

Photodistributed hyperpigmentation induced by antihypertensive drugs: two cases report

Dra Rosa Giménez Garcia

Clinical Assitant . Department of Dermatology. Hospital Rio Hortega. Valladolid. Spain

Associate Professor Faculty of Medicine . Valladolid.Spain



University of Valladolid is a public university in the city of Valladolid in the autonomous region of Castile-Leon .Spain

- **Established in the 13th century**
- **it is of the oldest universities in the world**



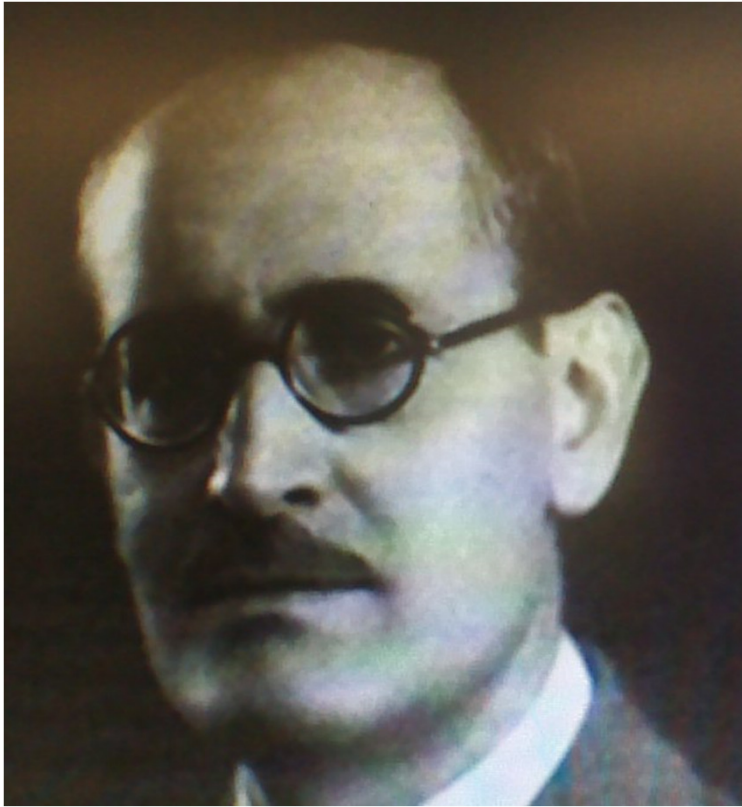
Photodistributed hyperpigmentation induced by antihypertensive drugs: two cases report



Associate Professor .
Department of Medicine, Dermatology and Toxicology.
Faculty of Medicine in Valladolid. Spain



Clinical Assistant. Department Dermatology
Hospital Rio Hortega. Valladolid. Spain



Dr Pio del Rio Hortega

Biography [\[edit\]](#)

Río Hortega was born in Portillo, Valladolid on 5 May in 1882.^[1] He studied locally and qualified to practice medicine in 1905. He obtained his doctorate at the University of Madrid by researching the pathology of brain tumours. In 1913 he was funded to study research histology in France and Germany but the outbreak of war between them forced him to return to Spain.^[1]

He worked with the histologist Santiago Ramón y Cajal and briefly with Wilder Penfield. Ramón y Cajal discovered neurons, Penfield helped explain oligodendroglia.^[2] whilst Rio Hortega discovered microglia.^[3] which are the cells that protect the brain from infection.

He managed to identify microglia between 1919 and 1921 by staining the cells with silver carbonate.^[3] His method of staining also led to the discovery of oligodendroglia in 1921, which both he and Penfield are now credited with.^[2] However it was Rio Hortega who named the cells.^[1]

Photodistributed hyperpigmentation induced by antihypertensive drugs: two cases report

Dra Rosa Giménez Garcia

Clinical Assitant . Department of Dermatology. Hospital Rio Hortega. Valladolid. Spain

Associate Professor Faculty of Medicine . Valladolid.Spain

Hypertension

- “**About one third of adults in most communities** in the developed and developing world have hypertension”
- Hypertension is the **most common chronic condition dealt with by primary care physicians** and other health practitioners

HOW IS HYPERTENSION DEFINED?

- Most major guidelines recommend that hypertension be diagnosed when a person's systolic blood pressure is ≥ 140 mm Hg or their diastolic blood pressure is ≥ 90 mmHg, or both, on repeated examination. The systolic blood pressure is particularly important and is the basis for diagnosis in most patients.

Weber et al. ASH hypertension guidelines. J Clin Hypertens 2014;16:14-26

Hypertension

- Systolic blood pressure (SBP) of 140 mm Hg or above and /or diastolic blood pressure (DBP) of 90 mm Hg or above (adults up to 80 years)
- **Hypertension is an increasing worldwide problem** and it is a well recognized risk factor for cardiovascular disease ; stroke and heart failure
- Often combined with smoking, obesity, physical inactivity and occurs commonly with diabetes

Hypertension

- **Treatment with drugs should be started in patients with blood pressures >140/90 mm Hg in whom lifestyle treatments have not been effective**
- **ANTIHYPERTENSIVE DRUGS ARE VERY COMMONLY PRESCRIBED ii**

Introduction

- **We describe the course of two patients who presented to the dermatology department at our hospital, with antihypertensive drugs induced photodistributed hyperpigmentation**
- **The antihypertensive culprit agents were lercanidipine and telmisartan**

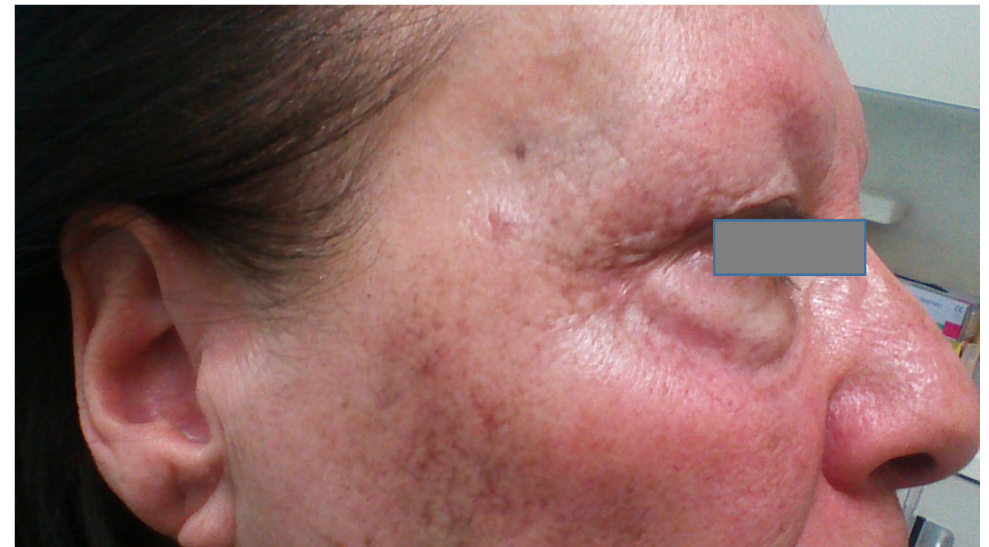
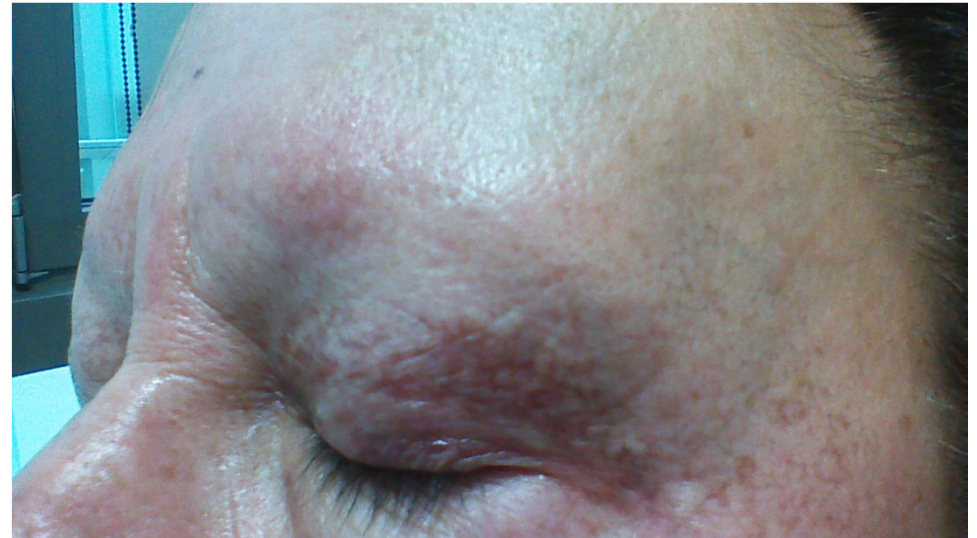
Report of cases. Case 1

- A 68-year-old woman with a past medical history of hypertension and frontal fibrosing alopecia, presented with a 3 months history of **hyperpigmentation on her face** that started in summer after sun exposure
- she had taken **Lercanidipine approximately 2 years before**
- Concomitant medications included simvastatin that she had started many years ago



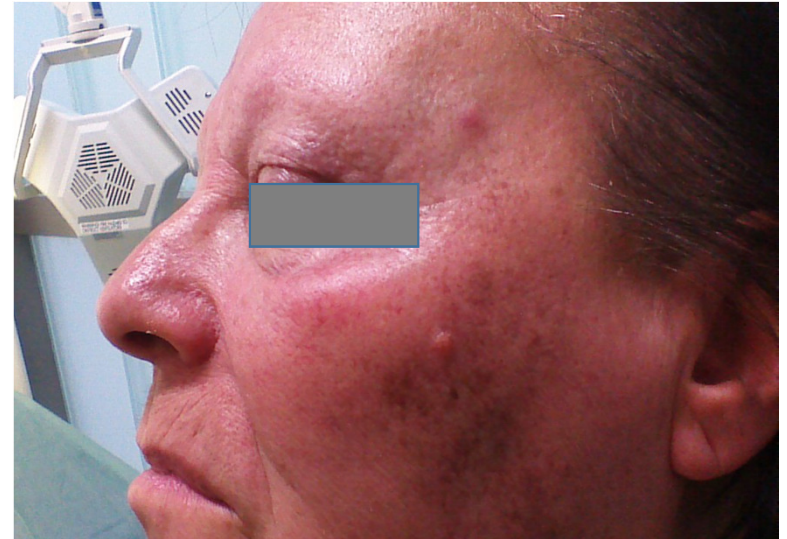
Report of cases. Case 1

- Physical examination showed reticulated, slate-gray to brown, pigmentation without infiltration on her face



Report of cases. Case 1

- Physical examination showed reticulated, gray to brown, pigmentation
- **On the cheek, temple, nose and eyelids regions**

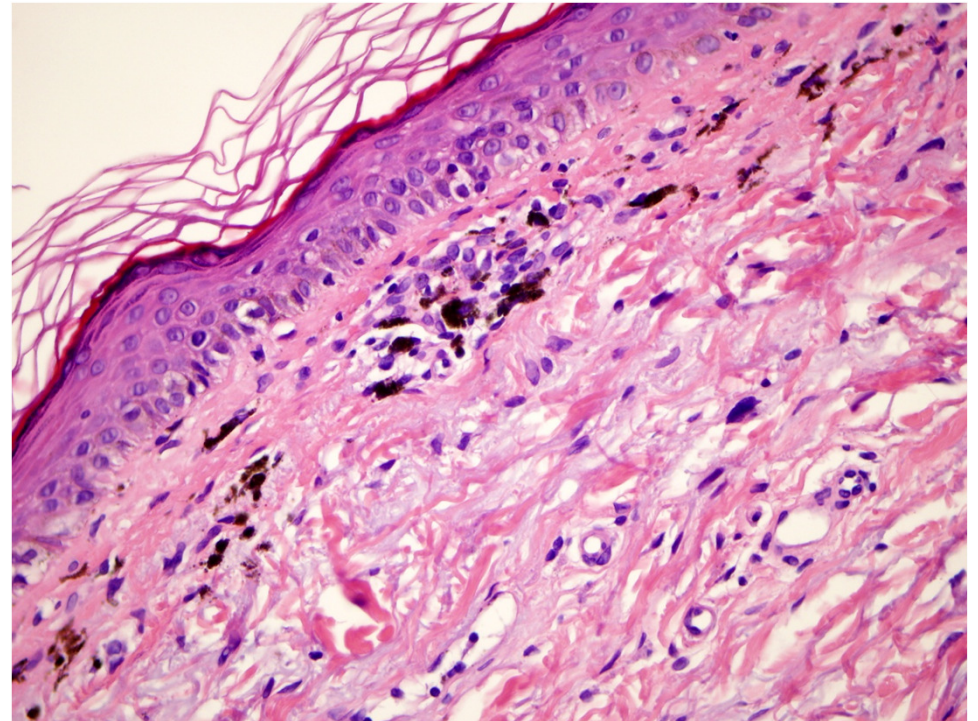


Report of cases. Case 1

Case 1

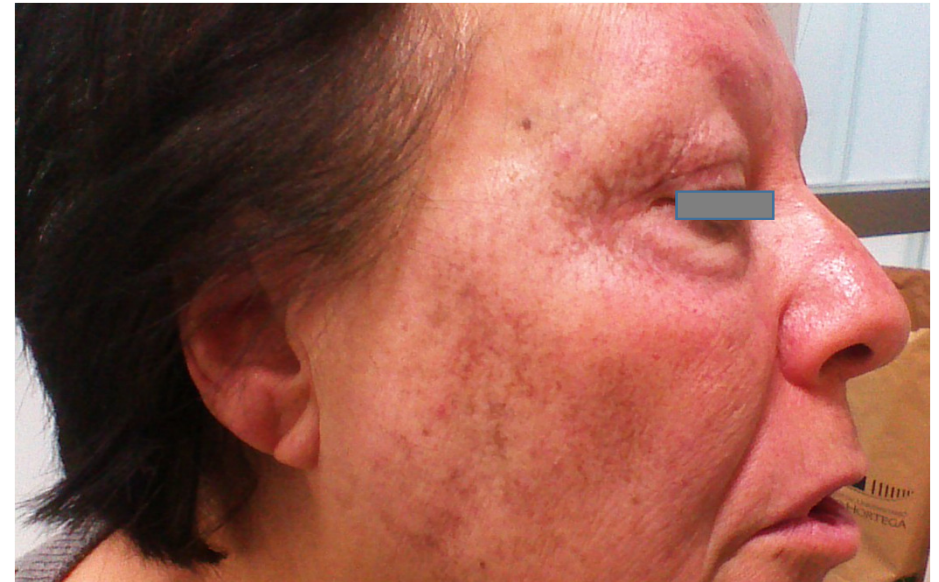
Histological examination revealed vacuolar alteration of the basal layer and prominent pigmentary incontinence

Laboratory testing included liver function test, complete blood cell count, serum urea and creatinine, serologic test for antinuclear antibodies were normal



Report of cases. Case 1

Photodistributed hyperpigmentation due to lercanidipine was suspected



Report of cases. Case 1

She has improved very slowly after discontinuation of lercanidipine

Lercanidipine was replaced with telmisartan- hydrochlorothiazide combination

Photoprotection was advised



4 months after cessation of lercanidipine



PHOTOPROTECTION



Photodistributed hyperpigmentation induced by antihypertensive drugs: two cases report.

Dra Rosa Giménez Garcia. Valladolid.Spain

Report of cases. Case 2

A 79-year-old man was referred to us for evaluation of hyperpigmented lesions

His medical history included prostate cancer and severe kidney disease

He had been given **telmisartan 80 mg** and **hydrochlorothiazide 12.5 mg** daily for essential hypertension for 3 years



Report of cases. Case 2

He had noticed **hyperpigmentation** and **pruritus** on sun exposed areas a few months after starting antihypertensive therapy

Examination showed slate-gray hyperpigmentation on the **face**, anterior aspect of his neck and dorsum of his hands



Report of cases. Case 2

Examination showed slate-gray hyperpigmentation on the face, **anterior aspect of his neck and dorsum of his hands**



Report of cases. Case 2

Laboratory testing revealed anemia and elevated urea and creatinine levels

Results from liver function test, antinuclear antibodies and cholesterol levels were all in normal ranges



Report of cases. Case 2

Photodistributed hyperpigmentation induced by telmisartan was suspected

Discontinuation of the drug and replacement with ramipril along with photoprotection caused gradual reduction of the symptoms and pigmentation had almost entirely faded after 3 months



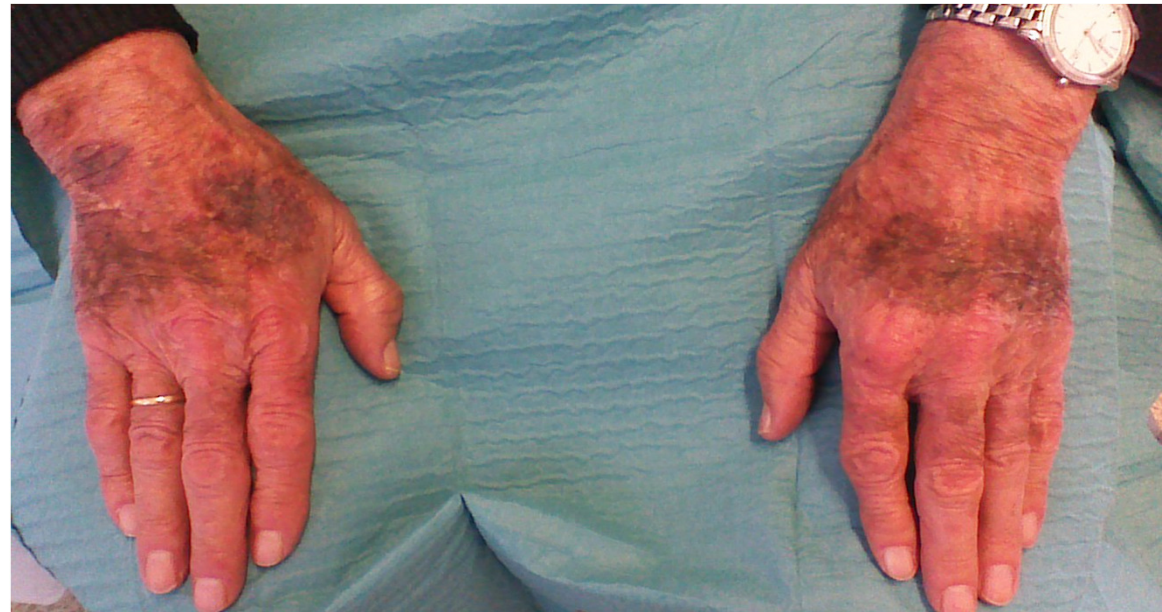
the house where the novelist, poet and playwright [Miguel de Cervantes](#) lived in the year 1605...in Valladolidiii

Discussion

- Drug-induced skin pigmentation is estimated to account for 10% to 20% of all cases of acquired hyperpigmentation
- It has been associated with many different types of medications including antimalarials, amiodarone, cytotoxic drugs, tetracyclines, heavy metals and psicotropic drugs (imipramine, phenothiazines)

Discussion. Drug-induced pigmentation

- Clinical features are variable, with a large range of patterns, colors and distribution

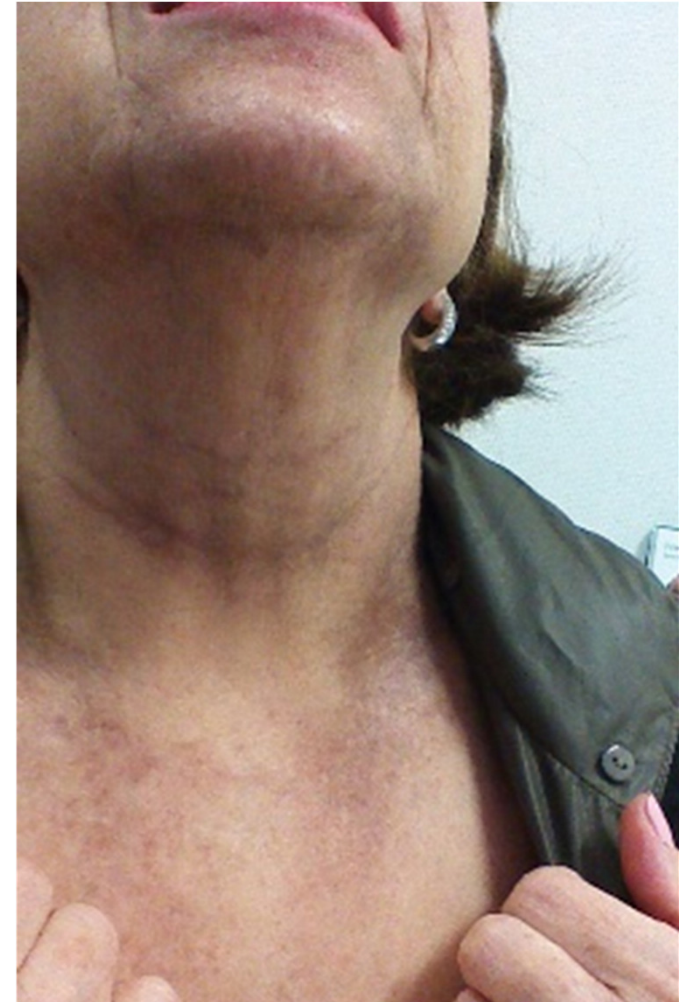


Amiodarone induced blue-gray pigmentation in photoexposed areas

Discussion.

Drug-induced pigmentation

- Clinical features are variable, with a large range of patterns, colors and distribution



antimalarials induced pigmentation

Discussion.

Drug-induced pigmentation

The pathogenesis is still not fully understood

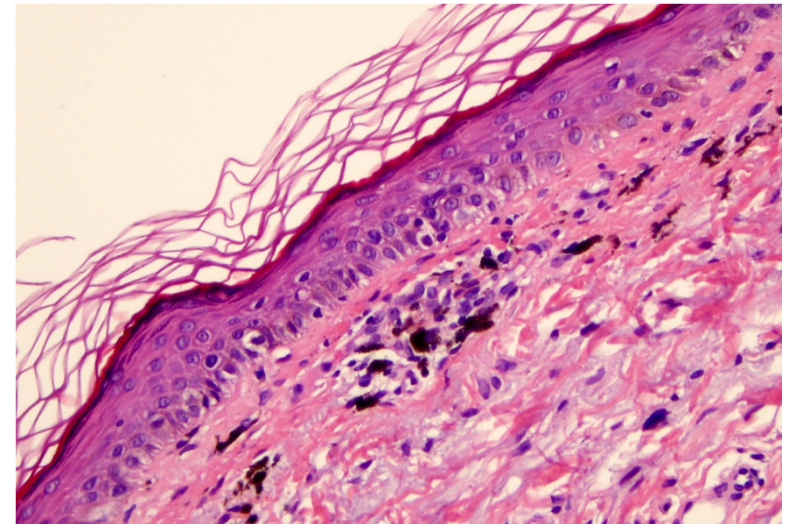
Related to a significant drug or light interaction? Leading to a phototoxic or photolichenoid reaction



Discussion.

Drud-induced pigmentation

- Common histological findings include **pigment deposition in dermal macrophages**, pigment deposition on elastic fibers, yellow-brown granules deposited on macrophages around blood vessels and dermal lipofuscin found in dermis



pigment deposition in dermal macrophages

Discussion. Drug-induced pigmentation

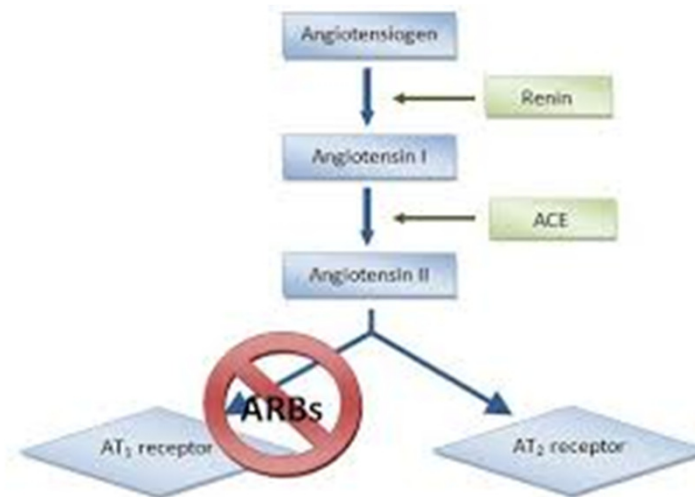
- Many isolated signals do exist reporting pigmentation disorders with ARBs



Gimenez-Garcia R. Hyperpigmentation induced by combination therapy with telmisartan-hydrochlorothiazide. J Clin Hypertens

ANGIOTENSIN RECEPTOR BLOCKERS

- Angiotensin receptor blockers (ARBs) selectively block the binding of angiotensin II to its subtype AT₁ receptor
- Used widely in everyday clinical practice because of their well known effectiveness and proven good tolerability



Dezsi CA. A review of clinical studies on angiotensin II receptor blockers and risk of cancer. *Int J Cardiology* 2014;177:748-53

ANGIOTENSIN RECEPTOR BLOCKERS

- Increasing prescribing rates of these antihypertensive agents are posing an appreciable rise in the amount of queries to pharmacovigilance centres.

AT1-receptor antagonists and psoriasis. Lareb Nederlands Pharmacovigilance Centre. Febr 2006

Taste disorders ARA II. Lareb Nederlands Pharmacovigilance Centre

ANGIOTENSIN RECEPTOR BLOCKERS

Cutaneous reactions described include life-threatening angioedema, urticaria, pruritus, bullous eruptions, generalized rashes, photosensitivity, lichenoid eruptions, psoriasis, erythema multiforme, pseudolymphomatous eruptions and eczematous reactions.

It has also been described cross reactivity between ACE inhibitors and ARBs.

- Tuoraud JP, Louguet C, Collet E, Sgro C, Dalac S, Dutronc Y, Lambert D. Cross-sensitivity between angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonist. *Ann Dermatol Venereol* 2002; 129:1033-6
- Steckelings UM, Artuc M, Wollschläger T, Wiehstutz S, Henz BM. Angiotensin-converting enzyme inhibitors as inducers of adverse cutaneous reactions. *Acta Derm Venereol* 2001; 81:321-325
- McCabe J, Stork C, Mailloux D, Su M. Penile angioedema associated with the use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. *Am J Health Syst Pharm* 2008; 65:420-1
- Vena GA, Cassano N, Coco V, De Simone C. Eczematous reactions due to angiotensin-converting enzyme or angiotensin II receptor blockers. *Immunopharmacol. Immunotoxicol.* 2013; 35:447-50
- Constable S, Farrell J, Naisbii D, King C, Leonard N, Pirmohamed M. Systemic illness with skin eruption, fever and positive lymphocyte transformation test in a patient on irbesartan. *Br J Dermatol* 2006; 155:491-3
- Pfab F, Athanasiadis GI, Kollmar A, Ring J, Ollert M. Lichenoid drug eruption due to an antihypertensive drug containing irbesartan and hydrochlorothiazide. *Allergy* 2006; 61:786-787
- Marquart-Elbaz C, Grosshans E, Alt M, Lipsker D. Sartans, angiotensin II receptor antagonists can induce psoriasis. *Br J Dermatol* 2002; 147:617-618
- Gambini D, Sala F, Gianotti R, Cusini M. Exanthematous reaction to irbesartan. *J Eur Acad Dermatol* 2003; 17:472-473
- Gimenez-Garcia R. Eritema Multiforme inducido por Irbesartan. *Emergencias* 2015;27

ANGIOTENSIN RECEPTOR BLOCKERS

- Nevertheless, there are very few reported cases of skin eruptions related to Telmisartan
- Ferreira O, Mota A, Morais P, Cunha AP, Azevedo F Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) induce by telmisartan Cut Ocul Toxicol 2010; 29:293-295
- Tandon VR, Mahajan A, Khajuria V, Gilani ZH. Angioedema due to fixed dose combination of telmisartan plus Ramipril. J Pharmacol Pharmacother 2014; 5:214-216
- Gimenez-Garcia R. Hyperpigmentation induced by combination therapy with telmisartan-hydrochlorothiazide. J Clin Hypertens 2016;18:361-368



Photodistributed hyperpigmentation induced by antihypertensive drugs: two cases report.

Dra Rosa Giménez Garcia. Valladolid.Spain

Calcium-channel blockers (calcium antagonists Cas)

- Group of antihypertensive medications introduced into clinical medicine in the 1960s
- Agents used for the treatment of a host of cardiovascular disease
- First-line treatment options for hypertension

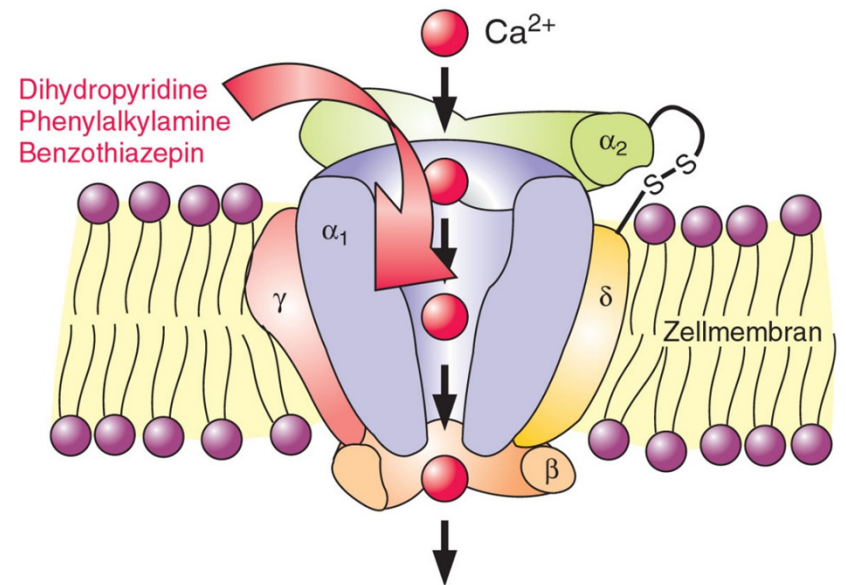
CCBs currently used for treatment of hypertension
Amlodipine
Barnidipine
Bepridil
Clinidipine
Diltiazem hydrochloride
Efonidipine
Felodipine
Fendilline
Isradipine
Lacidipine
Lercanidipine
Mibefradil
Nicardipine
Nisoldipine
Nitrendipine
Nifedipine
Nilvadipine

Sica DA. Pharmacotherapy review: calcium channel blockers. J Clin Hypertens 2006;8:

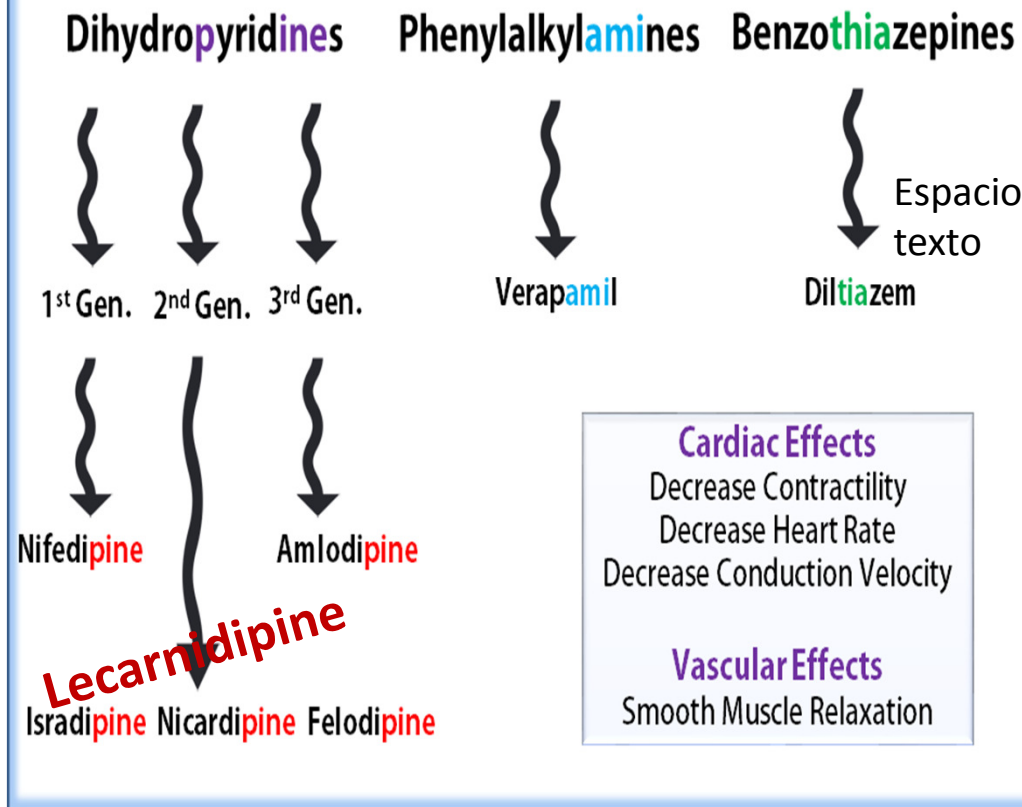
Calcium-channel blockers CCBs (calcium antagonists Cas)

- Property of blocking the transmembrane flow of calcium ions (into the cell through voltage-gated channels)

Binding to the L-type calcium channels in the heart and in smooth muscle of the peripheral vasculature



Calcium Channel Blockers



A group of compounds with distinctive structures and pharmacologic effects

Three subclasses:

Phenylalkylamines

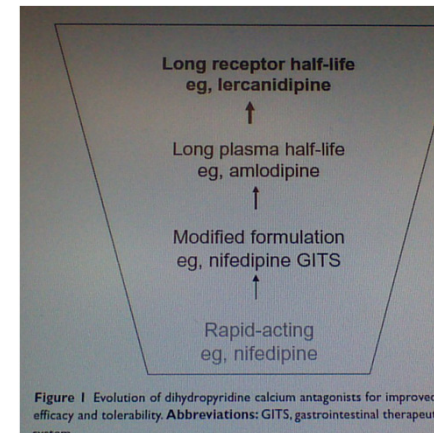
Benzothiazepines

Dihydropyridines DHP: have minimal effect on cardiac conduction or hearth rate while have potent action as arteriolar vasodilators....peripheral and coronary)

Lercanidipine

is a vasoselective lipophilic dihydropyridine calcium antagonist which causes systemic vasodilatation by blocking the influx of calcium ions through L-type calcium channels in cell membranes.

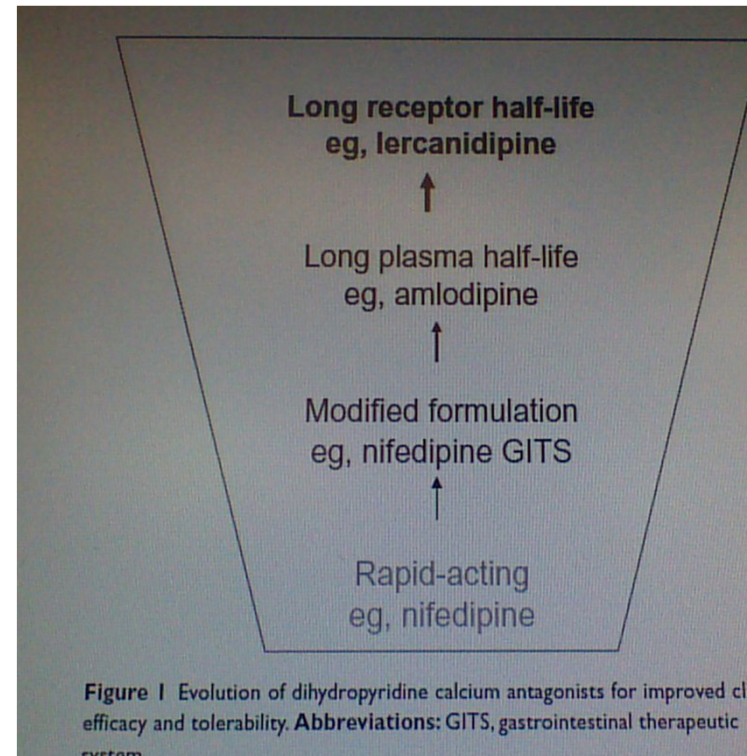
Has a slower onset and longer duration of action than a number of other CCBs



- Beckey Ch Lercanidipine in the treatment of hypertension. *Ann Pharmacother* 2007;41:465-74
- Borgui C. Lercanidipine in hypertension. *Vascular Health and Risk Management* 2005;2005:173-182
- Mc Clellan KJ. Lercanidipine: a review of its use in hypertension. *Drugs* 2000;60:1123-40
- Leonetti G et al . Tolerability of long-term treatment with lercanidipine versus amlodipine and lacidipine in elderly hypertensives. *Am J Hypertens* 2002;15:932-40

LERCANIDIPINE

- Once daily administration of lercanidipine 10 or 20 mg effectively reduce blood pressure
- Antihypertensive effect comparable to that of amlodipine but a better tolerability profile
- Edema –related symptoms (lower limb swelling and heaviness) occurred significantly more often with amlodipine



Borgui C. Lercanidipine in hypertension. *Vascular Health and Risk Management* 2005;2005:173-182

Cutaneous Adverse Reactions associated with Calcium Channel Blockers

- In spite of their widespread use, little data have been published about the spectrum of CAR by CCBs
- It appears that the frequency is low but **occasionally severe reactions** are associated with the use of these drugs
- Range from non serious reactions to serious and potentially fatal conditions , including **erythema multiforme, Steven-Johnson syndrome, toxic epidermal necrolysis(TEN) or exfoliative dermatitis**
- Most serious reactions occur within two weeks of initiating drug therapy

Stern R, Khalsa JH. Cutaneous adverse reactions associated with calcium channel blockers. Arch Intern Med 1989;149:829-832

Cutaneous Adverse Reactions associated with Calcium Channel Blockers

- Flushing, ankle or pedal edema and gingival hiperplasia are common side effects
- Photosensistivity reactions
- Photodistributed facial telangiectasia or on nonphotoexposed areas
- Lichenoid eruptions
- Psoriasiform eruptions (simultaneous intake of β blockers might have a synergist effect on the onset of psoriasis)

Ioulios P, Charalampos M, Efrossini T. The spectrum of cutaneous reactions associated with calcium antagonists: a review of the literature and the possible etiopathogenic mechanisms. Dermatol On line J 2003 ,9:6

Cutaneous Adverse Reactions associated with Calcium Channel Blockers

- Acute generalized exanthematous pustulosis
- Subacute cutaneous lupus erythematosus
- Pemphigus and pemphigoid
- Hypersensitivity syndrome (presented as exfoliative dermatitis or TEN)

Ioulios P, Charalampos M, Efrossini T. The spectrum of cutaneous reactions associated with calcium antagonists: a review of the literature and the possible etiopathogenic mechanisms. Dermatol Online J 2003 ,9:6

LERCANIDIPINE-INDUCED CUTANEOUS REACTIONS

- Drug reaction with eosinophilia and systemic symptoms (DRESS)
 - Macupapular rash
-
- Slim R et al. Drug reaction with eosinophilia and systemic symptoms due to lercanidipine. Indian J Dermatol Venereol Leprol 2016;82:324-326
 - Tuchinda P. et al. Cutaneous adverse reactions to calcium channel blockers. Asian Pac J Allergy Immunol 2014;32:246-50

Cutaneous Adverse Reactions associated with CCBs

- **Photodistributed hyperpigmentation (reticulated or homogenous)..Induced by diltiazem and amlodipine**
- **No previous cases of hyperpigmentation have been reported following exposure to lercanidipine**

.-Scherschun L et al. Diltiazem-associated photodistributed hyperpigmentation: review of 4 cases. Arch Dermatol 2001;137: 179-82

.-Chawla A, Goyal S. Diltiazem-induced hyperpigmentation in an African American woman. J m Acad Dermatol 2002; 46:468-9

.-Kubo Y. et al. Diltiazem-associated Photodistributed hyperpigmentation: report of two Japanese cases and published work review 2010;37.807-811

.-Erbagci Z. Amlodipine associated hyperpigmentation. Saudi Med J 2004; 25:103-105

Conclusions

Drugs-induced hyperpigmentation, in particular with antihypertensive medications must be considered in unexplained pigmented lesions in the elderly

Conclusions

Morphological appearance of the hyperpigmentation is most distinctive....

slate-gray to brown and reticulated

Conclusions

Long –term administration of lercanidipine -as well as diltiazem or amlodipine- may be associated with reticulated hyperpigmentation on sun-exposed areas

Telmisartan and ARBs can induce pigmentation disorders

Conclusions

A long interval between the initiation of antihypertensives therapy and the emergence of the hyperpigmentation (mean duration: 15months)

Conclusions

- Cessation of the suspicious drug results in a gradual fading of the rash, although in some cases it never resolves

Conclusions

- Prevention of photosensitivity involves **adequate protection from the sun with clothing and sunscreens**
- Diet supplementation with antioxidants may be beneficial in increasing the minimum erythemal UV radiation dose

Conclusions

- Hypertension management aims to prevent cardiovascular morbidity and mortality and involves **lifestyle modifications**, antihypertensive drug therapy and treatment of comorbid conditions

Vitamin D has some health benefits , particularly related to skeletal health and some solid tumors

Vitamin D levels in the highest quartile have around half the relative risk of hypertension, obesity, cardiovascular disease or all-cause mortality as those in the lowest quartile...Oral vitamin D supplementation has not effect.....

Liu D, et al UVA irradiation of human skin vasodilates arterial vasculature and lowers blood pressure independently of nitric oxide synthase. J Invest Dermatol 2014;134:1839-46





THANK YOU iiiiii



Photodistributed hyperpigmentation induced by antihypertensive drugs: two cases report.

Dra Rosa Giménez García. Valladolid.Spain