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Review Article

A Note on Diabetes: Anti Diabetic Drugs

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Abstract

This article provides an overview of the development of insulins, oral agents, and noninsulin injectable agents used in the management of hyperglycemia in patients with diabetes. It also briefly reviews the pharmacological impact and salient side effects of these medications. The management of diabetes has changed dramatically during the past several thousand years. The option preferred by "experts" of the pharaoh of Egypt 3,500 years ago was a mixture of "water from the bird pond," elderberry, fibers from the asit plant, milk, beer, cucumber flower, and green dates. Although our therapeutic options today are significantly more effective, they will likely be considered arcane by our successors 100 years from now if the current trajectory in treatment development continues. Clearly, however, the current pharmacological armamentarium used to manage diabetes has resulted in a dramatic reduction in morbidity and mortality. This article provides a brief overview of the development history and effectiveness of various agents used in the pharmacological management of diabetes.

Keywords: Diabetes, Drugs, Therapeutic, Pharmacological, Bird

INTRODUCTION

Before the 1920s, there were no effective pharmacological agents for the management of diabetes. Because of this, type 1 diabetes was a fatal malady. This changed dramatically with Frederick Banting's work. Dr. Banting served as a surgeon in World War I. Captain Banting initially spent some time in hospitals in England, but later was sent to the front as a battalion medical officer, where he was wounded by shrapnel. He received a Military Cross for his courage in action. After returning from the war, Dr. Banting opened an office outside of Toronto, Canada. After seeing only one patient in the first month of his practice (a patient seeking a prescription for ethanol), Banting embarked upon a career in academics. One of his first teaching assignments involved carbohydrate metabolism. This led to his interest in diabetes and his erroneous assumption that one needed to surgically ligate the pancreatic duct and then wait 6-8 weeks before extracting anything that might be useful from the endocrine portion of the gland. Over time, and without the ligation step, he was able to extract a substance from canine pancreas glands that had an impact on hyperglycemia in other diabetic animals. Banting and his student, Charles Best, continued working on various extraction processes. Patient a sterile abscess developed at the site of one of the injections, but the patient's blood glucose dropped. After that injection, the push to perfect the extraction process and commercialize insulin was on. Banting's team entered into an agreement with Eli Lilly and Company, and, by July 1922, the first bottles of Lilly's Iletin (insulin) arrived in Banting's office. Insulin was commercially available in the United States by 1923 (Anderson B et al., 2015) (Barnes J et al., 2013).

DISCUSSION

The next major advancement in insulin was its crystallization in 1926. The technique of insulin crystallization led to improved soluble (regular) insulin purity and also opened the door to insulin formulation modifications with different time-action profiles. There was a great need for extendedaction insulin. With the availability of only rapid-acting insulin, patients required multiple daily injections and had to be awakened at night for injections. Children not awaked for nigh time injections were at risk for a significant reduction in growth, or diabetic dwarfism syndrome. Children with diabetic dwarfism syndrome, which was also known as Mauriac's syndrome, suffered from stunted growth, hepatomegaly, and delayed puberty. In 1936, the first commercially available, extended-action insulin, PZI (Protamine Zinc Insulin), was released. This formulation was composed of an amorphous combination of protamine, zinc, and insulin. PZI continues to be used today in the management of cats with diabetes (Choquet A et al., 2018) (Clayton S et al., 2016)

All insulin preparations available before 1983 were derived from animal sources. This changed in 1983, when the first recombinant medication, human insulin, was approved. One of the primary problems at the time of the release of human insulin was the pharmacokinetic/pharmacodynamic profiles of the available insulins. The search for "flat" basal insulin and rapid-acting insulin that more closely approximated physiological insulin secretory patterns accelerated after the release of human insulin. In 1996, the first rapid-acting human insulin analog, lispro, was approved. This was followed in the past 15 years with a succession of additional insulin analogs, including the rapid-acting insulins aspart and glulisine and the long-acting basal analogs glargine and detemir. The U.S. Food and Drug Administration (FDA) declined to approve degludec, ultra-long-acting insulin in 2013. However this compound is available in Europe and will probably be resubmitted for approval in the United States (Dunn G et al., 2017) (Eigenbrode SD et al., 2007).

Type 2 diabetes mellitus is one of the leading causes of renal failure, ASCVD, non-traumatic lower limb amputation, blindness, and death worldwide. It is a serious chronic medical condition that requires a multidisciplinary team approach, consisting of healthcare professionals, dieticians, patient educators, patients, and their families. Lifestyle intervention designed to manage body weight and treat obesity, as well as patient education, are essential for all patients with diabetes. Treatment options may be individualized and medication(s) chosen based on a patient's risk factors, current HbA1C level, medication efficacy, and ease of use, patient's financial situation/insurance/costs, and risk of side effects such as hypoglycemia and weight gain. Effectiveness of therapy must be evaluated as frequent as possible using diagnostic blood tests (HbA1C), as well as monitoring for development of diabetic complications (e.g., retinopathy, nephropathy, and neuropathy). Furthermore, aggressive efforts from physicians and motivating patients for compliance are the two important aspects of the prevention and management of diabetes. Sociocultural issues should be carefully considered. For example, during religious fasting (e.g., during the holy month of Ramadan), the use of pharmacologic agents that induce hypoglycemia should be used with care and insulin doses (for example, premix formulations) should be appropriately titrated and the patient should be educated for blood glucose monitoring and breaking of fast as needed. With infectious diseases (such as AIDS and tuberculosis), Evidence from landmark T2DM prevention trials indicates that lifestyle modification is more effective, cheaper, and safer than medication and provides sustained benefits. Lifestyle modification may be promising approach to T2DM prevention in developing countries. This will be useful for many ethnic groups in the U.S. as well, such as South Asian, Latino, Pima Indians, and African-American populations, which may face socioeconomic challenges similar to what is seen in developing countries. Cost-contained strategies to identify at-risk individuals, followed by the implementation of groupbased, inexpensive lifestyle interventions ("comfortably uncomfortable" life, as lived by people in blue zones), seem to be the best options for resource-constrained settings. T2DM pathophysiology is increasingly understood as a mix of insulin resistance and secretory defects of β-cells (Fiksel J et al., 2014) (Glika DC et al., 2007).

CONCLUSION

Several options for pharmacologic therapy of lowering blood glucose are currently available, which have revolutionized long-term management of DM. Several antidiabetic drugs may have important CV complications, which the provider team should always be aware. The polypharmacy issues, management of diabetes, as well as hypertension, hyperlipidemia, and use of aspirin should be carefully explained to patients to ensure adherence to therapy to prevent significant CV morbidity and mortality. Careful attention should be paid to development of insulinopenic states by clinical assessment of C peptide and lack of control of HbA1C with multiple medications, and complete lack of secreted insulin conditions should be treated by initiation of appropriate insulin regimens. Every clinical encounter should also be utilized to explain the benefit of weight loss and motivated for such. Even though not yet conclusive, clinical trial and data support consideration of bariatric surgery as a possible strategy to monitor blood glucose levels and body weight, especially in morbid obesity. Balanced hypocaloric diets that cause weight loss must be adopted and regular interactions with dietician is a useful approach. Aerobic training and resistance training can control increasing lean mass in middle-aged and overweight/obese individuals. Behavioural strategies for weight loss should be encouraged in primary care settings and appropriate maintenance of body weight prior to conception may help after development of gestational diabetes. Weight loss may be particularly challenging for incapacitated patients and subjects with disabilities, so comprehensive approaches should be undertaken. Newer molecular studies have demonstrated the transcriptional link between inflammatory pathways and increased adipose tissue storage, contributing to insulin resistance. Drug

repurposing of the anti-inflammatory agent for aphthous stomatitis, amlexanox, is currently undergoing trials as newer agents for management of diabetes (Hoover E et al., 2015) (Maxwell K et al., 2014).

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None

CONFLICT OF INTEREST

None

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