DRUG-INDUCED CARDIOVASCULAR TOXICITY WITH TOXIC EFFECTS ON CARDIOMYOCYTES AND THE VASCULAR SYSTEM: A REVIEW

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Abstract

In the majority of developed nations worldwide, cardiovascular illnesses are the primary cause of morbidity and mortality. Toxins, illegal drugs, and pharmaceuticals can all considerably increase the stress on the cardiovascular system overall and should be taken seriously. An overview of medications that may cause specific cardiovascular toxicity is provided in this article. One major worry associated with the use of drugs, both legal and illegal, is cardiovascular damage. It may appear even after an overdose or even after only one injection. When it comes to novel drugs, the majority of what is currently known about these detrimental effects on the cardiovascular system is derived from extensive clinical studies or clinical experience. Because even slight variations in arterial blood pressure and heart rate have the potential to be later connected to increased cardiovascular mortality, all drugs that have such cardiovascular effects must be identified for their potential cardiac harm to the patient.

Keywords; Cardiovascular; Toxicity; Cardiomyocytes; Vascular system; review.

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1. Introduction

One major factor contributing to the attrition of compounds throughout preclinical and clinical development is drug-induced cardiotoxicity. It is recognized as one of the most harmful side effects brought on by a variety of drug types and is one of the most significant adverse consequences connected to the development of novel pharmaceuticals [1]. Anticancer drugs are not the only therapeutic medication classes that might cause unexpected cardiotoxicity; nearly all of them can. However, cardiotoxicity brought on by medications taken on a long-term basis, such as anticancer chemotherapeutic medicines and neurologic/psychiatric treatments, poses a serious issue because toxicity may not be apparent for some time after the drug or its metabolites have accumulated [2].

According to the International Conference of Harmonization Expert Working Group, evaluating the risk of drug-induced cardiotoxicity, including QT interval prolongation, is currently regarded as an essential component of the standard preclinical evaluation of new chemical entities for all medications under development [3]. Surprisingly, over 10% of medications have been taken off the clinical market globally in the last 40 years due to cardiovascular safety concerns. Examples of these medications include sibutramine, tegaserod, and rofecoxib. Despite significant efforts to identify cardiotoxicity during the preclinical stage of pharmaceutical development, the primary reason why cardiotoxicity remains a major safety concern is a lack of adequate understanding of the mechanisms underlying it [4].

Similar to this, there has been a great deal of research on the mortality rate from cardiovascular disease in patients with psychiatric illnesses. Antidepressants and antipsychotic medications, in particular, have a wide range of adverse effects on the cardiovascular system that can result in cardiac arrhythmias, which have occasionally been proven to be fatal in patients without a history of cardiac disease. For example, the most effective medication for resistant schizophrenia, clozapine, has limited use because of potentially fatal side effects such as myocarditis and cardiomyopathy. Myocarditis brought on by clozapine has been associated with up to 24% mortality. The co-occurrence of psychiatric problems in cardiac patients may have an impact on the clinical outcome and morbidity. Co-existing heart disease makes managing mental illness more difficult and prolongs the course of the illness [7, 8, 9]. This review aims to study the drugs and drug-related agents that may cause cardiovascular toxicity.

2. Drugs with toxic effects on cardiomyocytes and the vascular system

2.1 Indirect sympathomimetics

When it comes to toxicology, indirect sympathomimetics is crucial. Several illegal substances that are frequently abused fall within this group [7]. This is especially true for the most misused narcotics in Europe, cocaine and amphetamines, which are ranked second only to cannabis [8]. All indirect sympathomimetics have comparable effects, but they differ significantly in their primary modes of action and the neurotransmitter effects they produce (mostly in relation to dopamine and serotonin). Two mechanisms underlie indirect sympathomimetic effects that have therapeutic implications: (a) blocking noradrenaline plasmalemma synaptic transporters, and (b) catecholamines being released from synaptic vesicles **(Fig. 1).** The latter effects are more complicated and typically include inhibition of neuronal monoamine oxidase-A (MAO-A) as well as suppression of reuptake. Through their noradrenaline effects on α1-adrenergic receptors, indirect sympathomimetics influence the vascular system, and their noradrenaline actions on β1-adrenoreceptors affect the heart. Whereas the latter is linked to elevated cardiac excitability, heart rate, conduction velocity, and contractility, the former only shows up as elevated blood pressure. Such effects significantly raise the oxygen demand of the heart. Additionally, increased platelet aggregation brought on by sympathomimetics may be significant [9].

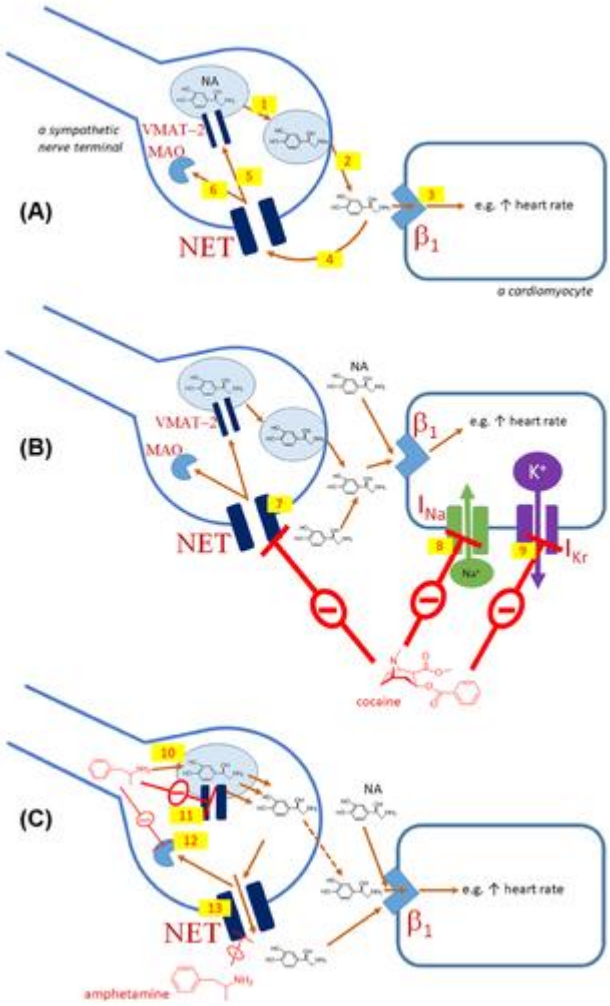

Figure (1): The impact of indirect sympathomimetics and noradrenaline release from sympathetic fibers at the heart's synaptic cleft.

2.2 Direct acting sympathomimetics

2.2.1 Endogenous catecholamines

In intensive care units, the endogenous catecholamines dopamine, noradrenaline, and adrenaline are frequently administered to treat shock symptoms related to acute cardiovascular problems. Regarding their selectivity for adrenergic receptors, they differ significantly from one another. While noradrenaline acts on α- and β1-adrenergic receptors but has minimal affinity for β2-adrenergic receptors, adrenaline generally stimulates both α- and β-adrenergic receptors. In physiological dosages, dopamin causes vasodilation by stimulating dopaminergic receptors on blood vessels; however, it also functions as a mild agonist at adrenergic receptors. Catecholamines have the potential to cause a variety of cardiotoxic effects, such as hypertension, heart ischemia, and dysrhythmias. When administered in the right conditions, clinically, the acute hemodynamic advantages on the heart outweigh the hazards; however, cardiovascular function should be closely monitored. These biogenic amines have shorter half-lives than other synthetic inotropes and vasopressors, which could be a significant benefit given their propensity to cause cardiotoxicity. However, continuous high-dose infusions of adrenaline or noradrenaline are not advised since they may directly cause cardiotoxic effects that lead to cardiomyocyte apoptosis or necrosis [10, 11].

2.2.2 Nonselective β-agonists and β2-agonists

Isoprenaline, sometimes referred to as isoproterenol, is a nonselective β-adrenoceptor agonist with a high potential for cardiac injury. Because of this, it has been widely employed in experimental settings to mimic the pathological state of acute myocardial infarction [12, 13]. Its intricate processes of cardiotoxicity entail the overstimulation of β-adrenoceptors and the generation of reactive oxygen species. Overstimulation of β-adrenoceptors causes an increase in the energy requirements of the heart. Furthermore, isoprenaline generates extensive vasodilation in the peripheral circulation as a result

of its powerful β2-adrenoceptor agonistic activity, which greatly lowers diastolic blood pressure and, in turn, myocardial perfusion [14, 15]. Because cardiac β1-adrenoceptors are stimulated, calcium excess is also frequently observed [16].

It is also possible that increased platelet aggregation has a role in toxicity [17]. ROS can be directly produced by ischemia or by the spontaneous or metal-catalyzed oxidation of high isoprenaline levels [18]. It is not unexpected that no one drug can completely prevent or reverse the damage produced by isoprenaline, or that it only acts when isoprenaline is taken at low dosages, given the complicated pathophysiology [19, 20].

2.3 Nicotine and smoking

In the twenty-first century, smoking tobacco poses a serious global health risk. Millions of smokers pass away every year, and an estimated 1 billion people smoke every day [21]. The health risk associated with using electronic cigarettes is somewhat reduced by current developments; nevertheless, more information is needed before firm conclusions can be made [22]. In addition to nicotine, cigarette smoke contains a variety of additional compounds that are produced when tobacco is burned, many of which are carcinogenic and can cause reactive oxygen species (ROS). Nicotine is also included in electronic cigarettes. The molecules generated have the potential to be hazardous to humans, even if the quantity of potentially toxic substances is reduced because of the lower temperature of thermal breakdown [22].

2.4 Drugs affecting the adrenergic system

Adrenergic α2-receptors are primarily found in the brain and pelvis. Inhibition of the central sympathetic tone is linked to stimulation of central α2-adrenergic receptors. This has practical implications, as agonists of α2-adrenoceptors, such as methyldopa and clonidine, are occasionally employed to treat hypertension. Children with ADHD are also treated with clonidine. Furthermore, tizanidine and other centrally acting α2-agonists are utilized in veterinary anesthesia for their sedative and myorelaxant effects, and xylazine and medetomidine are employed in vertebrogenic-algic syndromes because of their strong skeletal muscle myorelaxant effects. Hypotension and bradycardia resulting from α2-Adrenoceptor agonist intoxication can be treated with IV fluid replenishment, atropine, or catecholamines if necessary, or by administering the α2-antagonist atipamezole [23, 24]. Even with high dosages, the prognosis is usually favorable. Nevertheless, xylazine can be lethal when used in combination with other CNS depressants, such as when used as an adulterant (with heroin, for example) [25]. Peripheral α2-adrenergic receptor activation at large doses cause temporary moderate hypertension; however, this response usually goes unchecked [26].

α2-adrenergic receptor antagonists can have the reverse effect, raising sympathetic tone. Additionally, they antagonize peripheral α2-adrenergic receptors, causing vasodilation of the pelvic area, which may be advantageous in treating erectile dysfunction. Yohimbine, a naturally occurring alkaloid that may be extracted from the bark of the West African tree Pausinystalia yohimbe, has been used in the past to treat this illness. Modern methods of treating erectile dysfunction have essentially replaced yohimbine; yet, it is still used for bodybuilding, sports performance enhancement, and weight loss, while there is a lack of data or inconsistent information regarding these applications. Yohimbine-containing products are used extensively, and numerous incidents of intoxication are documented annually. Because of the above-indicated mechanisms pertaining to its cardiovascular effects, administering yohimbine causes dose-dependent increases in heart rate and blood pressure. Patients with hypertension experience a more noticeable impact on their blood pressure. Thankfully, yohimbine intoxications seldom result in fatal cases, and because of their brief half-lives, the majority of intoxications normally go away on their own [27, 28].

2.5 Drugs Causing Sympathetic Hyperactivity

Some medicines have little or no direct circulatory activity, but after intoxication, they can cause the sympathetic nervous system to become engaged as a stress response. As an illustration, consider cannabis, which is usually regarded as being extremely safe in terms of cardiovascular health [29]. It should be noted that certain contaminants—caffeine included—may exacerbate these cardiovascular risks [30].

2.6 Ca2+ channel blockers

Pharmacologically, dihydropyridines and nondihydropyridines, such as verapamil and diltiazem, are the two categories of Ca2+ channel blockers. While the former group also blocks cardiac L-type channels at therapeutic dosages, all of these medications block vascular L-type Ca2+ channels to varying degrees. This organ selectivity is mostly lost during intoxication, hence these medications will be covered collectively. One of the most frequent ways that therapeutically utilized

cardiovascular medications cause intoxication and mortality is through Ca2+ channel blockers. Conversely, these are thought to be fairly safe. Toxicology is more likely, nevertheless, when administered to very young infants or in combination with medications that work similarly (β-blockers, digoxin, amiodarone). They can cause brady-dysrhythmias during an overdose, which can include severe systemic hypotension, cardiovascular collapse, and sinus bradycardia with total atrioventricular (AV) block [31-33].

2.7 Tricyclic antidepressants (TCAs)

TCAs are a particular class of medications with a variety of effects. They work by inhibiting monoaminergic synaptic reuptake transporters, which have antidepressant properties. But they also have strong antagonistic activity against α1-, H1-, H2-, and M-receptors, and they inhibit Na+ and hERG (human ether-a-go-go) channels. Their effects on the cardiovascular system are so complicated. While additional atrial or ventricular dysrhythmias can be seen, sinus tachycardia is the most typical symptom following a TCA overdose. Because of IKr current blockage, they lengthen the QT interval; nevertheless, torsade de pointes are rarely caused by this because of heart rate rises. Another extremely prevalent adverse effect that usually has no tolerance is orthostatic hypotension. It is primarily induced by antagonistic interactions with α1-adrenoceptors, but cardiac Na+ channel inhibition may also be a contributing factor to decreased cardiac output and contractility. The latter is only important in overdose situations because, even in heart failure patients, adverse inotropic effects are not seen at therapeutic levels. Hypertension resulting from indirect sympathomimetic action may manifest at the start of therapy [34-36].

2.8 Ethanol

In general, moderate to low dosages of alcohol (ethanol) are thought to be cardioprotective; with excessive doses, however, the converse is true [37]. Given that 10% of women and 18% of males in the US population over the age of 18 have an alcohol use disorder within a year, this is extremely concerning. Approximately 50% of them drink moderately or heavily [38]. Hypotension and possibly a chance of cardiac failure are linked to acute alcohol overdose. The initial treatment measure is typically the delivery of fluids intravenously [39]. Mild elevations in arterial blood pressure have been linked to even moderate long-term alcohol use. Alcohol intake may be the cause of hypertension in 5–10% of cases, however, the prevalence of the disorder is almost 50% among younger individuals with alcohol use disorders. The effect appears to be dosage-dependent [40]. Although the exact mechanisms underlying the blood pressure responses are unknown, adrenergic hyperactivity is known to have a role, at least initially in the misuse process [41]. Alcoholic cardiomyopathy and dysrhythmias are caused by long-term heavy alcohol use. In many situations, a solitary episode of atrial fibrillation is the first clinical sign. About 15–40% of cases of idiopathic atrial fibrillation may be caused by alcohol consumption, which is a rather prevalent cause of atrial fibrillation [42].

2.9 Androgenic anabolic steroids

Only seldom is the male hormone testosterone utilized in therapy; but, massive dosages of its near relatives, the androgenic anabolic steroids, are abused to increase physical performance. Because it is against the law to use them in professional sports, information regarding their cardiovascular toxicities has not been thoroughly investigated. Furthermore, androgenic anabolic steroids are frequently used in combination with other medications, including diuretics, illegal sympathomimetics, β2-mimetics, and/or psychotropic substances [43]. The effects of testosterone on the circulatory system are not the same as those induced by supraphysiologic dosages of synthetic androgens, according to conflicting data [44]. Therefore, determining the cardiovascular effects of abusing anabolic androgenic steroids is difficult. The goal of abusing them is to gain leaner, striated muscular mass. But the heart also experiences similar effects. Cardiac hypertrophy is the most prevalent cardiac finding of long-term anabolic abuse [45], and it is more common than exercise-induced hypertrophy in professional athletes who do not take anabolic medications [46]. These medications generate maladaptive cardiac hypertrophy, which can progress to fibrosis and overt heart failure. It starts out predominantly concentric but can also be eccentric. The amount and duration of anabolic steroid use are positively connected with diastolic dysfunction. Furthermore, a changed heart structure may make a person more susceptible to the development of dysrhythmia, which may cause sudden cardiac death [47].

4. Conclusion

Cardiovascular toxicity is a significant concern that can arise from the use of both legal and illicit drug types. It can manifest itself even after a single injection or following an overdose. Since most of

what we currently know about these harmful effects on the cardiovascular system comes from long-term clinical trials or clinical experience, it is mostly unknown when it comes to innovative medications. All medications that cause such cardiovascular effects must be identified for their potential cardiac danger to the patient because even little changes in arterial blood pressure and heart rate have the potential to be later linked to greater cardiovascular mortality.

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