Telmisartan inhibits the progression of cardiomyopathy in daunorubicin treated rats: the role of advanced glycation end products

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Abstrak

Latar belakang: Antrasiklin diketahui dapat menimbulkan toksisitas pada jantung melalui mekanisme peningkatan pembentukan advanced glycation end-products (AGEs), yakni pentosidine dan Nε-(carboxylmethyl)lysine (CML).
Penelitian ini bertujuan mengetahui efek telmisartan (TLM) suatu antagonis reseptor angiotensin II (ARB) terhadap
toksisitas jantung yang diinduksi oleh antrasiklin.
Metode: Tikus galur Sprague Dawley dibagi secara acak menjadi 3 kelompok: kelompok pertama mendapat daunorubisin
(DNR) 3 mg/kgBB dua hari sekali hingga mencapai dosis kumulatif 9 mg/kgBB. Kelompok kedua mendapat DNR ditambah
TLM 10 mg/kgBB/hari, secara oral selama 6 minggu, sedangkan kelompok kontrol (CTL) hanya mendapat pelarut DNR.
Rerata tekanan darah (MBP), tekanan ventrikel kiri (LVP), tekanan diastolik akhir ventrikel kiri (LVEDP), dan kontraktilitas
ventrikel (±dP/dt) diukur dengan menggunakan Powerlab. Sedangkan fraksi ejeksi (EF) dan fraksi pemendekan (FS) dinilai
dengan ekokardiografi. Ekspresi reseptor AGE (RAGE), pentosidin, dan CML diperiksa dengan imunohistokimia dan
western blot.
Hasil: DNR menyebabkan perburukan beberapa parameter hemodinamik yang dapat diperbaiki oleh TLM, yakni :
LVP : 124,3 ± 6,0; 111 ± 7; dan 115,1 ± 5,4 mmHg, untuk kelompok CTL, DNR, dan DNR-TLM. LVEDP: 7,5 ± 0,9;
10,7 ± 0,3; 8,7 ± 0,4 mmHg, dan ; +dP/dt: 6813 ± 541; 4800 ± 345; 5950 ± 398 mmHg/s. Hal yang sama juga terlihat
pada parameter ekokardiografi, yakni: EF: 78,9 ± 1,8; 59.6 ± 1,4; 76,2 ± 2,75 %; FS: 42,8 ± 1,7; 29,1 ± 1,3; 41 ±
2,7 % untuk kelompok CTL, DNR and DNR-TLM. Ekspresi protein RAGE, pentosidine dan CML meningkat pada
pemberian DNR yang kemudian dihambat dengan pemberian bersama TLM.
Kesimpulan: AGE berperan pada toksisitas jantung akibat pemberian DNR. Telmisartan dapat menghambat efek tersebut
dengan menurunkan ekspresi RAGE.
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Abstract
Background: Anthracyclines have been reported to induce cardiotoxicity through mechanisms involving formation of
advanced glycation end-products (AGEs), including pentosidine and Nє-(carboxymethyl) lysine (CML). We investigated the
potential utility of telmisartan (TML), an angiotensin II receptor antagonists (ARB) on anthracycline-induced cardiotoxicity.
Methods: Three groups of Sprague-Dawley rats were treated as follows: The first group received daunorubicin (DNR)
3 mg/kgBW every alternating day to reach a cumulative dose of 9 mg/kg DNR . The second group received DNR plus
TLM at a dose10 mg/kgBW, by oral gavage for 6 weeks, and the third group served as control group (CTL) which only
received vehicle of DNR. Mean blood pressure (MBP) peak left ventricular pressure (LVP), LV end-diastolic pressure
(LVEDP), and intra-ventricular contractility (±dP/dt) were recorded by using Powerlab instrumentation. Ejection
fraction (EF), and fractional shortening (FS) were measured by echocardiography. Expression of receptor of AGE
(RAGE), pentosidine and CML were measured by immunohistochemistry and Western blot in LV tissue.
Results: DNR treatment was associated with significant weakening of some hemodynamic parameters which could
be reversed by TML (LVP: 124.3 ± 6.0; 111 ± 7; and 115.1 ± 5.4 mmHg, respectively in CTL, DNR and DNR-TLM
groups; LVEDP: 7.5 ± 0.9; 10.7 ± 0.3; 8.7 ± 0.4 mmHg, respectively; +dP/dt: 6813 ± 541; 4800 ± 345; 5950 ± 398
mmHg/s, respectively). The same phenomenons were also observed on echocardiographic parameters (EF: 78.9 ± 1.8;
59.6 ± 1.4; 76.2 ± 2.75 %, resepectively; FS: 42.8 ± 1.7; 29.1 ± 1.3; 41 ± 2.7 %) respectively. Expression of RAGE as
well as pentosidine and CML were increased in DNR-rats. TML treatment ameliorated these changes.
Conclusion: These results suggested the role of AGE formation in DNR-induced cardiotoxicity and telmisartan could
inhibit the progression of cardiac toxicity at least in part by reduction RAGE expressiom.