Use Of Oral Anti-Diabetic Agents In Diabetes With Chronic Kidney Disease

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INTRODUCTION

Diabetes is one of the leading causes of chronic renal disease and end stage renal disease. It was believed in the past that diabetic nephropathy is a common complication of type 1 diabetes as compared to type 2 diabetes, however the prevalence of diabetic nephropathy in type 2 diabetics is in fact on the rise because of improvement in the management of other complications like cardiovascular disease. However, it has been shown in multiple well designed trials that chronic renal disease in diabetes can be prevented with good glycaemic control in both type 1 and type 2 diabetes. The results of ADVANCE trial also support these findings showing a significant reduction of renal events, including new onset or worsening of nephropathy, recent onset microalbuminuria and macroalbuminuria in type 2 diabetics with strict control of blood sugar as compared to those without strict control. However, management of diabetic patients with chronic renal disease is a challenging issue with complexities in all areas on management including diagnosis, management of hyperglycaemia, prevention of hypoglycaemia, dietary management, and management of comorbid conditions. This article aims to review the role of oral anti-diabetic agents in the management of diabetic patients with chronic renal disease.

Insulin physiology differs markedly in patients without renal disease from that in patients without renal disease. Normally upto 50% of the insulin secreted from the pancreas into the portal circulation is metabolised in the liver during its first pass metabolism. Thus kidney has little physiological role in metabolism of insulin in normal persons. However, it plays a major role in the metabolism of insulin in the systemic circulation, thus exogenously administered insulin which is not subjected to first pass metabolism by the liver is primarily degraded by the kidney. Insulin is filtered by the glomeruli and extensively reabsorbed from the proximal tubules and is also degraded by the tubular cells into amino acids which are reabsorbed. The final result of all these processes is that only 1% of the filtered insulin appears in the urine.

In patients with renal disease, basal insulin levels are high. The reasons for this vary according to the stage of the renal disease. In early stages, it is due to reduction in the blood flow. In more severe cases, the process of degradation of insulin by the kidney is hampered due to loss of renal mass. In the most severe case (those with GFR<20 ml/min), the reduced clearance is in addition due to a decrease in the filtration. Such altered metabolism of insulin in diabetic patients with renal disease makes them particularly vulnerable to the hypoglycaemic effects of exogenously administered insulin and other insulin secretagogues.

Another aspect of insulin physiology which is affected in patients with renal disease is the sensitivity of insulin. It is usually observed that insulin sensitivity is decreased in diabetic patients with renal disease which is improved with hemodialysis. The exact basis of this phenomenon is debated, however.

At GFR below 50 ml/min, the secretion of insulin is also hampered. The speculated mechanism is the metabolic acidosis and hyperparathyroidism leading to an increase
in intracellular calcium and decrease in ATP and Na/K ATPase activity, leading to defect in insulin secretion by the pancreatic \( \beta \)-cells.

**EFFECTS OF DEVIATIONS IN INSULIN PHYSIOLOGY ON INSULIN REQUIREMENTS**

The overall effect of these deviations in metabolism of insulin is biphasic. In the initial stages, the insulin requirement increases due to the increased insulin resistance and decreased insulin secretion. However, in late stages, the insulin requirements fall due to decreased metabolism and clearance of insulin and lowered dietary intake due to decreased appetite.

**HYPOGLYCAEMIA IN DIABETIC PATIENTS WITH RENAL DISEASE**

The diabetic patients with renal disease are at increased risk of developing hypoglycaemic events. The reasons for such spontaneous hypoglycaemia are:

1. Altered insulin metabolism
2. Decreased appetite
3. Decreased renal gluconeogenesis
4. Impaired release of counter-regulatory hormones like epinephrine due to autonomic neuropathy
5. Concurrent hepatic disease
6. Decreased metabolism of drugs that might promote a reduction in plasma glucose concentrations such as alcohol, nonselective \( \beta \) blockers, and disopyramide.

**ORAL ANTI-DIABETIC AGENTS IN RENAL DISEASE**

Chronic renal disease is associated with decreased clearance of many oral hypoglycaemic agents and their metabolites, prolonging the duration of exposure to the drug and its metabolites, more so in patients with moderate to severe renal disease. Thus a diagnosis of renal disease in patients with diabetes merits attention to the revision of the drug therapy of the patient.

**Sulphonylureas**

The first generation sulphonylureas are practically not used now-a-days. So the discussion on sulphonylureas focuses on the second generation sulphonylureas only. Sulphonylureas are strongly bound to albumin. The problem that occurs due to high protein binding property of these drugs is that they cannot be removed from the circulation efficiently even by hemodialysis. Therefore these drugs should be used cautiously in patients in patients with renal failure.

Glibenclamide and Glimiperide are converted into metabolites in the liver which also possess some hypoglycaemic activity. The metabolites of these drugs have a predominant renal excretion, thus there is accumulation of these metabolites in patients with renal disease, which can lead to severe and prolonged hypoglycaemia. Therefore the use of these drugs is contraindicated in patients with severe renal disease and a reduction in dosage is advised in patients with mild to moderate renal disease.

Glipizide is also metabolized in the liver like glibenclamide but unlike glibenclamide its metabolites are inactive. Moreover, its plasma half-life is relatively short (2-4 hours), therefore if needed, glipizide should be the sulphonylurea of choice in patients with diabetes and renal disease.

**Insulin secretagogues**

Repaglinide is a non-sulphonylurea insulin secretagogue which is extensively metabolized in the liver and excreted in the bile. Its half-life is around 0.6-1.8 hours. It is minimally excreted by the renal route, therefore, although the half-life of the drug is increased in patients with renal failure, there is no need for any dose modification in these patients.

Nateglinide is also metabolised in the liver, however, many of the metabolites of nateglinide possess hypoglycaemic activity and accumulate in patients with renal disease. Thus the use of this drug in patients with renal disease is not free from the risk of hypoglycaemia, hence caution should be exercised in use of this drug in such patients.

**Biguanides**

Metformin is the only drug of this class which is used in diabetes. From the view-point of hypoglycaemia, metformin has been considered as one of the safer drugs. But its use in patients with renal disease is associated with significantly increased risk of lactic acidosis. This side effect is again a result of accumulation of the drug and its metabolites in patients with renal disease. Metformin is thus contraindicated in male patients with a serum creatinine > 1.5 mg/dl and in female patients with serum creatinine > 1.4 mg/dl.

**Thiazolidinediones**

The thiazolidinediones (Pioglitazone and Rosiglitazone) are exclusively metabolized in the liver. The metabolites of these drugs formed as a result of hepatic metabolism do not possess significant hypoglycaemic activity. Also, renal disease does not lead to significant accumulation of these
drugs or their metabolites. So risk of hypoglycaemic events is minimal. However a well known side effect of these drugs is fluid retention which is more so in patients given insulin along with these drugs\textsuperscript{10,11}. Therefore the use of these drugs in renal disease is associated with a significant risk of fluid overload and exacerbation of pre-existing cardiovascular disease.

**Alpha-glucosidase inhibitors**

Alpha-glucosidase inhibitors such as acarbose or miglitol are luminally acting anti-diabetic agents which delay the breakdown and hence absorption of the carbohydrates in the intestine, thus predominantly preventing the post-prandial surge in glucose. Acarbose is minimally absorbed from the intestine, however it is metabolised by the luminal flora into several breakdown products which may be absorbed. An important side effect that has been observed in patients with renal disease is a rise in the transaminases levels attributed to both the drug and its metabolites. Miglitol on the other hand is completely absorbed from the intestine and elimination is by the renal route. Hence both of these drugs have little if any role in management of patients with renal disease\textsuperscript{10}.

**DPP-4 inhibitors**

The two DPP-4 inhibitors available in India (Sitagliptin and Saxagliptin) have a predominant renal excretion\textsuperscript{12}. Hence dose adjustments have to be made in patients with moderate to severe renal insufficiency. These 2 agents can be used with good benefit in diabetic patients with renal failure albeit with dose adjustments.

Sitagliptin dose adjustments are as follows:

1. Creatinine clearance 50-80 ml/min - 100 mg qd (same as for normal persons)
2. Creatinine clearance 30-50 ml/min - 50 mg qd
3. Creatinine clearance < 30 ml/min or ESRD (approximate serum creatinine levels >3.0 mg/dl for men, >2.5 mg/dl for women, or on dialysis) - 25 mg qd\textsuperscript{13}.

The dose adjustments for saxagliptin are as follows:

1. Creatinine clearance > 50 ml/min - no dose adjustment (2.5 to 5 mg qd, taken regardless of meals).
2. Creatinine clearance < 50 ml/min - 2.5 mg qd\textsuperscript{14}.

**Amylin analogs**

Amylin is a neurohormone which is secreted along with insulin from the pancreatic $\beta$ cells. Its levels are low in patients with both type 1 (absolute deficiency) and type 2 (relative deficiency) diabetes. Pramlintide is the amylin analog which has been approved for use in type 1 and type 2 diabetes. Although it is primarily excreted by the renal route, no dose adjustment is required in patients with moderate to severe renal disease (creatinine clearance 20-50 ml/min). There are no data available on the safety in patients on dialysis or with end-stage renal disease\textsuperscript{15}.

**SUMMARY**

A summary of available oral anti-diabetic agents for diabetes and their dose adjustments is presented in Table I.

<table>
<thead>
<tr>
<th>Class of drug</th>
<th>Safety profile in renal disease</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{*} Generation Sulphonylureas</td>
<td>Unsafe</td>
<td>Risk of prolonged hypoglycaemia.</td>
</tr>
<tr>
<td>2\textsuperscript{nd} Generation Sulphonylureas</td>
<td>Gipizide safe</td>
<td>Gipizide is preferred. Others to be avoided.</td>
</tr>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>Unsafe</td>
<td>Possible hepatotoxicity.</td>
</tr>
<tr>
<td>Biguanides</td>
<td>Safe</td>
<td>Risk of lactic acidosis.</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Repaglinide safe</td>
<td>Volume retention may occur especially with insulin.</td>
</tr>
<tr>
<td>Meglinidines</td>
<td>Nateglinide not completely safe</td>
<td>Short half-life and minimal renal excretion of repaglinide.</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Relatively safe</td>
<td>Significant risk of hypoglycaemia with nateglinide.</td>
</tr>
<tr>
<td>Amylin analogs</td>
<td>Safe</td>
<td>Dose adjustment needed for moderate to severe renal disease.</td>
</tr>
</tbody>
</table>

Table I. Recommendations for the use of oral anti-diabetic agents in patients with diabetes and renal disease
REFERENCES


