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A) COMMENTS ON PUBLISHED ARTICLES

Antidiabetics in chronic kidney disease: new questions to new and traditional drugs

Nefrologia 2012;32(6):835

doi:10.3265/Nefrologia.pre2012.Aug.11678

To the Editor:

After reading the editorial by Martinez-Castelao A et al.,[1] I must congratulate the authors for the clarity and pragmatism of their article.

The topic of chronic kidney disease (CKD), diabetes mellitus, and hypoglycaemic drugs continues to be a source of controversy among nephrologists and doctors from all areas who come into contact with and must make decisions regarding patients with renal failure who require these drugs.

Although the aforementioned editorial removes many of the doubts that may arise for primary care physicians who read the original article,[2] it still leaves certain aspects somewhat unclear that we wish to highlight.

Why do classification systems for CKD continue to be in use when evaluating drugs that are not those proposed by the KDIGO several years ago?

The editorial includes the indications for new and traditional anti-diabetic drugs (Tables 2 and 3) based on the level of altered renal function in the patient, with glomerular filtration rates (GFR) >50ml/min, 30-50ml/min, or <30ml/min, referred to as mild, moderate, or severe, respectively. This classification system that differs from the more commonly used 5 stages established by the KDIGO (soon to undergo review) appear not only in this article, but also in the technical data sheets of several drugs, thus hindering the comparison between studies or protocols in the management of these drugs.

Due to what pathophysiological mechanisms, which are not sufficiently explained, is acarbose contraindicated in stage 4 and 5 patients, given that its mechanism of elimination is <2% renal?

A relatively large body of literature is available regarding the use of metformin, but very little is known regarding the adverse effects of acarbose.

New dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists are good resources to use when other drugs are contraindicated, but at times doubts can arise when treating patients with CKD, especially considering the fact that reduced doses for use in patients with CKD are often not available in Spain.

Has a pharmaco-toxic mechanism been isolated based upon which doses should be adjusted in the event of deteriorated capacity for renal elimination?

Should we guide ourselves based on dosage or administration interval based on which drug is being administered?

Although we are approaching a more updated and realistic version of the modern CKD patient with the imminent release of the S.E.N.-semFYC consensus document (and the debate continues whether a decrease in GFR<60 constitutes CKD, as held by the "huge" equation authors[3]), and while the precision of estimates of GFR with cystatin-C alone or combined with serum creatinine is increasing,[4] there are still doubts surrounding aspects of the treatment of this disease that have been around for some time.

Conflicts of interest

The authors declare that they have no conflicts of interest related to the contents of this article.

1. Martínez-Castelao A, Górriz JL, Sola E, Morillas C, Jover A, Coronel F, et al. A propósito de las discrepancias entre documentos de consenso, guías de práctica clínica y normativa legal en el tratamiento de la diabetes tipo 2. Nefrologia 2012;32(4):419-26.
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Authors reply: About the discrepancies between consensus documents, clinical practice guidelines, and legal regulations in the treatment of type 2 diabetes

Nefrologia 2012;32(6):835-7

doi:10.3265/Nefrologia.pre2012.Oct.11731

To the Editor:

In his letter to *Nefrología* published in this issue,[1] J. Serra Tarragon makes a

series of very interesting questions regarding clinical practice based on our original article, "About the discrepancies between consensus documents, clinical practice guidelines, and legal regulations for the treatment of type 2 diabetes",[2] which we agree still need some clarification.

Firstly, he makes allusions to the antiquated classification of chronic kidney disease (CKD) as mild, moderate, and severe, instead of the more modern KDOQI[3] and KDIGO[4] system of stages 1-5. We must keep in mind that both classification systems (KDOQI and KDIGO) were published relatively recently. The older of the two (KDOQI) only dates back to 2002, and many drug summary of characteristics have yet to be adapted to this new system.

However, in Table 1 and Figure 1 of our article,[2] we discuss the administration of oral anti-diabetic drugs (OAD) using the current KDOQI staging system. Even in Figure 3, in which we evaluate the appropriateness of using dipeptidyl peptidase-4 inhibitors (iDPP-4) for treating patients with renal failure (RF) and liver failure, while we do discuss this issue in terms of mild, moderate, or severe RF, we used the creatinine clearance cut-off value of <30ml/min/1.73m^2, which corresponds to stage 4 CKD in the current classification system.

Traditionally, the Cockcroft-Gault formula (C-G) was used for adjusting medication prescriptions for patients with RF. The adjustment tables published for this purpose were elaborated prior to the publication of the KDOQI guidelines, which established the 1-5 stage system. As such, these tables corresponded to the categories of mild, moderate, and severe. With the objective of analysing which is the most appropriate model for adjusting medication doses, Stevens et al.[5] examined 5504 patients from several studies to compare the MDRD and C-G formulas, incorporating parameters such as ideal weight and standardised creatinine values to perform a pharmacokinetic simulation. The MDRD equation was shown to be better aligned with renal function than the C-G formula, suggesting that the MDRD formula can and should be used for pharmacokinetic studies, as well as in medication adjustment tables. Although it is difficult to prompt an update to the technical data sheets for all medications that require adjustments based on renal function, we can at least hope that all new drugs that appear on the market follow the more updated recommendations from the KDOQI and KDIGO guidelines.

The next question refers to the contraindication against the prescription of acarbose in patients with stage 4-5 CKD, in light of the fact that this medication is not eliminated by the kidneys. Indeed, acarbose, as opposed to other ?-glucosidase inhibitors such as miglitol, is practically not absorbed by the body, and less than 2% of ingested molecules are eliminated through the urine in the form of active metabolites, for which this drug does not accumulate in cases of RF. To respond to the question posed by Dr. Serra, the contraindication against prescribing acarbose in patients with stage 4-5 CKD is based on two reasons: the first is the lack of studies performed among patients with RF using this drug, as mentioned by other authors,[6] but the primary reason is that the drug technical data sheet[7] states that patients with a creatinine clearance rate <25ml/min/1.73m^2 produce Cmax values and areas under the curve that are 6 and 5 times greater, respectively, than in healthy volunteers with normal renal function, which would indicate that a greater prevalence of secondary side effects would be expected in these patients. This, in addition to the possible interaction between acarbose and diuretics such as furosemide, makes the use of this drug more unadvisable than contraindicated in patients with RF.

As regards metformin, the dilemma here lies in the discrepancies between clinical guidelines, recommendations for clinical practice, and the drug technical data sheet. As long as this last element is not modified (a task that falls to the health authorities), it would be prudent to be cautious in using metformin in clinical practice. Our recommendation, especially in elderly patients, those with important atheromatous disease, and those receiving concomitant treatments with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, distal diuretics, or non-steroidal anti-inflammatory drugs, would be to closely monitor glycaemia, haemogram results, and renal function when estimated glomerular filtration rates (GFR) fall below 45ml/min/1.73m^2, and interruption of treatment when GFR falls below 30ml/min/1.73m^2.

As regards treatment with iDPP-4, the differences derive from the variable level of metabolisation of this compound in the kidneys. As such, several clinical trials and studies in patients with diabetes mellitus and RF of varying severity recommend reducing or suspending the dose of iDPP-4 below a fixed glomerular filtration rate cut-off value due to the possibility of hypoglycaemia. Linagliptin can be administered in any stage of CKD, since this is the only iDPP-4 that can be eliminated through the bile, with only a small percentage of molecules passing through the kidneys. As described in the ACCORD,[8] ADVANCE,[9] and other studies, strict control of HbA_{1c} in diabetic patients can produce increased morbidity and mortality rates, which are accentuated in the presence of RF and high comorbidity. On the other hand, HbA_{1c} does not appear to be the most reliable biochemical marker for ensuring proper control of glycaemia in patients with RF. Glycated albumin appears to be a more reliable option, especially in patients with CKD in stage 3 or higher.[10] The inconveniences of this technique are its high cost and the relative scarcity of laboratory analyses using this parameter.

Finally, another important issue is the measures to be taken in the case of patients with diabetes and acute renal failure. The 2011 updates to the KDIGO guidelines[11] reported on the conven-

ience of adapting the dosage of medications in patients with chronic vs. acute RF. In diabetic patients on treatment with OAD who suffer an episode of acute RF, and especially in those cases that require renal replacement therapy with dialysis, we suggest proceeding with great caution. The patient should be administered rapid-acting insulin and basal insulin analogues, with frequent monitoring and control of glycaemia in the context of the evolution of renal function parameters. This management should be carried out with special emphasis in patients with oligoanuria, since the dosage of insulin will have to be modified based on the recovery of diuresis in these patients.

We hope this has contributed to clarifying some of the aforementioned controversial aspects of this issue.

Conflicts of interest

The authors declare that they have no conflicts of interest related to the contents of this article.

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Discrepancies between the summary of characteristics and the recommended use of metformin in the treatment of type 2 diabetes mellitus patients

Nefrologia 2012;32(6):837-8

doi:10.3265/Nefrologia.pre2012.Sep.11656

To the Editor:

We read with great interest the editorial published in the last issue of *Nefrología* titled: "About the discrepancies between clinical consensus documents, clinical practice guidelines, and legal regulations in the treatment of type 2 diabetes mellitus",[1] and we would like to make a brief commentary on this article.

Firstly, we wish to state that this editorial inspired a great deal of interest since it updates and includes several innovative aspects, such as indications for use, based on the summary of characteristics information, for oral anti-diabetic medications (OAD), insulin, and glucagon-like peptide analogues, which are used in the treatment of patients with type 2 diabetes mellitus (DM2); however, we would also like to know the opinion of the authors regarding the legal aspects of the use of these drugs, especially in the case of metformin in renal failure patients.

In the section of the editorial dedicated to metformin, the authors specify that this molecule is eliminated through the kidneys, which supports the contraindi-