ejpmr, 2022,9(3), 106-111

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

CHRONOPHARMACOLOGY

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Article Received on 30/12/2021 **Article Revised on 20/01/2022** **Article Accepted on 10/02/2022**

ABSTRAC

Most facets of mammalian physiology and behavior vary according to time of day, thanks to endogenous circadian clocks. Therefore, it is not surprising that many aspects of pharmacology and toxicology also oscillate according to the same 24hr clocks. Daily oscillations in abundance of proteins necessary for either drug absorption or metabolism result in circadian pharmacokinetics, and oscillations in the physiological systems targeted by these drugs result in circadian pharmacodynamics. These clocks are present in most cells of the body, organized in a hierarchical fashion. Interestingly, some aspects of physiology and behavior are controlled directly via a "master clock" in the suprachiasmatic nuclei of the hypothalamus, whereas others are controlledBy "slave" oscillators in separate brain regions or body tissues. Recent re-Search shows that these clocks can respond to different cues and thereby show different phase relationships. Therefore, full prediction of Chronopharmacology in pathological contexts will likely require a systems biology approach that considers chronointeractions among different clock-regulated systems.

KEYWORDS: - Circadian rhythms, Drug metabolism, Chronotherapy, Cancer, Peripheral oscillators, Systems, biology.

INTRODUCTION

The pharmacotherapy of human diseases as a Rule is based on the hypothesis of homeostasis, which assumes that the effects of a drug are independent of their administration time during the 24 hr. However, there is a body of evidence accumulated from experimental studies on laboratory animals and investigations on patients and healthy volunteers demonstrating that this hypothesis does not hold true. Evidence against this hypothesis was first presented in 1814 by Virey in his thesis to the medical faculty of the university of Paris.[1] Virey described daily rhythms in human beings and their implications to health, disease and drug treatment. The publication of Virey was thus a cornerstone in The development of chronopharmacology from Chronobiology. The roots of these 'new' branches In science can be traced to the end of the 18th and the beginning of the 19th century. In 1801 and 1802 the 'Offentliche Lehrer der Arzneykunst in Tubingen', Johann Heinrich Ferdinand AutenRieth, described in his Handbuch der empirischen Mmschlichen physiologic that the pulse was slower in the morning than the evening and that daily changes occurred also in body temperature.[2] Similar observations were reported by Wil-Helm in 1806[3] and others. Since those early times, daily, 24-hr or circadian [from the Latin Circa and dies about 24 hr, as introduced by Halberg[4] rhythms have been described for Nearly all physiological functions or parameters In human beings as well as laboratory animals. Life on a rotating planet with a day-night cycle of about 24 hr has evidently subjected organisms to a temporal origination which has allowed successful adaptemporation to cyclic alterations of the environment. During the last two decades, clinical and Experimental research in the fields of chrono-Biology and chronopharmacology has gained Importance for medicine. It is increasingly recognized today that circadian rhythms in physiological functions call for careful reappraisal of traditional diagnostic and therapeutic procedures. Similarly, studies describing administration time dependent differences in the effects And kinetics of most medications strongly suggest that the optimization of drugs can be achieved by careful selection of their timing with regard to the staging of critical biological rhythms. As will be apparent from the examples and discussion given in this paper as well as the other contributions to this special issue, chronopharmacology adds a new dimension to conventionally conceived therapeutic regimens.

Circadium rhythm

Circadium Rhythm and Glucose metabolism

From a chronobiological point, glucose metabolism in humans follow a circadian rhythm through diurnal

variation of glucose tolerance that typically peaks during day light hours, when food consumption usually happens and reduces when it comes to night-dark hours when fasting usually occurs. Several hormones involved in glucose metabolism, such as insulin and cortisol, exhibit circadian oscillation. For example, experiments in rodents have shown the importance of the circadian system in glucose metabolism with changes in insulin sensitivity and insulin secretion patterns inducing highly rhythmic changes, thus affecting blood glucose levels. Therefore, insulin secretion and sensitivity are closely regulated by circadian control and have strong effects on glucose metabolism.

Unusual meal timings can cause glucose intolerance by affecting the phase relationship between the central circadian pacemaker and peripheral oscillators in cells of the liver and pancreas in rodents. Similarly in humans,timed meal intake is also driven by the SCN, play a role in synchronization of circadian rhythms in peripheral tissues, thereby affecting glucose metabolism. The effects of diet on circadian rhythmicity clearly involves a relationship between factors such as meal timings and nutrients (chrononutrition), that can contribute to circadian perturbance and influence the manifestation of metabolic disorders such as type 2 diabetes.

Diabetes managementmanagement

The term diabetes includes several different metabolic disorders that all, if left untreated, result in abnormally high concentration of a sugar called glucose in the blood. Diabetes mellitus type 1 results when the pancreas no longer produces significant amounts of the hormone insulin, usually owing to the autoimmune destruction of the insulin-producing beta cells of the pancreas. Diabetes mellitus type 2, in contrast, is now thought to result from autoimmune attacks on the pancreas and/or insulin resistance. The pancreas of a person with type 2 diabetes may be producing normal or even abnormally large amounts of insulin. Other forms of diabetes mellitus, such as the various forms of maturity onset diabetes of the young, may represent some combination of insufficient insulin production and insulin resistance. Some degree of insulin resistance may also be present in a person with type 1 diabetes.

The main goal of diabetes management and control is, as far as possible, to restore carbohydrate metabolism to a normal state. To achieve this goal, individuals with an absolute deficiency of insulin require insulin replacement therapy, which is given through injections or an insulin pump. Insulin resistance, in contrast, can be corrected by dietary modifications and exercise. Other goals of diabetes management are to prevent or treat the many complications that can result from the disease itself and from its treatment.

Diet

Because high blood sugar caused by poorly controlled diabetes can lead to a plethora of immediate and long-term complications, it is critical to maintain blood sugars as close to normal as possible, and a diet that produces more controllable glycemic variability is an important factor in producing normal blood sugars.

People with type 1 diabetes who use insulin can eat whatever they want, preferably a healthy diet with some carbohydrate content; in the long term it is helpful to eat a consistent amount of carbohydrate to make blood sugar management easier.

There is a lack of evidence of the usefulness of low-carbohydrate dieting for people with type 1 diabetes. Although for certain individuals it may be feasible to follow a low-carbohydrate regime combined with carefully managed insulin dosing, this is hard to maintain and there are concerns about potential adverse health effects caused by the diet.In general people with type 1 diabetes are advised to follow an individualized eating plan.

Medications

Currently, one goal for diabetics is to avoid or minimize chronic diabetic complications, as well as to avoid acute problems of hyperglycemia or hypoglycemia. Adequate control of diabetes leads to lower risk of complications associated with unmonitored diabetes including kidney failure (requiring dialysis or transplant), blindness, heart disease and limb amputation. The most prevalent form of medication is hypoglycemic treatment through either oral hypoglycemics and/or insulin therapy. There is emerging evidence that full-blown diabetes mellitus type 2 can be evaded in those with only mildly impaired glucose tolerance.

Patients with type 1 diabetes mellitus require direct injection of insulin as their bodies cannot produce enough (or even any) insulin. As of 2010, there is no other clinically available form of insulin administration other than injection for patients with type 1: injection can be done by insulin pump, by jet injector, or any of several forms of hypodermic needle. Non-injective methods of insulin administration have been unattainable as the insulin protein breaks down in the digestive tract. There are several insulin application mechanisms under experimental development as of 2004, including a capsule that passes to the liver and delivers insulin into the bloodstream.There have also been proposed vaccines for type I usinglutamic acid decarboxylase (GAD), but these are currently not being tested by the pharmaceutical companies that have sublicensed the patents to them.

For type 2 diabetics, diabetic management consists of a combination of diet, exercise, and weight loss, in any achievable combination depending on the patient. Obesity is very common in type 2 diabetes and

contributes greatly to insulin resistance. Weight reduction and exercise improve tissue sensitivity to insulin and allow its proper use by target tissues. Patients who have poor diabetic control after lifestyle modifications are typically placed on oral hypoglycemics. Some Type 2 diabetics eventually fail to respond to these and must proceed to insulin therapy. A study conducted in 2008 found that increasingly complex and costly diabetes treatments are being applied to an increasing population with type 2 diabetes. Data from 1994 to 2007 was analyzed and it was found that the mean number of diabetes medications per treated patient increased from 1.14 in 1994 to 1.63 in 2007.

Patient education and compliance with treatment is very important in managing the disease. Improper use of medications and insulin can be very dangerous causing hypo or hyperglycemic episodes.

Insulin

For type 1 diabetics, there will always be a need for insulin injections throughout their life, as the pancreatic beta cells of a type 1 diabetic are not capable of producing sufficient insulin. However, both type 1 and type 2 diabetics can see dramatic improvements in blood sugars through modifying their diet, and some type 2 diabetics can fully control the disease by dietary modification.

Insulin therapy requires close monitoring and a great deal of patient education, as improper administration is quite dangerous. For example, when food intake is reduced, less insulin is required. A previously satisfactory dosing may be too much if less food is consumed causing a hypoglycemic reaction if not intelligently adjusted. Exercise decreases insulin requirements as exercise increases glucose uptake by body cells whose glucose uptake is controlled by insulin, and vice versa. In addition, there are several types of insulin with varying times of onset and duration of action.

Several companies are currently working to develop a non-invasive version of insulin, so that injections can be avoided. Mannkind has developed an inhalable version, while companies like Novo Nordisk, Oramed and BioLingus have efforts undergoing for an oral product. Also oral combination products of insulin and a GLP-1 agonist are being developed.

Insulin therapy creates risk because of the inability to continuously know a person's blood glucose level and adjust insulin infusion appropriately. New advances in technology have overcome much of this problem. Small, portable insulin infusion pumps are available from several manufacturers. They allow a continuous infusion of small amounts of insulin to be delivered through the skin around the clock, plus the ability to give bolus doses when a person eats or has elevated blood glucose levels. This is very similar to how the pancreas works, but these pumps lack a continuous "feed-back" mechanism. Thus, the user is still at risk of giving too much or too little insulin unless blood glucose measurements are made.

A further danger of insulin treatment is that while diabetic microangiopathy is usually explained as the result of hyperglycemia, studies in rats indicate that the higher than normal level of insulin diabetics inject to control their hyperglycemia may itself promote small blood vessel disease. While there is no clear evidence that controlling hyperglycemia reduces diabetic macrovascular and cardiovascular disease, there are indications that intensive efforts to normalize blood glucose levels may worsen cardiovascular and cause diabetic mortality.

Dental care

Diabetic patients have greater chances of developing oral health problems such as tooth decay, salivary gland dysfunction, fungal infections, inflammatory skin disease, periodontal disease or taste impairment and thrush of the mouth.The oral problems in persons suffering from diabetes can be prevented with a good control of the blood sugar levels, regular check-ups and a very good oral hygiene. By maintaining a good oral status, diabetic persons prevent losing their teeth as a result of various periodontal conditions.

To prevent further diabetic complications as well as serious oral problems, diabetic persons must keep their blood sugar levels under control and have a proper oral hygiene. A study in the Journal of Periodontology found that poorly controlled type 2 diabetic patients are more likely to develop periodontal disease than well-controlled diabetics.

Dental care is therefore even more important for diabetic patients than for healthy individuals. Maintaining the teeth and gum healthy is done by taking some preventing measures such as regular appointments at a dentist and a very good oral hygiene. Also, oral health problems can be avoided by closely monitoring the blood sugar levels. Patients who keep better under control their blood sugar levels and diabetes are less likely to develop oral health problems when compared to diabetic patients who control their disease moderately or poorly.

Diabetic persons are advised to make morning appointments to the dental care provider must make sure both their physician and dental care provider are informed and aware of their condition, medical history and periodontal status.

Diagnosis

Symptoms of type 1 diabetes often appear suddenly and are often the reason for checking blood sugar levels. Because symptoms of other types of diabetes and prediabetes come on more gradually or may not be evident, the American Diabetes Association (ADA) has recommended screening guidelines. The ADA

recommends that the following people be screened for diabetes.

Anyone with a body mass index higher than 25 (23 for Asian Americans), regardless of age, who has additional risk factors, such as high blood pressure, abnormal cholesterol levels, a sedentary lifestyle, a history of polycystic ovary syndrome or heart disease, and who has a close relative with diabetes.

Anyone older than age 45 is advised to receive an initial blood sugar screening, and then, if the results are normal, to be screened every three years thereafter.Women who have had gestational diabetes are advised to be screened for diabetes every three years. Anyone who has been diagnosed with prediabetes is advised to be tested every year.

Treatment

Depending on what type of diabetes you have, blood sugar monitoring, insulin and oral medications may play a role in your treatment. Eating a healthy diet, maintaining a healthy weight and participating in regular activity also are important factors in managing diabetes.

Treatments for type 1 and type 2 diabetes

Treatment for type 1 diabetes involves insulin injections or the use of an insulin pump, frequent blood sugar checks, and carbohydrate counting. Treatment of type 2 diabetes primarily involves lifestyle changes, monitoring of your blood sugar, along with diabetes medications, insulin or both.

People with type 1 diabetes need insulin therapy to survive. Many people with type 2 diabetes or gestational diabetes also need insulin therapy.

Many types of insulin are available, including short-acting (regular insulin), rapid-acting insulin,long-acting insulin and intermediate options. Depending on your needs, your doctor may prescribe a mixture of insulin types to use throughout the day and night.

Insulin can't be taken orally to lower blood sugar because stomach enzymes interfere with insulin's action. Often insulin is injected using a fine needle and syringe or an insulin pen — a device that looks like a large ink pen.

An insulin pump also may be an option. The pump is a device about the size of a small cellphone worn on the outside of your body. A tube connects the reservoir of insulin to a catheter that's inserted under the skin of your abdomen.

A tubeless pump that works wirelessly is also now available. You program an insulin pump to dispense specific amounts of insulin. It can be adjusted to deliver more or less insulin depending on meals, activity level and blood sugar level.

In September 2016, the Food and Drug Administration approved the first artificial pancreas for people with type 1 diabetes who are age 14 and older. A second artificial pancreas was approved in December 2019. Since then systems have been approved for children older than 2 years old.

An artificial pancreas is also called closed-loop insulin delivery. The implanted device links a continuous glucose monitor, which checks blood sugar levels every five minutes, to an insulin pump. The device automatically delivers the correct amount of insulin when the monitor indicates it's needed.

There are more artificial pancreas (closed loop) systems currently in clinical trials.

Monitoring your blood sugar. Depending on your treatment plan, you may check and record your blood sugar as many as four times a day or more often if you're taking insulin. Careful monitoring is the only way to make sure that your blood sugar level remains within your target range. People with type 2 diabetes who aren't taking insulin generally check their blood sugar much less frequently.

People who receive insulin therapy also may choose to monitor their blood sugar levels with a continuous glucose monitor. Although this technology hasn't yet completely replaced the glucose meter, it can significantly reduce the number of fingersticks necessary to check blood sugar and provide important information about trends in blood sugar levels.

Even with careful management, blood sugar levels can sometimes change unpredictably. With help from your diabetes treatment team, you'll learn how your blood sugar level changes in response to food, physical activity, medications, illness, alcohol, stress — and for women, fluctuations in hormone levels.

In addition to daily blood sugar monitoring, your doctor will likely recommend regular A1C testing to measure your average blood sugar level for the past two to three months.

Compared with repeated daily blood sugar tests, A1C testing better indicates how well your diabetes treatment plan is working overall. An elevated A1C level may signal the need for a change in your oral medication, insulin regimen or meal plan.

Your target A1C goal may vary depending on your age and various other factors, such as other medical conditions you may have. However, for most people with diabetes, the American Diabetes Association recommends an A1C of below 7%.

Transplantation. In some people who have type 1 diabetes, a pancreas transplant may be an option. Islet

transplants are being studied as well. With a successful pancreas transplant, you would no longer need insulin therapy.

But transplants aren't always successful — and these procedures pose serious risks. You need a lifetime of immune-suppressing drugs to prevent organ rejection. These drugs can have serious side effects, which is why transplants are usually reserved for people whose diabetes can't be controlled or those who also need a kidney transplant.

Treatment for prediabetes

If you have prediabetes, healthy lifestyle choices can help you bring your blood sugar level back to normal or at least keep it from rising toward the levels seen in type 2 diabetes. Maintaining a healthy weight through exercise and healthy eating can help. Exercising at least 150 minutes a week and losing about 7% of your body weight may prevent or delay type 2 diabetes.

Sometimes medications — Such as metformin (Glucophage, Glumetza, others) — also are an option if you're at high risk of diabetes, including when your prediabetes is worsening or if you have cardiovascular disease, fatty liver disease or polycystic ovary syndrome.

In other cases, medications to control cholesterol — Statins, in particular — and high blood pressure medications are needed. Your doctor might prescribe low-dose aspirin therapy to help prevent cardiovascular disease if you're at high risk. However, healthy lifestyle choices remain key.

Symptoms

Diabetes symptoms vary depending on how much your blood sugar is elevated. Some people, especially those with prediabetes or type 2 diabetes, may sometimes not experience symptoms. In type 1 diabetes, symptoms tend to come on quickly and be more severe. Some of the signs and symptoms of type 1 diabetes and type 2 diabetes are:

Increased thirst
Frequent urination
Extreme hunger
Unexplained weight loss
Presence of ketones in the urine (Ketones are a byproduct of the breakdown of muscle and fat that happens when there's not enough available insulin)
Fatigue
Irritability
Blurred vision
Slow-healing sores
Frequent infections, such as gums or skin infections and vaginal infections
Type 1 diabetes can develop at any age, though it often appears during childhood or adolescence.

Type 2 diabetes, the more common type, can develop at any age, though it's more common in people older than 40.

Risk factor

Risk factors for diabetes depend on the type of diabetes
Risk factors for type 1 diabetes

1. Family history
2. Your risk increases if a parent or sibling has type 1 diabetes.
3. Environmental factors : Circumstances such as exposure to a viral illness likely play some role in type 1 diabetes.
4. The presence of damaging immune system cells (autoantibodies)
5. Sometimes family members of people with type 1 diabetes are tested for the presence of diabetes autoantibodies. If you have these autoantibodies, you have an increased risk of developing type 1 diabetes. But not everyone who has these autoantibodies develops diabetes.

Geography

Certain countries, such as Finland and Sweden, have higher rates of type 1 diabetes.
Risk factors for prediabetes and type 2 diabetes
Researchers don't fully understand why some people develop prediabetes and type 2 diabetes and others don't. It's clear that certain factors increase the risk, however, including:

1. **Weight:** The more fatty tissue you have, the more resistant your cells become to insulin.
2. **Inactivity:** The less active you are, the greater your risk. Physical activity helps you control your weight, uses up glucose as energy and makes your cells more sensitive to insulin.
3. **Family history:** Your risk increases if a parent or sibling has type 2 diabetes.
4. **Age:** Your risk increases as you get older. This may be because you tend to exercise less, lose muscle mass and gain weight as you age. But type 2 diabetes is also increasing among children, adolescents and younger adults.
5. **High blood pressure:** Having blood pressure over 140/90 millimeters of mercury (mm Hg) is linked to an increased risk of type 2 diabetes.

Prevention

Type 1 diabetes can't be prevented. However, the same healthy lifestyle choices that help treat prediabetes, type 2 diabetes and can also help prevent them:
Eat healthy foods
Choose foods lower in fat and calories and higher in fiber. Focus on fruits, vegetables and whole grains. Strive for variety to prevent boredom.
Get more physical activity
Aim for about 30 minutes of moderate aerobic activity on most days of the week, or at least 150 minutes of moderate aerobic activity a week.
Lose excess pounds

If you're overweight, losing even 7% of your body weight — for example, 14 pounds (6.4 kilograms) if you weigh 200 pounds (90.7 kilograms) — can reduce the risk of diabetes.

Don't try to lose weight during pregnancy, however. Talk to your doctor about how much weight is healthy for you to gain during pregnancy.

To keep your weight in a healthy range, focus on permanent changes to your eating and exercise habits. Motivate yourself by remembering the benefits of losing weight, such as a healthier heart, more energy and improved self-esteem.

Sometimes medication is an option as well. Oral diabetes drugs such as metformin (Glumetza, Fortamet, others) may reduce the risk of type 2 diabetes — but healthy lifestyle choices remain essential. Have your blood sugar checked at least once a year to check that you haven't developed type 2 diabetes.

CONCLUSION

Chronopharmacology is the study of how the effects of drugs vary with biological timing and endogenous periodicities. The goal is to improve our understanding of periodic and thus predictable (eg circadian) changes in both desired effects (Chrono effectiveness) and tolerance (Chrono tolerance) of medications. In the management of diabetes, the target is to maintain the patient in normoglycemia. Chronopharmacological aspects are highly relevant in the management of diabetes mellitus since time of day, patient activities and timing of medication may impact on the risk of occurrence of peaks and troughs in blood glucose levels. It is well known that shift workers have increased diabetes and obesity, worse glucose control, and higher rates of cardiovascular disease and mortality.

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