

## ORAL ANTI DIABETIC POLYCHEMOTHERAPY IN TYPE 2 DIABETES MELLITUS

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**SUMMARY** - The therapeutic guidelines of the seventies for type 2 diabetic patients was a monotherapy which choice was based on the BMI of the patient and a bitherapy in case of a blood glucose increase. The pathophysiologic knowledge on type 2 diabetes has moved and the disease is nowadays more complex with a loss of the  $\beta$  cell mass and an insulin resistance state of the liver, muscle and adipocyte tissue associated with a defect in gastro-intestinal hormones in the postprandial state. The pathophysiologic knowledge and the existence of new therapeutic agents led us to discuss oral antidiabetic polychemotherapy at the first drug prescription. This intuitive proposition has no evidence-based arguments with prospective long-term studies that would demonstrate the benefit of such a proposition.

Moreover, if nowadays we can imagine a tritherapy proposition, progress in chemistry research will conduct to a quadri- and penta-therapy with expected difficulties in therapeutic compliance of the patient.

*Key-words:* type 2 diabetes melitus, oral antidiabetic drugs.


**RÉSUMÉ** - Polychimiothérapie antidiabétique orale pour le diabète de type 2.

Les recommandations thérapeutiques des années 70 pour le traitement du diabète de type 2 comportaient une monothérapie dont le choix était basé sur le BMI du patient et une bithérapie en cas d'échappement glycémique. Les progrès dans la connaissance physiopathologique du diabète de type 2 font état d'une maladie plus complexe avec perte de la masse cellulaire  $\beta$  et état d'insulinorésistance du foie, du muscle et du tissu adipeux, associé à un défaut des hormones gastrointestinales dans la phase postprandiale.

La connaissance physiopathologique et l'existence de nouveaux agents thérapeutiques nous ont conduit à proposer une polychimiothérapie antidiabétique en première intention. Cette proposition intuitive ne repose pas sur des preuves, des études prospectives à long terme seront nécessaires pour démontrer le bien fondé de cette proposition.

En outre, si de nos jours on peut imaginer un schéma de trithérapie, les progrès de l'industrie pharmaceutique nous conduiront à des quadri- et penta-thérapies exposant à des problèmes probables de compliance thérapeutique.

*Mots-clés :* diabète de type 2, hypoglycémisants oraux.

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**T**ype 2 diabetes is a serious disease because of its life-long chronicity exposing to micro- and macrovascular complications. The disease is increasing in frequency due to modern way of life, modification of food intake, population sedentarity and prolongation of life expectancy.

The complications of the disease are more threatening as a longer exposition to the risk is associated with an increase in life expectancy. The pathophysiology of the disease is complex, with the association at various degrees of an insulin-resistance state [1], a defect in insulin-secretion [2] and a loss of  $\beta$  cell mass [3], and perhaps a modification in postprandial hyperglycaemic kinetics [4].

European guidelines of the seventies regarding therapeutic choice in type 2 diabetes after failure of dietetic recommendations are well known. The choice was based upon the patient's weight: a too heavy patient was at the same time considered in an hyperinsulinemic state and this hyperinsulinism was considered as a risk factor for weight increase, so insulin secretion enhancing drugs were excluded and metformin was used in first intention until it failed in controlling blood glucose; then sulfonylureas were added. On the other hand, when the patient did not feature any weight excess, a sulfonylurea was a first choice and metformin was introduced after their failure. It ended up that every type 2 diabetic patient was then treated with both drugs, metformin and sulfonylurea in a therapeutic choice of stacking.

Since the seventies, the pathophysiological knowledge has progressed and antidiabetic drugs are more numerous with the development of new drugs ( $\alpha$  glucosidase inhibitors, thiazolidinediones, ...).

Different ways of drug prescription may exist. On one hand, the therapeutic prescription may use a first agent and then a second and thereafter a third one as blood glucose level increases. On the other hand, we can consider that type 2 diabetes is a complex disease with association of multiple factors as soon as it begins; so, as soon as the therapeutic is set, the best choice will be a low dose association of each drug acting at different targets of the disease with a progressive increase of each dosage as blood glucose worsens. This strategy is based on the fact that each therapeutical class can improve only one of the different mechanisms of the disease.

The therapeutic association of several drugs as soon as diabetes is diagnosed is a realistic proposition as the UKPDS [5] has clearly demonstrated that three years after the initiation of a first monotherapy prescription, 50% of the patients treated with a single drug failed with uncontrolled blood glucose values; they were 75% nine years later. Thus it is established that initial monotherapy fails to control blood glucose for a long time. This justifies to try a new therapeutic strategy.

## ■ TYPE II DIABETES PATHOPHYSIOLOGY

### Insulin secretion

Insulin secretion disturbances in type 2 diabetes mellitus are characterised by a defect in the early peak of secretion, but a loss in  $\beta$  cell mass is also evidenced leading to a relative insulin deficiency at the first stage of the disease [5]. The  $\beta$  cell mass loss is probably due to gluco- and lipotoxicity but also to the acceleration of  $\beta$  cell apoptosis [6, 7]; a high blood glucose level can induce an overexpression of pro-apoptotic genes (BAD, BID) in the  $\beta$  cell. The pro-apoptotic balance seems genetically determined [8].

This direct effect of the hyperglycaemic level on the  $\beta$  cell mass loss means that a strict blood glucose control is needed as soon as diabetes is diagnosed [9]; the insulin deficiency requires the use of insulin secretion enhancing drugs from the onset of the disease. We can also expect that new drugs protecting against the induction of  $\beta$  cell apoptosis will be developed.

### Insulin resistance state

Insulin resistance is known since a long time and is a determinant factor for type 2 diabetes. The insulin sensitive tissues are muscles, liver and adipocytes. Each of them can be the site of insulin resistance. Liver is insulin resistant on the endogenous production of glucose, featuring a continuous non adapted glucose production with a constant flooding of the body by a glucose excess, leading to an hyperglycaemic state all day long [10].

Muscles and adipocytes also are insulin resistant, particularly in their glucose storage and oxidation aspects. It seems that the mechanism leading to the resistance state is different in each tissue.

No ubiquitous drug is available, but rather different drugs that act in different tissues. Metformin particularly acts against insulin resistance in the liver, while thiazolidinediones act against insulin resistance in muscles and adipocytes [11].

### Post prandial state

High post prandial glucose level is a cofactor for micro- and macroangiopathy [12]. It also largely contributes to the increase in HbA<sub>1c</sub> level [13].

The post prandial state is complex with a large number of contributing factors: food, nutriment, gastric emptying, intestinal glucose transport and gastrointestinal hormones such as GIP and GLP1, that are deficient in type 2 diabetes [4]. GLP1 can also regulate glucagon secretion [14], an hyperglycaemia-promoting hormone.

Specific drugs are currently available that act on glucose transport at the (glucosidase level [15] and GLP1 is also under investigation in type 2 diabetic patients.

Type 2 diabetes is a complex disease with multiple abnormalities at different sites. An optimal treatment of the disease needs to be effective at each site and this, at the same time. Rather than a first step treatment targeting one abnormality and a second step initiated only once the first one fails, it seems more appropriate to propose a therapeutic association as soon as the disease is diagnosed. However, if health care institutions lead us to choose low dose association of different drugs as soon as diabetes is diagnosed, long term studies are needed to establish the superiority of such a strategical choice.

## ■ IS THERE EVIDENCE THAT DRUG ASSOCIATIONS ARE MORE EFFICIENT THAN MONOTHERAPY?

### Association of insulin secretion-enhancing drugs and metformin

The association of sulfonylurea + metformin is largely used because both drugs are ancient. A large number of studies have demonstrated their synergistic effects [16]. However, UKPDS 34 has led to a doubt [17]. A cohort of 537 patients, badly controlled with sulfonylurea alone, was randomised to association with metformin or sulfonylurea alone. An improvement in blood glucose level and HbA<sub>1c</sub> was solely observed with the association of both drugs but a 96% increase in mortality due to diabetes was observed in this group. These results must be confirmed by other studies, but justify to be cautious. Another recent study has reported similar results [18].

The association of glinides with metformin also is interesting. Glinides (repaglinide, nateglinide) are rapid and short-acting insulin secretagogues. They lead to a new insulin drug-induced profile, different from the sulfonylurea profile. The association with metformin is complementary as glinides act in the postprandial state and metformin in the basal state. Studies report an improvement of  $1.4\% \pm 0.2$  in HbA<sub>1c</sub> levels with both drugs in comparison with monotherapy (metformin or repaglinide alone). This result confirms the synergistic effect of an association that act on two different sites of pathophysiologic abnormalities of type 2 diabetes [19].

### Association of insulin secretagogues and thiazolidinediones

This association is quite new as thiazolidinediones were introduced recently. Since their use in human studies, this association in many different trials has

reported an improvement of 1 to 2% in HbA<sub>1c</sub> with bitherapy in comparison with monotherapy [20, 21]. However, there is no study of sulfonylurea + thiazolidinedione *versus* sulfonylurea + metformin, and so the choice between these two associations is still difficult.

The glinide - thiazolidinedione association has been studied and similar results as sulfonylurea-thiazolidinedione association were reported [22].

### Association of metformin with thiazolidinedione

Both metformin and thiazolidinediones are drugs of the insulin resistance state but metformin acts preferentially on the glucose production from the liver [23] while thiazolidinediones act on the insulin resistance state of muscles and adipocytes [24]. The clinical application of the action of these drugs at different sites has been well demonstrated by Inzucchi [11]: 29 type 2 diabetic patients have been treated with metformin alone, thiazolidinedione alone and then with both drugs. Metformin alone and thiazolidinedione alone share the same glycemic effect with similar results on blood glucose level in the post absorptive or post prandial state. Both drugs together lead to a 1.5 mmol/l glucose improvement. Both drugs were synergistic. In the same study, the use of glucose isotopic tracer evidenced a 18% improvement in endogenous glucose production with metformin and a 80% increase in peripheral glucose disposal with thiazolidinedione. These two effects on two different sites of insulin action lead to the same results in terms of blood glucose level when the drugs were used separately, but when they were used together, their effects and their results were summed up. This study has been confirmed by others [25].

### The triple association of insulin secretagogues + metformin and thiazolidinediones

This association may be useful but there are few studies. One study involving 200 patients reported an 1% improvement in HbA<sub>1c</sub> with tritherapy in comparison with bitherapy [26], another study with 837 patients [27] reported the same results. So tritherapy association seems to be effective.

### Is there a place for medications of the post prandial state?

Many studies that used a drug that acts on the postprandial state ( $\alpha$  glucosidase inhibitors) have always demonstrated an improvement in HbA<sub>1c</sub> level [13, 28, 29]. There is an additive effect of these drugs to the others. New drugs acting on the postprandial state are in process of investigation such as GLP1 and amylin analogs. So new association choices may be discussed in the future.

## ■ FROM KNOWLEDGE TO PRACTICE

Type 2 diabetes pathophysiology knowledge leads us to the polychemotherapy concept but progress in pharmaceutical industry may rapidly move us from a tritherapy to a penta- and perhaps hexatherapy. The association of an insulin secretagogue drug with one or two drugs that act on insulin resistance state seems to be logical, but we must also think to a postprandial drug regulator as the postprandial glucose level is a vascular risk factor; in a few years from now, we may choose between different drugs acting on the postprandial state.

On the other hand, if an anti-apoptotic drug is developed, it shall be used within all the therapeutic associations as soon as the disease is diagnosed. In the same way, if the effect of thiazolidinediones on beta cell mass is demonstrated, this will promote their use within all the associations.

So the question is between a low dose of three or four compounds as soon as the disease is diagnosed or the introduction step by step of different drugs as blood glucose increases. We need long term prospective studies to answer this question. But practice will perhaps be different and we also must look for potential adverse effects of polychemotherapy and question the compliance of the patient to this daylong and lifelong multiple drug regimen.

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