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Pregledni članak Review article

Mogući kardiovaskularni učinci anksiolitika

Potential cardiovascular effects of anxiolytics

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SAŽETAK: *Uz tradicionalne čimbenike rizika nastanka kardiovaskularnih bolesti, različiti psihosocijalni čimbenici privlače sve više pozornosti, a među njima, sve se češće spominje anksioznost. Narušavanjem ravnoteže autonomnog živčanog sustava i smanjenom barorefleksnom kontrolom, anksiozni poremećaji povećavaju rizik pojave ventrikulskih aritmija i nastanka iznenadne srčane smrti. Također, anksiozne osobe imaju nešto veći rizik nastanka koronarne bolesti srca i infarkta miokarda. Lijekovi iz skupine anksiolitika mogli bi imati povoljne kardiovaskularne učinke koji bi bili posredovani smanjivanjem anksioznosti i ukupne simpatičke aktivnosti, prevencijom aritmogeneze, smanjivanjem perifernog vaskularnog otpora, snižavanjem arterijskog tlaka, tlaka u aorti i pulmonalnoj arteriji, kao i tlaka u lijevom srcu na kraju dijastole te nizom drugih mehanizama.*

KLJUČNE RIJEČI: *anksiolitici, anksioznost, iznenadna srčana smrt, kardiovaskularne bolesti.*

SUMMARY: *Besides traditional risk factors of the occurrence of cardiovascular diseases, various psychological and social factors attract ever greater attention, whereby anxiety is the factor that is more and more mentioned among them. Anxiety disorders increase a risk of occurrence of ventricular arrhythmia and occurrence of sudden cardiac death as a consequence of damaged balance of autonomic nervous system and reduced baroflex control. Anxious persons also show a higher risk of occurrence of coronary heart disease and myocardial infarction. The drugs from the group of anxiolytics could have positive cardiovascular effects that would be mediated by decreased anxiety and total sympathetic activity, prevented arrhythmogenesis, reduced peripheral vascular resistance, lowered blood pressure, aortic pressure and pressure in pulmonary artery and the pressure in the left heart at the end of the diastole and a series of other mechanisms.*

KEYWORDS: *anxiolytics, anxiety, sudden cardiac death, cardiovascular diseases.*

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Kardiovaskularne bolesti predstavljaju jedan od najznačajnijih javnozdravstvenih problema diljem svijeta, pa tako i u Republici Hrvatskoj[1]. Uz tradicionalne čimbenike rizika njihovoga nastanka poput arterijske hipertenzije, dijabetesa, hiperlipidemije, pušenja, pretilosti, genetskih čimbenika, sve se češće spominju i depresivni poremećaji, agresivnost, ukupni psihosocijalni stres te posebice anksioznost. Obzirom na veliku učestalost anksioznosti, njena uloga mogućeg čimbenika kardiovaskularnog rizika ima potencijalno veliko javnozdravstveno značenje, kako u primarnoj tako i sekundarnoj prevenciji. U isto vrijeme i na istome tragu, lijekovi iz skupine anksiolitika nalaze se među lijekovima koji se danas najčešće propisuju[2]. Dosadašnja istaživanja o djelovanju nekih od lijekova iz ove skupine ukazala su na mogući pozitivni učinak na različite kardiovaskularne funkcije, čime se otvara pitanje njihove izdašnije primjene u akutnim i kroničnim kardiovaskularnim bolestima.

Patofiziologija kardiovaskularnih posljedica anksioznosti

Anksiozni poremećaji narušavaju ravnotežu autonomnog živčanog sustava putem izražene simpatičke aktivacije uz reduciranje vagalne srčane komponente[3,4]. Narušavanje te ravnoteže vjerojatno igra ključnu ulogu u izazivanju ventrikulskih aritmija[3,5] i nastanku iznenadne srčane smrti[3,6-8]. Kao najznačajniji prilog tome, u anksioznih osoba opisana je reducirana barorefleksna kontrola srčanog rada[4]. Štoviše, čini se da je stupanj anksioznosti razmjeran riziku iznenadne srčane smrti[9,10]. Također, čini se da

Cardiovascular diseases are one of the most significant public healthcare problems all around the world and in the Republic of Croatia as well[1]. Besides traditional risk factors of their occurrence such as hypertension, diabetes, hyperlipidaemia, smoking, obesity, genetic factors, the factors such as depressive disorders, aggressive behavior, overall psychological and social stress, especially anxiety are more frequently mentioned. Considering high frequency of anxiety, its role as a potential factor of cardiovascular risk has potentially a great public healthcare importance not only in the primary, but also in the secondary prevention. At the same time the group of anxiolytics are included in the drugs that are nowadays the most frequently prescribed drugs[2]. The recent researches on effects of some of the drugs from this group showed a possible positive effect on different cardiovascular functions, thereby opening an issue of their more frequent use in acute and chronic cardiovascular diseases.

Pathophysiology of cardiovascular consequences of anxiety

Anxiety disorders damage the balance of autonomic nervous system by a high level of sympathetic activation followed by reduction of vagal cardiac component[3,4]. The damage of this balance probably plays a key role in causing ventricular arrhythmia[3,5] and occurrence of sudden cardiac death[3,6-8]. The best evidence of this is the fact that the reduced baroflex control of the heart function is described in anxious persons[4]. Moreover, the degree of anxiety seems to be proportionate to the risk of sudden cardiac death[9,10].

anksiozne osobe imaju povećani rizik za nastanak koronarne bolesti srca (KBS), u prosjeku 11 godina nakon dijagnosticiranja anksioznog poremećaja, a anksioznost je neovisni prediktor smrtnosti od kardiovaskularnih bolesti[11]. Osim toga, kod starijih muškaraca anksioznost predstavlja neovisni čimbenik rizika pobola od infarkta miokarda, a u tih je bolesnika nakon preboljelog događaja anksioznost također povezana sa smanjenom barorefleksnom kontrolom srčanog rada[12,13].

Mogući povoljni kardiovaskularni učinici benzodiazepina

Amplificirajući inhibitorni učinak neurotransmitera GABA-e u središnjem živčanom sustavu, anksiolitici iz skupine benzodiazepina ostvaruju svoje djelovanje u smislu smanjenja anksioznosti, postizanja sedacije i miorelaksacije te mogućeg povoljnog djelovanja na kardiovaskularni sustav[14-16]. Ovi lijekovi također djeluju i periferno preko benzodiazepinskih receptora koji se nalaze na srcu i leukocitima, čemu se dodatno pripisuje njihov ukupni kardiovaskularni učinak[17-20].

Neka od dosadašnjih istraživanja klinički potvrđuju osnovanost ideje o povoljnom djelovanju benzodiazepina na kardiovaskularne funkcije. Intravenska primjena diazepama u dozi od 5 mg u zdravih normotenzivnih pacijenata uzrokovala je značajan pad sistoličkog i srednjeg arterijskog tlaka (AT) bez utjecaja na srčanu frekvenciju, vjerojatno centralno posredovanim snižavanjem ukupne simpatičke aktivnosti[21]. Kod pacijenata s bolešću mitralne valvule tijekom dijagnostičke kateterizacije srca, primjena diazepama je uzrokovala snižavanje tlaka u aorti i pulmonalnoj arteriji te pad srčane frekvencije[22]. Nekoliko istraživanja povezuje primjenu benzodiazepina sa smanjenjem tlaka u lijevom atriju na kraju dijastole i sa smanjenjem perifernog otpora[23-25]. U bolesnika s ishemijom ili infarktom miokarda, benzodiazepini bi mogli smanjivati razinu kateholamina u krvi, vaskularni otpor koronarnih arterija te pripomoći inhibiciji agregacije trombocita[23]. Izazivajući koronarnu vazodilataciju, snižavajući srčanu frekvenciju, a možda i mehanizmima koji uključuju djelovanje na autonomni živčani sustav, postoji mogućnost da benzodiazepini u stanovitoj mjeri imaju protektivni učinak protiv ventrikulskih poremećaja ritma[5,23]. S druge pak strane, rezultati nekih istraživanja ne podupiru vjerojatnost povoljnog djelovanja benzodiazepina na AT, srčanu frekvenciju ili na razvitak fatalnih i nefatalnih aritmija[26,27].

Zaključak

Kardiovaskularne bolesti su prioritetni javnozdravstveni problem u većini zemalja razvijenog svijeta. Obzirom na veliku učestalost anksioznosti, kao i narastajuće spoznaje o njenoj ulozi kao neovisnog čimbenika u nastanku ateroskleroze, ali i drugih akutnih i kroničnih kardiovaskularnih bolesti, čini se da je važnost otkrivanja i liječenja anksioznosti u ovom smislu trenutno podcijenjena. Istovremeno, barem neki od lijekova iz skupine anksiolitika mogli bi imati povoljne kardiovaskularne učinke, neke u kroničnom liječenju, a neke i u akutnoj primjeni. Stoga, ne bi bilo neočekivano da boljim i potpunijim liječenjem anksioznosti možda ujedno djelujemo na pojavu ili prognozu

The anxious persons also seem to show a higher risk of occurrence of coronary heart disease (CHD) on average, 11 years following the diagnosed anxiety disorder and the anxiety is an independent predictor of mortality from cardiovascular diseases[11]. Besides, in elderly men, anxiety represents an independent factor of risk of morbidity from myocardial infarction and in such patients the anxiety is, following the survived event, also related with reduced baroflex control of the heart function[12,13].

Potential more positive cardiovascular effects of benzodiazepine

By amplification of inhibitory effect of GABA neurotransmitters in the central nervous system, anxiolytics from the group of benzodiazepines exert their effects in terms of reduction of anxiety, achievement of sedation and myorelaxation and potential positive effects on cardiovascular system[14-16]. These drugs are also effective peripherally through benzodiazepine receptors that are found in the heart in leukocytes, whereas their total cardiovascular effect is additionally exerted[17-20].

Some of the recent researches clinically verify the reasonableness of the idea of positive effect of benzodiazepine on cardiovascular functions. Intravenous application of diazepam in dose of 5 mg in healthy normotensive patients has caused a significant decrease in systolic and medium blood pressure (BP) without impact on heart rate, probably by centrally mediated lowering of total sympathetic activity[21]. In patients suffering from mitral valve disease during diagnostic cardiac catheterization, the application of diazepam has caused lowering of pressure in the aorta and pulmonary artery and decreased heart rate[22]. Several researches relate the application of benzodiazepine to lowered pressure in the left atrium at the end of diastole and to lowered peripheral resistance[23-25]. In patients with ischemia and myocardial infarction, benzodiazepine could reduce the level of catecholamine in blood, vascular resistance of coronary arteries and help the inhibition of blood platelets[23]. By causing coronary vasodilatation, lowering heart rate, and applying mechanisms that include the effects on the autonomic nervous system, it is possible for benzodiazepines to have certain protective effect against the ventricular arhythmias[5,23]. On the other hand, some research findings do not support the probability of positive effects of benzodiazepine on BP, heart rate or development of fatal and non-fatal arrhythmia[26,27].

Conclusion

Cardiovascular diseases are the prioritized public healthcare problem in the most of the countries in the developed world. Considering high frequency of anxiety and more information about its role as the independent factor in occurrence of atherosclerosis and other acute and chronic cardiovascular diseases, the importance of diagnosing and treatment of anxiety in this sense seems to be underestimated. At the same time, at least some of the drugs from the group of anxiolytics may have positive cardiovascular effects, some in chronic treatment and some in acute application. Therefore, it is likely that better and more thorough

kardiovaskularnih bolesti, no za provjeru ove hipoteze neophodna su daljnja dobro osmišljena istraživanja.

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treatment of anxiety may lead to occurrence or prediction of cardiovascular diseases, but further well designed researches are required for checking this hypothesis.

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