Guest Editorial

Maximally Utilizing the Available Agents for the Treatment of Type 2 Diabetes

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In this issue of *Clinical Medicine & Research*, Dr. Michael T. Sheehan in a comprehensive article describes the newer agents for the treatment of type 2 diabetes and discusses questions that have arisen because of the availability of these new drugs. However, whatever drug you start with, how much of the drug you use, when you add a second or third drug, or when you add insulin are unimportant when compared with the results obtained (i.e., the HbA1c you achieve).

We have had evidence from cross-sectional studies for a number of years that glycemic control is associated with the time of appearance and severity of diabetic complications. Prospective studies such as the Diabetes Control and Complications Trial (DCCT), United Kingdom Prospective Diabetes Study (UKPDS), and the Kumamoto study (Glycemic Control in Type 2 Diabetes) confirmed these findings. The UKPDS demonstrated that in the type 2 patient the lower the HbA1c, the lower the rate of cardiac events, down to a level of 5.5% and there was no lower threshold. In fact, in the European Prospective Investigation of Cancer and Nutrition Study (EPIC-Norfolk cohort), a population study in the English county of Norfolk, the lower the HbA1c within the accepted normal range the lower the rate of cardiac events, cardiac mortality and total mortality.

What then should be our goal for the HbA1c in our type 2 diabetic patients? The American Diabetes Association suggests the HbA1c should be below 7% based on the DCCT study of type 1 diabetes. In the type 1 patient getting to a level of 7% or below even with the help of fast-acting analog insulins given multiple times per day in combination with a long-acting insulin is very difficult. It is still difficult with fast-acting analog insulins in insulin pumps. This is because frequent and severe hypoglycemia bedevil our efforts to get to these goals in type 1 patients.

The goal of the American College of Endocrinology and the International Diabetes Federation is a HbA1c of 6.5% or below, based on the UKPDS of type 2 diabetic patients. These goals are more realistic in the type 2 diabetic patient where hypoglycemia is much less common. This is due to retention of some endogenous insulin production, which acts as a buffer and prevents hypoglycemia by turning off endogenous insulin production when serum glucosees are lowered. Type 2 diabetic patients unlike type 1 patients maintain glucagon production and sympathetic response to hypoglycemia.
However, based on the data outlined above we should not be content to stop at 7.0% or 6.5%. We should try to lower the HbA\textsubscript{1c} to as low a level as possible without causing severe or frequent hypoglycemia. Lower levels are difficult to achieve with insulin or secretagogues because of the hypoglycemic risk. However, neither the biguanide metformin or the thiazolidinediones (TZDs: pioglitazone and rosiglitazone) are associated with severe hypoglycemia and utilization of these drugs either as monotherapy or in combination can achieve a HbA\textsubscript{1c} within the normal range, without the risk of severe hypoglycemia.\textsuperscript{4} This makes these drugs attractive as initial therapy in the type 2 diabetic patient.

If, as outlined in Dr. Sheehan’s article, TZDs improve β-cell function then the two of the three defects of type 2 diabetes (insulin resistance and insulin deficiency) are being addressed by the TZDs. The third defect (increased hepatic glucose production) is addressed by metformin and to a lesser extent the TZDs making the combination of a TZD and metformin even more attractive.\textsuperscript{5} Furthermore, if this improvement in β-cell function is maintained then it may be a considerable time before another drug and/or insulin will need to be added. A TZD (or a combination of metformin and TZD) would seem to be an ideal therapy with which to start treatment of type 2 diabetes based on the decrease in cardiac risk factors.

To lower the HbA\textsubscript{1c} and reduce cardiac events we should not delay starting insulin when oral therapy is no longer effective. There is a reluctance on the part of both the physician and the patient to start insulin therapy, with the threshold for initiating insulin therapy being a fasting glucose of approximately 200 mg/dl. Insulin injections are no longer painful or inconvenient so why should starting insulin be a “hang-up?” Patients perceive starting insulin as failure on their part to stick to their regimen. This has been repeatedly emphasized by their physicians, who tell them that if they cannot adhere to their diet or take their medication, the result will be the need for insulin. Of course this is not true. The need for the patient to start insulin is due to the natural progression of the disease and not the patient’s indiscretions. Furthermore, most type 2 patients have relatives with type 2 diabetes. They remember that after starting insulin these relatives developed the complications of diabetes. They therefore mistakenly associate insulin, and not hyperglycemia, with diabetic complications.

Insulin should be added to the oral agent regimen at the earliest possible time. Long-acting insulin started at anytime of the day with a small dose that is built up slowly is the most usual therapy at this time. Other appropriate approaches could be the addition of premixed insulin at supper with coverage of the large evening meal, or isophane insulin suspension (NPH) at night to cover the dawn phenomenon (the increase in insulin resistance around the time of awakening due to nocturnal growth hormone surges). Head to head studies of these regimens have not been done and are urgently needed.

When more than one insulin injection is required insulin should be used with one or two sensitizers. With the TZDs this is not the usual higher doses, but 15 mg or 30 mg of pioglitazone, or 2 mg or 4 mg of rosiglitazone. Studies of metformin used with insulin have shown not only better glycemic control but lower insulin needs and less weight gain. Therefore, in the type 2 insulin resistant patient utilization of sensitizers with insulin is appropriate.

From Dr. Sheehan’s article and this editorial, the message to the primary care physician should be that we have available new and old agents that will decrease the HbA\textsubscript{1c} to appropriate levels. The problem is that in the United States HbA\textsubscript{1c} is still too high. This poor glycemic control will result in increased mortality and morbidity in the diabetic patient. With the current and future epidemic of type 2 diabetes an astronomical increase in diabetic complications, due to this poor glycemic control, will place a financial burden on the community at large.

**REFERENCES**