RINGKASAN

Pengaruh dosis dan lama pemberian amlodipin terhadap gingiva tikus putih *(Rattus norvegicus)*

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Amlodipin merupakah salah satu obat golongan dihidropiridin yang banyak digunakan untuk perawatan kelainan kardiovaskuler. Salah satu efek yang tidak dinginkan akibat penggunaan amlodipin adalah terjadinya hiperplasi gingiva. Prevalensi terjadinya hiperplasi gingiva akibat penggunaan amlodipin ini hanya 20-30%, namun karena pada saat ini obat ini banyak digunakan dan hiperplasi gingiva diduga ada hubungannya dengan terjadinya tumor, sehingga hal ini perlu mendapat perhatian.

Tujuan penelitian ini adalah membuktikan adanya pengaruh dari dosis dan lama pemberian amlodipin terhadap gingiva ditinjau dari parameter nilai indeks stimulasi proliferasi limfosit T, kadar sitokin IL-1β, TNF α, dan IL-6 serta perubahan histopatologis pada hewan coba tikus putih.

Dilakukan penelitian eksperimen laboratorium dengan rancangan *factorial design*. Sampel penelitian ini adalah tikus putih *(Rattus norvegicus)* galur Sprague Dawley, jenis kelamin jantan, berumur 6-7 minggu dengan berat badan antara 200-250 gram. Dosis amlodipin yang diberikan kepada tikus adalah 0 (kontrol), 0,45, 0,90 dan 1,80 mg/kg BB, sedangkan lama pemberian amlodipin adalah 30, 60 dan 90 hari. Eksperimen pertama adalah mengukur nilai indeks stimulasi proliferasi limfosit T dari biakan sel darah tepi yang distimulasi dengan concanavalin A, PHA-P, distimulasi dengan concanavalin A dan diberi paparan amlodipin, dan diberi paparan amlodipin saja. Darah tepi diambil dari sudut mata kanan pada plexus retroorbitalis, selanjutnya dilakukan isolasi sel limfosit T dengan ficoll-isopaque. Limfosit T kemudian dilakukan kultur, sebagian sumuran pada plate kultur diberi MTT untuk dilakukan pengukuran indeks stimulasi proliferasi sel limfosit T. Eksperimen kedua adalah mengukur kadar IL-1β, IL-6 dan TNF-α dari biakan sel darah tepi dengan metode Elisa. Supernatan yang diukur kadarnya berasal dari kultur limfosit T. Eksperimen ketiga adalah mengukur kadar IL-1β, IL-6 dan TNF-α dari jaringan lokal gingiva dengan metode Elisa. Sampel yang digunakan untuk pemeriksaan berasal dari gingiva yang diambil dari bagian anterior rahang bawah yang dilakukan homogenisasi, selanjutnya supernatannya digunakan untuk pemeriksaan kadar ketiga sitokin tersebut. Eksperimen keempat adalah menghitung jumlah sel fibroblas gingiva dari sediaan histopatologis dengan mikroskop cahaya yang dilengkapi dengan occular grid. Sampel yang digunakan untuk membuat sediaan histopatologis adalah gingiva rahang bawah regio anterior yang diambil beserta tulang alveolarnya, kemudian dilakukan dekalsifikasi menggunakan EDTA 10% dalam solusi 7,5% *polyvinylpyrolidone*. Setelah gigi dan jaringan kerasnya lunak, kemudian dilakukan proses pembuatan sediaan histopatologis dengan pewarnaan hematoksilin eosin.

Data penelitian dianalisis menggunakan anava dua jalur, LSD dan analisis regresi. Hasil penelitian menunjukkan bahwa: 1) dosis amlodipin berpengaruh terhadap gingiva tikus putih dengan parameter nilai indeks stimulasi proliferasi limfosit T, kadar IL-1β, IL-6 dan TNF-α dari jaringan lokal gingiva serta jumlah sel

fibroblas gingiva ($p<0,05$); 2) lama pemberian amlodipin berpengaruh terhadap gingiva tikus putih dengan parameter kadar IL-1β, IL-6 dan TNF-α dari jaringan lokal gingiva, serta jumlah sel fibroblas gingival ($p<0,05$); 3) interaksi dosis dan lama pemberian amlodipin berpengaruh terhadap kadar IL-1β, IL-6 dan TNF-α dari jaringan lokal gingiva serta terhadap jumlah sel fibroblas gingiva ($p<0,05$); 4) ada hubungan proliferasi limfosit T dengan kadar IL-1β, IL-6 dan TNF-α dari biakan sel darah tepi ($p<0,05$); 5) ada hubungan kadar IL-1β, IL-6 dan TNF-α dari jaringan lokal gingiva dengan jumlah sel fibroblas gingiva ($p<0,05$).

Dari hasil penelitian dapat disimpulkan bahwa dosis dan lama pemberian amlodipin berpengaruh terhadap terjadinya hiperplasi gingiva pada tikus putih.

SUMMARY

The effect of dosage and duration of amlodipine given orally on the gingival of rats (Rattus norvegicus)

A. Haris Budi Widodo

Currently, amlodipine, a dihydropyridine calcium antagonist is being used increasingly for treatment of cardiovascular disorders. One of some adverse reactions from long use of amlodipine is gingival hyperplasia. Prevalence of gingival hyperplasia because of amlodipine use is about 20-30%, however, since this drug is used increasingly and there is a possible relation between gingival hyperplasia and tumorogenesis, it is important to review intensively such side effect.

The aim of this study was to examine the effects of different dosage and duration of amlodipine given orally on rat gingival using the following parameters value of stimulation index of T lymphocyte proliferation, level of IL-1β, IL-6, TNF-α and account of gingival fibroblast cell from histophatological picture.

An experimental laboratory research was performed with factorial design application. Sample of this research was rats (Rattus norvegicus) Sprague Dawley strain, male, 6-7 weeks and body weight 200-250 grams. Dosage of amlodipine given to rats was 0 (control); 0.45; 0.90; and 1.80 mg/kg BW, duration of treatment was divided into 30, 60 and 90 days. The first experiment-measured stimulation index of T lymphocyte proliferation from PBMC which was stimulated by concanavalin A, PHA-P, concanavalin A and amlodipine, and amlodipine only. Blood peripheral was taken from right corner eye in plexus retroorbitalis, then T lymphocyte was isolated by ficoll isopaque. Then, PBMC was cultured, a part of well on culture plate was treated with MTT to measure of T lymphocyte proliferation. Second experiment measured the level of IL-1β, IL-6 and TNF-α from PBMC. Supernatant measured was from T lymphocyte cultured. Third experiment measured the level of IL-1β, IL-6 and TNF-α from local gingival tissues. The sample used was from gingival mandibular anterior region which was homogenized. Then its supernatant was taken for measuring the level of IL-1β, IL-6 and TNF-α. Fourth experiment was counting gingival fibroblast cell number from histopatological preparation using light microscope with ocular grid. The gingival which was used for histophatological preparation from mandibular anterior region was taken with their alveolar bone. Then its was decalcified using 10% EDTA in 7,5% polyvinilpyrolidone solution. After bone alveolar became soft, it was made into histophatological preparation and colored by hematoxylin-eosin.

Research data were analyzed using two way anova, LSD and regression analyses. The result demonstrated that: 1) different dosage of amlodipine had effects on rat gingival with parametric level of IL-1β, IL-6 and TNF-α from local gingival tissue; as well as the number of fibroblast gingival cell ($p<0,05$); 2) different duration of amlodipine use had effects on rat gingival with parametric level of IL-1β, IL-6 and TNF-α from local gingival tissue; as well as the number of fibroblast gingival cell ($p<0,05$); 3) interaction of different amlodipine dosage and duration had effects on rat gingival with parametric level of IL-1β, IL-6 and TNF-α from local gingival tissue; as well as the number of fibroblast gingival cell ($p<0,05$); 4) there was a relation

between T lymphocyte proliferation with the level of IL-1β, IL-6 and TNF-α from PBMC ($p<0,05$); 5) there was a relation between the level of IL-1β, IL-6 and TNF-α from local gingival tissues with the fibroblast cell number ($p<0,05$).

The results of this research concluded that different dosage and duration of amlodipine use had caused gingival hyperplasia on rats.

ABSTRACT

The effect of dosage and duration of amlodipine given orally on the gingival of rats *(Rattus norvegicus)*

A. Haris Budi Widodo

Amlodipine, a calcium channel blocking agent has been widely used in medical practice for cardiovascular disorders management. However, this drug has several adverse reactions such as gingival hyperplasia. This study was conducted to examine the effects of different dosage and duration of amlodipine given orally on rat gingival using indicators namely stimulation index of T lymphocyte proliferation value, IL-1β, IL-6, TNF-α levels and gingival fibroblast cell number.

This research used 108 male Sprague Dawley rats. The rats were divided into 12 groups randomly. Rats in each group daily-received amlodipine orally at a dosage of 0 (control), 0,45; 0,90 and 1,8 mg/kg body weights for 30, 60 and 90 days. The rats blood was taken from plexus retroorbitalis according to their group then PBMC was cultured. Then stimulation index of T lymphocyte proliferation value and IL-1β, IL-6 and TNF-α levels were measured. At the end of this study, rats were sacrificed to obtain their gingival tissues for histophatologic preparation then their gingival fibroblast cells were counted. Other part of gingival tissues was used as a sample for measured of IL-1β, IL-6 and TNF-α levels.

Research data were analyzed using two way anova, LSD and regression analyses. The result demonstrated that: 1) different dosage of amlodipine had effects on rat gingival with parametric level of IL-1β, IL-6 and TNF-α from local gingival tissue; as well as the number of fibroblast gingival cell ($p<0,05$); 2) different duration of amlodipine use had effects on rat gingival with parametric level of IL-1β, IL-6 and TNF-α from local gingival tissue; as well as the number of fibroblast gingival cell ($p<0,05$); 3) interaction of different amlodipine dosage and duration had effects on rat gingival with parametric level of IL-1β, IL-6 and TNF-α from local gingival tissue; as well as the number of fibroblast gingival cell ($p<0,05$); 4) there was a relation between T lymphocyte proliferation with the level of IL-1β, IL-6 and TNF-α from PBMC ($p<0,05$); 5) there was a relation between the level of IL-1β, IL-6 and TNF-α from local gingival tissues with the fibroblast cell number ($p<0,05$).

The results of this research concluded that different dosage and duration of amlodipine use had caused gingival hyperplasia on rats.

Key word: Amlodipine, IL-1β, TNF-α, IL-6, fibroblast, gingival hyperplasia