Editorial

Untapped diamonds for untamed diabetes: The α-glucosidase inhibitors

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That the diabetes pandemic grows unabated is no secret. As the syndrome scales brobdingnagian heights, in term of its epidemiological, patho-physiological, and clinical spectrum, it is hardly surprising that we seem unable to tame this condition.

Many authors explore the barriers which prevent physicians from prescribing, and patients, form accepting, appropriate therapy. Yet others discuss the limitations of currently available anti-diabetes drugs. Experts write of the need to ensure safety and tolerability along with efficacy that is necessary to control hyperglycemia. Some bemoan the lack of cardiovascular safety data with modern glucose-lowering drugs, while a few hype "side effects" in pursuit of pseudo-scientific sensationalism.

Although modern anti-diabetic therapy now includes effective drugs, both oral and injectable, we still seem to need more. Opinion leaders discuss various options for diabetes care in detailed algorithms, elevating relatively risky and relatively untested molecules to second-line status, in spite of concerns about safety and tolerability. The search for the elusive panacea in diabetes pharmacotherapy, however, seems to have neglected already discovered diamonds, the alpha glucosidase inhibitors (AGIs).

The Path of Development

Modern medicine seems to follow to a set pattern of drug discovery and development. Learnings from epidemiology (documentation of the existence of a disease) and clinical medicine (its impact on human health) lead to advances in physiology, which further our understanding of pathophysiology. This, in turns, identifies suitable molecular and other targets for intervention, which are used by pharmaceutical researchers to help create appropriate drugs. Thus, pathophysiology informs pharmacology in medical practice. This pattern is familiar to all clinicians working in the field of diabetology. The concept of insulin deficiency was known before drug insulin was synthesized. Similarly, the identification of insulin resistance as a key mediator of dysglycemia preceded the development of insulin sensitizers such as thiazolidinediones. The journey from discovery of the incretin effect and of glucagon dysfunction to the crafting of incretin-based, glucagon-lowering therapy, though an exceptionally long one, has followed the same path.

The Path of Understanding

At times, however, drug development takes the opposite direction. Metformin, for example, was synthesized long before its actual mechanism of action was delineated (the actual mode of action is still being worked out!). It is this anomaly in the 'natural history' of the molecule, perhaps which prevented its use for so many decades in the United States. Now that it has been accepted, it holds absolute sway as the only first-line drug for diabetes. So much is metformin's power that no other (equally deserving) molecules are allowed to be used as first-line monotherapy by some guidelines.

The same seems to be true for another class of oral anti-diabetic drugs, the α-glucosidase inhibitors (AGIs). Developed and used before the real import of the diabetes epidemic was realized, and before the full spectrum of their pleotropic benefits could be appreciated, they seem to have been overshadowed by newer molecules. Just as metformin's use in earlier years was limited not by its

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shortcomings, but by ours, AGIs seem to be unable to realize their full therapeutic utility.

Metformin and α–Glucosidase Inhibitors: Similarties

One advantage that metformin has is its long history of safe use. Available since the 1950s, it has a proven track record of cardiovascular safety. It can also be used in prediabetes, in all age groups from adolescence to the elderly, and in special situations such as pregnancy. Its cautious use in conditions such as renal impairment is also expanding, while adverse gastrointestinal effects are minimized by pharmacotherapeutic and physiological advances and improvization. The lack of hypoglycemia, multiplicity of pleotropic effects attributed to metformin, and ability to be used as monotherapy as well as combination therapy also add to metformin's appeal.

The dependable class of AGIs, too, has a nearly two decade-long history of use cardiovascular safety in both diabetes[1] and prediabetes[2] has been demonstrated conclusively. With low risk of hypoglycemia, drugs are safe for use in all age groups. ADA's multidisciplinary Professional Practice Committee stated that among the oral antidiabetic agents, metformin and acarbose are classified as category B (no evidence of risk in humans) and all others as category C.[3] Acarbose is also safe to prescribe in mild to moderate renal impairment. The gradual realization that AGIs have multiple pleotropic, beneficial effects, also adds to their allure [Table 1].

Current Status

The International Diabetes Federation (IDF) recommends AGIs as first-line, second-line, or third-line treatment options.[4] AGIs can be combined with metformin, sulfonylurea, DPP4 inhibitors, thiazolidinedione, and insulin. The American Association of Clinical Endocrinology suggests use of AGIs at all stages, irrespective of entry level HbA1c. The AGIs are classified as being safe, but less potent as compared to other choices.[5] National guidelines from China, Japan, Taiwan, Korea, and Singapore all support the use of AGIs, as do expert recommendation from an Asian-Pacific panel.[6]

These properties explain why AGIs are the largest prescribed oral anti-diabetic drugs in China and Japan, both countries which figure in the list of top 10 diabetes-afflicted countries. Yet, for some, the AGIs seem to be untapped diamonds. While popular guideline authors are quick to highlight the benefits of newer therapy, in spite of various limiting factors, AGIs still do not figure in the list of first-line or second-line drugs. Why this happens is unclear.

The American Diabetes Association- European Association for Study Diabetes algorithm, for example, tends to be dismissive of AGIs. These seem to be no valid reason for this. AGIs address an important aspect of glycemic dysfunction, viz., postprandial hyperglycemia (PPHG). PPHG is independently associated with macro-as well as micro-vascular complications of diabetes, through well-delineated patho-physiological pathways. It is recommended to implement treatment strategies which lower PPHG in persons with diabetes.[7]

The Pharmacology of α-Glucosidase Inhibitors

The AGIs act by competing with oligosaccharides for binding size at the α–glucosidase enzyme. This slows down the rate of digestion carbohydrates, and alternates the postprandial rise in glucose levels. This insulin-sparing mechanism helps in reducing the degree of hyperinsulinemia that is often seen in diabetes. This insulin-sparing action process translates in to clinical benefits, viz., a low frequency of hypoglycemia and weight neutrality. In some studies, weight loss has been reported with AGI use years.[8,9] A Cochrane systematic review[9], considering a meta-analysis of 41 studies, reports beneficial effects of AGIs on fasting glucose, post-load glucose, post-load insulin, and body mass index (BMI). The highest dose suggested is 50 mg thrice daily. Long-term studies[10] have also demonstrated that this glycemic control is multifaceted (fasting, postprandial glucose, and HbA1c control) and is sustained up to 5 years.

Both as monotherapy and in combination, the AGIs have been found to be potent glucose- lowering agents, although without the risks of hypoglycemia or weight gain. This evidence is supported by data form India as well.[10-12]

Table 1: Similarities between metformin and α-glucosidase inhibitors

Property	Similarity
Mode of administration	Oral
Time of administration	With meals
Dosage range	Wide range
Insulin sparing	Yes
Use in pregnancy	In specific settings
Use in mild to moderate renal failure	Yes
Use in prediabetes	Yes
Use in all age groups	Yes
Cardiovascular safety	Proven
Weight neutral/weight loss	Yes
Hypoglycemia	Low risk
Gastrointestinal intolerability	Possible

Similar data is seen in recently published reports from multinational cohorts.

The available literature confirms acarbose to be a well-tolerated and effective agent, when combined with diet and insulin therapy, for the treatment of type 1 diabetes. Studies show that postprandial glucose fluctuations are minimized, post-breakfast hyperglycemia is reduced and the pre-noon glucose level is optimized in patients receiving two to four injections of insulin per day.[13]

AGIs also have an excellent safety profile. The commonest adverse effects, which are gastrointestinal in nature, are dose-dependent, mild and transient. The tolerability of acarbose can be improved by gradual uptitration of dose in a 'start low, go slow' manner. The upregulation of glucosidase enzyme intestine helps in reduction of frequency and severity of gastrointestinal side effects.[13] While the most frequent adverse event was flatulence, it is noteworthy that a recent Japanese study has postulated a cardioprotective effect for this symptom.[14]

Apart from these benefits, acarbose has proven cardiovascular benefits. In a meta-analysis of 7 randomized controlled trials, which studied 2180 subjects with type 2 diabetes (MeRIA), acarbose significantly reduced the risk of myocardial infarction (hazard ratio 0.36; 95% confidence interval 0.16-0.80) (P = 0.012) and any cardiovascular event (0.65; 0.48-0.88) (P = 0.0061).[1]

Multiple mechanisms have also been postulated to explain the cardio protective effect of AGIs. These include reduction of pro-inflammatory markers (nuclear factor kappa-B), platelet activation (thromboxane A2), oxidative stress (Prostaglandin F2a), coagulation markers, blood pressure, and modification of lipid metabolism.[15]

Acarbose has also been shown to stimulate the release of glucagon-like peptide 1 (GLP1) after administration.[16] This property makes it similar to the newly developed incretin-based therapies, including GLP1 receptor agonists and dipeptidyl peptides-4 inhibitors.

Conclusions

One reason for the suboptimal use of AGIs may be in their perception as being less potent, poorly tolerated glucose-lowering drugs. Evidence from randomized controlled trials and observational studies, however, supports a contrarian view point. These effective molecules are well tolerated, if used correctly. A slow upward titration of dose, preferably with each meal, for an adequate length of time is required. It must be noted that specific timing of administration is not an absolute necessity for AGI use: Acarbose maintains its efficacy even if ingested up to half an hour after meals.

As we continue to discover and utilize, newer drugs for the control of diabetes, we must not lose sight of, or forget to reap the benefits of, already existing tools which have proven their worth. It took nearly four decades for metformin to occupy its rightful center-stage position at the high table of diabetes therapy: We hope AGIs do not have to wait that long.

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