Use of antidiabetic drugs in elderly patients

J Doucet

SUMMARY
The objective of this review of the literature is to analyze the results of studies including diabetic patients aged 70 years and older. Although the risk of treatment is greater in this population because of co-morbid conditions and altered renal function, information on the pharmacokinetics and pharmacodynamics of antidiabetic drugs remains limited. Long-term experience with sulfonylureas is sufficient to establish certain general rules of use; but for biguanides and α-glucosidase inhibitors, problems of tolerance limit use; further data are needed on glinides and glitazones. Use of insulin or insulin analogs is frequent and prescription should be adapted to achieve an acceptable balance between the risk of hypoglycaemia and therapeutic goals.

Key-words: Diabetes mellitus · Treatment · Clinical pharmacology · Oral antidiabetic drugs · Insulin.

RÉSUMÉ
Utilisation des médicaments antidiabétiques chez le sujet âgé
L’objectif de cette revue de la littérature est d’analyser les résultats d’études publiées ayant inclus des diabétiques âgés de 70 ans et plus. Les modalités d’utilisation des médicaments antidiabétiques chez les sujets âgés disposent d’informations pharmacocinétiques et/ou pharmacodynamiques globalement limitées, alors que les risques sont plus importants en raison d’une comorbidité importante où prédomine l’altération de la fonction rénale. L’utilisation des sulfonylurées dispose d’un recul suffisant pour permettre d’établir quelques modalités générales d’utilisation ; celle des biguanides et des inhibiteurs de l’α-glucosidase est limitée par des problèmes de tolérance ; celle des glinides ou des glitazones demande à être précisée. Le recours aux insulines ou aux analogues de l’insuline est plus fréquent et doit être principalement adapté aux risques hypoglycémiens et aux objectifs thérapeutiques.

Mots-clés : Diabète · Traitement · Pharmacologie clinique · Antidiabétiques oraux · Insuline.
Our overall knowledge of the action of oral antidiabetic drugs in elderly subjects is limited due to evidence provided by a small number of pharmacokinetic, efficacy and/or tolerance trials which have been conducted with sufficiently robust methodology in a sufficient number of old patients, particularly above the age of 75, or even 70 years. This has lead to an extrapolation of evidence obtained in young diabetics or patients with renal impairment but not diabetes [1, 2]. Furthermore, no midterm morbidity-mortality study is available. Guidelines are thus difficult to set up and generally have to rely on data coming from other than geriatric sources [1, 3, 4]. This explains the limitations of current therapeutic guidelines as well as their imprecision [1, 4]. The purpose of the present review of the literature was to analyze the results of prospective studies (generally published since 1990) which have included diabetic patients aged 70 years and older in order to detail the modalities for prescribing antidiabetic drugs to elderly subjects.

Oral antidiabetic drugs

For the geriatric population, two groups of oral antidiabetic drugs can be distinguished as a function of the quality of evidence obtained from prospective studies. Sulfonylureas and metformin are two relatively old drugs; clinical experience with α-glucosidase inhibitors, glinides and glitazones, more recently marketed, is limited.

We will not discuss here combination formulations of oral antidiabetics because the information available for each component remains of course valid, while trials have not been conducted in geriatric patients.

Sulfonylurea therapy

Few studies have been devoted to efficacy and/or tolerance [3, 5]. Most sulfonylurea drugs were first marketed decades ago when marketing approval for new compounds did not entail pre-clinical and clinical studies with the rigor required today. Documents published over the last fifteen years on these compounds are generally review articles and have not always been based on geriatric studies [1, 6]. It can be recalled that the prescription of the slow-release formulation of glipizide was limited to diabetics below the age of 65 years after reports of serious hypoglycaemic episodes in older diabetics who were given this drug without prior evaluation! Conversely, we do have interesting and recent pharmacological data from studies where these drugs were used for the reference arm of trials of new drug classes [7].

Pharmacokinetics

Although it is generally considered that the half-life elimination time of renally excreted compounds increases with age, pharmacokinetic studies in older diabetics are rare. The pharmacokinetic properties of glibenclamide were not found to be modified by age [7, 8], but the C-peptide response was greater in elderly diabetics [8].

Pharmacodynamics: efficacy and tolerance

To our knowledge, there has been no overall study detailing the influence of the drugs themselves, their dosage, and their formulation on efficacy and/or tolerance. Thus despite certain claims [9], the absence of a difference in efficacy between the different sulfonylurea drugs has thus not been proven. Comparative studies examining the risk of hypoglycaemia with sulfonylurea drugs must take into consideration the blood glucose level obtained, which varies with the clinical situation and the goals set for the elderly diabetic as well as respective frequency of prescription.

One randomized study concluded that the glucose lowering effect of glibenclamide is twice that of glipizide at the same dose [10]. Another randomized study, which did not however have a titration protocol, concluded that the glucose lowering effect of glibenclamide and glitazide were comparable, with however more episodes of hypoglycaemia with glibenclamide [11]. More recently, an analysis of 294 diabetics aged over 65 included in a randomized double-blind study comparing the efficacy and tolerance of glimepiride with modified-release glipizide (both drugs administered once a day for 27 weeks) was unable to demonstrate any difference in efficacy between the two drugs (and compared with younger diabetics), but revealed a 2-fold higher rate of hypoglycaemic events in the glimepiride group for an equivalent glucose level [12].

Besides the classical factors favoring hypoglycaemia, and keeping in mind the frequency of drug interactions, there is a consensus among clinicians that the risk (in terms of frequency and severity) of hypoglycaemia is greater with drugs having a long elimination half-life and predominantly excreted via the kidney (particularly carbutamide and chlorpropamide) [1, 2, 13, 14]. Similarly, the risk of prolonged severe hypoglycaemia is greater with certain long-action formulations (Ozidia®) [3].

Practical implications

Drugs with a long plasma elimination half-life (carbutamide, chlorpropamide) should be avoided [1, 4]. Professionals have reached a consensus in favor of short half-life products with moderate hypoglycaemic effect and without an active metabolite, given at a low dose initially then progressively increased [3, 6, 15-18]. Glibenclamide is generally not recommended for first-intention use [4]. There is no clinical proof favoring glipizide based solely on the shorter plasma elimination half-life, hepatic metabolism, and absence of active metabolites [16]. In any case, there is a professional agreement on the indispensable need for patient and family education, particularly to limit the risk of hypoglycaemia.

The most frequent contraindication for sulfonylureas in the elderly diabetic is advanced-stage renal failure, the non-consensual creatinine clearance cutoff being between 30 and 50 ml/min [17-19].
Biguanides (metformin)

The problems of analyzing use of biguanides in the geriatric population are the same as with sulfonylureas. There have been only a few studies, often with small cohorts and limiting inclusion criteria, all non-randomized [20-22]. Recommendations are based on agreement among professionals, excepting patients with renal failure.

Pharmacokinetics

Metformin is excreted unchanged via the kidney. Metformine clearance is greater than that of creatinine [review in ref. 20]. There is no correlation between serum metformin and lactate concentrations, nor between serum metformin and creatinine [20]. Serum lactate cannot be used to monitor metformin treatment in the elderly subject [20, 22].

Pharmacodynamics: tolerance

Gastrointestinal disorders are the most frequent adverse effects of biguanides: epigastralgia, diarrhea in about 30% of patients [21]. The most severe adverse effect is lactic acidosis. Lactic acidosis is favored by non-specific conditions but is found more frequently in old patients with renal failure and tissue hypoxia. Biguanides do not expose the patient to a risk of hypoglycaemia.

Practical implications

Lactic acidosis occurs in certain conditions which are more frequently encountered in geriatric patients and constitute criteria for contraindication. Metformin is thus contraindicated in patients with renal failure, although the creatinine cutoff level remains a question of debate: the “official” cutoff is 135 µmol/l in men and 110 µmol/l in women, but the American Geriatrics Society only mentions “altered renal function” in their recommendations [1, 2, 6]. This term is however preferable over a set creatinine level known to be of limited value in geriatric patients. The AFSSAPS recently set the cutoff at 40 ml/min. Metformin is also contraindicated in situations exposing the patient to tissue hypoxia (heart or respiratory failure, obliterating arteriopathy of the lower limbs) and in patients with liver failure.

The risk of lactic acidosis thus places a limitation on the use of biguanides in people aged over 70 years; serum creatinine must be monitored regularly. Biguanides must also be discontinued during intercurrent events (dehydration, surgery, injection of iodine contrast agent).

α-glucosidase inhibitors (acarbose and miglitol)

Pharmacokinetics

Bioavailability is low (1%), so systemic circulation is negligible; most of the drug is eliminated in feces. The plasma elimination half-life is six to eight hours. The pharmacokinetic properties of acarbose are not affected by aging [7, 23].

Pharmacodynamics: efficacy

Several pharmacodynamic studies, including a few randomized double-blind comparisons with placebo, have been conducted with acarbose in obese patients with type 2 diabetes treated for several months to one year. The results agree on a significant decrease in fasting blood glucose (10-20%), a greater decrease in post-prandial blood glucose (25-40%), and a decrease in HbA1c (0.8% in absolute values and 10-20% in relative values). Decreased fasting insulinemia and especially post-prandial insulinemia reflect increased sensitivity to insulin [24, 25]. Acarbose efficacy does not appear to be dose related [26].

There has only been one randomized study, comparing miglitol with a sulfonylurea, glibenclamide, in subjects aged 68 years on average: miglitol led to a lower decrease in fasting blood glucose and HbA1c than glibenclamide, but post-prandial glycaemia was reduced more with miglitol [7].

Pharmacodynamics: tolerance

α-glucosidase inhibitors do not provoke hypoglycaemia [7, 27]. Certain undesirable effects (flatulence, or even diarrhea in 30-80% of patients) are frequent and can be poorly tolerated. There is no age relationship. It has been reported faster colonic transit time, about 20% faster, in constipated elderly diabetics, with no particular inconvenience [28]. There have however been a few reports of isolated cases of digestive complications suggesting there could be a more serious gastrointestinal risk for patients with history of digestive tract disease, autonomic neuropathy, or taking anticholinergic drugs concomitantly [29].

Practical implications

The absence of a hypoglycaemia risk is an important property of this class. Nevertheless, use of α-glucosidase inhibitors could be limited by the frequent adverse gastrointestinal effects. The initial dose should thus be limited and taken at the beginning of the three daily meals, to be titrated according to tolerance thereafter.

Contraindications of α-glucosidase inhibitors include obstructive-like syndromes, inflammatory bowel diseases, intestinal hernia, and severe renal failure (creatinine clearance less than 25 ml/min), conditions which are frequent in geriatric patients.

Glinides (repaglinide)

Pharmacokinetics

Repaglinide is mainly metabolized in the liver via cytochrome P450 isoenzyme 3A4, without an active metabolite, and eliminated in bile and feces [30].

Pharmacokinetic profiles have been determined with therapeutic trials in elderly subjects which only included diabetics aged less than 70 years. These comparative trials demonstrated the lack of any difference in the pharmacokinetic properties of repaglinide between elderly subjects and non-diabetic younger adults, nor between “old” diabetics and “old” non-diabetic subjects. The plasma elimination half-life ranged from 1 to 1.7 hours while the Cmax and the area under the curve (AUC) tended to increase with age [31, 32].
The pharmacokinetic parameters of repaglinide are not modified for creatinine clearance ≥ 40 ml/min in the young adult. There is however evidence of an increased AUC with a 4 to 6-fold slower elimination of repaglinide when the creatinine clearance is less than 40 ml/min, the mechanism proposed being partially related to changes in the liver metabolism resulting from the impaired kidney function [30, 33, 34].

**Pharmacodynamics: efficacy and tolerance**

To our knowledge, efficacy data are not available in the elderly diabetic.

Considering the drug’s mode of action, there would be a risk of hypoglycaemia with repaglinide (particularly if meal-time calorie intake is insufficient). The risk of hypoglycaemia is positively correlated with the severity of the renal failure in young adults; this result can be transposed to the elderly diabetic [35]. Minor gastrointestinal disorders may also occur.

**Practical implications**

The short onset of action (30 min) and the short plasma half-life of repaglinide enable administration a few minutes (15 minutes) before meals, even if food intake is retarded. Nevertheless, since there is no specific clinical study in geriatric patients, repaglinide is not currently recommended after the age of 75 years.

The initial dose should be lowered to 0.5 mg per intake in patients with moderate renal impairment (creatinine clearance between 30 to 60 ml/min).

Contraindications are severe renal failure (creatinine clearance < 30 l/min), liver disease, and association with gemfibrozil.

Clinical studies have not demonstrated to date any clinically significant interaction between repaglinide and cytochrome P450 isoform 3A4 inducers or inhibitors [36].

**Thiazolidinediones or “glitazones” (pioglitazone and rosiglitazone)**

**Pharmacokinetics**

To our knowledge, there has been no published pharmacokinetic study conducted in the elderly, just some reported data [37]. In the young adult, the plasma half-lives of rosiglitazone and pioglitazone are 3 to 4 hours, with protein binding greater than 99% and hepatic metabolism via cytochrome P450 isoenzyme 2C8, with no active metabolites. To date, there have been no reports of drug interaction with other agents interfering with isoenzyme 2C8 (digoxin, warfarin). Renal elimination predominates (about 65%).

Interestingly, changes in the pharmacokinetic properties have not been reported in patients with chronic renal failure (mild to severe) irrespective of age [38].

**Pharmacodynamics: efficacy**

Only two articles have been published concerning the efficacy and safety of pioglitazone and rosiglitazone in elderly diabetics [37, 39]. The conclusion of these two studies was that efficacy is similar in old and young type 2 diabetics [37, 39], with a non-significant trend towards more adverse events (notably edema, anemia and heart failure) in older diabetics. It must be noted however that the methodology lacked rigor: these were post hoc studies pooling data from earlier randomized double-blind studies (which were not specifically geriatric studies) with different therapeutic protocols and different comparators both in terms of the agent and dose, and also with numerous exclusion criteria (notably heart failure) in order to compare subgroups of diabetics aged less than 75 years with the subgroup of young diabetics, without statistical analysis.

A third article has been published on troglitazone, which has been withdrawn from the market due to hepatic complications [40].

**Pharmacodynamics: tolerance**

The approved Summary of Product Characteristics (SPC) monographs states that glitazones can cause fluid retention leading to weight gain and/or edema, or even mild anemia (by hemodilution). Cardiac decompensation is also possible, particularly in older subjects, with pre-existing moderate renal impairment or heart disease or taking nonsteroidal anti-inflammatory drugs or insulin [41, 42]. There has not however been any report of liver toxicity with either of the two glitazones currently on the market [43].

**Practical implications**

The absence of risk of (excepting association with a sulfonylurea) hypoglycaemia and extra-glycaemic actions of glitazones could be interesting for the geriatric population. But the contraindications as well as the mandatory surveillance required currently limit use of these drugs in the geriatric population until further information becomes available.

Patients should be regularly monitored to record weight and liver enzyme levels (before the initial prescription in all patients, then regularly depending on the individual clinical situation). Care should be taken to avoid the risk of hypoglycaemia, which can be high in two-drug regimens associating sulfonylurea via the synergetic hypoglycaemic effect, and which can appear several weeks after onset of the combination regimen.

The main contraindications for glitazones are association with insulin, end-stage renal failure (creatinine clearance < 4 ml/min), liver disease (particularly liver failure), and heart failure (all stages).

Precaution is necessary in the event of pre-existing anemia or creatinine clearance less than 30 ml/min.

**Insulins and insulin analogs**

European, American, and French recommendations for the use of insulin or insulin analogs in elderly diabetics are generally based on studies conducted in non-elderly diabetics [1, 3, 4]. Several situations do exist however where insulin use is more frequent than in young diabetics (altered renal func-
tion, acute intercurrent disease, insufficient efficacy of oral antidiabetics); the risk of hypoglycaemia is greater in these older patients [6, 44].

**Specific benefits of insulin therapy**

It is known that insulin therapy improves the general and nutritional status of the elderly diabetic [3, 19]. One non-randomized study compared 30 type 2 diabetic patients aged 73 years on average who were treated with one or two insulin injections per day with ten type 2 diabetics taking oral antidiabetics. This study demonstrated improvement in certain quality-of-life criteria after four weeks of treatment in the insulin treated group without change in glucose control. However, the absence of randomization did not enable confirmation of a link with insulin therapy [45]. Another randomized study in 57 type 2 diabetics aged 69.9 years on average with poor glucose control on oral antidiabetics demonstrated a statistically significant improvement from the third month in certain quality-of-life criteria (including an anxiety scale), as well as in HbA1c, in the group of patients treated with a basal-bolus insulin regimen (intermediate insulin and short-acting insulin analog) while this improvement was not noted in the group given two injections of intermediate-action insulin per day [46]. Insulin therapy also contributes to more effective glucose monitoring (the nurse measuring capillary blood glucose before each injection) enabling these patients to maintain their autonomy [3, 19].

**Type of insulin or insulin analog**

The type of insulin and the insulin therapy regimens proposed for geriatric patients are not based on comparative studies. They depend on the therapeutic goals, the risk of nighttime hypoglycaemia, and conditions of administration. Nearly all of the classical regimens are proposed in accordance with publications: two daily injections of intermediate-action insulin or of a premixed (rapid + intermediate action) insulin (30% rapid + 70% intermediate), one injection morning or at evening of intermediate insulin or a single injection of long-acting insulin analog (glargine) in the morning, with or without an oral antidiabetic drug [3, 6, 47, 48].

To our knowledge, there are no comparative data on the efficacy and/or tolerance of insulin analogs compared with conventional insulin in elderly diabetics. Similarly, there are no data with an analysis distinguishing a subgroup of elderly diabetics [49, 50]. It would be interesting to perform clinical studies in elderly diabetics to assess the usefulness of the low variability of action provided by insulin analogs in terms of reduced risk of hypoglycaemia, particularly nighttime hypoglycaemia [49-52].

On the other hand, the short onset of action enabling injection at mealtime can be an advantage in frail elderly patients whose food intake is irregular [52]. One randomized cross-over study conducted for twelve weeks compared preprandial injection with postprandial injection using pre-mixed biphasic aspart insulin (30/70) in 93 type 2 diabetics aged 70.3 years on average and did not demonstrate any difference in the patterns of post-prandial glycaemia, HbA1c, or hypoglycaemia prevalence [53].

**Dose adaptation**

It is well accepted that renal elimination of insulin is slower and insulin needs reduced with aging in older patients. This requires adjusting doses and number of administrations to limit the risk of hypoglycaemia, particularly nighttime hypoglycaemia. Outside an acute context, a moderate initial dose (to the order of 0.3-0.5 U/kg/d) is arbitrarily recommended [54].

**Modalities of injection**

Depending on the clinical situation, the injection can be performed by the patient, a family caregiver or a nurse. Several criteria must be taken into consideration: lifestyle, autonomy, neuropsychic context (cognitive or praxia disorders), visual acuity. Underestimating the difficulties encountered by elderly subjects to self-administer insulin can lead to serious and frequent mistakes and problems [55].

Autonomous patients can use pens [19, 55-58]. More recent interest in the InnoLet® system for geriatric patients has been reported in two studies. The most relevant study was a 12-week cross-over trial in 79 type 1 or 2 diabetic patients aged 68.2 years on average, with visual and/or motor impairments [55]. This study demonstrated less need for an outside person and less health care cost with this system [55]. In the second study with a less rigorous methodology conducted in 25 type 2 diabetics aged 65.6 years on average, two daily injections of NPH insulin with this system enabled a significant improvement at three months in terms of patient satisfaction and glucose control [58].

**New insulin formulations**

New formulations being studied for insulin are still in the early development stage, explaining the lack of complete information, particularly pharmacokinetic data in geriatric diabetics [59]. There is one study which compared the pharmacokinetic and pharmacodynamic properties of a short-acting insulin after a single pulmonary inhalation in 27 young diabetics and 28 aged diabetics (mean age 70.1 yrs), all with type 2 diabetes [60]. This study demonstrated no difference between the pharmacokinetic parameters, but a lesser decline in blood glucose in the older diabetics, which might be explained by a more pronounced insulin resistance.

**Therapeutic strategy**

Globally, the therapeutic strategy in diabetes remains similar for elderly patients compared with younger patients [3, 4].

The issue examined in geriatric studies is the attitude which should be adopted for elderly subjects with type 2 dia-
betes who have an insufficient glucose control with sulfonylurea [44, 61-63]. Two of these studies included enough patients after randomization. The first was unable to demonstrate a difference in glucose control at six months when one daily NPH insulin injection (morning or evening) was combined with glibenclamide or when glibenclamide was replaced by two daily injections of NPH insulin [44]. The second study, in patients free of renal impairment, also failed to demonstrate any difference in glucose control at 18 months between increasing sulfonylurea dose to a maximum and association with metformin [61]. These studies however concerned a limited aspect of the therapeutic management in elderly diabetic subjects.

In practice, the therapeutic strategy must be adapted to the glucose goals (which are not always the same as in young diabetics). The therapeutic strategy is usually based on three recognized arguments which favor the switch to insulin therapy as soon as needed:

1°) insulin has a favorable effect independent of glucose control, particularly for undernourished patients;

2°) there are many contraindications and precautions for use of oral antidiabetics in the geriatric population because of the important comorbidity;

3°) certain frequently encountered individual clinical and/or social situations favor use of insulin therapy: cognitive impairment, social or familial isolation, poor observance, loss of autonomy. In these situations, a health care network must be organized to implement monitoring and surveillance, including daily home visit by a nurse [3].

Conclusion

Although available informations are often incomplete, it can be considered that the aging process does not theoretically modify the major pharmacokinetic and/or pharmacodynamic properties of antidiabetic drugs having a moderate elimination half-life in patients with preserved renal function. But this clinical situation does not correspond to the majority of diabetic patients aged over 70 years. Good use of antidiabetic drugs is strongly related to therapeutic goals which must be adapted to each individual patient. Pre-market approval therapeutic evaluation (before submission of the marketing authorization) of new compounds including a sufficient number of old patients is indispensable and must be strongly encouraged, as must be drug post-marketing surveillance programs, in order to obtain more precise data concerning the risk-benefit ratio which is different from that observed in young diabetics.

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