Certain kinds of non-cardiac drugs have been demonstrated to induce heart rhythm disorders. Although most of them are not clinically significant, lethal events have been reported. QT prolongation, a repolarization abnormality that is also referred to as secondary long QT syndrome, is a well-known disorder that is caused by non-cardiac drugs. It mainly arises due to reduced potassium channel activity.\(^1\) This syndrome is associated with an increased risk of polymorphic ventricular tachycardia, also known as torsades de pointes (TdP).\(^2\) By contrast, eicosapentaenoic acid (EPA), an omega-3 (n-3) fatty acid, has been reported to have favorable effects on the potassium channels.\(^3,4\)

A reduction in ischemic cardiovascular events in healthy adults and patients with established coronary artery disease was demonstrated following the use of n-3 polyunsaturated fatty acids (n-3 PUFAs) (i.e., EPA and docosahexaenoic acid) in randomized controlled trials.\(^5,6\) A significant improvement was also established in left ventricular end-systolic volume and myocardial fibrosis after acute myocardial infarction (MI) by Omega-3 Acid Ethyl Esters.\(^7\) A reduction of platelet aggregation by blocking platelet-derived thromboxane A\(_2\) by EPA is reported to be a major mechanism to reduce ischemia cardiovascular risk.\(^8\)

The consumption of n-3 PUFAs has been also associated with a reduction in arrhythmic risk. EPA directly affects atrial and ventricular myocyte electrophysiology via modulating cardiac potassium channel function.\(^9\) This causes a reduction in sudden cardiac death and ventricular fibrillation.\(^9\) Such results, however, have been obtained in preclinical or in vitro studies, and evidence of a direct antiarrhythmic effect of n-3 PUFAs on humans was limited.

Recently, the positive impact of n-3 PUFAs (i.e., a reduction in atrial fibrillation) has been reported in a few observational studies in human.\(^10,11\) In addition, Endo, \textit{et al.} reported that J-waves were found more frequently on acute phase of MI in patients with low levels of serum EPA.\(^11\) Low-serum EPA levels were associated with an increased incidence of ventricular arrhythmia after MI, suggestive that EPA is efficacious in reducing ventricular arrhythmia.\(^11\) However, it remained uncertain as to whether serum EPA levels influence the frequency of J-waves in healthy adults.

To address these questions, Kimura, \textit{et al.} evaluated the association between the existence of J wave and serum EPA levels in 1052 persons participating in a community-based health-promotional study in Japan.\(^12\) A significant relationship between J-waves and serum EPA levels could not be established in these healthy subjects, as was the case for MI patients. Instead, male gender and the R-R interval were found to novel factors that were independently associated with the presence of J-waves.\(^12\)

In the case of MI, differences in the activation of ATP-sensitive potassium channels (K\(_{ATP}\)), or in its distribution between epicardial and endocardial myocardium, contributes to J wave manifestation.\(^13\) This finding is supported in another study in which ischemic myocardium caused the reduction of intracellular adenosine triphosphate, leading to K\(_{ATP}\) channel activation.\(^14\) These changes of K\(_{ATP}\) channel after MI might facilitate specificity of favorable effects of EPA on J wave manifestation after MI, but not in healthy humans.

Although EPA was not originally intended for use as a cardiac drug, it has been shown to have a beneficial pharmacological impact on cardiac electrical activity.\(^15\) Similarly, certain non-cardiac drugs like antihistamines, antipsychotic drugs and antibodies have been reported to affect cardiac electrical activity.\(^15\) Of all the cardiac electrical disorders caused by non-cardiac drugs, QT prolongation is a major one and has been identified as a risk factor for malignant TdP. Therefore, careful attention should be exercised when handling non-cardiac drugs. Erythromycin, a macrolide antibody, prolongs the QT interval and is especially used with drugs metabolized by cytochrome P450 3A. It is associated with a five times higher incidence of sudden death compared with no medication.\(^15\)
Haloperidol and cisapride have the resembling structural formula, which are characteristic to block human ether-a-go-go-related gene potassium leading to QT prolongation. $K_{ATP}$ channel is consists of the sulfonylurea receptor and the Kir6.2 channel subunit. Kir6.2 channel subunits constitute the pore of channel, and the sulfonylurea receptor controls the pore activity.22) Eicosapentaenoic acid binds to sulfonylurea receptor, inducing the conformation change of the Kir6.2 subunit structure. As a result, potassium current reduces, leading to the reduced risk of J wave manifestation.

Haloperidol, an antipsychotic drug, is often used in the management of delirium in the intensive care unit and also induces QT prolongation, especially when administered intravenously, as opposed to intramuscularly or orally.16) Of all the antipsychotic drugs, haloperidol and thioridazine, when administered intravenously, are considered to be high risk factors for TdP. These drugs are still used in clinical practice, despite the risk of QT prolongation and TdP. Meanwhile, other drugs, such as cisapride, terfenadine, and astemizole, have been removed from the market due to their association with TdP. The latter was identified in 1:120000 patients who had been prescribed cisapride; this incidence of TdP was considerably lower than that caused by antiarrhythmic drugs.17) Nevertheless, this level of risk is obviously unacceptable for drugs used to treat non-life-threatening gastrointestinal disorders.

The QT interval increases when potassium channels are inhibited.1) Potassium-selective channels have diverse structures and functions, including maintenance of the resting membrane potential and the termination of action potentials in excitable cells. Of these, the rapid delayed rectifier potassium current, which is conducted by the human ether-a-go-go-related gene (hERG) potassium channels, is essential for normal electrical activity in the heart. Inhibition of this channel activity also leads to QT prolongation.18,19)

The hERG channel possesses four units comprising six $\alpha$-helical transmembrane domains (i.e., S1-S6).20) The role of S1-S4 is to sense transmembrane potential, while that of S5 and S6 relates to permeation of the voltage-gated potassium channels, respectively. Tyr652 and Phe 656, key amino acids that are located on the S6 domain, are not conserved in the other potassium channels, are unique binding sites, and are unusually susceptible to drug blockage.20) Three common important features of the hERG potassium channel blockers are hydrophobic and aromatic ring features, and hydrogen bond acceptor lipids.21) Since Tyr652 and Phe656 are aromatic residues, the abovementioned features have a strong affinity for these residues. Indeed, some of these features can be attributed to QT prolongation-inducing non-cardiac drugs (Figure).

Certain non-cardiac drugs have been found to modulate potassium channel including hERG and $K_{ATP}$ channel through increase or reduction of potassium current. These effects, however, depend on patients’ conditions.

Disclosures

Conflicts of interest: None.

References

5. Dietary supplementation with n-3 polyunsaturated fatty acids
and vitamin E after myocardial infarction: results of the GISSI-
Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvi-
acids and risk of coronary heart disease among Japanese: the
Japan Public Health Center-Based (JPHC) Study Cohort I. Cir-
Acid Ethyl Esters on Left Ventricular Remodeling After Acute
Myocardial Infarction: The OMEGA-REMODEL Randomized
Platelet-membrane fatty acids, platelet aggregation, and
thromboxane formation during a mackerel diet. Lancet 1980; 1:
441-4.
9. Leaf A, Kang JX, Xiao YF, Billman GE. Clinical prevention of
sudden cardiac death by n-3 polyunsaturated fatty acids and
mechanism of prevention of arrhythmias by n-3 fish oils. Circu-
10. Mozaffarian D, Psaty BM, Rimm EB, et al. Fish intake and risk
11. Brouwer IA, Heeringa J, Geleijnse JM, Zock PL, Witteman JC.
Intake of very long-chain n-3 fatty acids from fish and inci-
dence of atrial fibrillation. The Rotterdam Study. Am Heart J
rum Eicosapentaenoic Acid Levels with J-Waves in a General
Population: Analysis of the Iwaki Health Promotion Project. Int
13. Antzelevitch C. Genetic, Molecular and Cellular Mechanisms
K+ channels, and cellular K+ loss during hypoxia, ischemia,
and metabolic inhibition in mammalian ventricle. Circ Res
15. Ray WA, Murray KT, Meredith S, Narasimhulu SS, Hall K,
Stein CM. Oral Erythromycin and the Risk of Sudden Death
16. Beach SR, Celano CM, Noseworthy PA, Januzzi JL, Huffman
JC. QTc prolongation, torsades de pointes, and psychotropic
17. Vitola J, Vukanovic J, Roden DM. Cisapride-induced torsades de
18. Trudeau MC, Warmke JW, Ganetzky B, Robertson GA. HERG,
a human inward rectifier in the voltage-gated potassium channel
19. Sanguinetti MC, Tristani-Firouzi M. hERG potassium channels
20. Vandenberg JI, Perozo E, Allen TW. Towards a Structural View
of Drug Binding to hERG K(+) Channels. Trends Pharmacol
21. Garg D, Gandhi T, Gopi Mohan C. Exploring QSTR and toxi-
cophore of hERG K+ channel blockers using GFA and Hypo-
and stoichiometry of K(ATP) channel subunits. Neuron 1997;
18: 827-38.