MINI REVIEW

NON INSULIN-DEPENDENT DIABETES MELLITUS (TYPE 2) SECONDARY FAILURE. METFORMIN-GLIBENCLAMIDE TREATMENT

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The goal of sulphonylurea (S) treatment in Non-Insulin-Dependent Diabetes Mellitus (NIDDM - type 2 diabetes) subjects should be to obtain a satisfactory glycaemic control (fasting glycaemic levels < 140 mg%). The loss of an adequate blood glucose control after an initial variable period of S is known as *secondary failure* (SF). The number of SF are extremely variable among different trials for many reasons, some of which are patient-related: increased food intake, weight gain, non-compliance, poor physical activity, stress, diseases and/or impaired pancreatic beta cell function, desensitization after S chronic therapy, reduced absorption, concomitant therapies.

Many therapeutic strategies have been proposed to achieve an adequate metabolic control in type 2 diabetes patients: switch to intensive insulin therapy and subsequent return to S therapy; association with insulin; association with sulphonylureas plus biguanides. The association biguanides and S, in particular glibenclamide plus metformin, is now widely used by diabetologists in SF since glibenclamide improves insulin secretion while metformin exerts its antidiabetic effect by different mechanisms.

The biguanides

Metformin: Krall and Camerini-Davalos defined biguanides as enigmatic compounds (1). This definition could be accepted for many reasons: first, for their unclear antidiabetic activity after the incidental discovery of the antihyperglycaemic activity of Guanidin-clorure by Watanabe in 1918 (2) and other derivates of Guanidin-Sintalin A in the 1950s like phenetilbiguanide (phenformin), butilbiguanide (buformin) and dimetylbiguanide (metformin); second, because the mode of action and efficacy among the different compounds are unlikely to be the same (3-13) and, third, because the possibility to develop lactic acidosis, the main metabolic complication that can occur in association with biguanides, is not the same for each one of them (14-18).

In the mid'70s, one long-term prospective clinical study publicated by University Group Diabetes Program (UGDP) in 1027 type 2 diabetic subjects, treated with phenformin and designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications established: "*the mortality findings coupled with the findings for nonfatal events gave no evidence that phenformin therapy, as used in the UGDP, was as efficacious as diet alone or than diet plus insulin and suggested that it was less efficacious than diet alone or than diet and insulin for prolonging life. For these reasons the use of this drug was terminated in the UGDP*" (19).

Phenformin was avoided for medical use in the United States and, at present, is only used in association in other countries (20). After phenformin

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was taken off the market in 1977 in the USA, researchers focused their interest towards Metformin, another biguanide used in France and in other countries since 1970. Medline search can reflect this change in the evaluation of the number of publications on both of these biguanides (Table 1).

Metformin, Buformin and Phenformin are considered antidiabetic drugs since they decrease hepatic gluconeogenesis and intestinal absorption of glucose and increase anaerobic glycolysis, while insulin secretion remains unchanged (21-27). Despite some controversies regarding its mechanism of action, Metformin decreases glucose output from the liver and seems to increase glucose uptake by peripheral tissues, particularly muscular tissue. In type 2 diabetes subjects, Metformin decreases hepatic glucose production without changing in glucose uptake in muscular forearm tissue preparations. To the contrary, Butterfield and coll. documented an increased muscolar captation for Phenformin and Buformin (28-33). Moreover, some investigators documented an insulin-receptor action by Metformin but this effect was not verified by others (34-41). Recently, the possibility that Metformin determines protein GLUT 1 redistribution from the intracellular compartment to the plasmatic membrane of skeletal muscle, stimulating the peripheral glucose uptake and utilization by muscular tissue has been considered (42-44).

Lipid profiles may be favorably influenced by Metformin. Type 2 diabetes patients treated with Metformin showed decreased total cholesterol and LDL-cholesterol values while HDL-cholesterol and serum triglycerides tended to remain unchanged. These effects are reversible after drug discontinuation suggesting that they are correlated Metformin therapy and not to glycaemic levels (45-47).

In obese NIDDM patients some therapeutic strategies may be used:

- promote weight loss throughout lifestyle modifications (hypocaloric diet and exercise) and anti-obesity drugs (orlistat, sibutramine,etc.);
- improve blood glucose control, essentially by reducing insulin resistance (metformin, eventually thiazolidinediones) or insulin requirements (alpha-glucosidase inhibitors);
- promoting the correction of defective insulin secretion (sulphonylureas, repaglinide) or lowering circulating insulin levels (exogenous insulin);
- treat common associated risk factors, such as hypertension and dyslipidemias, for cardiovascular disease prevention (49).

Recently, Flechtner et al. evaluate the effects of metformin on basal and catecholamine-stimulated lipolysis in abdominal subcutaneous adipose tissue of obese hyperinsulinaemic hypertensive subjects. A reduction of lipolysis in the large body fat mass of these subjects may contribute to decrease VLDL synthesis in the liver, resulting in lowered plasma triglyceride concentrations. In addition, Metformin is considered a first-line drug for obese diabetics since it improves blood glucose control by reducing insulin resistance (50-51). For these reasons, Metformin is an effective, safe and well tolerated drug in obese type 2 diabetics, presenting secondary failure to sulphonylurea treatment, and it not only improves the metabolic control but also favorably modifies other parameters such as weight, total cholesterol and triglyceride values.

Other effects of Metformin are documented in untreated diabetic subjects: metformin increased diastolic chamber stiffness associated with collagen-linked glycation in the myocardium compared with control animals. The effects of metformin in non-diabetic subjects with android-type obesity and hypertriglyceridaemia are also of interest. Lastly, other studies indicate that Metformin appears to affect plasma concentration of insulin-like growth factor (IGF) and IGF-binding protein (IGFBP-1) in polycystic ovary syndrome patients, and it could be useful in the treatment of the devastating metabolic effects in HIV-patients (52-56).

As other biguanides, Metformin can provoke lactic acidosis. As suggested by Leo Krall and Camerini Davalos, the documented deaths in lactic acidosis cases with Phenformin use were probably associated with an inadequate use of this drug (1). In 330 patients with lactic acidosis, half of which died, 71% were also affected by other diseases: 64% by heart diseases, 51% by renal failure, 28% by infection, 25% by pulmonary disorders and 28% by hepatic diseases as demostrated by Luft et al. (17). In this study only 4% of patients were treated with Metformin in contrast with 86% treated with Phenformin and 10% treated with Buformin (57-61).

The reports on Metformin toxicity are extremely variable: a French study documented an association

between serious renal failure and Metformin mortality by lactic acidosis, since Metformin is mainly excreted by the kidneys and does not undergo hepatic metabolism as Phenformin. For this reason, Metformin should not be used in diabetic patients with renal dysfunction (59). Phenformin is also contraindicated in patients with impaired hepatic function. Lactic acidosis in Metformin-treated patients could not only be due to lactic acidosis type B but is also found in hypoxiemic patients (type A or anaerobic). A recent study suggests that Metformin is safe in the treatment of type 2 diabetic pregnant women and in patients with Gestational Diabetes whose hyperglycaemia cannot be satisfactorily managed with diet alone, since it does not cross the placental barrier (62-64).

Glibenclamide: In 1969, Ernest Pfeiffer concluded in his report on oral antihyperglycaemic drugs that: "*always taking tolbutamide as hypoglycaemic reference drug, a qualitatively rather than quantitatively different action of HB 419 (glibenclamide) might be assumed, presumably originating from some support or facilitation of glucose metabolism inside or energy production of the diabetic Langerhans islet included. Perhaps, literally a representative of a "new class of sulphonylureas" has been found. This aspect might fully explain the new interest in that (13 years) old subject*". Glibenclamide represents the first second-generation sulphonylurea. Glicazide is the most recent second-generation S, and Glimeperide is the first third generation sulphonylurea (65).

As for the Biguanides, the hypoglycaemic activity of a sulphonylurea was discovered accidentally. In 1942, Janbon et al. noted that para-aminosulfonamyde - isopropil - tiodazole administered to a patient with typhoid fever caused a serious hypoglycaemia (66). Subsequent studies by Loubatieres pointed out some characteristics of the S. They can be summarized as follows: a) the sulphonamide group is essential for hypoglycaemic activity; b) they are active in animals that had undergone partial but not total removal of the organ; c) when the S are injected into a normal dog whose pancreatic duodenal vein was collected with anastomosis to the jugular vein of a dog whose pancreas had been removed, they lowered plasma glucose levels in the second dog.

In the years that followed, carbutamide and tolbutamide were developed and later, acetohexamide, tolazamide and chlorpropamide. Many trials studied the mechanisms of these drugs in lowering hyperglycaemia in diabetic and non-diabetic subjects. This researches demostrate that S, unlike Biguanides, should be consider hypoglycaemic agents (67-69).

Pancreatic and extrapancreatic effects of S are shown in Table 2.

Pancreatic effects of S: S stimulate the release of insulin in perfused pancreas *in vitro* and *in vivo*; the insulin release *in vivo* occurs by increasing pancreatic beta-cell sensitivity to glucose. It has been hypotesized that S inhibit the efflux of potassium -channels of pancreatic beta-cell and inhibit phosphodiesterase, resulting in increased cyclic adenosine monophosphate (cAMP) levels (70-71). There is no evidence that S can increase the synthesis of insulin and it is unclear if they may also inhibit the release of glucagon after prolonged administration (chronic therapy) in normal and diabetic subjects (72-73).

In 1975, the results of the University Group Diabetes Program, a long term study on the efficacy of Tolbutamide, a first-generation S, showed that the combination of diet and Tolbutamide therapy lacked efficacy compared with diet alone or diet and insulin in diabetes treatment. Furthermore, Tolbutamide was associated with an increased risk of cardiovascular mortality. For this reason, the UGDP discontinued the research on tolbutamide (74). The conclusions of this study were subsequently criticate, but the Food and Drug Administration (FDA) still requires that each drug-box of tolbutamide should include an insert that warns of "the increased risk of cardiovascular mortality" (75-80). Recently, the United Kingdom Prospective Diabetes Study (UKPDS) concluded that:

a) despite the differents opinions, all sulphonylureas have similar mechanisms of action;

b) although the second-generation sulphonylureas, particularly Glibenclamide, are not, as suggested by Pfeiffer, "new hypoglycemic drugs", their pharmacokinetic properties (effectiveness, elimination, side effects) conferred them a safety;

c) in type 2 diabetic patients, sulphonylureas

should be considered first-line drugs if adequate glycaemic control has not been achieved with diet alone (81-83).

Despite the criticized UGDP results and the FDA decision on Tolbutamide, the studies on S, especially on Glibenclamide – the first of the second-generation S, increased as documented by the number of publications in the last years (84-85) (table 3).

Extrapancreatic effects of S: S alone do not reduce plasma glucose levels in experimental animals whose islet beta cells have been destroyed or in animals that had undergone total pancreasectomy and they are considered ineffective in patients with type 1 Diabetes.

Nevertheless, there are some evidence that these agents may reduce hyperglycaemia in patients with type 2 Diabetes by other mechanism besides insulin secretion increase (86-90).

In patients treated for long periods with sulphonylureas, plasma glucose levels decrease despite unmodified insulin concentrations; the mechanism of this effect is unclear. The initial reports on the eventual increase of insulin-receptor binding have not been confirmed by other studies (91-100).

The S effects on the liver and skeletal muscle are numerous: increase of fructose 2,6 biphosphatase, decreased hepatic gluconeogenesis, decreased fatty acid oxidation and increase of hepatic glycolysis. However, some of the demonstrated effects on insulin-sensitive tissues in vitro could not be documented in vivo (101-102). Sulphonylureas may also increase glycogen synthesis and hepatic lipogenesis, and adipose tissue levels, they can reduce lipolysis and enhance insulin glucose transport (103-104).

Recent studies emphasize the cardiovascular advantages of S treatment. Klepzig et al. documented a better maintenance of ATP-dependent potassium channel mediated ischaemic myocardial preconditioning. In this experiment, the time of angina occurrance during ballon occlusion slightly increased by 30% in the placebo and glimeperide groups and remained unchanged in the glibenclamide group (105).

Recently, Ouedraogo et al. suggested that the secretory capacity of BM 208 and BM 225, two isoesters of glibenclamide, depended by the inhibition of ATP-sensitive potassium channels with subsequent increase in calcium influx (106). Glibenclamide seems to eliminate ischaemic preconditioning during coronary angioplasty; this drug prevents the increase of the ischaemic threshold observed during the exercise tests. These findings confirm that ischaemic preconditioning plays a key role in the warm-up phenomenon and that, in this setting is, at least partially, mediated by activation of ATP-sensitive potassium channels (107). Hospital mortality in type 2 diabetes patients is higher than in non-diabetic patients suffering from acute myocardial infarction, regardless of whether or not they have been treated with sulphonylureas. Furthermore, glibenclamide does not enlarge myocardial necrosis (108). Glibenclamide has been shown to inhibit prostanoid-induced contraction in a number of blood vessels. The inhibitory effect of glibenclamide on peripheral blood vessels is not restricted to prostanoid-induced contraction. Some authors suggest that these effects might be mediated by an interaction with voltage – sensitive calcium channels (109-110).

Primary and Secondary failure of the Sulphonylureas: the goal of S treatment should be the normalization of both fasting and postprandial glucose concentrations according to the recent parameters established by American Diabetes Association: normal fasting plasma glucose < 7.8 mmol/l (140 mg/dl) and normal HbA1c < 7.5 (111).

If the patient does not obtain an adequate glycaemic control during initial therapy with S, it is considered a *primary failure*, as reported in about 2 to 5% of treated type 2 diabetic patients. The ineffectiveness of S in lowering blood glucose values to a target level over a period of time is known as *secondary failure*. The reasons of a secondary failure are unknown but probably the hypoglycaemic activity of these drugs decreases for a progressive decrease in insulin secretion due to many factors (table 4). The UKPD Study evaluated the number of secondary failures in a group of type 2 diabetic patients receiving sulphonylureas and assessed the percentage of patients that should be switched to combined therapy with biguanides or insulin. In this study, a group of 2.500 diabetic patients, managed with diet alone and with abnormal fasting glycaemic levels in the last 3 months, was treated with glibenclamide, metformin or insulin. In the glibenclamide treated group, the 76% of

Tab. I. *Publications on Metformin and Phenformin between 1965 and 2000.*

	Metformin	Phenformin
1965-1969	19	94
1970-1974	34	158
1975-1979	61	149
1980-1984	63	41
1985-1989	71	14
1990-1994	131	10
1995-2000	343	12

source PUB MED

Tab. II. *Potential mechanisms of pancreatic and extrapancreatic hypoglycaemic action of Sulphonylureas.*

Pancreatic:
Improved insulin secretion
Reduced glucagon secretion
Hepatic:
Increased fructose 2.6 biphosphatase
Increased glycolysis
Reduced gluconeogenesis
Decreased plasma free fatty-acid concentrations
Increased glycogen synthesis
Increased hepatic lipogenesis
Reduced hepatic insulin extraction
Skeletal muscle:
Increased glucose transport
Increased fructose 2.6 biphosphatase
Enhanced of insulin activity on glucose uptake.
Adipose tissue:
Adenosin-3'5'-monophosphate diesterase increase and lipolysis inhibition.
Increased glycogen synthetase.
Enhance insulin glucose transport by the increased production of glucose transport molecules.

from Gerich JE (84)

Tab. III. *Publications on Tolbutamide and Glibenclamide between 1964 and 2000.*

	Tolbutamide	Glibenclamide
1964-1969	293	17
1970-1974	309	148
1975-1979	198	95
1980-1984	131	83
1985-1989	105	109
1990-1994	85	214
1995-2000	90	216

source PUB MED

Tab. IV. *Causes of secondary failure with sulphonylurea treatment.*

Patient
Increased food intake and weight gain
Noncompliance
Poor physical activity
Stress
Intercurrent illness
Disease
Islet beta-cell exhaustion
Increased insulin resistance
Therapy
Inadequate doses
Desensitization after chronic therapy with S
Poor drug absorption due to hyperglycaemia
Concomitant use of hyperglycaemic drugs

from Groop et al. (113)

obese type 2 diabetics and 81% of non obese type 2 diabetics continued to take the drug after 3 years of treatment, while the percentage of diabetics with satisfactory glycaemic control increased up to 91% when metformin was added (112).

Secondary failure may be due to differents causes, as shown in table 4, in type 2 diabetic patients. Patients who do not achieve an adequate glycaemic control with a second-generation S alone, may achieve this goal with insulin therapy or

Tab. V. *Recommendations on therapy (if fasting plasma glucose>7.8 mmol/l and HbA1c>7.5).*

Therapy	Modified therapy
➢ Only diet	Diet plus S at low dose
➢ Diet plus S	Increased S dose
➢ Diet plus S at maximum dose ➢ Metformin at maximum dose	S plus Metformin To begin basal and prandial insulin

combination therapy (S plus insulin or biguanide plus S). Another possibility is to initiate intensive insulin therapy and return to S therapy after a variable period of time as suggested by Groop et al (113).

A model of combined therapy after primary or secondary failure is shown in table 5.

Nevertheless, there is no general agreement on the necessity to treat patients with secondary failure with insulin therapy immediatly. Some authors consider that insulin therapy is useful only after a long period of unsatisfactory oral antidiabetic treatment.

Association of a second-generation sulphonylurea (Glibenclamide) with a Biguanide (Metformin). The rationale: In the 1960s, after the first experiences of Krall and Balodimos and Clarke et al. respectively in treating secondary failures in type 2 diabetic patients with biguanides and S, several trials were undertaken using different associations (114-115).

A great number of diabetologists consider diabetes as a progressive disorder and, although oral monotherapy is initially successful, often it is associated with a high secondary failure rate. The combination therapy using oral antidiabetic drugs with different mechanisms of action may be highly effective in achieving satisfactory blood glucose levels (116-130). One of the most studied combinations is the association glibenclamide plus metformin (129, 131-138).

In conclusion the scientific data above discussed show that metformin increases insulin action by reducing glucose absorbtion, increasing glucose uptake by peripheral tissues (as Phenformin), promoting oxidation and utilization by non oxidative pathways. Furthermore, new evidences showed that the synergic action of metformin and glibenclamide improves lipid metabolism in diabetics and non diabetics, by reducing triglycerides and increasing HDL-cholesterol.

The key messages of the UKPDS experts in more than 5000 patients with type 2 diabetes recruited in 23 centers in the United Kingdom during the 20-year study, were the following:

- the aim of UKPDS was to determine the impact of intensive blood glucose control on 24 predetermined clinical endpoints using sulphonylureas or insulin therapy and the impact of intensive blood pressure control on macro- and microcomplications of diabetes;
- therapy with glibenclamide or metformin are equally effective and more effective than diet alone;
- sulphonylureas can cause weight gain and increase insulinemia, increasing the related risks;
- metformin doesn't cause weight change nor hyperinsulinemia;
- there was no evidence of a major detrimental effect of the drugs or insulin on survival or outcome other than the expected risk of hypoglicaemia;
- among patients on intensive blood glucose control, metformin showed a greater effect than chlorpropamide, glibenclamide or insulin for any diabetes-related end points;
- since intensive glucose control with metformin appears to decrease the risk of diabetes-related end points in overweight diabetic patients and it is associated with less weight gain and fewer hypoglycaemic attacks compared with insulin and sulphonylureas, it may be considered the first-line pharmacological therapy in these patients;
- early addition of metformin improved blood glucose control in patients with suboptimal glycaemic control while taking maximum sulphonylurea therapy, irrespective of obesity or baseline fasting blood glucose concentrations;
- long-term follow-up will be necessary to establish the exact cost-benefit ratio of each treatment.

In a recent metanalysis by Johansen K. on the efficacy of metformin for the treatment of type 2 diabetes, based on data from 9 recent studies, it is confirmed that metformin compared with placebo is effective in reducing blood glucose values and glycosylated haemoglobin, without body weight modifications as found in association with glibenclamide therapy (139-142).

In the UKPDS there are reported 21% of hypoglycaemic episodes/year in patients receiving glibenclamide, which is significantly lower than the 52% reported among patients treated with ultralente insuline (141). The frequency of sulphonylureas-induced hypoglycaemia (SIH) is still a debate; in a review of the cases reported in the literature between 1940 and 1982, Campbell found 843 cases of SIH, with 670 cases occurring in patients receiving sulphonylurea treatment as monotherapy, with an 8.4% mortality (143).

In this context, the hypoglycaemic role of prolonged and unusual physical exertion may have been underestimated. We found a higher risk for "holiday-hypoglycaemia" in patients with a lower educational level, with a sedentary occupation or among the ex-farmers. The pathogenesis of hypoglycaemic events should also consider other two mecanisms: first, the circadian rhythm of insulin response to stimulus hypoglycaemic; second, the variation of blood sugar levels during the 24 hours after the administration of insulin or tolbutamide (144-148).

Recently, newer oral antihyperglycaemic drugs have been experimented and some have been approved for use in Italy. Among these, one of the better known is glimepiride, a third-generation sulphonylurea with high affinity towards the proteic receptor 65kD, from which it rapidly dissociates allowing a once-daily administration (149). Another oral hypoglycaemic agent is repaglinide, a benzoic acid derivate that binds, to the sulphonylurea receptors with different binding kinetics than the sulphonylureas and with a short duration of action it can be used in association with metformin (150-151). Furthermore, we must mention troglitazone, member of thiazolidinediones, which was approved in the United States for insulin-resistant patients. This class of drugs does not stimulate insulin secretion but it favors glucose utilization by peripheral tissues and has a lipolytic action on VLDL triglycerides. The thiazolidinediones can be used in association with metformin or sulphonylureas, although potential adverse effects have been reported, as weight gain, elevation of LDL-cholesterol, fluid retention and hepatic toxicity.

Lastly, other agents as a phenilalanine derivate and glucagon-like peptide GLP1 are currently under investigation for the therapy of type 2 diabetes (152-155).

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