

Kožne nuspojave povezane s primjenom amlodipina

Cutaneous Adverse Drug Reactions Induced by Amlodipine

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SAŽETAK: Kožne nuspojave povezane s korištenjem amlodipina su rijetko opisane. Najčešća kožna reakcija povezana s tim lijekom je pojava flushinga. Ostale kožne promjene, osim pojave urtikarije i eritematoznog makulopapuloznog osipa, koje su najčešće posljedica alergijske reakcije na ovaj lijek, uključuju i pojavu rosacee i fotodistribuirane teleangiektazije, koje zbog slične kliničke prezentacije ne bi smjelo pogrešno dijagnosticirati kao flushing. Iako su spomenute nuspojave većinom blaže do srednje klinički izražene, one uzrokuju značajnu nelagodu u bolesnika i mogu utjecati na terapijsku suradljivost. Osim spomenutih, primjena amlodipina je povezana i s nekoliko ozbiljnih i nepredvidivih kožnih nuspojava koji uključuju vaskulitis uzrokovan lijekovima te pojavu Steven Johnsonova sindroma. Spomenute kožne nuspojave su karakterizirane visokim morbiditetom te čak mogućim smrtonosnim ishodom. Iako su te reakcije općenito rijetke i neuobičajene za primjenu amlodipina, važno ih je identificirati kao moguće reakcije preosjetljivosti uzrokovane tim lijekom.

SUMMARY: Cutaneous adverse reactions associated with amlodipine have been rarely reported. Its most prevalent cutaneous side effect is flushing. Other recognized amlodipine associated skin eruptions, apart from urticaria and erythematous maculopapular rash which are most common allergic reactions, are rosacea and photodistributed telangiectasia which it is important not to misdiagnose as flushing, due to similarities in clinical presentations. Although these are usually mild to moderate skin side effects, they can cause serious discomfort and affect the patient's treatment compliance. Apart from these mild drug reactions, amlodipine use is associated with other more severe and non-predictable skin disorders including drug induced vasculitis and Steven Johnson syndrome. These cutaneous adverse drug reactions are characterized with high morbidity and even possible lethal outcome. Although these reactions are in general rare and uncommon in the use of amlodipine, it is important to acknowledge them as a possible hypersensitivity syndrome induced by this drug.

KLJUČNE RIJEČI: kožna nuspojava, amlodipin, fotodistribuirana teleangiektazija, Steven Johnsonov sindrom.

KEYWORDS: cutaneous adverse drug reaction, amlodipine, photodistributed telangiectasia, Steven Johnson syndrome.

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Uvod

Najčešća kožna nuspojava amlodipina, kao i ostalih blokatora kalcijevih kanala (BKK), je flushing, koji je prolazan, pojavnost mu se smanjuje nakon dužeg razdoblja liječenja¹⁻³, a pojavljuje se u približno 5% bolesnika, s većom incidencijom u muškaraca¹⁻⁵. Iako su kožne nuspojave uzroko-

Introduction

The most common cutaneous side effect of amlodipine as well as other calcium channel blockers (CCBs) is flushing, which is transient, diminishes in intensity with continued treatment¹⁻³ and is experienced by approximately 5% of patients, with greater incidence in women

vane amlodipinom rijetke, od velike je važnosti utvrditi sve moguće kliničke prezentacije s obzirom na to da je prestanak uzimanja lijeka najvažniji korak u liječenju tih nuspojava^{6,7}.

Rosacea i fotodistribuirana teleangiektazija

U novije vrijeme postoji sve više dokaza kako i vazoaktivni lijekovi, primarno BKK kao što je amlodipin, mogu biti provocirajući čimbenici za nastanak rosacee ili pogoršanje već postojeće bolesti^{5,8,9}. S obzirom na to da BKK pripadaju u prvu liniju antihipertenzivnih lijekova koji se koriste u liječenju arterijske hipertenzije⁵, a s obzirom na to da i rosacea spada u najčešće kožne poremećaje, potrebna je daljnja procjena moguće povezanosti. Nadalje, kad god je to moguće te kada su klinički simptomi kožnih nuspojava izraženi, preporučuje se izabrati drugi lijek iz skupine prve linije antihipertenzivnih lijekova umjesto lijekova iz skupine BKK⁵. Osim opisanih promjena, do sada su zabilježeni i slučajevi koji ukazuju na povezanost primjene BKK i pojave fotoosjetljivih reakcija poput pojave teleangiektazija na licu i drugim fotoeksponiranim područjima, koja s vremenom postaju sve izraženija^{7,10-15}.

Iako je patofiziološki mehanizam nastanka iatrogene teleangiektazije još uvijek nedovoljno razjašnjen^{7,10,15}, mogući čimbenici koji mogu pridonijeti nastanku ove promjene su vazodilatatorno djelovanje lijeka kao i moguća interakcija lijeka i sunčeve svjetlosti^{10,15}. Da bi se dijagnostički potvrdile spomenute kožne nuspojave uzrokovane lijekom, potrebno je isključiti prijašnju pojavu rozaceje, teleangiektazija ili flushinga kao i nedavno izlaganje sunčevoj svjetlosti ili korištenje lokalnih kortikosteroidnih pripravaka^{7,10-15}. Iako su spomenute kožne nuspojave uzrokovane amlodipinom blažeg kliničkog tijeka, ako se ne liječe, mogu imati značajan utjecaj na kvalitetu života u bolesnika kao i na terapijsku suradljivost.

Ozbiljne kožne nuspojave uzrokovane lijekovima

Idiosinkratične reakcije povezane s primjenom amlodipina, a koje mogu uzrokovati ozbiljan morbiditet kao i mortalitet, uključuju vaskulitis uzrokovan lijekovima te Steven Johnsonov sindrom. Steven Johnsonov sindrom se pojavljuje kao oblik reakcije preosjetljivosti na neki lijek, a očituje se zahvaćenošću sluznica i razvojem brojnih vezikula i bula te erozija po koži¹⁶⁻¹⁸. Tu kožnu reakciju je karakterizira brzi nastanak te brzo napredovanje i razvoj^{16,17}. Promjene na koži se brzo šire, najčešće su lokalizirane na području trupa s tendencijom konfluiranja i karakterizirane su odvajanjem epidermisa¹⁹. Iako se te reakcije primarno povezuju s korištenjem sulfonamida, nesteroidnih protuupalnih lijekova, antiepileptika te alopurinola, postoje i slučajevi koji ukazuju na povezanost razvoja tih teških kožnih nuspojava s amlodipinom²⁰⁻²³. Vaskulitis uzrokovan lijekovima je druga kožna nuspojava povezana s amlodipinom koja može uzrokovati značajan morbiditet^{24,25}. Ozbiljne kožne nuspojave zahtijevaju hitno obustavljanje lijeka te započinjanje specifične suportivne terapije koja uključuje korištenje kortikosteroida, ciklosporina te intravenskih imunoglobulina ovisno o samom slučaju.

than in men¹⁻⁵. Although cutaneous adverse drug reactions to amlodipine are rare, it is important to identify all possible drug induced clinical presentations since prompt withdrawal of the incriminated agent is the most important step in the treatment of these side effects^{6,7}.

Rosacea and photodistributed telangiectasia

Evidence is emerging that vasoactive drugs, primarily CCBs such as amlodipine, could be triggering factors for rosacea development or aggravation of a pre-existing condition^{5,8,9}. Considering that CCBs belong to the class of recommended first line antihypertensive drugs for the treatment of arterial hypertension⁵, and rosacea being one of the most common skin disorders, this possible association should be carefully evaluated. Furthermore, some researchers suggest that in cases of pronounced clinical symptoms another first-line antihypertensive drug should be recommended instead of CCBs⁵. Additionally, there have also been a few reports suggesting association between use of CCBs and photosensitive reactions with telangiectasia appearing on the face and photoexposed sites, becoming more noticeable with time^{7,10-15}.

Although the underlying pathological mechanism of provoking iatrogenic telangiectasia is still poorly understood^{7,10,15}, potential contributing factors could be the vasodilatory action of the drug as well as possible drug and light interaction^{10,15}. Prior medical history of rosacea, flushing, sun exposure, and the use of topical corticosteroids has to be excluded in order to confirm this diagnosis^{7,10-15}. Although clinical presentation of all of these cutaneous adverse effects is mild or moderate, if left untreated they can affect the patient's quality of life as well as treatment compliance.

Severe cutaneous adverse reactions

Idiosyncratic drug reactions that can cause severe morbidity and even mortality associated with the use of amlodipine include drug induced vasculitis and Steven Johnson syndrome. Steven Johnson syndrome occurs as a hypersensitivity reaction to a particular drug, characterized by the affection of mucous membranes and development of multiple vesiculous/bullous lesions and erosions on the skin¹⁶⁻¹⁸. This cutaneous reaction is characterized by acute onset and rapid progression^{16,17}. The skin lesions are widespread and predominantly on the trunk, with a tendency to become confluent, characterized by detachment of the epidermis¹⁹. Although these reactions have been primarily associated with the use of sulfonamides, nonsteroidal anti-inflammatory drugs, anti-convulsants, and alopurinol, there have been reports on the development of these severe cutaneous reactions after initiation of amlodipine²⁰⁻²³. Drug induced vasculitis is another cutaneous adverse drug reaction associated with amlodipine intake that can cause severe morbidity^{24,25}. Severe cutaneous adverse reactions need prompt withdrawal of the incriminated drug and initiation of specific supportive therapy including corticosteroids, cyclosporine, and intravenous immunoglobulin, depending on the case.

Limfomatoidne reakcije uzrokovane lijekom

Limfomatoidne reakcije uzrokovane lijekom su relativno rijetke promjene^{26,27} koje se mogu očitovati od difuznog eritema s prisutnom deskvamacijom do makula, papula i anularnih plakova na koži, imitirajući tako kožne limfome histološki i/ili klinički²⁷⁻²⁹. Do sada je bilo nekoliko objavljenih slučajeva pojave pseudolimfoma uzrokovanih amlodipinom³⁰⁻³². Prepoznavanje tih promjena može pomoći kliničaru da učini odgovarajuću procjenu i liječenje³¹.

Zaključak

Kožne nuspojave uzrokovane lijekovima, kao što su rosacea, fotodistribuirana teleangiectazija, Steven Johnsonov sindrom, vaskulitis uzrokovan lijekovima te limfomatoidne reakcije uzrokovane lijekovima, povezane su s korištenjem amlodipina. Iako su spomenute nuspojave tog lijeka rijetke, vrlo je važno prepoznati navedene reakcije s obzirom na važnost ranog otkrivanja nuspojave i hitnog obustavljanja lijeka kao najvažnijega koraka u liječenju.

Lymphomatoid drug reactions

Lymphomatoid drug reactions are relatively rare^{26,27} presenting as diffuse erythema with desquamation to macules, papules, and annular plaques on the skin, mimicking cutaneous lymphoma histologically, clinically, or both²⁷⁻²⁹. A few cases of pseudolymphoma induced by amlodipine have been reported³⁰⁻³². Recognition of these findings may help clinicians to prepare appropriate clinical evaluation and treatment³¹.

Conclusion

Cutaneous adverse drug reactions such as rosacea, photodistributed telangiectasia, Steven Johnson syndrome, drug induced vasculitis, and lymphomatoid drug reactions have been associated with use of amlodipine. Although these are rare side effects of this drug, it is important to acknowledge the possibility of these reactions because of the importance of early detection and prompt withdrawal of the incriminated drug as the main therapeutic strategy.

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