes
Coexisting medical problems	Hyptn CHD OA	Hyptn Hyplip Hypothy	Hyptn CHD COPD	CHD Hyptn Hyplip	Hyptn Hyplip CVD
Medication	Perindopril Amlodipine Furosemide Isosorbide-mononitrate Atenolol Aspirin Nicorandil Fenofibrate Hydroxyzine Mebeverine	Candesartan Verapamil Doxazosin Aspirin Atorvastatin Ezitembe Levothyroxine	Ramipril Furosemide Aspirin Nicorandil Isosorbide-mononitrate Atorvastatin Spironolactone Temazepam Gabapentin Co-dydramol Salmeterol Combivent Fluticasone	Candesartan Atenolol Amlodipine Nicorandil Isosorbide-mononitrate Atorvastatin Aspirin Co-dydramol Tolterodine Cetirizine Paroxetine cimetidine	Doxazosin Bendrofluzide Amlodipine Ramipril Aspirin Atorvastatin

Hyptn, hypertension; Hyplip, hyperlipidaemia; Hypothy, hypothyroidism; CHD, coronary heart disease; CVD, cerebrovascular disease; OA, osteoarthritis; COPD, c chronic obstructive pulmonary disease.

regimen was converted to glargine 120 units daily plus Humalog 25 units thrice daily and her gliclazide was stopped. Her own blood glucose monitoring then showed significant deterioration in glycaemic control that did not respond to insulin adjustment. When gliclazide was restarted after four weeks there was an immediate improvement in her glycaemic control. Her insulin regimen was then revised to glargine 136 units daily plus Humalog 25 units thrice daily. Her dietary regimen was not changed.

In one patient (AB) the pioglitazone was stopped after four months because of oedema. None had total dose of insulin increased.

RESULTS

At three months all five showed an improvement in glycaemic control with a mean reduction in HbA1c of 1.4% (range 0.9% to 2.5%). One patient (CD) had a large reduction. If CD is excluded the mean reduction in HbA1c in the remaining four patients is 1.1%, which still represents a significant improvement in glycaemic control. At six months four of five people had HbA1c below base line level and the mean reduction was 1.2% (range minus 4.2% to plus 0.1%) but this was powerfully influenced by one patient (CD). One other patient (JK) had also maintained a clinically significant reduction (0.9%) but the other three had not.

Table 2 Background medical history of patients excluded

	LM	NO	PQ
Age (y)	21	61	48
Age at onset diabetes (y)	12	42	41
Duration diabetes (y)	9	19	7
Number of years taking insulin (y)	9	8	3
Family history of diabetes	no	no	yes
Coexisting medical problems	Coeliac disease	CHD Hyptn PVD CCF CRF	Hyptn CHD Hyplip Ast
Medication	Gluten free diet products	Candesartan Furosemide Aspirin Amlodipine Propantheline Fluvastatin Doxazosin	Ramipril Doxazosin Isosorbide Mononitrate Indapamide Mebeverine Aspirin Atorvastatin Supralip Salbutamol inhaler Beclomethasone inhaler

PVD, peripheral vascular disease; CRF, chronic renal failure; CCF, congestive cardiac failure; Ast, asthma. Other abbreviations as in table 1.

Table 3 Results from patients included

Patient	AB age 52	CD age 53	EF age 64	GH age 57	JK age 68
Insulin regimen	Basal bolus Humulin I 80 units am 40 units pm Humulin S 80 units thrice daily	Hybrid—fixed mixture/basal bolus Humalog mix 25 100 units twice daily Humalog 60 units at midday	Basal bolus Glargine 24 units daily NovoRapid 4 units thrice daily	Twice daily fixed mixture Mixtard 30 40 units am 34 units pm	Twice daily fixed mixture Mixtard 30 38 units am 34 units pm
Oral diabetes drug	Me 1 g thrice daily Pi 45 mg daily Or 120 mg thrice daily Ac 100 mg thrice daily	Me 500 mg daily Pi 45 mg daily Or 120 mg thrice daily	Me 1 g twice daily	Me 850 mg thrice daily	Me 1 g twice daily
HbA1c range over preceding 12 months	9.2% to 12.2%	12.3% to 13.4%	9.9% to 11.2%	7.9% to 8.4%	8.5% to 9.5%
Dose gliclazide added	80 mg twice daily	160 mg twice daily	160 mg am 80 mg pm	30 mg mr daily	80 mg daily
Week 0					
Weight	125 kg	82 kg	—	89 kg	82 kg
BMI	42	35	—	33	35
HbA1c	9.2%	13.4%	9.9%	8.4%	9.1%
3 months					
Weight	120 kg	83 kg	—	94 kg	80 kg
BMI	40	35	—	35	34
HbA1c	8.0%	10.9%	8.7%	7.1%	8.2%
6 months		Insulin regimen change at 3 months			
Weight	116 kg	85 kg	—	92 kg	80 kg
BMI	39	36	—	34	34
HbA1c	8.9%	9.2%	9.5%	8.5%	8.2%

Pi, pioglitazone; Ac, acarbose; Me, metformin; Or, orlistat. No weight or BMI available for EF because she is housebound due to complications after coronary angiography. mr, modified release.

However, AB stopped her pioglitazone at four months because of oedema and GH had stopped her evening dose of insulin between three and six months without reference to medical advice.

DISCUSSION

Many people with type 2 diabetes will eventually need insulin to maintain glycaemic control when their pancreatic β cells start to fail and it is common practice to add a long acting insulin such as insulin glargine or isophane insulin to oral medication with metformin and a sulphonylurea such as gliclazide.²

It is assumed that the meal time insulin peaks are achieved by the effect of the sulphonylurea on the remaining pancreatic β cells.

Many type 2 diabetes patients controlled like this will eventually progress to need either a twice daily fixed mixture combination of short and long acting insulin or a basal bolus regimen of short and long acting insulin at which point the sulphonylurea is stopped but metformin is frequently continued.

The use of sulphonylurea drugs (of which gliclazide is one) in combination with insulin is not a new concept. A meta-analysis, Pugh *et al*³ and three literature reviews, Peters and Davidson,⁴ Groop *et al*,⁵ and Lebovitz and Pasmantier⁶ all conclude that combinations of sulphonylurea and insulin showed at best only minor improvements in glycaemic control compared with insulin alone and that those who were moderately obese and in the early stages of the disease with well preserved β cell function were the most likely to

Table 4 Results from patients excluded

Patient	LM	NO	PQ
Insulin regimen	Fixed mixture Humalog mix 25 90 units twice daily	Fixed mixture Mixtard 30 68 units am 72 units pm nil	Fixed mixture Humalog mix 25 62 units am 60 units pm Metformin 1 gm twice daily
Oral diabetes drug	Metformin mr 500 mg daily	—	Metformin 1 gm twice daily
HbA1c range over preceding 12 months	10.5% to 9.3%	8.3% to 9.6%	7.6% to 11.4%
Dose gliclazide added	30 mg mr daily	30 mg mr	30 mg mr
Week 0			
Weight	88 kg	—	80 kg
BMI	34	—	30
HbA1c	9.3%	9.6%	8.7%
3 months			
Weight	92	—	79 kg
BMI	36	—	30
HbA1c	9.5%	8.0%	7.4%
Reason for exclusion	Type 1 diabetes	(1) Dietary intervention (2) Restarted metformin (3) Serum creatinine 167–200 μ mol/l	Dietary intervention

No weight record for NO because he is housebound after amputation of leg. mr, modified release.

benefit. However, a few patients did show a significant improvement in glycaemic control using combinations of insulin and sulphonylurea drugs. CD may be an example of this.

However, all these studies were conducted before the publication of UK PDS (1998), which changed the emphasis from control of symptoms to tight glycaemic control to prevent long term complications.

In only one of those studies was the HbA1c reduced below 8%.

More recently Janka *et al*⁷ have concluded that a once daily injection of insulin glargine added to oral medication including metformin and a sulphonylurea (glimipiride) was safer and more effective in improving glycaemic control than a fixed 30/70 mixture of soluble and isophane insulin given twice daily with oral diabetic drug stopped.

However, Raskin *et al*⁸ found that a combination of metformin and pioglitazone with twice daily 30/70 fixed mixture of short acting analogue insulin and isophane insulin was more effective than a regimen of once daily insulin glargine combined with metformin and pioglitazone.

Was it the glimipiride that made the once daily insulin regimen of Janka *et al*⁷ more effective than the once daily regimen of Raskin *et al*⁸?

Davidson⁹ commenting on these two studies concludes that it probably makes little difference which insulin regimen is used to treat type 2 diabetes patients who fail to maintain glycaemic control with oral agents alone.

The five patients reported here all, with the possible exception of EF received significant amounts of exogenous insulin and it is unlikely that the addition of gliclazide is working simply by stimulating additional insulin secretion.

In 1989 Bak *et al*¹⁰ showed that gliclazide increased insulin sensitivity in skeletal muscle in type 2 diabetes patients.

Kumar and Dey¹¹ in an in vitro study on mouse skeletal muscle showed that gliclazide increased insulin sensitivity in insulin resistant skeletal muscle.

Ammarit *et al*¹² found that in Asian patients with type 2 diabetes treated with gliclazide 30 mg (modified release) there was a significant fall in fasting blood glucose that was not accompanied by a rise in fasting plasma insulin. This might suggest that the extra-pancreatic effects of gliclazide may be having a significant effect in reducing blood glucose.

At three months mean reduction in HbA1c was between 1.1% and 1.4%, which is significant if it is maintained. UK PDS (1998) predicts a sustained 1% reduction in HbA1c results in a 30% reduction in risk of complications.

A 4.2% reduction in HbA1c at six months as shown in case of CD represents a significant risk reduction. In two patients

(AB and GH) who did not maintain reduction of HbA1c there are clear reasons why this may have occurred.

Patients with MODY (maturity onset diabetes of the young) do sometimes show good responses to sulphonylurea drugs but none of the patients reported here meet the diagnostic criteria:

- None had onset of non-insulin dependent diabetes under 25 years
- None had family history of a relative with onset of non-insulin dependent diabetes under 25 years.
- None had a family history suggesting an autosomal dominant inheritance pattern.
- All had been taking sulphonylurea drugs before transfer to insulin.

Could the improvements seen be explained by lifestyle changes? All five had been taking insulin for a minimum of four years. All received encouragement in healthy eating as part of routine review but none had a specific dietetic review. CD who showed the most significant change did have a change in her insulin regimen after three months but this was not accompanied by dietetic review and she did not make daily adjustments to her insulin regimen in response to changes in diet pattern. In CD the improvement in glycaemic control was shown before the insulin regimen change and the effect of stopping and re-starting gliclazide shown by her own blood glucose monitoring was quite dramatic.

Could this be placebo effect? New drug and increased interest from a clinician may effect patient adherence to a dietary regimen and emphasises the need for further investigation

In the five patients reported re-introduction of gliclazide seems to improve glycaemic control without increasing the dose of exogenous insulin. If this is because of increased insulin sensitivity in skeletal muscle then this could have significant benefits in reducing hyperinsulinaemia because of exogenous insulin and therefore reducing vascular risk and also in improving glycaemic control. It is not current common practice to re-introduce gliclazide in patients with type 2 diabetes with suboptimal control while taking combinations of short and long acting insulin plus metformin, but there is some past evidence for a possible beneficial effect. Gliclazide is a safe, inexpensive, and well tolerated drug and we must now evaluate whether this effect of gliclazide is sustained and whether it can be reproduced in a double blind randomised placebo controlled study.

CONCLUSION

In the five patients reported on re-introduction of gliclazide, which is a safe, inexpensive, and well tolerated drug seems to improve glycaemic control. The mechanism of that improvement is unclear. The time has come for a double blind randomised control study to re-evaluate the role of gliclazide in type 2 diabetes patients with suboptimal glycaemic control taking combinations of short and long acting insulin plus maximum tolerated metformin.

Funding: the study was not sponsored. The observations were made during routine diabetic surveillance. The measurements of HbA1c were carried out at the George Eliot Hospital, Nuneaton using a DCCT aligned method as part of the routine assessment and management of the diabetic care of the people involved.

Conflicts of interest: none.

Ethical approval was not sought for this retrospective observational study because gliclazide is widely used in the management of patients with type 2 diabetes controlled with insulin. The variation from standard practice was to re-introduce gliclazide only when suboptimal control was achieved with insulin and maximum tolerated metformin.

Key points

- Gliclazide improved glycaemic control after three months in all five patients and this was maintained at six months in two patients
- There is previous evidence that one of the extra-pancreatic effects of gliclazide is to increase insulin sensitivity in skeletal muscle.
- Gliclazide is a safe, inexpensive, and well tolerated drug
- double blind randomised placebo control study is necessary to re-evaluate the role of gliclazide in type 2 diabetes with suboptimal control while taking insulin and maximum tolerated metformin.

Consent: verbal consent was obtained from patients before re-introduction of gliclazide: written consent for publication was obtained subsequently.

REFERENCES

- 1 **BMA/Royal Pharmaceutical Society of Great Britain.** *British National Formulary*. Issue 1. London: BMA/RPSGB, 2005.
- 2 **Riddle M**, Rosenstock J, Gerich J. Treatment to target in trial: randomised addition of glargine or human NPH insulin added to oral therapy of type 2 diabetic patients. *Diabetes Care* 2003;**26**:3080–6.
- 3 **Pugh J**, Wagner M, Sawyer J, *et al.* Is combination sulfonylurea and insulin therapy useful in NIDDM patients? *Diabetes Care* 1992;**15**:953–9.
- 4 **Peters A**, Davidson M. Insulin plus a sulfonylurea agent for treating type 2 diabetes. *Ann Intern Med* 1991;**115**:45–53.
- 5 **Groop L**, Groop P, Stenman S. Combined insulin-sulfonylurea therapy in treatment of NIDDM. *Diabetes Care* 1990;**13**(suppl 3):47–52.
- 6 **Lebovitz H**, Pasmantier R. Combination insulin-sulfonylurea therapy. *Diabetes Care* 1990;**13**:667–75.
- 7 **Janka H**, Plewe G, Riddle M, *et al.* Comparison of basal insulin added to oral agents versus twice daily premixed insulin as initial therapy for type 2 diabetes. *Diabetes Care* 2005;**28**:254–9.
- 8 **Raskin P**, Allen E, Hollander P, *et al.* Initiating insulin therapy in type 2 diabetes. A comparison of biphasic and basal insulin analogues. *Diabetes Care* 2005;**28**:260–5.
- 9 **Davidson M**. Starting insulin therapy in type 2 diabetic patients. *Diabetes Care* 2005;**28**:494–5.
- 10 **Bak J**, Schimtz O, Niels S, *et al.* Postreceptor effects of sulfonylurea on skeletal muscle glycogen synthetase activity in type 2 diabetic patients. *Diabetes* 1989;**38**:1343–50.
- 11 **Kumar and Dey**. Gliclazide increases insulin receptor tyrosine phosphorylation but not p38 phosphorylation in insulin resistant skeletal muscle cells. *J Exp Biol* 2002;**205**:3739–46.
- 12 **Ammarit F**, Davies M, Koppikert N, *et al.* The effect of gliclazide on plasma insulin, intact and 23/33 split proinsulin in South Asian subjects with type 2 diabetes mellitus. *Diabet Med* 1999;**16**:142–6.

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