Metformin: 50 years old, fit as a fiddle, and indispensable for its pivotal role in type 2 diabetes management

S Halimi

Head of department, Department of Endocrinology, Diabetes Studies and Nutrition (DUNE), CHU Grenoble, Grenoble, France.

Biguanides are by-products of guanidine, an active substance extracted from Galega officinalis (Goat’s rue), a plant used as early as the Middle Ages for its antidiabetic virtues. The glucose-lowering effect of guanidine was discovered in 1918. Several derivates were extracted, many of which turned out to be toxic and therefore were not produced or were withdrawn from the market, as was phenformin in 1976. The career of metformin dates back to 1957 along with the only other oral antidiabetics drugs (OAD) available at that time, glucose-lowering sulfonylureas. However, it would take 40 years and the publication of the huge UK Prospective Diabetes Study (UKPDS) in 1998 [1] to demonstrate its utility, its therapeutic specificities, its safety, its potential cardiovascular benefits, as well as its glucose-lowering effects in the treatment of type 2 diabetes. Another 10 years were required to make metformin a first-line treatment and the linchpin of type 2 diabetes treatment in today’s national and international guidelines [2]. Finally, metformin is the star of the latest publications comparing it in single-drug therapy with pioglitazone over 1 year [3] and even more recently with rosiglitazone over 4–5 years (ADOPT), where its specific and irreplaceable qualities have yet again brought it into the limelight [4].

Before the UKPDS results were reported, the molecule’s passage across the Atlantic in the middle of the 1990s ensured its renown with a number of high-quality preclinical and clinical studies [5]. Europe, where metformin was born and had its most widespread use for 30 years, was not able to produce enough decisive studies on the subject until the UKPDS. The Americans, who had completely ignored it until that time, thus discovered an oral antidiabetic drug that does not cause weight gain, does not lead to hypoglycaemia in single-drug therapy, and acts in synergy with the insulin secretogogues, at that time the only OADs available in the US. What a godsend for a population where obesity is even more severely rampant among type 2 diabetics than in Europe. Finally, we should also remember the fear taught and carefully maintained in Europe of the much dreaded and terrifying complication of lactic acidosis, without a doubt real, but the danger was vastly overestimated (compared to the risk of the other OADs) and received far too much media coverage [6]. How and why did this occur? It would long harm the use of metformin by general practitioners.

Its remarkable effects on weight maintenance and often weight loss should particularly be noted. Its detractors too often attributed its weight control benefits solely to its digestive side effects – diarrhea and nausea – certainly real in approximately 20% of users, but which could only be explained as such.

In sum, now that the molecule is no longer questioned, what should we retain?

– this is clearly an OAD that does not stimulate insulin secretion. Therefore, no hypoglycaemia can result in single-drug therapy, even for beginning cases of diabetes or in diabetes prevention (although there is no drug marketing approval for the latter indication), nor is there hypoglycaemia when used in association with all the other OADs, except the insulin secretogogues and insulin because of their own effects;

– its main site of action: the liver, lower production of glucose by lowering gluconesgenesis, with the resulting favorable effects on nighttime, fasting, and interprandial blood glucose. The effects on glucose utilization by the muscles are more debatable;

– reduction of the HbA1c level by 1.5%–2% depending on the starting level;

– a favorable effect on weight, in single-drug therapy on the one hand (–1 to –3 kg compared to the initial weight), and a weight difference in initial single-drug therapy of –3 kg compared to sulfonylureas, and –4 to –7 kg of weight benefit compared to both glitazones with a comparable glucose-lowering effect after 1–5 years of treatment [3, 4]. What better therapeutic initiation could we hope for in a disease where 70% of the subjects are overweight, especially if we aim to attack the disease at even moderately high blood glucose levels, which

Address correspondence and reprint requests to:

S Halimi. Head of department, Department of Endocrinology, Diabetes Studies and Nutrition (DUNE), CHU Grenoble, Grenoble, France.
shalimi@chu-grenoble.fr

should be our goal, by using the maximum tolerated dose? We should also note the efficacy on blood glucose levels even in diabetics of normal weight [4];

– these favorable weight effects are very useful in moderating the extent of the weight gain induced by all the other treatments: the weight gain induced by the glitazones (it is therefore recommended preferably in double therapy), by glycose-lowering sulfonylureas, and by insulin, which is why continuing metformin is advised when the patient begins insulin [3,4];

– the favorable effects on the lipid profile, although they are less than the favorable effects of pioglitazone [3,7] but equal to rosiglitazone [4];

– other effects on the factors and markers of cardiovascular risk shown by the UKPDS are its own specific cardiovascular benefit, today recognized by the drug-marketing approval board [1];

– finally, metformin is a very low-cost drug, ideal for a mass disease that is experiencing epidemic progression in emerging countries with few resources.

In sum, metformin is advised in all the recommendations as the initial OAD at the maximum dose tolerated if there are no contraindications (rare at the beginning of the disease) and no intolerance (digestive effects are reduced if the dosage is reached progressively) as soon as the HbA1c level reaches 7% after ADA EASD consensus diet only [8] and 6.5% in France [9] for the AFSSAPS-HAS 2006 recommendations and, like certain other North American groups, with the objective of lowering this parameter as much as possible to 6% or less [9]. Then its use in double therapy [7] associated with all the other OADs, then in triple therapy associated with insulin secretagogues and the glitazones [10], or even with insulin thereafter.

Today metformin is the indispensable entryway to treatment of this illness and the best road companion throughout the history of the disease: sweet revenge for this 50-year-old that is more youthful and lively than ever and that will not be easily dethroned, even by the new wave of incretins that are expected, whose only thought is to work in association with metformin to potentiate and increase the value of their truly promising effects [11]. Although the prescription of metformin is progressing everywhere in Europe, the relative underuse of this OAD by practitioners is regrettable, as shown again by a recent European study [12]. The message should be continued to be transmitted to GPs so as to encourage the use of metformin as first-line treatment of type 2 diabetes.1

References


1 Conflict of interest: none in relationship with this editorial.