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An Overview of Antipsychotic Drugs Overdose

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Abstract:
Antipsychotics include the 'typical' agents (phenothiazines, thioxanthines, and butyrophenones) as well as the more recently introduced agents referred to as 'atypical' (dibenzodiazepines, diphenylbutylpiperidines and benzamides). There are significant differences between these drugs in their toxicity in overdose. For example, thioridazine has been observed to be more cardiotoxic in overdose than other antipsychotic drugs, whereas clozapine and loxapine are the most likely to cause seizures. Many antipsychotic overdoses will result in mild sedation and no other ill effects. Most patients can be safely discharged 6 hours after the poisoning, but it is critical to recognize the more seriously poisoned patient who will develop cardiotoxicity or seizures. These patients have ECG changes (QRS and/or QT prolongation) and decreased level of consciousness and therefore require intensive care unit admission. Treatment of antipsychotic overdose includes supportive care of the comatose patient, effective gastrointestinal decontamination with activated charcoal, intravenous fluids, and ECG monitoring. Cardiotoxicity in antipsychotic overdose may manifest as ventricular arrhythmia, various degrees of conduction delay, or hypotension. The primary treatment of cardiotoxicity is plasma alkalinization with sodium bicarbonate and hyperventilation. Neurotoxicity is manifest as coma and seizures. Treatment consists of intubation, hyperventilation, and plasma alkalinization.

Keywords: Antipsychotic, Overdose, Toxicity.

Introduction:

The 1950s saw the release of the first generation of antipsychotic drugs. Antipsychotics were mostly prescribed to individuals with severe psychotic illnesses before to the 1990s. such as agitation, confusion in delirium, schizophrenia, Tourette's syndrome, Huntington's illness, acute manic episodes, bipolar disorder or psychotic depression, and transient psychosis [1, 2].

The landscape of antipsychotic treatment was later altered by the more recent atypical antipsychotics, which are thought to be safer than typical antipsychotics and have fewer extrapyramidal adverse effects [3, 4].

One of the top five drugs most commonly implicated in human poisoning is antipsychotic toxicity [5]. According to Rasheed et al. [6], antipsychotic medication poisoning was the second most frequent pharmaceutical drug poisoning affecting the central nervous system that patients brought to the National Poisoning Center's emergency room at Cairo University in Egypt. Furthermore, 13% of all inebriated patients that were seen in the emergency rooms of Assiut University Hospital in 2020 involved antipsychotic medications [7].

Antipsychotic medication classification: Antipsychotic medications can be divided into normal and atypical categories based on their receptor binding characteristics or chemical structure. According to their relative affinities for the dopamine D2 receptor, typical or first-generation antipsychotics are also divided into two potencies: low potency (like thioridazine) and high potency (like haloperidol). Second- and third-generation antipsychotics are examples of atypical antipsychotics (figure 1) [8].

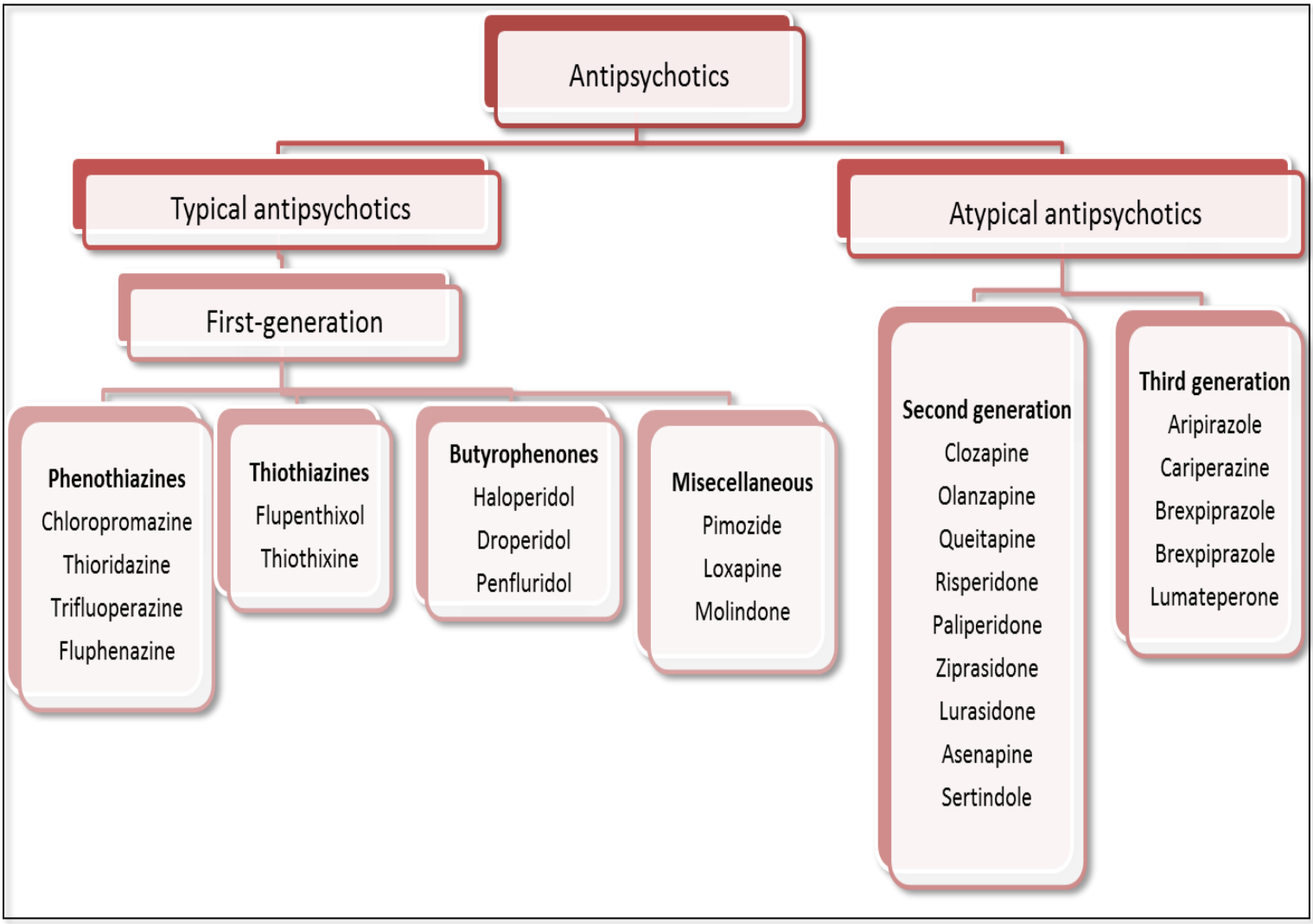

Figure (1): Classification of antipsychotic drugs **[9]**

Pharmacokinetic and toxicokinetic of antipsychotic drugs:

The gastrointestinal tract readily absorbs antipsychotic medications, and plasma peak levels appear one to four hours after intake. Blood level monitoring is ineffective because of their strong lipophilia and broad volume of distribution [1].

The liver is primarily responsible for their metabolism, which includes oxidation, reduction, methylation, and hydroxylation. The existence of cytochrome p450 enzymes, particularly 2D6, 1A3, and 3A4, is necessary for it. Genetic variation in 2D6 metabolism helps explain why some proteins respond differently to slow or fast metabolism. Enzyme inhibitors and inducers may have an impact on them [1]. They are not well eliminated by the kidney. Accordingly, patients with renal insufficiency can safely use them [10].

How antipsychotic medications work:

The activities of typical antipsychotics in the central nervous system are complicated and not fully understood. It is believed that their primary mechanism of action is antagonism of the central dopaminergic receptor (D) type 2. Their antagonistic actions also extend to α1-adrenergic, serotonergic (5-HT), muscarinic (M), and H1-hitaminergic receptors [11].

The effects of atypical antipsychotics on D, 5-HT, H, and M receptors vary. Clozapine and olanzapine bind to serotonin and dopamine receptors (D1–D5). Additionally, they inhibit H1 histamine receptors, M1 receptors, α1, α2 adrenergic receptors, and others [12].

Risperidone has a low affinity for the M1 receptor but a high affinity for the 5-HT, D2 dopamine, α1 adrenergic, and H1 histamine receptors. Quetiapine is a strong antagonist of α1 adrenergic and H1 receptors but a mild antagonist of D2, M1, and 5-HT receptors. Ziprasidone exhibits agonist action at 5-HT 1A receptors but antagonistic activity at D2, α1 adrenergic receptors, and several serotonin receptors (5-HT 2A\1C, 5-HT 1D, and 5-HT 7). Partial D2 agonists include bifeprunex and aripirazole [13].

In the event of an overdose, a number of antipsychotics also block voltage-gated fast sodium channels. Along with blocking the delayed rectifier potassium current, this blockade may also impede cardiac conduction and reduce myocardial contractility. Torsade de pointes is more likely to occur during maintenance therapy and following an overdose if this blockage causes QT prolongation [10].

Side effects of antipsychotic medications:

The majority of antipsychotics cause several side effects through one or two pathways, which may be idiosyncratic or dose-related. Individual vulnerability, which is typically pharmacogenetic and only partially associated with dose, is the cause of idiosyncratic side effects, which can arise during routine therapeutic usage [14]. Table 1 lists side effects that are dose-dependent **[10]**.

Table (1): Adverse effects of antipsychotic drugs

System	Adverse effects
Cardiovascular system	Tachycardia, hypotension (orthostatic or resting), myocardial depression, QRS widening, QT prolongation, Torsade de pointes
Central nervous system	Extrapyramidal syndromes, seizures, central anticholinergic syndrome, somnolence, coma, respiratory center depression, hyperthermia
Endocrine system	Breast tenderness, galactorrhea, amenorrhea,

	oligomenorrhea, or metrorrhagia, weight gain
Dermatological system	Impaired sweat production, cutaneous vasodilatation
Gastrointestinal tract	Dry mouth, impaired peristalsis and constipation
Ophthalmological effects	Mydriasis or miosis, visual blurring
Genitourinary system	Urinary retention, ejaculatory dysfunction, priapism

Clinical presentation of antipsychotic drug overdose:

Antipsychotic medication overdose effects primarily affect the brain and cardiovascular system [15].

Pediatric patients may be more susceptible to symptoms following a single antipsychotic pill due to their small stature and lack of tolerance [16].

a) Signs of cardiovascular disease:

Antipsychotics are known to cause cardiotoxicity and raise the risk of abrupt cardiac arrest and potentially fatal arrhythmias such tachycardia and QT prolongation. They may result in left ventricular failure, cardiomyopathy, and myocarditis [17].

Peripheral vasodilation with reflex tachycardia and the ensuing orthostatic hypotension are frequent due to strong α1-receptor antagonistic effects. Another possible cause of tachycardia is the antagonistic interaction of muscarinic receptors. A prolonged QT interval on an ECG and subsequent Torsade de pointes, also known as polymorphic ventricular tachycardia, can result from antagonistic interactions with the delayed rectifier potassium channel (KIR) [18].

Torsade de pointes is rare when antipsychotic medication is used without a risk factor, such as hypokalemia, multiple drug consumption, or perhaps specific hereditary channelopathies, even though QT prolongation occurs [19]. Following an individual atypical antipsychotic overdose, monomorphic ventricular dysrhythmias are rare [20].

b) Central nervous system manifestation: After an antipsychotic drug overdose, central nervous system depression can appear as sedation, coma, respiratory center depression, and in extreme cases, loss of airway reflexes [21].

The seizure threshold can be lowered by any antipsychotic. Following an overdose, clozapine carries the highest risk of seizures [15, 22]. Furthermore, because of its anticholinergic properties, clozapine, olanzapine, and quetiapine overdoses might result in delirium [23].

Unwanted drug-induced movement abnormalities known as extrapyramidal syndromes cause symptoms that impair and disrupt daily activities and motor skills. First-generation antipsychotics

and other medications that inhibit dopamine D2 receptors are more likely to cause these disorders [24].

They fall into two categories: non-reversible symptoms like tardive dyskinesia and parkinsonism, and reversible syndromes like neuroleptic malignant syndrome, acute dystonia, and acute akathisia. Similarly, these extrapyramidal syndromes are not limited to acute consumption; they can also develop over time as negative effects [25].

A rare, unique, and sometimes fatal side event linked to the recent start or increase in the therapeutic dose of antipsychotic drugs is neuroleptic malignant syndrome (NMS). The following symptoms are suspected: leukocytosis, elevated serum creatinine phosphokinase, tachycardia, lead-pipe muscle rigidity and hypertonicity, gradual onset of pyrexia, autonomic instability, and neuromuscular and central nervous system (CNS) abnormalities [26].

Acute dystonia, a movement disorder marked by prolonged involuntary contractions of a single muscle or muscle group, can appear within a few hours of medication consumption but can also take days or weeks to manifest. Although the limbs may be impacted, the head and neck, especially the tongue and extraocular muscles, are more frequently affected. Common symptoms include torticollis, tongue protrusion, facial grimacing, and oculogyric crises. One uncommon but potentially fatal form is laryngeal dystonia [27].

Unease and a need to move around are hallmarks of akathisia, which typically coexists with anxiety [28]. Similar to idiopathic Parkinson's disease, Parkinsonism is typified by postural instability, akinesia or bradykinesia, and rigidity [29].

Many other symptoms, such as orobuccal, lingual, and masticatory movements, chorea, dystonia, myoclonus, blepharospasms, and tics, are indicative of tardive dyskinesia, which often manifests months to years after starting therapy [30].

Other expressions

Within an hour of acute overdose intake, antipsychotic overdose can cause anticholinergic symptoms such as dry mouth and mucosal surfaces, mydriasis, reduced bowel noises, heated and flushed skin, urine retention, constipation, and agitation. In addition, severe heart blockages, respiratory depression, tachycardia, hypertension, and potentially fatal arrhythmias (such as supraventricular tachycardia) can happen. Sleepiness, sedation, ataxia, amnesia, coma, paranoia, hallucinations, delirium, and confusion are examples of neurological and psychiatric symptoms [31].

Miosis can happen even when anticholinergic toxicity is present because atypical antipsychotic drugs have a higher affinity for α-receptors in the eye than for muscarinic receptors [32].

Management of Antipsychotic Drugs Overdose

Diagnosis of antipsychotic drugs overdose:

Overdosing on antipsychotic medications is mostly diagnosed by appropriate history and physical presentation. Although there are no distinguishing characteristics for overdose, the co-occurrence of CVS symptoms and CNS depression may be indicative of an overdose of antipsychotics. To rule out hypoglycemia in a state of altered mental state, blood sugar should be taken at random. To rule out co-ingestion, levels of salicylate and paracetamol must be measured. X-ray of the chest to rule out aspiration in patients who are unconscious [10].

For the likely extension of the QT interval, a widely recognized surrogate sign for a drug's pro-arrhythmic potential, an ECG must be performed [33].

Handling overdoses of antipsychotic and antidepressant medications:

1. Stabilization of the patient

Supportive care is the cornerstone of treating overdoses caused by antidepressant and antipsychotic medications. Patients who have co-ingestion or massive overdoses may require intubation and ventilation. They are rarely required for single-drug intake, though. Thiamine and dextrose are recommended for patients with changed mental status [32].

2. Cleaning

If the patient is awake and present within an hour of consumption, activated charcoal should be used to decontaminate the gastrointestinal tract; however, if the patient is at risk of aspiration, this procedure should not be performed. The results will not be improved by whole bowel irrigation or orogastric lavage. It is not recommended to use ipecac syrup or induce vomiting [34].

Hemodialysis, hemoperfusion, and forced diuresis are not advised and are unlikely to be helpful due to the high volume of distribution and substantial protein binding of antipsychotic medications [35].

3. Supportive and symptomatic care:

Antipsychotic overdose is mostly treated with supportive care based on the patient's clinical status when there is no specific antidote available [36].

• Management of cardiovascular issues:

Hypotension is treated with a parenteral infusion of 0.9% sodium chloride. Vasopressors will be started if the 0.9% sodium chloride infusion is not successful. Dopamine is not preferred over norepinephrine or phenylephrine as vasopressors [22].

The first line of treatment for ventricular arrhythmia and QT prolongation is sodium bicarbonate (1-2 mEq/kg). It is advised to administer bicarbonate boluses repeatedly in order to achieve a blood pH of roughly 7.5. Because it can function as a sodium channel antagonist, lidocaine is the second-line antiarrhythmic medication [37].

During treatment, hypokalemia must be avoided as it can worsen heart block, lengthen the QT interval, and cause Torsade de Pointes. Torsade de pointes should be treated with magnesium sulfate. Overdrive pacing with isoproterenol or transcutaneous or transvenous pacing may be considered if the patient does not respond to magnesium sulfate; however, this may exacerbate the rate-dependent sodium channel blockage. Unless ischemia is present, anticholinergic-related tachycardia does not require treatment [38].

Alpha-adrenergic receptor-blocking medications, such as phentolamine or phenoxybenzamine, are advised for the treatment of severe hypertension brought on by MAOIs [39].

Patients with substantial overdoses of highly lipophilic medications with a high risk of cardiotoxicity, such as sertin, olanzapine, and quetioine, are advised to get lipid emulsion therapy [36].

• Management of extrapyramidal symptoms:

Parenteral anticholinergic medications are used to treat acute dystonia, and they typically result in a quick recovery. Diphenhydramine (50 mg IV or IM in adults; 1 mg/kg up to 50 mg in children) or benztropine (2 mg IV or IM in adults; 0.05 mg/kg up to 2.0 mg in children) may be utilized. In addition to being an effective first line of treatment, benzodiazepines should be taken into consideration if patients do not respond to anticholinergic medications alone [40].

In cases of chronic use, akathisia is treated by tapering or stopping the offending medication; in cases of overdose, benzodiazepines can help reduce symptoms more rapidly [27].

Anticholinergic augmentation, dopamine agonists, and/or medication dose decrease are commonly used to treat Parkinsonism [29].

Tardive dyskinesia typically develops after long-term antipsychotic medication use rather than an overdose. Anticholinergic medications have the potential to exacerbate symptoms, and stopping the medication may not always cause them to go away. Gamma-aminobutyric acid (GABA)-nergic agent treatment, drug substitution, and dose modifications are examples of management techniques [30].

• Management of neuroleptic malignant syndrome: Benzodiazepines and internal and exterior cooling techniques should be used to treat hyperthermia. Theoretically, hyperthermia and severe muscle rigidity can be treated with dantrolene [26].

• Seizures caused by antipsychotics typically don't require treatment, but when they do, diazepam, phenobarbitone (phenobarbital), phenytoin, and paraldehyde have all been shown to be useful in reducing convulsions, either by themselves or in combination. When anticonvulsant medications are ineffective in treating convulsions, neuromuscular paralysis, and artificial breathing are necessary [22].

• Management of anticholinergic effects: delirium and other central anticholinergic symptoms can be treated with physostigmine. Benzodiazepines are also an option [41].

It is possible to reverse peripheral anticholinergic symptoms using physostigmine and neostigmine. Peripheral anticholinergic symptoms, such as uncomfortable urine retention, have few indications for treatment. Catheterization is suggested to physostigmine in more severe instances so that urine flow may be continuously monitored [41].

Diagnostic Biomarkers

In order to discover a "measurable and quantifiable biological parameter used to assess the health and physiology of patients in terms of disease risk and diagnosis," the word "biomarker" (derived from "biological marker") was created in 1989. It can be described as "any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease" or as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (table 2) **[42]**.

Table 2: Characteristics of an ideal biomarker and possible types of biomarkers

Characteristics of an ideal biomarker	Types of biomarkers
• Has been thoroughly tested • Is cheap, easily measure, and interpreted, with well-known characteristics • Reflects a pivotal pathophysiological pathway • Provides additional information to those already available • Allows a better definition of disease diagnosis, prognosis, or management	• **Antecedent biomarker** • **Screening biomarker** • **Diagnostic biomarker** • **Staging biomarker** • **Prognostic biomarker** • **Treatment response biomarker** • **Surrogate endpoint**

Suppression of tumorigenicity 2 protein

One of the most intricate and promising biomarkers, suppression of tumorigenicity 2 protein (ST2), plays a significant part in a number of illnesses. ST2 was initially identified as a crucial component of cell proliferation that influences the development of cancer twenty years ago. It was later linked to autoimmune and other inflammatory illnesses once its inflammatory and immunomodulatory properties were discovered. The use of ST2 has expanded steadily ever since [43].

The interleukin (IL)-1 receptor family includes the suppression of tumorigenicity 2 protein, which can be found as a soluble decoy receptor (sST2) or as a trans-membrane receptor (ST2L) [44].

Tumorigenicity 2 protein pathway suppression for cardiovascular protection :

inhibition of carcinogenicity Tissue plasminogen activator, pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNFα) and IL-1, as well as numerous inflammatory cell growth factors (platelet-derived, acidic fibroblast, and primary fibroblast growth factor) stimulate the ST2 gene, resulting in the expression of two protein molecules. Many types of cells, including immunological, hematopoietic, tumor, and embryonic cells, can synthesize the ST2 receptor molecule thanks to its expression. Additionally, fibroblasts and myocytes in the cardiac muscle express and contain it [45].

Myocytes, vascular structures (endothelial cells), and fibroblasts of the heart increase the expression, formation, and release of both forms of ST2 as well as IL-33 in response to elevated cardiac loads (increased biomechanical stress, pressure, and tension of the muscular structures) brought on by acute (infarct) or progressive heart failure (HF). According to Li et al. [44], myocytes in heart muscle express ST2L, a transmembrane receptor .

Numerous investigations have verified that the immune response, homeostasis, and the repair of injured (heart muscle) tissue are all significantly impacted by the binding of IL-33 to ST2L. Because of this interaction, cells exposed to ischemia and inflammatory processes—which are brought on by infarction or diminished circulation through the heart muscle tissue—are less likely to undergo apoptosis. Additionally, it lessens cardiomyocyte hypertrophy and cardiac fibrosis, preserving ventricular function and extending patient survival (figure 2) [46].

By competitively binding to IL-33 and disrupting its binding to ST2L, the soluble receptor sST2, on the other hand, is released from fibroblasts and vascular structures at the same time. This inhibits the cardioprotective effects of IL-33 on heart muscle. Thus, elevated sST2 expression and release promote cell death, fibrosis formation, hypertrophy, heart muscle remodeling, and the advancement of heart failure [47].

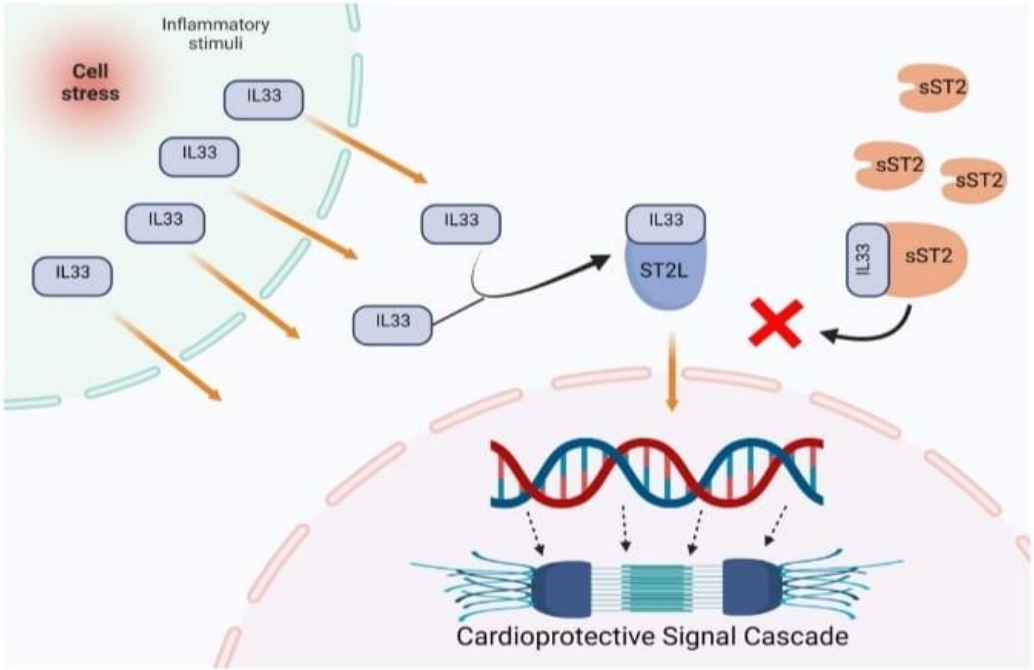

Figure 2: Cardioprotective relation of IL-33 with ST2L and sST2 [48].

Importance of suppression of tumorigenicity 2 protein as a biomarker:

Tumorigenicity 2 protein suppression has been linked to gastrointestinal disorders, sepsis, chronic renal disease, and pulmonary disorders [45].

Since it is a reliable indicator of cardiovascular outcomes in both acute and chronic heart failure (HF), soluble ST2 is acknowledged as a significant prognostic marker of HF. With multiple recent studies supporting its use in illness follow-up and therapy monitoring of patients with HF, the significance of sST2 is increasing [49].

Natriuretic peptide B-type

In 1988, the brain natriuretic peptide, also known as B-type natriuretic peptide (BNP), was first identified in the brain of a pig. BNP belongs to a family of peptide hormones that share structural similarities, which also includes urodilatin, C-type natriuretic peptide (CNP), and atrial natriuretic peptide (ANP). Although the left ventricle is the primary location for BNP production, both atrial and ventricular myocytes release BNP [50, 51].

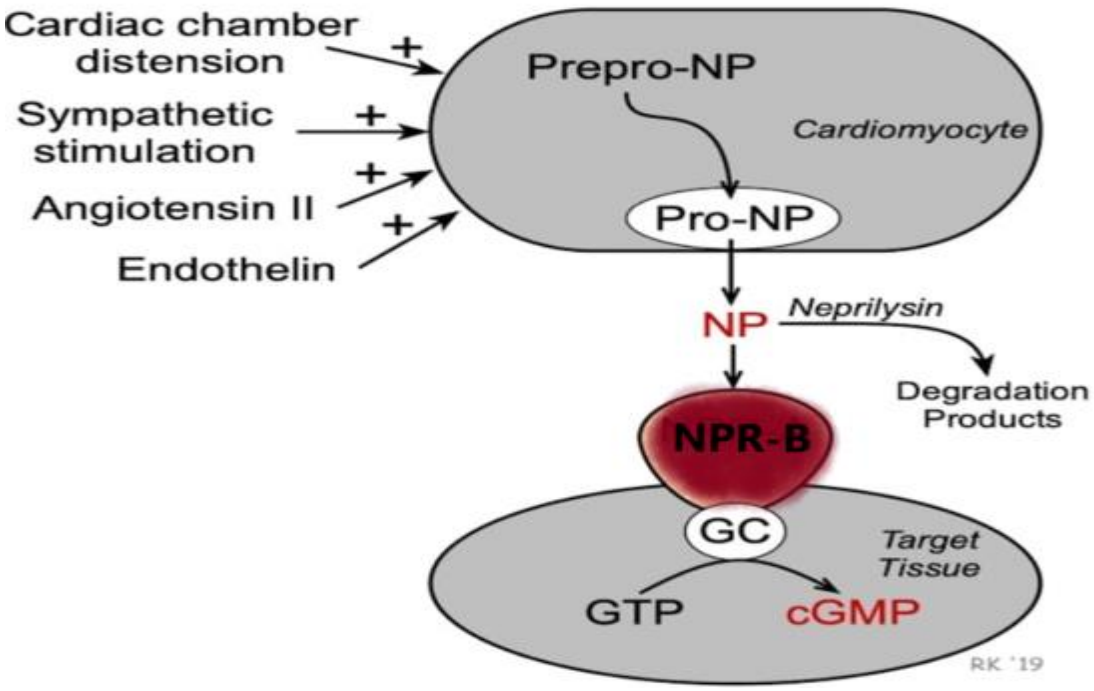

Figure (3): B-type natriuretic peptide pathway in cardiovascular protection [50].

A precursor protein (proBNP) is cleaved into BNP and the biologically inactive peptide NT-proBNP in response to atrial cardiomyocyte stretch. This results in natriuresis, diuresis, vasodilatation, smooth muscle relaxation, antiproliferation, antifibrosis, and antihypertrophic action by binding guanosine 3′,5′-cyclic monophosphate (cGMP), the second intracellular messenger, to particular receptors (figure 3) [50].

Cardiovascular protection through the B-type natriuretic peptide system [52]. (NP: natriuretic peptide, NPR-B, B type natriuretic peptide receptor, pre pro-NP: premature precursor of natriuretic peptide, pro-NP: precursor of natriuretic peptide, Guanosine triphosphate, or GTP, c GMP: guanosine monophosphate cyclic.

B-type natriuretic peptide's significance as a biomarker

Incorporated into HF clinical practice guidelines, natriuretic peptide testing is currently routinely utilized to help the diagnosis, prognostication, and management of patients with HF [53].

Natriuretic peptides are used as diagnostic and prognostic indicators because of their increased synthesis and release in heart failure. Patients with HF who have the worst prognosis, the most severe symptoms, and ventricular dysfunction had greater BNP values [54].

Troponin I

First described in 1965, serum troponin was detected in 1990 using a sensitive and accurate radioimmunoassay. Regulatory proteins called cardiac troponins govern the calcium-mediated

interaction between actin and myosin, which causes striated muscle to contract and relax. Three subunits make up the troponin complex: troponin T, which links to tropomyosin and promotes contraction; troponin I, which prevents actin-myosin connections; and troponin C, which binds calcium [55, 56].

Troponin isoforms are differentiated by the amino acid structure of their molecules, which varies according to where they are located in muscles. Accordingly, there are three different kinds of troponin I: cardiac troponin I, fast-twitch skeletal muscle fiber troponin I, and slow-twitch skeletal muscle fiber troponin I [57].

Molecular genetic research indicates that there is a 40–60% difference in the amino acid sequences of cardiac troponin I and cardiac troponin T and the corresponding isoforms of skeletal troponins found in skeletal muscle fibers. The utilization of cardiac troponins T and I as particular biomarkers for laboratory diagnoses of myocardial injury in myocardial infarction and other noncardiac pathological situations is made possible by this significant structural characteristic. Because cardiac troponin C and muscular (skeletal) troponin C have exactly the same amino acid structure, elevated blood levels of this protein will not allow us to reliably distinguish between damage to the skeletal muscles and injury to the cardiac muscle tissue. As a result, cardiac troponin C cannot be used as a cardiac marker for myocardial infarction diagnostics [58].

The role of the troponin I pathway in cardiovascular defense:

In the absence of calcium ions in the cell cytoplasm, muscle contraction is prevented by troponin I, the inhibitory member of the tropomyosin complex, which binds to actin during relaxation and inhibits the ATPase activity of actomyosin [59].

According to Chaulin [57], the following may be the mechanisms underlying the release of troponin molecules and the rise in their serum levels:

a) consequence of myocardial cell renewal and regeneration is the release of cardiac troponins.

b) When myocardial cells undergo apoptosis, cardiac troponins are released.

c) When membrane vesicles form on the surface of myocardial cells, cardiac troponins are released.

d) Heart troponin molecules are broken down by intracellular proteolytic degradation into tiny pieces, which are then released through the intact myocardial cell membrane.

g) Myocardial cells' increased membrane permeability causes the release of cardiac troponins.

f) Small-scale (subclinical) cardiomyocyte necrosis leading to the release of cardiac troponins.

g) Non-cardiac cells release cardiac troponins.

Heart troponin I's significance as a biomarker

For the non-invasive identification of myocardial damage in a variety of cardiovascular disorders, especially in patients with coronary heart disease who exhibit acute chest discomfort, troponin I concentration has grown in importance. Accordingly, increased troponin I levels are regarded as the gold-standard biomarker of myocardial infarction and are widely recognized as an indication of myocyte necrosis [58].

A number of cardiac and non-cardiac conditions, including heart failure, pulmonary embolism, myopericarditis, kidney disease, sepsis, tachycardia, toxic injury, and even healthy individuals following high-intensity exercise, are associated with elevated troponin I in addition to cardiomyocyte necrosis brought on by coronary ischemia [60].

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