Newsletter for the TDM and Toxicology Division of AACC

Fall 2012

Therapeutics & Toxins News

Inside this issue:

"Diabetes Mellitus diabetes is now a global epidemic with an estimated 285 million patients in 2010, and growing rapidly."

Therapeutic Drug Monitoring in Diabetes Mellitus

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Diabetes Mellitus (DM), or diabetes is now a global epidemic with an estimated 285 million patients in 2010, and growing rapidly. In 2010, nearly 26 million people have diabetes in the United States, of whom 7 million people remain undiagnosed. Another 57 million people are estimated to have pre-diabetes (a condition defined not yet as diabetes, but leading to the disease). (1) The American Diabetes Association has predicted that at the current rate of growth, one in three Americans born after 2000 will develop diabetes in their lifetimes. (2) According to the ADA, about 18.3% (8.6 million) of Americans age 60 and older have diabetes. (3)

Logo for Therapeutic and Toxin Newsletter

Diabetes is a metabolic disease with increased glucose concentrations in blood. The disease fall in 3 main groups: Type 1 or "insulin-dependent diabetes mellitus" (T1DM, IDDM), Type 2 or "non insulin-dependent diabetes mellitus" (T2DM, NIDDM), and gestational diabetes. T1DM is a disease of low insulin (hypoinsulinemia), and can start early in life (teen or pre-teen); it has, however, increasingly been seen in adults today. The etiology of disease progression is still unknown, with presumed genetic and environmental factors playing parts. The disease mechanism, however, is destruction of body's insulin producing cells (the islet cells of Langerhorn in the pancreas). T2DM is a disease that includes insulin resistance and insulin ineffectivity. T2DM is the most prevalent form of diabetes, making up about 90% of diabetic cases. T2DM is more common in more developed countries, probably because of more sedentary lifestyles and a "Western-style" diet there. The exact mechanism for developing this disease is unclear, though it has a high genetic correlation (50%+). An alarming fact in US health today is the increasing obesity across the whole population, including children, and thus earlier onset of T2DM. The third main form, gestational diabetes occurs when pregnant women without a previous diagnosis of diabetes develop a high blood glucose level. It occurs in about 2%–5% of all pregnancies and may improve or disappear after delivery. It may precede and may be closely related to development of T2DM. (4)

The high blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger) in diabetic patients.

Spotlight on Pregabalin (Lyrica®)

Kamisha Johnson-Davis, PhD, University of Utah

Indications: Pregabalin, marketed by Pfizer under the trade name Lyrica, was FDA-approved in 2004 for the treatment of neuropathic pain associated with diabetic peripheral neuropathy, neuropathic pain associated with herpes zoster (postherpetic neuralgia), and is also indicated for adjunctive therapy for partial onset seizures in adults and fibromyalgia[1]. In addition, studies have shown that the drug is also effective for treating anxiety disorders, spinal cord injury, and has a positive effect on sleep.

Mechanism of Action: Pregabalin is structurally similar to the inhibitory neurotransmittter gamma-aminobutyric acid (GABA), yet it does not bind to $GABA_A$ or $GABA_B$ receptors. The mechanism of action is not fully illucidated; however, it is known to bind to the $alpha_2$delta subunits of the calcium channels on nerves and functions to inhibit the release of excitatory neurotransmitters by reducing calcium influx and depolarization[2]. Ultimately, for the indication for pain, the drug reduces pain signals to the brain.

Pharmacokinetics[1]

Absorption	Rapid (empty stomach)
Oral Bioavailability	$\geq$ 90%
Peak plasma concentrations	0.7 – 1.5 h
Half-life ($T_{1/2}$ - plasma)	4.6 – 6.8 h
Volume of Distribution (Vd)	0.5-0.6 L/kg
Plasma Protein Binding	Minimal
Elimination	Renal – 98% excreted unchanged in urine Elimination proportional to creatinine clearance

"Pregabalin use may cause angioedema, peripheral edema, hypersensitivity reactions, creatinine kinase elevations, decreased platelet count, weight gain, dizziness, somnolence, and blurred vision."

Metabolism: Pregabalin undergoes negligible metabolism in humans, with approximately 98% of the drug unchanged in urine, and a small amount of the major metabolite, N-methyl pregabalin, present at 0.9%.[3]

Adverse effects: Pregabalin use may cause angioedema, peripheral edema, hypersensitivity reactions, creatinine kinase elevations, decreased platelet count, weight gain, dizziness, somnolence, and blurred vision.[1] The drug has a low potential for abuse and is classified as a Schedule V drug. However, if the drug is discontinued abruptly, it may also cause withdrawal effects in patients after long-term use. Withdrawal symptoms include restlessness, insomnia, nausea, headache, diarrhea, and anxiety.[1] Thus, pregabalin should be reduced gradually before discontinuing therapy. The drug is also catagorized as Pregnancy Category C, due to animal studies that have demonstrated tumorigenic and teratogenic potential.[1]

Laboratory testing: There are no immunoassay methods available for analysis. Chromatographic methods (GC/MS, HPLC, LC-MS/MS) are used to quantify pregabalin.

References

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Therapeutic Drug Monitoring in Diabetes Mellitus (continued from page 1)

If untreated, increased blood glucose may cause acute complications which include hypoglycemia, diabetic ketoacidosis, or non-ketotic hyperosmolar coma. Serious long-term complications include macro and micro-vascular damages, leading to cardiovascular disease, chronic renal failure, and diabetic retinopathy (retinal damage). (4) Overall, DM can be a devastating and costly chronic disease; the National Diabetes Information Clearinghouse estimates diabetes costs $132 billion in the United States alone every year.

Lab Test of Diabetes

Currently, the main lab tests used to diagnose diabetes are (whatever method is used, is applied on two separate days): (4)

- Fasting Blood (Plasma) Glucose (FBS) level ≥ 7.0 mmol/L (126 mg/dL)
- Oral Glucose Tolerance Test (OGTT): Plasma glucose ≥ 11.1 mmol/L (200 mg/dL) two hours after a 75 g oral glucose load
- Glycated hemoglobin (Hb A1c, in whole blood) ≥ 6.5% (5)
- Glycated proteins (or Fructosamine, in serum or plasma) ≥ 270 mmol/L

While FBS has traditionally been the preferred test for screening, FBS levels may be highly variable. Thus, a positive result of two FBS levels, in the absence of unequivocal hyperglycemia, should be confirmed by the OGTT. OGTT, though considered a 'reference test' is difficult and time-consuming. With all this in mind, HbA1c is increasingly becoming the mainstay not only to monitor the disease, but to diagnose diabetes as well. With improvements in automation, precision, and universal standardization, HbA1c tests are highly dependable. Both glucose and HbA1c tests are now available on small Point-Of-Care (patient bedside) instruments. Since the half life of red blood cells is 50-55 days, HbA1c test presents an 'average' condition of hyperglycemia over 3 months. There have been numerous studies linking the HbA1c levels to the severity of disease, and its clinical complications. (4) Successful treatments lower HbA1c levels, and can indicate treatment success and a decrease in disease progression. Fructosamine also gives an average glycemic level for about a month. This test is less used because of lack of universal standardization. New developments in diabetes testing include non-invasive (by IR spectra) or continuous (where the glucose sensing electrode is surgically embedded in blood stream) measurements of blood glucose.

"Increased blood glucose may cause acute complications which include hypoglycemia, diabetic ketoacidosis, or non-ketotic hyperosmolar coma. Serious long-term complications include macro and micro-vascular damages, leading to cardiovascular disease, chronic renal failure, and diabetic retinopathy."

Therapeutic Drug Monitoring (TDM) for Diabetes:

T1DM is caused by the lack of insulin. Originally, pig insulin was mostly used to treat T1DM; currently, however, 'humanized' insulin and insulin analogs are more commonly used. While insulin, a peptide hormone, had to be injected before, modern developments include computerized injection of micro incremental doses (depending on continuous monitoring of blood glucose) and non-injection sprays.

The TDM of insulin may be done by blood glucose monitoring, or by measurements of insulin or C-peptide (which is a side product released in serum, when pro-insulin is cleaved into active insulin) in serum. Immunoassay methods are used to measure serum insulin or C-peptide levels. This can, in fact, allow for distinguishing between T1DM and T2DM as well.

T2DM treatments include (1) agents that increase the amount of insulin secreted by the pancreas (secretagogues), (2) agents that increase the sensitivity of target organs to insulin, and (3) agents that decrease the rate at which glucose is absorbed from the gastrointestinal tract. The effectivity of a treatment is monitored by HbA1c measurements. A single drug, or combinations of drugs that use different physiological pathways are used to treat T2DM. Often the therapy includes titrating up the doses of one drug (since the starting dose of the drug may lose affectivity over time), transitioning to a combination of drug,

TDM in Diabetes Mellitus (continued from page 3)

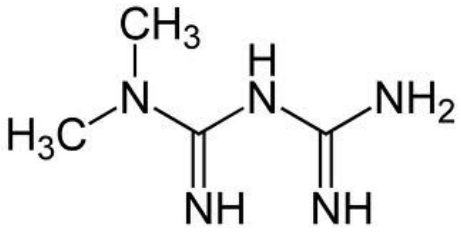
finally, if required, using insulin directly. TDM of these drugs are usually not done directly, but rather via HbA1c measurements.

Drugs for type 2 DM

1. Biguanides, in particular metformin, reduce hepatic glucose output (a process called gluconeogenesis) by up to 1/3, increase insulin sensitivity, and increase uptake of glucose by the periphery, including skeletal muscle. Although, it has a low risk of hypoglycemia, metformin must be used with caution in patients with impaired liver or kidney function (since it is largely renally cleared), due to decreased metformin and lactic acid clearance, which, when combined with the inhibited gluconeogenic process, may result in lactic acid build up – a lactic acidosis that can be dangerous, if not fatal. Still, metformin has become the most commonly used agent for T2DM, because among common diabetic oral drugs, metformin is the one of the few that do not cause weight gain. Typical reduction in HbA1c for metformin is 1.5–2.0%. Among the other biguanides, the earlier drugs, Phenformin and Buformin are now rarely prescribed, in particular for an elevated lactic acidosis risk. (5)

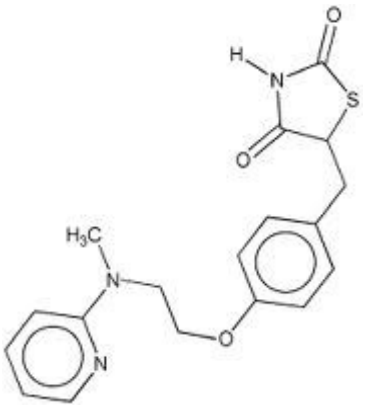
"Metformin has become the most commonly used agent for T2DM. Although, it has a low risk of hypoglycemia, metformin must be used with caution in patients with impaired liver or kidney function."

Metformin is usually the first-line medication used for treatment of T2DM. There is an immediate release as well as an extended-release formulation, typically reserved for patients experiencing GI side-effects that can occur with metformin administration. It is also available in combination with other oral diabetic medications.



Metformin

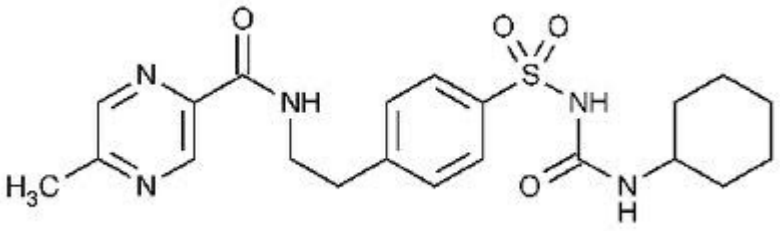
2. Thiazolidinediones, also known as "glitazones," reduce insulin resistance by binding to PPAR-γ, a type of nuclear regulatory protein involved in transcription of genes regulating glucose and fat metabolism. These PPARs act on peroxysome proliferator responsive elements (PPRE). The PPREs influence insulin-sensitive genes, which enhance production of mRNAs of insulin-dependent enzymes. The final result is better use of glucose by the cells. Typical reductions in HbA1c values are 0.5–1.0%. Some examples of this class of drugs are rosiglitazone (Avandia), pioglitazone (Actos), and troglitazone (Rezulin). Elevated cardiovascular risks have been reported with this group of drugs, particularly in heart failure, due to their association with fluid retention. Hepatotoxicity has also been reported, warranting liver function test monitoring. In fact, Troglitazone, used in 1990s, has been withdrawn due to hepatitis and liver damage risk. (6)



Rosiglitazone

TDM in Diabetes Mellitus (continued from page 4)

3. Sulfonylureas are *insulin secretagogues*, triggering insulin release by inhibiting the K_{ATP} channel of the pancreatic beta cells. The 'second-generation' agents of this family are most commonly used; examples include: glipizide (Glucotrol), glyburide or glibenclamide (Diabeta, Micronase, Glynase), glimepiride (Amaryl), and gliclazide (Diamicron). Though these drugs typically reduce HbA1c by 1-2%, their main side effects are weight gain and potential hypopglycemia. The weight gain can potentially be attributed to the long half life of the drugs, which can induce patients to consume food more readily. A 2012 study found sulfonylureas raise the risk of death compared with metformin, which has a much lower risk of hypoglycemia than sulfonylureas. Sulfonylureas bind strongly to plasma proteins. Sulfonylureas are useful only in Type II diabetes, as they work by stimulating endogenous release of insulin. They work best with patients over 40 years old who have had T2DM for under ten years. They can be safely used with metformin or glitazones. The primary side-effect is hypoglycemia.



Glipizide

4. Meglitinides help the pancreas produce insulin and are often called "short-acting secretagogues." They act on the same potassium channels as sulfonylureas, but at a different binding site. By closing the potassium channels of the pancreatic beta cells, they open the calcium channels, thereby enhancing insulin secretion. Typical reductions in HbA1c values are 0.5–1.0%. Examples are: repaglinide (Prandin), nateglinide (Starlix). Adverse reactions include weight gain and hypoglycemia. (7)

5. Alpha-glucosidase inhibitors do not have a direct effect on insulin secretion or sensitivity. They slow the digestion of starch in the small intestine, so that glucose from the starch of a meal enters the bloodstream more slowly, and can be matched more effectively by an impaired insulin response or sensitivity. These agents are effective by themselves only in the earliest stages of impaired glucose tolerance, but can be helpful in combination with other agents in T2DM. Typical reductions in HbA1c values are 0.5–1.0%. Examples are: miglitol (Glyset), acarbose (Precose/Glucobay), voglibose. Severe side-effects (flatulence and bloating) are often observed.(8)

6. Glucagon-like peptide (GLP) agonists/analogues and Dipeptidyl peptidase-4 (DPP-4) inhibitors primarily function in the incretin pathway. GLP-1 agonists bind to a membrane GLP receptor. As a consequence, insulin release from the pancreatic beta cells is increased. Furthermore, GLP-1 analogues can increase sensations of satiety, decreasing food intake. Examples include Exenatide (also Exendin-4, marketed as Byetta) and Liraglutide (long acting GLP-1 analogue; brand name Victoza). Typical reductions in HbA1c values are 0.5–1.0%. (9) DPP4 inhibitors increase blood concentration of the incretin GLP-1 by inhibiting its degradation by dipeptidyl peptidase-4. They, however, have a much shorter action than the GLP-1 analogues. Examples are: sitagliptin (Januvia), vildagliptin (Galvus), saxagliptin (Onglyza) and linagliptin (Tradjenta). This class of drugs typically lower HbA1c values by 0.74%. (9)

"Sulfonylureas are insulin secretagogues, triggering insulin *release by inhibiting the K_{ATP} channel of the pancreatic beta cells. "*

TDM in Diabetes Mellitus (continued from page 5)

In summary, type 2 DM is growing globally at a high rate, together with urbanization. Many classes of drugs exist to manage the disease, most of which are monitored by HbA1c. Insulin is always the final drug that is used. It can be used effectively, when patients can learn to administer the hormone depending on the glycemic condition. However, excess insulin levels may cause severe hypoglycemia leading to death, and so careful monitoring (mostly by measurements of blood sugar) is needed.

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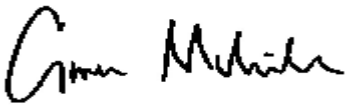
FROM THE HOT SEAT:

Greetings Division Members!

Thank-you to all those that joined us for the lunchtime business meeting at the 2012 annual meeting of the AACC in Los Angeles! It was exciting to see so many of you there!!! We enjoyed a fabulous scientific presentation, delivered by Dr. Matt Krasowski, our 2011 young investigator award winner. We also honored our 2012 award recipients, announced the election results, reviewed the Division activities and accomplishments over the past year, and discussed our plans for the coming year. For those of you who could not attend our lunch meeting, look for minutes to be posted on the Division website. Please contact me directly with questions or comments, and plan to attend the lunchtime meeting that we will host in 2013!

As you might expect, the Division has supported submission of several scientific sessions for presentation at the 2013 annual meeting of the AACC in Houston, and it will be exciting to see the program evolve over the next few months. The Division is also supporting the 2013 Congress for the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT), that will be held September 22-26 in Salt Lake City, Utah. See the website for current details about the conference, and check back later in the year, as it will be much more complete near the end of 2012: http://iatdmct.com/ Note also that the deadline for submission of abstracts for posters and platform presentations is February 28, 2013. This will be a very good opportunity for us to present our research, and acquire an international perspective on clinical toxicology and therapeutic drug management issues, including pharmacogenetics, novel devices, and trends in drug and non-drug toxicants. I would love to see you all there in Salt Lake City next year!

Sincerely,



"The Congress for the International Association of Therapeutic Drug Monitoring and Clinical Toxicology will be held in Salt Lake City, Utah from Sept. 22-26, 2013."

UPCOMING MEETINGS OF INTEREST

CALIFORNIA ASSOCIATION OF TOXICOLOGISTS (CAT)
Annual Meeting
November 2-3, 2012, Hilton Los Angeles North, Glendale, CA
www.cal-tox.org

AMERICAN COLLEGE OF TOXICOLOGY
Annual Meeting
November 4-7, 2012, Omni Orlando Resort & Spa, ChampionsGate, FL.
www.actox.org

SOCIETY OF TOXICOLOGY (SOT)
Annual Meeting
March 10-14, 2013, Henry B. Gonzalez Convention Center, San Antonio, TX.
www.toxicology.com

MIDWEST ASSOCIATION FOR TOXICOLOGY AND THERAPEUTIC DRUG MONITORING (MATT) Annual Meeting
April 25-26, 2013, Cleveland Clinic, Cleveland, OH
www.midwesttox.org

Please contact Dr. Kamisha Johnson-Davis at kamisha.johnson-davis@aruplab.com if you are interested in joining the editorial board or if you have ideas or article contributions for this newsletter.

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DRUGS IN THE NEWS

Fungal Meningitis Outbreak — The FDA has observed fungal contamination of methylprednisolone acetate from the New England Compounding Center (NECC). There has been an outbreak of meningitis in patients that received the steroid injection.

Recent FDA Approved Drugs

Stivarga (regorafenib)
Treatment for **Colorectal Cancer**

Aubagio (teriflunomide)
Treatment for **Multiple Sclerosis**

Bosulif (bosutinib)
Treatment for **Chronic Myelogenous Leukemia**

Quillivant XR (methylphenidate) —Extended-Release Oral suspension
Treatment for **Attention Deficit Disorder**

Xtandi (enzalutamide)
Treatment for **Prostate Cancer**

Stribild (cobicistat, elvitegravir, emtricitabine and tenofovir)
Treatment for **HIV Infection**