

## 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 N<sup>ε</sup>-(carboxymethyl)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 ( $\pm dP/dt$ ) 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 :  $124,3 \pm 6,0$ ;  $111 \pm 7$ ; dan  $115,1 \pm 5,4$  mmHg, untuk kelompok CTL, DNR, dan DNR-TLM. LVEDP:  $7,5 \pm 0,9$ ;

$10,7 \pm 0,3$ ;  $8,7 \pm 0,4$  mmHg, dan ;  $+dP/dt$ :  $6813 \pm 541$ ;  $4800 \pm 345$ ;  $5950 \pm 398$  mmHg/s. Hal yang sama juga terlihat

pada parameter ekokardiografi, yakni: EF:  $78,9 \pm 1,8$ ;  $59,6 \pm 1,4$ ;  $76,2 \pm 2,75$  %; FS:  $42,8 \pm 1,7$ ;  $29,1 \pm 1,3$ ;  $41 \pm$

$2,7$  % 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 N<sup>ε</sup>-(carboxymethyl) lysine (CML). We investigated the

potential utility of telmisartan (TLM), 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 dose 10 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 ( $\pm$ 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 TLM (LVP:  $124.3 \pm 6.0$ ;  $111 \pm 7$ ; and  $115.1 \pm 5.4$  mmHg, respectively in CTL, DNR and DNR-TLM

groups; LVEDP:  $7.5 \pm 0.9$ ;  $10.7 \pm 0.3$ ;  $8.7 \pm 0.4$  mmHg, respectively;  $\pm$ dP/dt:  $6813 \pm 541$ ;  $4800 \pm 345$ ;  $5950 \pm 398$

mmHg/s, respectively). The same phenomenons were also observed on echocardiographic parameters (EF:  $78.9 \pm 1.8$ ;

$59.6 \pm 1.4$ ;  $76.2 \pm 2.75$  %, respectively; FS:  $42.8 \pm 1.7$ ;  $29.1 \pm 1.3$ ;  $41 \pm 2.7$  %) respectively. Expression of RAGE as

well as pentosidine and CML were increased in DNR-rats. TLM 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 expression.