Fotodistribuirana hiperpigmentacija uzrokovana diltiazemom

Photodistributed Hyperpigmentation Induced by Diltiazem

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SAŽETAK: Fotoosjetljivost uzrokovana lijekovima uključuje pojavu promjena na koži kao posljedicu interakcije lijeka i UVA i UVB zraka. U toj skupini fotodermatoza primarno se radi o fototoksičnim reakcijama koje se očituju različitim kliničkim slikama. Hiperpigmentacije na koži su jedna od najčešćih kliničkih prezentacija tih reakcija. Pojava tih kožnih promjena je dosad bila povezana s uzimanjem određenih antibiotika, antiepileptika, antihipertenziva te antidepresiva. Međutim, u novije vrijeme neka istraživanja ukazuju na povezanost pojave fotodistribuirane hiperpigmentacije s korištenjem diltiazema. Hiperpigmentacije uzrokovane lijekovima u većini slučajeva ne reagiraju na konvencionalnu terapiju stečenih poremećaja pigmentacije. Najvažniji korak u terapiji jest ukidanje diltiazema, koji bi trebao biti zamijenjen drugim antihipertenzivnim lijekom, kao jedina mjera koja omogućuje postupnu regresiju kožnih promjena. Bolesnik bi također trebao biti upućen u to da će uz primjenu adekvatnih mjera regresija promjena biti potpuna, međutim, tek kroz razdoblje od nekoliko mjeseci. Prevencija te kožne nuspojave uzrokovane diltiazemom je moguća, i to primjenom krema sa zaštitnim faktorom, s obzirom na to da UVA i UVB zrake imaju značajnu ulogu u nastanku tih promjena.

SUMMARY: Drug-induced photosensitivity refers to the development of cutaneous disease as a result of the interaction of the drug and UVA and UVB light. These are primarily phototoxic reactions presenting in different clinical patterns. Skin hyperpigmentation presents as one of the most frequent phototoxic reactions. It has been associated with the use of certain antibiotics, antiepileptics, antihypertensive drugs as well as antidepressant medications. Recently, there have been reports suggesting association between use of diltiazem and appearance of photodistributed hyperpigmentation. This drug-induced hyperpigmentation is usually refractory to conventional treatment options. The most important step in treatment management is withdrawal of the incriminating agent. Once hyperpigmentation has been established, diltiazem should be discontinued and replaced with another antihypertensive agent, as it is essential for improvement and gradual resolution of the hyperpigmentation. The patient should be reassured that with proper management, the hyperpigmentation is a reversible process, but informed that for total resolution of skin lesions it may take many months. Prevention of this cutaneous adverse drug reaction may be possible with the use of appropriate photoprotection. Consequently, for all patients on diltiazem, it is imperative to recommend a broad-spectrum sunscreen, as UVA and UVB radiation may both play a significant role in diltiazem-induced photodistributed hyperpigmentation.

KLJUČNE RIJEČI: fotodistribuirana hiperpigmentacija, hiperpigmentacija uzrokovana lijekovima, diltiazem, fototoksična reakcija, fotoprotekcija.

KEYWORDS: photodistributed hyperpigmentation, drug-induced hyperpigmentation, diltiazem, phototoxic reaction, photoprotection.

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Uvod

Diltiazem hidroklorid je antihipertenzivni lijek iz skupine blokatora kalcijskih kanala, koji je do sada povezivan s razvojem velikog broja kožnih nuspojava[1-6]. Kad govorimo o hiperpigmentacijama uzrokovanih lijekovima, diltiazem je jedan od najčešćih lijekova povezanih s tim poremećajem[1-4,7-23]. Cilj ovog članka je ukazati na kliničku prezentaciju te kožne nuspojave uzrokovane lijekom, identificirati moguće čimbenike rizika, kao i optimalne terapijske opcije.

Klinička slika

Fotodistribuirana hiperpigmentacija je dosad bila povezana s uzimanjem lijekova kao što su amiodaron, minociklin, fenotiazin i imipramin, a očitovala se kao pojava progresivne plavičastosivkaste diskoloracije na fotoeksponiranim područjima na koži[7,24,25]. Odnedavno, postoje istraživanja i prikazi slučajeva koji ukazuju na pojavu fotodistribuirane hiperpigmentacije vezane uz primjenu diltiazema[2-4,7-23]. Iako je taj antihipertenziv u uporabi više od 20 godina, ta kožna nuspojava nije bila opisana do 2001. godine[1,15]. Klinička prezentacija uključuje pojavu karakteristične perifolikularne i retikularne hiperpi-

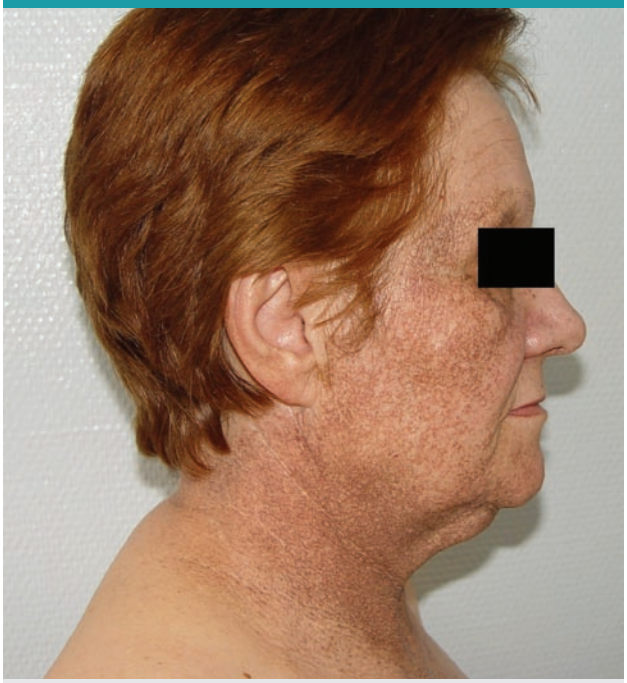
Introduction

Diltiazem hydrochloride, a member of the calcium channel blocker family of antihypertensive medications, has been found to produce many cutaneous reactions[1-6]. In terms of drug induced hyperpigmentation, diltiazem is one of the most common drugs associated with development of this skin disorder[1-4,7-23]. The aim of this review is to describe the clinical presentation of this cutaneous adverse drug reaction, the possible risk factors involved, and optimal therapy management.

Clinical presentation

Photodistributed hyperpigmentation has been associated with drugs such as amiodarone, minocycline, phenothiazines, and imipramine, which produce patterns of progressive blue-gray pigmentation in areas exposed to the sun[7,24,25]. Recently, there have been reports suggesting development of photodistributed hyperpigmentation associated with diltiazem[2-4,7-23]. Although this antihypertensive has been in use for over 20 years, this particular hyperpigmentation was not described until 2001[1,15]. Clinical presentation includes the appearance

FIGURE 1A.



Distribution of hyperpigmentations on the lower two-thirds of the face and neck.

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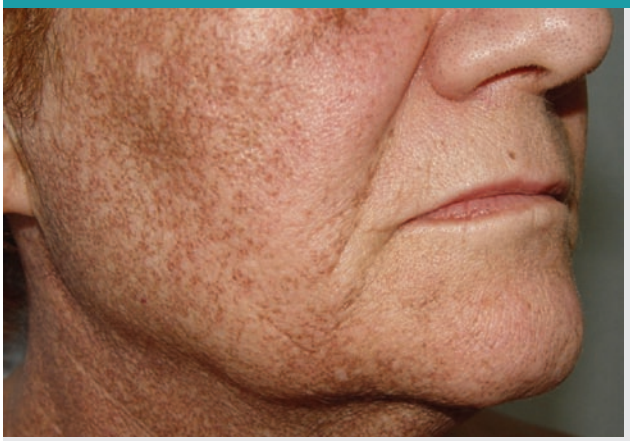
FIGURE 1B.



Appearance of the characteristic gray-brown perifollicular and reticulated hyperpigmentation.

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gmentacije na fotoeksponiranim područjima, primarno na području oko očiju i obraza[1,8,12,20] (**slike 1A** i **1B**). Sama pojava i izgled fotodistribuirane hiperpigmentacije se također mogu razlikovati od retikularne blago sivkaste promjene do sivkastoplavičastih ili tamnosmeđih mrlja[7]. Diferencijalna dijagnoza hiperpigmentacija na licu uključuje melasmu, egzogenu ohronozu, postupalnu hiperpigmentaciju, hiperpigmentaciju uzrokovanu lijekovima, sistemski lupus, alkaptonuriju, makularnu amiloidozu, Addisonovu bolest te hemokromatozu[17].

Čimbenici rizika i patofiziološki mehanizam

Istraživači upućuju na to kako bi čimbenici poput dobi, spola, rase te dužine trajanja terapije mogli imati utjecaj na razvoj fotodistribuirane hiperpigmentacije[16-18]. Tamniji fototipovi kože, posebice osobe afroameričkog, južnoameričkog te azijatskog podrijetla češće su pogođene tim poremećajem[7,12,13,18,20], a pojavnost je također češća u žena, i to u dobi između petog i sedmog desetljeća života[7,8,17,18]. S obzirom na dužinu uzimanja terapije, fotodistribuirana hiperpigmentacija se obično javlja tek nakon 6-8 mjeseci uzimanja lijeka[1,7,8,12,17]. Na temelju dosadašnjih objavljenih slučajeva ne može se povući poveznica između doze diltiazema i pojave hiperpigmentacija[7]. Iako je patogeneza tog poremećaja još uvijek nepoznata, smatra se kako izlaganje sunčevoj svjetlosti može dovesti do stvaranja slobodnih radikala lijeka ili njegovih metabolita[18]. Iako se smatra da je učinak UVA zraka najznačajniji u razvoju fotoosjetljivih reakcija, UVB zrake bi također mogle imati značajnu ulogu u razvoju fotodistribuirane hiperpigmentacije uzrokovane diltiazemom[8]. Lijekovi koji uzrokuju fotoosjetljive reakcije apsorbiraju valne dužine u spektru UVB (290–320 nm)[1], UVA (320–400 nm)[1] ili vidljivom svjetlu (>400 nm) nakon čega dolazi do razvoja fototoksičnog odgovora kože, uzrokovanoga djelovanjem stvorenih slobodnih radikala ili zbog prijenosa energije koji uzrokuje molekularne promjene[1,23-25].

Terapijske opcije i preventivne mjere

Hiperpigmentacija uzrokovana diltiazemom je najčešće refrakterna na terapijske opcije koje se najčešće koriste u dermatologiji u terapiji pigmentacija, a uključuju primjenu hidrokinona, tretinoina te azelaične kiseline[17]. Prekid inkriminirajućega lijeka je jedina terapijska mjera koja omogućuje postupno povlačenje hiperpigmentacije, obično u potpunosti, nakon nekoliko mjeseci od prekida uzimanja lijeka[1,6,12,13,17-19].

Zamjena s drugim blokatorom kalcijskih kanala je opravdana i sigurna, s obzirom na to da se ostali lijekovi iz ove grupe ne povezuju s nastankom fotoosjetljive hiperpigmentacije[1,12,14,18]. Nadalje, preporučuje se odmah uvesti fotoprotektivne mjere, uključujući korištenje krema s visokim zaštitnim faktorom koje apsorbiraju ili mehanički blokiraju UVA i UVB zrake[12]. Na kraju, bolesnik treba biti upoznat da je, uz pravilno poduzete terapijske mjere, hiperpigmentacija reverzibilna[12].

Prevencija te kožne nuspojave je moguća primjenom krema s visokim zaštitnim faktorom koje bi se trebale početi svakodnevno koristiti kod svih bolesnika koji započinju antihipertenzivnu terapiju diltiazemom.[1,12,18]

of the characteristic gray-brown perifollicular and reticulated hyperpigmentation on photoexposed areas, primarily on the periocular area and cheeks[1,8,12,20] (Figure 1A and 1B). The appearance of the photodistributed pigmentation also varies, from reticulated slate gray or blue-gray to darker brown patches[7]. Differential diagnoses of face hyperpigmentation includes melasma, exogenous ochronosis, postinflammatory hyperpigmentation, drug-induced hyperpigmentation, systemic lupus erythematosus, alkaptonuria, macular amyloidosis, Addison disease, and hemochromatosis[17].

Risk factors and pathophysiological mechanism

Researches have suggested that age, sex, race, and duration of therapy could have an impact on the development of photodistributed hyperpigmentation[16-18]. Darker skin phototypes, especially those of African American, Hispanic, and Asian descent, are more commonly affected[7,12,13,18,20] and it is also more frequently found in women between the fifth and seventh decade of life[7,8,17.18]. Regarding the duration of therapy, photodistributed hyperpigmentation usually appears after at least 6-8 months of drug intake[1,7,8,12,17]. Based on the cases reported, no correlation can be found between the dosage of diltiazem and the time of onset of pigmentation[7]. The pathogenesis is unknown, but it has been postulated that sun exposure may lead to the formation of free radicals of the drug or its metabolites[18]. While UVA has been thought to be the main culprit in drug-induced photosensitive reactions, UVB may also possibly play a role in diltiazem-induced photodistributed hyperpigmentation[8]. Drugs that cause photosensitive reactions should exhibit an absorption wavelength in one of the following ranges: UVB (290–320 nm)[1], UVA (320–400 nm)[1], or visible light (>400 nm) after which a phototoxic skin response occurs, either through the development of free radicals or through energy transfer causing molecular change[1,23-25].

Therapy options and preventive measures

Diltiazem induced hyperpigmentation is usually refractory to any treatment options including hydroquinone, tretinoin, and azelaic acid as the most frequently used bleaching agents[17]. Withdrawal of the incriminating agent is the only therapeutic measure which provides gradual resolution of the hyperpigmentation, with full resolution usually occurring several months after the discontinuation of the drug[1,6,12,13,17-19].

For medical management, switching to another calcium channel blocker has been found to be safe, as other calcium channel blockers have not been shown to cause the same photosensitive hyperpigmentation[1,12,14,18]. Additionally, photoprotective measures should be introduced, including the use of a UVB and UVA absorbing or blocking sunscreen[12]. Lastly, patients should be instructed that when proper therapeutic measures are taken, the hyperpigmentation is a reversible process[12].

Finally, prevention of this eruption may be possible with the use of appropriate broad-spectrum sunscreen photoprotection which should be introduced to all patients starting antihypertensive treatment with diltiazem[1,12,18].

Zaključak

Primjena diltiazema u liječenju bolesti srca i krvnih žila je česta te je stoga važno prepoznati taj lijek kao mogući uzrok nastanka fotodistribuirane hiperpigmentacije. Rana detekcija hiperpigmentacije uzrokovane diltiazemom je važna s obzirom na to da je prekid uzimanja lijeka ključni korak u terapiji tog poremećaja kože. Nadalje, provođenje preventivnih mjera, poput fotoprotekcije kod svih bolesnika koji koriste diltiazem, ključno je u prevenciji razvoja te kožne nuspojave povezane s uzimanjem lijeka.

Conclusion

The use of diltiazem in the treatment of cardiovascular diseases is common and should thus be identified as a potential causative medication in the development of photodistributed hyperpigmentation. Early recognition of diltiazem-induced hyperpigmentation is important because discontinuation of the drug is a key aspect of treatment management. In addition, following preventive measures as mandatory photoprotection in all patients using diltiazem is crucial to preventing this cutaneous drug adverse reaction to occur.

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