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Drugs and Hypoglycemia

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1. Introduction

Manifested hypoglycemia is relatively frequent cause of out-patient office visit at general practitioner, diabetologist and in severe cases represents emergent situation requiring transport to hospital and hospitalization. Severe and untreated hypoglycemia can even lead to death. The aetiology of hypoglycemia is variable, and includes drugs, insulinoma, liver failure, renal failure, hormonal deficiencies, alcohol abuse and reactive hypoglycemia. The medication history is an integral part in the evaluation of a patient with hypoglycemia. A variety of medications have been associated with hypoglycemia, and the list of these medications is expanding (Comi, 1993). The common causes of acute hypoglycemia are related to therapy for diabetes mellitus – insulin and its analogues or oral antidiabetic drugs (OAD). Determining the aetiology of hypoglycemia poses little difficulty in patients known to be taking parenteral or oral hypoglycaemic agents. Severe hypoglycemia, associated with coma or requiring assistance of another person for reversal occurs at least once a year in 10% of patients treated with insulin, with a mortality of 2-4%. There is difficulty assessing the absolute rates but the frequency of iatrogenic hypoglycemia is substantially lower in type 2 than in type 1 diabetes. Thus, the rates of severe hypoglycemia in type 2 diabetes are approximately 10% of those in type 1 diabetes even during aggressive insulin therapy (Marks, 1981).

Episodes of hypoglycemia may occur also in patients without diabetes mellitus, insulin or OAD therapy. In these patients, hypoglycemia absents often among diagnostic concerns what might worsen subsequently their prognosis. It is necessary to consider the possibility of drug induced hypoglycemia after excluding its organic aetiology (endocrinopathies, malnutrition, cancer etc.). There are various groups of drugs with provable hypoglycemic effects that may potentiate diabetes mellitus treatment or lead to hypoglycemia in nondiabetic patients as well (Table 1). Some prospective studies carried out in last decade

• Insulin and its analogues	• Trimetoprim/sulfametoxazol
• Sulfonylurea derivates	• Tetracyclins
• Betablockers	• Disopyramide
• Salicylates	• Pentamidine
• Chinine and chinidine	• Ethanol

Table 1. The most common drugs with hypoglycemic effects

find that hypoglycemia is present in 12% patients with beta-blocker poisoning and in 30.9% patients with salicylate poisoning. Among drug-induced hypoglycemias in non-diabetic subjects, alcohol represents the most frequent cause, followed by beta-blockers, and salicylates (Guettier & Gorden, 2006).

2. Most common drugs leading to hypoglycemia

2.1 Insulin and its analogues

Insulin is a hormone central to regulating carbohydrate and fat metabolism in the body. Insulin causes cells in the liver, muscle, and fat tissue to take up glucose from the blood, storing it as glycogen in the liver and muscle. cells. Insulin also influences other body functions, such as vascular compliance and cognition. Once insulin enters the human brain, it enhances learning and memory and benefits verbal memory in particular. Enhancing brain insulin signalling by means of intranasal insulin administration also enhances the acute thermoregulatory and glucoregulatory response to food intake, suggesting central nervous insulin contributes to the control of whole-body energy homeostasis in humans. Insulin is a peptide hormone composed of 51 amino acids and has a molecular weight of 5808 Da (Fig. 1). It is produced in the islets of Langerhans in the pancreas (Chang et al., 1997).

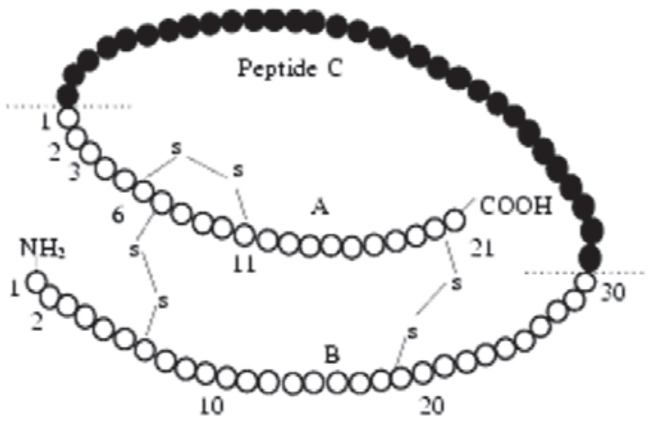

Fig. 1. Pro-insuline with C-peptide.

Insulin replacement therapy has witnessed several major developments since its inception in the early 20th century, allowing for treatment approaches that seek to mimic normal insulin physiology and achieve tight glycemic control. Hypoglycemia can hinder these efforts as the glycemic control trials in both type 1 and type 2 diabetes have shown (UK Hypoglycaemia Study Group, 2007).

The data on the frequency of hypoglycemia in diabetic subjects is uncertain. Depending on the severity of the hypoglycemic event, hypoglycemia is defined as asymptomatic, mild or severe. While there is much more information on the frequency of severe hypoglycemia, little is known on the real frequency of asymptomatic and mild hypoglycemia. (MacLeod et al., 1993)

Insulin resistance with hyperinsulinemia is a prominent feature in the early stages of the disease. Thus, type 2 diabetics benefit from measures to improve insulin sensitivity, such as caloric restriction, exercise and weight management, early in their disease. With progression

of type 2 diabetes, there is ultimately a progressive loss of pancreatic b-cell function and endogenous insulin secretion. At this stage, most patients require exogenous insulin therapy to achieve optimal glucose control (Abraira et al, 1995).

A relative or absolute excess in insulin mainly occurs in excessive dose of insulin or when an incorrect dose is given at the wrong time. Hypoglycemia also occurs during prolonged fasting, after exercise, in renal or liver failure. The risk of severe hypoglycemia in insulin-requiring patients with type 2 diabetes has consistently been reported to be significantly reduced compared with the risk in type 1 diabetic patients undergoing intensive insulin therapy. The lower incidence of severe hypoglycemia in type 2 diabetes may result from insulin resistance. In the randomized Diabetes Control and Complications Trial (DCCT), hypoglycemia occurred approximately once per week in the standard insulin treatment group (under 3 doses of insulin daily) and approximately twice per week in the intensive treatment group (3 and more doses of insulin daily). Most patients with type 1 diabetes lose their ability to secrete glucagon in response to hypoglycemia shortly after developing diabetes, and thus the incremental secretion of epinephrine assumes a primary role in the hormonal response to hypoglycemia in this disease (DCCT Research Group, 1993). Basdevant et al. reported that during a one-year period of observation, 17% of patients with type 1 diabetes mellitus on the intensive insulin treatment had a severe hypoglycemic reaction. Because the ability to secrete epinephrine is also impaired in approximately 25% of patients with longstanding type 1 diabetes mellitus, such patients may manifest the syndrome of "hypoglycemic unawareness", resulting in a tendency to develop frequent, severe and prolonged hypoglycemia (Basdevant et al, 1982).

In the DCCT study 9.8% of subjects in the standard treatment diabetic group had severe hypoglycemia during the 12 months of study. In the same study, subjects the intensive treatment group had a threefold increase in the incidence of serious hypoglycemia compared with those in the standard treatment group. Other authors have also noted an increased risk of hypoglycemia in patients with diabetes controlled very rigidly (DCCT Research Group, 1993).

On the other side, tight glycemic control has been shown to reduce mortality in surgical intensive care patients and in long-term medical intensive care patients. But, the high incidence of hypoglycemia may override the potential beneficial effects of intensive insulin therapy. In the studies by van den Berghe et al., the proportion of patients experiencing severe hypoglycemia in the intensive treatment group was 5.1% in surgical and 18.7% in medical patients, whereas in the conventionally treated group the incidences were 0.8% and 3.1%, respectively (Van den Berghe et al., 2001).

2.2 Sulfonylurea derivates

Sulfonylureas were introduced into medical practice in 1955 for the treatment of diabetes and other conditions, and have been used by both diabetic and nondiabetic subjects.

Sulfonylureas bind to an ATP-dependent K^+ (K^+ATP) channel on the cell membrane of pancreatic beta cells. This inhibits a tonic, hyperpolarizing efflux of potassium, thus causing the electric potential over the membrane to become more positive. This depolarization opens voltage-gated Ca^{2+} channels. The rise in intracellular Ca^{2+} leads to increased fusion of insulin granulae with the cell membrane, and therefore increased secretion of pro-insulin. The structure of sulfonlyureas is on the fig. 2.

Fig. 2. Structure of the sulfonylureas

Sulfonylureas also sensitize β-cells to glucose, and hey limit glucose production in the liver,, they decrease lipolysis,, and decrease clearance of insulin by the liver. Sulfonylureas produce hypoglycemia by releasing preformed insulin from b-cells by a direct action, and possiblyby sensitizing them to the action of certain endogenous insulinotrophs such as leucine (Kunte H et al, 2007).

The sulfonylureas resemble one another more than they differ, and the greatest differences are found in their blood glucose-lowering potencies and in the way in which they are eliminated from the body . The hypoglycemic potency of an individual agent is a function of the biological half-life of the drug itself and its active metabolites.

Sulfonylureas, as opposed to metformin, the thiazolidinediones, exenatide, symlin and other newer treatment agents may induce hypoglycemia as a result of excesses in insulin production and release. This typically occurs if the dose is too high, and the patient is fasting. Some people attempt to change eating habits to prevent this, however it can be counter productive. Like insulin, sulfonylureas can induce weight gain, mainly as a result of their effect to increase insulin levels.

Sulfonylureas are potentially teratogenic and cannot be used in pregnancy or in woman who may become pregnant. Impairment of liver or kidney function increases the risk of hypoglycemia, and are contraindications for the use of sulfonylureas (Campbell, 1985).

Second-generation sulfonylureas have increased potency by weight, compared to first-generation sulfonylureas. All sulfonylureas carry an FDA-required warning about increased risk of cardiovascular death. The ADVANCE trial (Action in Diabetes and Vascular Disease), found no benefit from tight control with gliclazide for the outcomes of heart attack (myocardial infarction), cardiovascular death, or all-cause death (Patel et al, 2005).

Similarly, ACCORD (Action to Control Cardiovascular Risk in Diabetes) and the VADT (Veterans Affairs Diabetes Trial) studies showed no reduction in heart attack or death in patients assigned to tight glucose control with various drugs (Gerstein et al., 2007; Reaven et al., 2004).

Various sulfonylureas have different pharmacokinetics. The choice depends on the propensity of the patient to develop hypoglycemia. Long-acting sulfonylureas with active metabolites can induce prolonged hypoglycemia. The shorter-acting agents may not control blood sugar levels adequately, but the hypoglycemia does not last so long.

Due to varying half-life, some drugs have to be taken twice or three times a day rather than once. The short-acting agents may have to be taken about 30 minutes before the meal, to ascertain maximum efficacy when the food leads to increased blood glucose levels.

Some sulfonylureas are metabolised by liver metabolic enzymes and inducers of this enzyme system (e.g rifampicin) can therefore increase the clearance of sulfonylureas. In addition, because some sulfonylureas are bound to plasma proteins, use of drugs that also

bind to plasma proteins can release the sulfonylureas from their binding places, leading to increased clearance.
Mild sulfonylurea-induced hypoglycemia produces only few symptoms and mostly they are of a subacute neuroglycopenic variety. Although mild hypoglycemia causes unpleasant symptoms and disrupts patients daily activities, severe hypoglycemia can result in coma, seizures and death (Herbel & Boyle, 2000)
Hypoglycemia due to ingestion of sulfonylures has been documented as a accidental ingestion and also when ingested in a suicide attempt leading to death. Sulfonylurea compounds have also been reported to cause severe hypoglycemia when prescribed simultaneously with either a second blood glucose-lowering agent or a nonhypoglycemic drug that prolongs the activity of the sulfonylurea. The different drugs which were involved include phenformin or buformin, salicylate, alcohol, phenylbutazone, sulfadimidine or sulfamethoxazole for urinary tract infection (Bandyopadhyay, 2004).

2.3 β-blockers

Beta blockers block the action of endogenous catecholamines (adrenaline and noradrenaline) on β-adrenergic receptors. There are three known types of beta receptor, designated β1, β2 and β3 receptors. β1-adrenergic receptors are located mainly in the heart and in the kidneys. β2-adrenergic receptors are located mainly in the lungs, gastrointestinal tract, liver, uterus, vascular smooth muscle, and skeletal muscle. β3-adrenergic receptors are located in fat cells. Stimulation of β2 receptors induces smooth muscle relaxation induces tremor in skeletal muscle, and increases glycogenolysis in the liver and skeletal muscle. Stimulation of β3 receptors induces lipolysis.
Spontaneous hypoglycemia may occur in diabetic and nondiabetic patients receiving β-adrenoceptor antagonists. This complication of treatment with β-blockers was first described by Kotler et al. in 1966. Mechanism of β-blocker-induced hypoglycemia includes inhibition of hepatic gluconeogenesis, which is normally potentiated by the sympathetic nervous system. Reduction of lipolysis with decreased plasma concentrations of nonesterified fatty acid increase β-blockers the glucose uptake of skeletal muscles. Non-selective β-blockers, which are currently used only in a limited way, may intensify hypoglycemia-induced hypoglycemic therapy or delay and suppress clinical manifestations of hypoglycemia (tachycardia, tremor) (Abramson et al, 1965). Sweating as a symptom of hypoglycemia remains preserved even when taking β-blockers, therefore, attention or this symtome should be given in the absence of other symptoms of hypoglycemia and neuroglycopenia. In addition, β-adrenergic antagonists block the effect of adrenaline as a counter-regulatory mechanism, resulting in a reduction in glycogenolysis. However, cases of severe hypoglycemia were also described with the use of therapeutic doses of cardioselective beta-blockers (Miller et al., 2001).
At risk of hypoglycemia are particularly insulin-dependent diabetics, but severe hypoglycemia while taking β-blockers have been described as well in non-diabetic hemodialysated patients during dialysis (Murata et al., 1981). The literature has described the emergence of severe hypoglycemia in the treatment of glaucoma with eye drops containing timolol in patients with diabetes mellitus type 1 (Angelo-Nielsen, 1980).

2.4 ACE inhibitors

Angiotensin converting enzyme inhibitors (ACEI) are potent antihypertensive agents with multiple pleiotropic effects, which are used for the treatment of hypertension, heart failure

or in patients after myocardial infarction. ACE inhibitors block the conversion of angiotensin I to angiotensin II. Under normal conditions, angiotensin II will have the following effects:

- vasoconstriction, which lead hypertension
- constriction of the efferent arterioles of the kidney, leading to increased perfusion pressure in the glomeruli
- contribute to ventricular remodeling and ventricular hypertrophy of the heart
- stimulation of the adrenal cortex to release aldosterone, with sodium retention.
- stimulation of the posterior pituitary to release vasopressin (anti-diuretic hormone - ADH), which acts on the kidneys to increase water retention.
- decrease renal protein kinase C (Acharya et al, 2003)

With ACE inhibitor use, the effects of angiotensin II are prevented.

Unlike other groups of drugs they have a relatively low incidence of adverse effects. Hypertension, chronic heart failure and coronary heart disease in diabetics are very frequent co morbidities and ACEI are due they indifferent effect on the metabolism of glucose and lipids and proven renoprotective effect in these patients the drugs of first choice. The association between use of ACE inhibitors and episodes of hypoglycemia in patients with diabetes mellitus is controversial. Were the cases illustrated the need to reduce doses of insulin or oral hypoglycemic agents failure after initiation of ACEI therapy and few cases of ACEI-associated hypoglycemia, although it has been reported particularly in patients with the presence of severe co-morbidities - heart failure, chronic kidney disease and the like (Herings et al., 1995)

Possible mechanism of the hypoglycemic effect of ACEI is not yet well understood, may involve increased insulin sensitivity of peripheral tissues, blocking of angiotensiogen II as one of the counter-regulatory hormones with similar effects as adrenaline, speeding up absorption of subcutaneous insulin etc. (Buchanan et al., 1993).

Nevertheless, it appears that some episodes of hypoglycemia associated with ACEI use were the result of potentiation of hypoglycemic effects of other drugs and ACE inhibitors remain a safe choice for treatment of patients with diabetes mellitus (Seghieri et al., 1992).

2.5 Salicylates

Salicylic acid is a monohydroxybenzoic acid, a type of phenolic acid and a beta hydroxy acid. It is derived from the metabolism of salicin. This colorless crystalline organic acid is widely used in organic synthesis and functions as a plant hormone. The salts and esters of salicylic acid are known as salicylates.

Salicylates in the past short period of use as hypoglycemic drugs, but to achieve the hypoglycemic effect, administration of high doses was necessary, which had many adverse effects (Baron, 1982). Since diabetics are at increased incidence of coronary heart disease, myocardial infarction or cerebrovascular diseases, today we meet with frequent use of antiplatelet drugs in this population, especially acetylsalicylic acid, which is used in the primary and secondary prevention of cardiovascular events. Symptomatic hypoglycemia was described in many cases of the use of salicylates, especially in young children. Salicylates in therapeutic doses have the hypoglycemic potential similar to some sulphonylurea agent or metformin (Micossi et al, 1978). On the other hand, lotions containing salicylates are used to treat certain skin disorders, and the drug can be absorbed through the skin and has been associated with life-threatening complications. A case of

severe refractory hypoglycemia in a man with terminal kidney disease using a salicylate lotion for treatment of psoriasis has been described in the literature (Raschke et al, 1991). Intentional salicylate overdose usually occurs predominantly in adolescents and young adults. Overdoses in children are usually accidental and in the elderly they occur as therapeutic misadventures. Elderly patients with chronic salicylate overdose tend to present with nonspecific findings such as deterioration of cognition, or self care, pulmonary edema or failure to thrive. Important clinical clues may be tachypnea, hyperpnea and an unexplained positive ion gap metabolic acidosis (Marks & Teale , 1999)

The mechanism of the hypoglycemic effect of salicylates is not precisely known, yet. Possible mechanisms include a reduction of hepatic gluconeogenesis and increase of insulin secretion, increases glucose utilization in peripheral tissues due to disconnection of oxidative phosphorylation or reduction of the concentration of circulating nonesterified fatty acid by suppression of lipolysis. Meanwhile organic acids (pyruvate and lactate) accumulate in the periphery because ATP is no longer being generated through the Krebs cycle, as several of the Krebs cycle enzymes are blocked by excess salicylate. The body becomes increasingly dependent on the less efficient anaerobic energy pathways by way of which more energy is dissipated as heat. This produces fever and increased utilization of glucose. This inhibition of glucose oxidative metabolism is particularly hazardous to the brain because of the inability of neuronal tissue to employ fatty acids. The resulting lipolysis increases production of ketones and organic acids culminating in metabolic acidosis when the body's buffering capacity becomes sufficiently depleted. These metabolic changes eventually lead to renal depletion of fluid and electrolytes, hypoglycemia, hypokalemia and a mixed picture of respiratory and metabolic alkalosis coupled with metabolic acidosis (Rumore & Kim, 2010).

2.6 Paracetamol

Paracetamol (acetaminophen - fig.3) intoxication, most frequently in suicidal intent, may lead to liver necrosis with severe hypoglycemia. Paracetamol toxicity is one of the most common causes of poisoning worldwide. In the United States and the United Kingdom it is the most common cause of acute liver failure (Khashab et al, 2007).

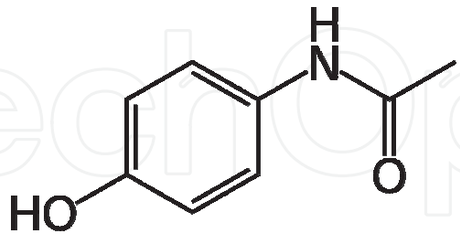

Fig. 3. Structure of the paracetamol (acetaminophen)

Hypoglycemia while taking paracetamol in the usual therapeutic doses has been described in a child, but also had documented hypoglycemia after salicylates. Two case reports of patients with anion gap metabolic lactic acidosis and hypoglycemia were presented in literature. Both patients subsequently died of acute liver failure secondary to paracetamol hepatotoxicity. The development of lactic acidosis with hypoglycemia might have been caused by a deficit in gluconeogenesis secondary to severe hepatic failure and/or a toxic metabolite of paracetamol (Bandyopadhyay, 2004).

2.7 Antibiotics and chemotherapeutics

2.7.1 Trimethoprim-sulfamethoxazole

Trimethoprim-sulfamethoxazole or Co-trimoxazole is a sulfonamide antibiotic combination of trimethoprim and sulfamethoxazole, in the ratio of 1 to 5, used in the treatment of a variety of bacterial infections. The synergy between trimethoprim and sulfamethoxazole was first described in a series of in vitro and in vivo experiments published in the late 1960´s. Trimethoprim and sulfamethoxazole have a greater effect when given together than when given separately, because they inhibit successive steps in the folate synthesis pathway. Sulfamethoxazole acts as a false-substrate inhibitor of dihydropteroate synthetase. Sulfonamides such as sulfamethoxazole are analogues of para-aminobenzoic acid (PABA) and are competitive inhibitors of the dihydropteroate-synthetase, and, thus, inhibiting the production of dihydropteroic acid. Trimethoprim acts by interfering with the action of bacterial dihydrofolate reductase, inhibiting synthesis of tetrahydrofolic acid. Folic acid is an essential precursor in the de novo synthesis of the DNA nucleosides (fig. 4) (Brumfitt & Hamilton-Miller, 1993).

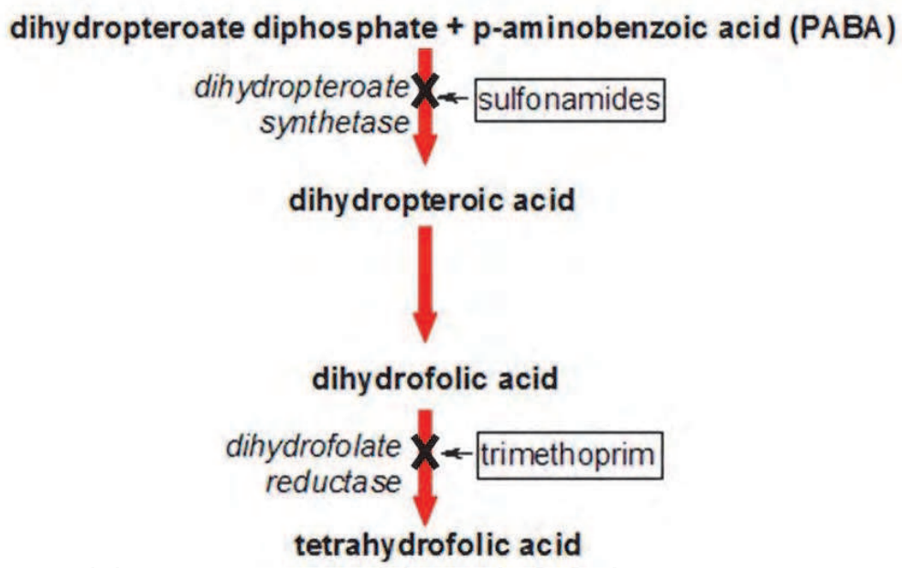

Fig. 4. Mechanism of co-trimoxazole effects

Bacteria are unable to take up folic acid from the infection host and, thus, are dependent on their own synthesis. Inhibition of the enzyme starves the bacteria of two bases (thymidine and uridine) which are necessary for DNA replication and transcription.

Sulfonamide antibiotics may potentiate the hypoglycaemic effect of sulphonylureas, but can also cause hypoglycemia in patients not taking this type of OAD. Several cases of severe and fatal hypoglycemia especially in combination of sulfamethoxazole with older types of sulphonylureas have been described (Hekimsoy et al., 1997). For structural similarity of sulfamethoxazole and sulphonylureas it is assumed to have the similar mechanism of action on pancreatic cell, namely that in the perceptive group of patients there is an increased release of insulin due to the modification of K^+ channel of the β-cells (Mihic et al., 1975). Hyperinsulinemic hypoglycemia associated with trimethoprim-sulfamethoxazole has generally been reported in adults who had renal impairment or in patients with AIDS using

high dose of trimethoprim-sulfamethoxazole. High insulin and C-peptide levels were documented at the time of hypoglycemia (Rosinini et al. 2008).

2.7.2 Ciprofloxacin and other fluoroquinolons

Ciprofloxacin is a synthetic chemotherapeutic antibiotic of the fluoroquinolone drug class. It is a second-generation fluoroquinolone antibacterial. It functions by inhibiting DNA gyrase, a type II topoisomerase, and topoisomerase IV, enzymes necessary to separate bacterial DNA, thereby inhibiting cell division. Thus, it kills bacteria by interfering with the enzymes that cause DNA to rewind after being copied, which stops synthesis of DNA and of proteins (Kawahara, 1998).

Ciprofloxacin is one of the most commonly used fluoroquinolones in clinical practice. Hypoglycemia after its administration has been described only in isolated cases so far, especially in patients concomitantly receiving older types of sulphonylureas. Fluoroquinolones are widely associated with dysglycemias, particularly in diabetic patients receiving hypoglycemic agents. Renal insufficiency has been also implicated to precipitate hypoglycemia after fluoroquinolones combinated with sulfonylureas. The cellular mechanisms by which sulfonylureas and ciprofloxacin interact to produce hypoglycemia are poorly described but likely to be complex and multifactorial. Mechanisms might include interactions at one or more of the P450 isoenzymes or ciprofloxacin-related blockage of ATP-potassium channels that are responsible for insulin control (Roberge et al., 2000). Since the bounding of the ciprofloxacin to plasma proteins is relatively weak, probably it does not interact with OAD at that level. Sulfonylurea-induced hypoglycemia after using of ciprofloxacin can be serious and refractory to traditional therapy. In the report by Roberge et al, the patient developed hypoglycemia after treatment with ciprofloxacin for one week (Roberge et al., 2000). On the other hand, in the case report of Lin et al,, a 68-year-old man with a history of coronary artery disease, atrial fibrillation, and type 2 diabetes on OAD therapy (glyburide) developed significant hypoglycemia after one dose of ciprofloxacin (Lin et al., 2004).

Other fluoroquinolones can also induce severe hypoglycemia, especially in the combination with sulfonylurea derivates. Sporadic published case reports have linked administration of fluoroquinolone antibiotics, in particular gatifloxacin, with early-onset hypoglycemia in patients with diabetes. Most reported patients were aged over 65 years and were concomitantly receiving the sulfonyureas. fluoroquinolones have been demonstrated to augment insulin release in a dose-dependent manner from isolated pancreatic islet cells and to increase insulin levels in patients with type 2 diabetes mellitus. Gatifloxacin therapy is associated with a higher incidence of hypoglycemia than therapy with non-fluoroquinolones in the group of older patients (LeBlanc et al 2004; Baker & Hangii , 2002).

2.7.3 Tetracyclines

Tetracyclines are broad-spectrum polyketide antibiotics. Tetracyclin alone is produced by the Streptomyces genus of Actinobacteria. They are protein synthesis inhibitors. Tetracyclines bind to the 30S subunit of microbial ribosomes. They inhibit protein synthesis by blocking the attachment of charged aminoacyl-tRNA. Thus, they prevent introduction of new amino acids to the nascent peptide chain. The action is usually inhibitory and reversible after withdrawal of the drug (Olson et al., 2006).

The mechanism of tetracyclins-induced hypoglycemia is still not clear. Increased sensitivity to insulin and decreased clearance if insulin were implicated. Miller reported ocytetracyclin-

induced hypoglycemia in a patient with diabetes with initially uncontrolled glycemia because of glandular fever (Miller, 1966). In the case report of Basaria et al., severe hypoglycemia occurred in young non-diabetic man with Marphan´s syndrome with doxycyklin therapy due to acne (Basaria et al, 2002). Moreover, severe hypoglycemia occurred in non-diabetic patient after intrapleural administration of tetracycline, for the purpose of pleurodesis.

2.7.4 Pentamidine

Pentamidine is a biguanide, which was originally used in the treatment of trypanosomiasis. However, in recent decades, it is also often used to treat pneumocystis pneumonia (PCP) caused by Pneumocystis jirovecii (formerly known as Pneumocystis carinii), predominantly in patients with HIV infection. Pentamidine is also used as a prophylactic against PCP in patients receiving chemotherapy, as they also have a depressed immune system as a direct side-effect of the drugs used. Additionally, pentamidine has good clinical activity in treating leishmaniasis, and yeast infections caused by Candida albicans (Nguewa et al.). Hypoglycemia occurs in about 10-40% of patients treated with pentamidine at higher doses and is considered the most common metabolic abnormality associated with this treatment (Waskin et al., 1988). The prevalence of hypoglycemia is more common in patients with AIDS infection than in other patients treated with pentamidine. Hypoglycemic reaction is usually seen after several days from the start of the treatment. However, several cases of hypoglycemia were described after several hours of pentamidine treatment. Episodes of hypoglycemia can be frequent, severe and can lead to irreversible damage of central nervous system (Satler & Waskin, 1987). The mechanism of hypoglycemia includes mainly cytolytic response of pancreatic cells with subsequent release of insulin. Prolonged treatment with pentamidine may lead to destruction of pancreatic cells and the onset of insulin-dependent diabetes mellitus. Hypoglycemia have also been reported after pentamidine aerosol therapy (Hauser et al., 1991).

2.7.5 Quinine and quinidine

Quinine (fig. 5) is a natural white crystalline alkaloid having antipyretic, antimalarial, analgesic and anti-inflammatory properties. Though it has been synthesized in the laboratory, the bark of the cinchona tree is the only known natural source of quinine. Quinine was the first effective treatment for malaria caused by Plasmodium falciparum, appearing in therapeutics in the 17th century. It remained the antimalarial drug of choice until the 1940s, when other drugs replaced it. Since then, many effective antimalarials have been introduced, although quinine is still used to treat the disease in certain critical situations. As of 2006, quinine is no longer recommended by the WHO as first line treatment for malaria and should be used only when artemisinins are not available. It is sometimes also used in the treatment of lupus erythematodes and rheumatoid arthritis (Kaufman & Rúveda, 2005).

Quinine-induced hypoglycemia is dose-dependent and, several fatal cases of hypoglycemia by the treatment of tropical malaria were reported. Quinine sulfate causes hypoglycemia also in nondiabetic patients, particular by increasing insulin release. Quinine is excreted by the kidneys, so the presence of chronic kidney disease increases the risk of quinine-induced hypoglycemia (Harats et al, 1984).

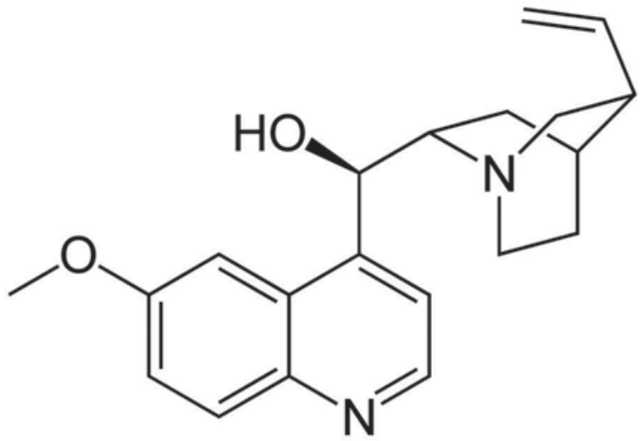

Fig. 5. Structure of quinine

Quinidine is a stereoisomer of quinine, and it acts as a class I antiarrhythmic agent in the heart. Quinidine primarily works by blocking the fast inward sodium influx (I_{Na}). Quinidine's effect on I_{Na} is known as a use dependent block – at higher heart rates, the block increases, while at lower heart rates the block decreases. The effect of blocking the fast inward sodium influx causes decrease of the cardiac action potential in the phase 0 of the heart depolarization (Jones et al., 1986).

2.8 Disopyramide

Disopyramide, group I antiarrhythmic drug, is mainly used for the treatment of ventricular and supraventricular rhythm disturbances. Commonest side effects result from disopyramide's anticholinergic activity. It is also used in ventricular arrhythmia and supraventricular arrhythmia that might follow myocardial infarctions. It has no effect on alpha or beta adrenergic receptors. Disopyramide is an analogue of quinidine and hence has similar effects, that means, it stimulates insulin secretion and may lead to hyperinsulinemic hypoglycemia. It is excreted by the kidneys, therefore older patients and patients with chronic kidney disease using this drug are at risk of hypoglycemic episodes (Cacoub et al., 1989).

2.9 Sertraline

Unlike other groups of antidepressants from the selective serotonin reuptake inhibitors (SSRI) group, sertraline has linear pharmacokinetics, so an increase in dose leads to a proportional increase in its plasma concentrations. Sertraline is primarily used to treat major depression in adult outpatients as well as obsessive–compulsive, panic, and social anxiety disorders in both adults and children. In 2007, it was the most prescribed antidepressant on the U.S. retail market. Hypoglycemia has been described in several cases, mostly in diabetic patients stabilized on long-term treatment of OAD, in which treatment with sertraline was added. The most likely mechanism of potentiating effect of antidiabetic agents is inhibition of cytochrome P-450. Although the mechanism of action of SSRIs is usually thought to involve an increase of the synaptic concentration of serotonin secondary to blockade of its reuptake by nerve terminals, it is also possible that nonneuronal mechanisms contribute. Sertraline treatment may have potentiated hypoglycemia-induced epinephrine secretion by a direct action in the adrenal medulla (Pollak et al., 2001).

2.10 Vacor

Vacor is a rodenticide containing N-3-pyridylmethylurea (PNU), which is chemically related to alloxan and streptozotocin. Vacor is a potent b-cell toxin that initially produces severe hypoglycemia by washing out stored insulin, followed by complete destruction of b-cells and fatal diabetes. Accidental ingestion of Vacor has resulted in severe hypoglycemia. It is suggested that the mechanism of Vacor toxicity involves niacinamide antagonism (Johnson et al, 1980)

2.11 Ethanol

Substance use disorders are a major public health problem facing many countries. The most common substance of abuse/dependence in patients presenting for treatment is alcohol. The World Health Organization (WHO) estimates that there are about 2 milliards people worldwide who consume alcoholic beverages, about 140 million people throughout the world suffer from alcohol dependence, and 76.3 million patients with diagnosable alcohol use disorders. Alcohol causes 1.8 million deaths (3.2% of total) and a loss of 58.3 million (4% of total) of Disability-Adjusted Life Years (DALY). Unintentional injuries alone account for about one third of deaths, while neuropsychiatric conditions account for approximately 40% of the 58.3 million DALYs. Alcohol consumption is the leading risk factor for disease burden in low mortality developing countries and the third largest risk factor in developed countries (White et al., 1993). Generally, the WHO European Region has the highest proportion in the world of total ill health and premature death due to alcohol. At a societal level, the European Union is the heaviest-drinking region in the world, with over one fifth of the European population aged 15 years and above reporting heavy episodic drinking (five or more drinks on an occasion, or 50g alcohol) at least once a week (Fig 6).

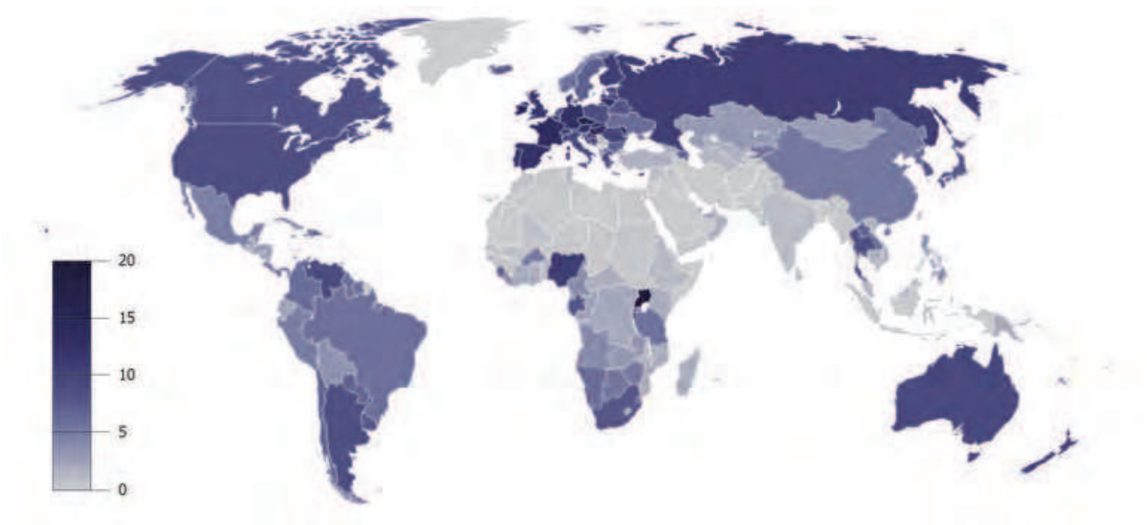

Fig. 6. Alcohol consumption in the world (litres per capita)

Heavy episodic drinking is widespread across all ages and all of Europe, and not only among young people or those from northern Europe. Alcohol consumption has health and social consequences via intoxication (drunkenness), alcohol dependence, and other biochemical effects of alcohol. Overall there is a causal relationship between alcohol consumption and more

than 60 types of disease and injury. Alcohol is estimated to cause about 20–30% of oesophageal cancer, liver cancer, cirrhosis of the liver, homicide, epileptic seizures, and motor vehicle accidents worldwide. The risk of death from a chronic alcohol-related condition is found to increase linearly from zero consumption in a dose–response manner with the volume of alcohol consumed (WHO Global Status Report on Alcohol, 2004).

Although alcoholism is a very common condition, alcohol related hypoglycemia is a relative rare complication of alcohol abuse. In one older clinical study authors proved that alcohol associated hypoglycemia at an emergency department constituted only 0.9% of ethanol detectable cases over 3-month period. On the other hand, only a few hypoglycemic clinical features are exhibited other like coma, and many symptoms and signs of hypoglycemia are identical to those of alcohol intake. Thus, hypoglycemia in these patients could be unrecognised even by first aid or emergency physician. Assessment of plasma glucose is cheap, quick and reproducible and prolongated hypoglycemia may lead to irreversible brain damage or death. Alcohol related hypoglycemia often develops slowly and probably accounts for some deaths of chronic alcohol abusers and drunks who are confined in police cells to sober up overnight. That's why the assessment of plasma glucose level is necessary in chronic abusers admitted to emergencies (Fishbain & Rotundo).

In healthy individuals 2-3 days of fasting are necessary for depletion of hepatic glycogen reserve. Alcohol-related fasting hypoglycemia results from depletion of glycogen storage by starvation, and impairment of gluconeogenesis in liver cells. Thus, in chronically malnutricient patient it could develop within 6-36 hours after ingestion of a moderate to high dose of alcohol. In addition, suppression of counter-regulatory mechanisms (e.g. glucagon, growth hormone or epinephrine secretion) is also contributing to development of hypoglycemia (Chen & Ng, 2003).

Alcohol-related reactive hypoglycemia often occurs after drinking alcohol with some calories rich beverages (gin-tonic, rum-cola). This combination can lead to profound hypoglycemia 3-4 hours afterward, probably due to attenuation of counter-regulatory mechanism. Acute and sustained alcohol use can suppress growth hormone release in response to insulin-induced hypoglycemia. At night, acute and chronic alcohol administration is associated with a 75% reduction in the usual night time sleep-related release of growth hormone (Flanagan et al, 1998).

Many drugs interact with alcohol resulting in undesirable outcomes. There are two types of alcohol-drug interactions: pharmacokinetic and pharmacodynamic. Acute alcohol use increases the risk of severe hypoglycemia in patients with 2. type diabetes mellitus treated with derivates of sulfonylurea. Alcohol may prolong glipizide's effect on blood glucose by delaying glipizide absorption and elimination. In addition, alcohol enhanced glucose-lowering action of insulin Weathermon & Crabb , 1999).

3. Conclusion

The most common cause of medication-induced hypoglycemia is improper management of diabetes. Missing meals, overexertion, and intentional or unintentional overdose of medications used to treat the condition can all cause blood glucose levels to drop.

Cases of hypoglycemia were also described for other pharmaceuticals, but rather of sporadic outbreaks which do not meet very often in clinical practice. It should be noted that any quantitative disturbance of consciousness or sudden change in behavior in patients with diabetes mellitus with far offset the amount of glucose patterns, or an elderly patient with

polypolymorbid possibly with chronic kidney disease may be caused by the effect of hypoglycemic drugs. In the clinical practice, it is necessary to think about this eventuality and carry out blood glucose testing for each suspected hypoglycemia. Acute treatment of dru-induced hypoglycemia is different from the treatment of hypoglycemia from other causes. When relapse hypoglycemia after discontinuation of the suspect drug it is necessary to revise the diagnosis and rule out organic causes of hypoglycemia (endocrinopathy, malignancy, insulinoma, etc.). Table 2 summarised the most common drugs with hypoglycemic effects.

Drug	**Mechanism of Action**	**Clinical Significance**
Alcohol (ethanol)	Impairs gluconeogenesis and increases insulin secretion.	+++
Pentamidine	Cytolytic response in pancreas accompanied by insulin release.	+++
Triazole antifungals	Enhance the effect of sulfonylureas.	+++
Case Series		
β-Adrenergic antagonists	Inhibit glycogenolysis; attenuate signs and symptoms of hypoglycemia.	++
Chloramphenicol	May inhibit metabolism of sulfonylureas.	++
Chloroquine	Unknown (hypoglycemia leading to death has been reported in overdose).	++
Disopyramide	Unknown; appears to result from endogenous insulin secretion.	++
Phenylbutazone	Reduces clearance of sulfonylureas.	++
Salicylates	Increase insulin secretion and sensitivity; may alter pharmacokinetic disposition of sulfonylureas.	++
Case reports		
Anabolic steroids	Decrease glucose tolerance.	+
Angiotensin-converting enzyme inhibitors	May improve insulin sensitivity, particularly in skeletal muscle.	+
Clofibrate	Unknown.	+
Gatifloxacin	Unknown.	+
Monoamine oxidase inhibitors	May increase insulin release and decrease sympathetic response to hypoglycemia.	+
Saquinavir	Unknown.	+
Sulfonamides	Alter clearance of sulfonylureas.	+

Table 2. Most common hypoglycemic pharmaceuticals and their clinical significance.

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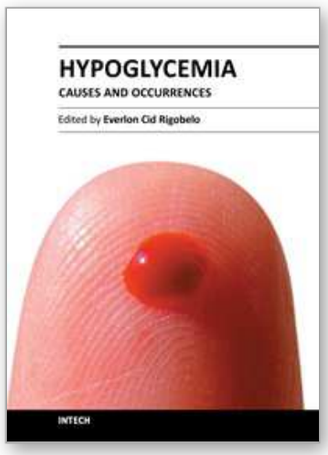

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Glucose is an essential metabolic substrate of all mammalian cells being the major carbohydrate presented to the cell for energy production and also many other anabolic requirements. Hypoglycemia is a disorder where the glucose serum concentration is usually low. The organism usually keeps the glucose serum concentration in a range of 70 to 110 mL/dL of blood. In hypoglycemia the glucose concentration normally remains lower than 50 mL/dL of blood. This book provides an abundance of information for all who need them in order to help many people worldwide.

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