Photodistributed hyperpigmentation induced by antihypertensive drugs: two cases report

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

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

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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 Río Hortega who named the cells.[1]
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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

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
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.

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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
Photodistributed hyperpigmentation induced by antihypertensive drugs: two cases report.
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 colesterol levels were all in normal ranges.
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](http://example.com) lived in the year 1605...in Valladolid
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 psychotropic drugs (imipramine, phenothiazines).
Discussion. Drud-induced pigmentation

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

Amiodarone induced blue-gray pigmentation in photoexposed areas

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Discussion.
Drud-induced pigmentation

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

antimalarials induced pigmentation
Discussion.
Drud-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.
Discussion. Drud-induced pigmentation

• Many isolated signals do exist reporting pigmentation disorders with ARBs

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

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.

- Pfab F, Athanasiadis GI, Kollmar A, Ring J, Ollert M. Lichenoid drug eruption due to an antihypertonic drug containing irbesartan and hydrochlorothiazide. Allergy 2006; 61:786-787
- 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


• 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

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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

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<table>
<thead>
<tr>
<th>CCBs currently used for treatment of hypertension</th>
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<tbody>
<tr>
<td>Amlodipine</td>
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<td>Barnidipine</td>
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<tr>
<td>Bepridil</td>
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<tr>
<td>Clinidipine</td>
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<td>Diltiazem hydrochloride</td>
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<td>Nicardipine</td>
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<td>Nitrendipine</td>
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<tr>
<td>Nifedipine</td>
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<tr>
<td>Nilvadipine</td>
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</tbody>
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Sica DA. Pharmacotherapy review: calcium channel blockers. J Clin Hypertens 2006;8:

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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 hearth and in smooth muscle of the peripheral vasculature
A group of compounds with distinctive structures and pharmacologic effects

Three subclasses:
- **Phenylalkylamines**
- **Benzothiazepines**
- **Dihydropyridines (DHP):** have minimal effect on cardiac conduction or heart rate while have **potent action as arteriolar vasodilators...peripheral and coronary**

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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.

• Mc Clellan KJ. Lercanidipine: a review of its use in hypertension. Drugs 2000;60:1123-40

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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

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 cannal blockers. Arch Inter 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
- Photosensitivitiy 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)


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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)


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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
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

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: 15 months)
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 no effect.....

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