Cardioprotective effect of metformin against doxorubicin cardiotoxicity in rats

To the Editor,

Doxorubicin (Adriamycin), an anthracycline antibiotic, is used in the treatment of a variety of cancers, often in combination chemotherapy. Despite being a potent antitumor reagent, the use of doxorubicin is severely limited by its well-documented, dangerous, dose-dependent side effect of development of cardiomyopathy leading to congestive heart failure. The incidence of cardiotoxicity is in direct correlation with the cumulative dose of doxorubicin; however, cardiomyopathy may develop in some patients at lower doses.

There has been a growing effort in research aiming to eliminate or palliate doxorubicin-induced cardiotoxicity. Many mechanisms of doxorubicin-induced cardiomyopathy have been proposed, with mitochondrial dysfunction and generation of oxidative stress being most frequently mentioned (1). Interestingly, among the many drugs that are being proposed to ameliorate doxorubicin-induced cardiotoxicity, metformin, (N,N-dimethylimidodicarbonimidic diamide), a broadly used oral drug with few side effects, is used for the treatment of type 2 diabetes (2). The molecular mechanism of action of metformin is believed to be via the activation of AMP-activated protein kinase (AMPK) (3). The notion that metformin may reduce cancer risk came from a retrospective type 2 diabetes cohort study in the United Kingdom (4). Metformin monotherapy was shown to be associated with lower risk of colon and pancreatic cancers but not breast or prostate cancers (4). Later, it was confirmed that metformin use was indeed associated with lower cancer mortality in type 2 diabetes (5). In a mouse breast cancer cell xenograft study, metformin was also shown to synergistically enhance the effect of doxorubicin and prevent recurrence (6). Therefore, it is now a generally accepted concept that metformin use is beneficial with better outcomes in cancer treatment, particularly in type 2 diabetes patients. The question is how exactly metformin works in ameliorating the cardiotoxicity induced by doxorubicin? To date, activation of AMPK seems to be the most plausible candidate, at least according to in vitro studies (7). Many in vivo studies revealing the effects of metformin in alleviating the adverse side effects of doxorubicin have focused on biochemical changes such as reduction in free radical generation and mitochondrial damage (1, 8). The paper by Argun et al. (9) entitled "Cardioprotective effect of metformin against doxorubicin cardiotoxicity in rats" published in this issue of the Anatolian Journal of Cardiology took a slightly different approach. In this in vivo study, the authors used echocardiography as a direct readout to demonstrate the beneficial effect of metformin. Rats treated with doxorubicin had significant deterioration in their left ventricular (LV) functions. Metformin cotreatment, however, effectively reversed the many adverse side effects induced by doxorubicin, including histopathological changes in cardiac tissue, cardiomyocyte apoptosis, and LV functions. Specifically in M-mode measurements, changes in LV end-systolic dimension and interventricular septum thickness were effectively reversed. Ejection fraction and fractional shortening were also somewhat improved with metformin cotreatment.

However, there are several limitations to this study. First, the dosage of metformin seems on the higher end (250 mg/kg/day for 14 days). The normal suggested maintenance dose of metformin for adult type 2 diabetes patients is about 2.000 mg/day. Therefore, the metformin dose used in this study greatly exceeded the normal accepted clinical guidelines for type 2 diabetes treatment. Although metformin generally has few side effects, the authors did not mention any abnormal signs with the animals treated with metformin. Second, cardiac functions were only measured by echocardiography. Addition of hemodynamic assessments, including dP/dt (Doppler- or catheter-derived), would have been complementary and confirmatory for the echocardiography results.

This study is not the first to use echocardiography to assess cardiac functions in the research field of doxorubicin. For example, recently, Chang et al. (10) demonstrated the beneficial effects of angiotensin receptor blockers (ARBs) in preventing doxorubicin-induced cardiotoxicity in rats. Although the clinical application of ARBs for reducing doxorubicin-induced adverse effects is debatable, the use of metformin is so far reached now such that the study by Argun et al. (9) should have much more translational value. To date, the majority of the clinical investigations have focused on cancer survival rate in type 2 diabetes patients. Maybe it is time that more efforts are put into the cardiac protection effect of metformin in patients receiving doxorubicin treatment.

Yi-Tang Tseng
Department of Pediatrics, Women&Infant's Hospital of Rhode Island, the Warren Alpert Medical School of Brown University, Providence-*USA*

Address for correspondence: Yi-Tang Tseng, Ph.D., Department of Pediatrics, Women & Infant's Hospital of Rhode Island, the Warren Alpert Medical School of Brown University, Providence RI 02905-*USA*
Phone: 1-401-274-1122, extension 48006 E-mail: ytseng@wihri.org
Accepted Date: 09.03.2016 **Available Online Date:** 15.04.2016

DOI:10.14744/AnatolJCardiol.2016.18505

References

1. Ashour AE, Sayed-Ahmed MM, Abd-Allah AR, Korashy HM, Maayah ZH, Alkhalidi H, et al. Metformin rescues the myocardium from doxorubicin-induced energy starvation and mitochondrial damage in rats. Oxid Med Cell Longev 2012; 2012: 434195.
2. American Diabetes Association. Standards of medical care in diabetes—2009. Diabetes Care 2009; 32 Suppl 1: S13-61. [CrossRef]
3. Rena G, Pearson ER, Sakamoto K. Molecular mechanism of action of metformin: old or new insights?. Diabetologia 2013; 56: 1898-906.
4. Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia 2009; 52: 1766-77. [CrossRef]
5. Landman GW, Kleefstra N, van Hateren KJ, Groenier KH, Gans RO, Bilo HJ. Metformin associated with lower cancer mortality in type 2 diabetes: ZODIAC-16. Diabetes Care 2010; 33: 322-6.
6. Vallianou NG, Evangelopoulos A, Kazazis C. Metformin and cancer. Rev Diabet Stud 2013; 10: 228-35. [CrossRef]
7. Kobashigawa LC, Xu YC, Padbury JF, Tseng YT, Yano N. Metformin protects cardiomyocyte from doxorubicin induced cytotoxicity through an AMP-activated protein kinase dependent signaling pathway: an in vitro study. PLoS One 2014; 9: e104888. [CrossRef]
8. Aleisa AM, Al-Rejaie SS, Bakheet SA, Al-Bekari AM, Al-Shabanah OA, Al-Majed A, et al. Effect of metformin on clastogenic and biochemical changes induced by adriamycin in Swiss albino mice. Mutat Res 2007; 634: 93-100. [CrossRef]
9. Argun M, Uzum K, Sönmez MF, Özyurt A, Karabulut D, Soyersarıca Z, et al. Cardioprotective effect of metformin against doxorubicin cardiotoxicity in rats. Anatol J Cardiol 2016; 16: 234-41.
10. Chang SA, Lim BK, Lee YJ, Hong MK, Choi JO, Jeon ES. A novel angiotensin type I receptor antagonist, fimasartan, prevents doxorubicin-induced cardiotoxicity in rats. J Korean Med Sci 2015; 30: 559-68.