

Eventos adversos e interacciones de medicamentos tradicionales en psoriasis

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Medicamentos tradicionales en psoriasis

Tópicos:

- Medidas generales: emolientes, sustitutos del jabón
- Corticoides tópicos: de potencia variable y en vehículos apropiados a la zona a tratar, solos o combinados con queratolíticos
- Derivados de alquitranes: en crema, loción o champú.
- Antralina: más usada en Europa.
- Derivados de la vitamina D: calcitriol o calcipotriol
- Retinoides tópicos : Tazaroteno

Efectos adversos e interacciones de los corticoides tópicos

- Taquifilaxis o disminución del efecto
- Bloqueo eje adrenal
- Telangectasias
- Estrias de distensión
- Discromías
- Foliculitis

NO > 100gr corticoide potente/mes
Rotación con emolientes y queratolíticos

Efectos adversos e interacciones de alquitranes

Interacciones o combinaciones

- Se usa combinado con UVB banda ancha Goeckerman
- También descrito con nbUVB con excelentes resultados (Lee, Koo J. Dermatol. Treat., 2005)
- Uso combinado con corticoides potencia efecto

Efectos adversos

- Irritación
- Mal olor, mancha la ropa
- Contraindicado en embarazo, lactancia
- Carcinogénico? Por contenido de HAPc No existe evidencia epidemiológica (Zackheim Cutis, 2004)

Efectos adversos e interacciones de antralina

Uso combinado o interacciones

- Su uso con UVB aumenta en período de remisión en Ingram tradicional o de corto contacto

Efectos adversos

- Irritación
- Mancha ropa, piel y muebles

Contraindicado en Ps. Eritrodermica y pustulosa
embarazo y lactancia

Derivados de vitamina D

Efectos adversos

- **Irritación**; principalmente en cara y zonas de pliegues
- **Hipercalcemia e hipercalciuria**; especialmente si se usa en áreas extensas por mucho tiempo
 - calcipotriol 100mg/semana adultos, 75-50mg/sem niños ≥ 12 años
 - calcitriol NO $> 35\%$ sup corporal o 30mg/día
 - tacalcitol \ll irritante se usa cara y manos NO > 10 gr/día

Derivados de vitamina D

Interacciones

NO recomendable en embarazo ni lactancia

- El ácido salicílico 6% y el lactato de amonio 12% lo inactivan si se usan combinados, la aplicación previa aumenta riesgo de hipercalcemia
- UVA lo inactiva, uso luego de aplicación ↓ # dosis total

Combinaciones

- Corticoides de alta potencia, aumenta su efectividad en menor tiempo
- Combinado con UVB banda ancha mejora efecto y ↓ # sesiones, no así con UVB nb

Interactions between calcipotriene and ultraviolet light

Mark Lebwohl, MD,^a David Hecker, MD,^a Joseph Martinez,^a Allen Sapadin, MD,^a and Bhiku Patel, PhD^b *New York and Buffalo, New York*

Background: Calcipotriene is often used with UVB or PUVA, but interactions between UV radiation and calcipotriene have not been examined extensively.

Objective: Our purpose was to examine interactions between calcipotriene and UV light.

Methods: Minimal erythema doses (MEDs) were determined with UVB and immediate pigment darkening was measured for UVA. The effect of calcipotriene ointment applied before phototesting was examined. Thick and thin applications of calcipotriene were compared. Calcipotriene ointment was applied to a small area on the skin before phototherapy. Patients received either UVB, PUVA, UVA, or no phototherapy. After phototherapy, the ointment was collected and assayed by reverse-phase, high-performance liquid chromatography.

Results: MEDs for UVB and immediate pigment darkening for UVA were unaffected by calcipotriene. Thick application of calcipotriene, however, increased the MED. UVA caused substantial reductions in the concentration of detectable calcipotriene.

Conclusion: When used in conjunction with PUVA, calcipotriene should be applied after exposure to UVA.

(*J Am Acad Dermatol* 1997;37:93-5.)

Calcipotriene is a vitamin D₃ analog that has been introduced for the topical treatment of psoriasis.¹ Addition of topical calcipotriene to a regimen of PUVA resulted in a reduction in the number of treatments and the total UVA dosage required for clearing.² Regimens combining phototherapy with UVB have also been tried,^{3,4} although photosensitivity has been reported after topical calcipotriene was introduced in patients already receiving high doses of UVB.⁵

Various topical psoriasis treatments, such as tars and salicylic acid, block UVB and should not be used immediately before phototherapy.⁶ Concern over the use of calcipotriene before phototherapy has already been expressed.⁷ Our pur-

pose was to study the impact of calcipotriene on the short-term clinical effects of UVA, UVB, and PUVA. In addition, we examined the effects of UVA, UVB, and PUVA on topically applied calcipotriene.

METHODS

Impact of topical calcipotriene on short-term clinical effects of UV light

This protocol was approved by Mount Sinai Medical Center's institutional review board, and informed consent was obtained from participants.

Phototesting was performed on 10 subjects to determine the minimal erythema dose (MED) for UVB and the minimal dose required for immediate pigment darkening for UVA.

Patients had skin types I to IV. MEDs were determined by irradiating 4.0 cm² of uninvolved skin on the back with Light Sources FS72 T12-UVB-HO bulbs. Subjects were irradiated with 20 to 120 mJ/cm² at 20 mJ/cm² increments. The minimal dose required for UVA-induced immediate pigment darkening was determined by irradiating 4.0 cm² of uninvolved skin on the back with Light Sources F72 T12-BL HO/50R bulbs. Subjects were irradiated with 3 to 18 J/cm² at 3 J/cm² increments.

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Presented at the annual meeting of the Society for Investigative Dermatology, Chicago, Ill., May 25, 1995.

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Retinoides tópicos; tazaroteno

Se une específicamente al subtipo β y γ del receptor RAR
↓ inflamación > diferenciación

Interacciones

- Con UVB aumenta la efectividad pero también el riesgo de quemaduras, por lo que debe bajarse la dosis en 1/3

Efectos adversos

- Irritación > a >concentración, ↓ al combinarlo con mometasona al 0.1% o con clobetasol
- Prurito, eritema y ardor local
- Contraindicado en embarazo y lactancia y relativamente en niños

Tazarotene gel, a new retinoid, for topical therapy of psoriasis: Vehicle-controlled study of safety, efficacy, and duration of therapeutic effect

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Irvine and Santa Monica, California; Salt Lake City, Utah; Houston, Texas; Providence, Rhode Island; Pittsburgh, Pennsylvania; Winston-Salem, North Carolina; Columbia, South Carolina; and Albuquerque, New Mexico

Background: Topical therapy providing initial improvement and maintenance of effect after treatment of the large majority of patients with limited, mild to moderate psoriasis is not presently available. Previous topical retinoids have generally been either ineffective or too irritating for therapy of psoriasis.

Objective: Our purpose was to evaluate a new topical retinoid, tazarotene, in the treatment of stable plaque psoriasis during treatment and posttreatment periods.

Methods: In a double-blind manner, 324 patients were randomly selected to receive tazarotene 0.1% or 0.05% gel, or vehicle control, once daily for 12 weeks and were then followed up for 12 weeks after treatment.

Results: Of the total, 318 patients could be evaluated. Tazarotene gels were superior ($p < 0.05$) to vehicle, often as early as treatment week 1, in all efficacy measures: plaque elevation, scaling, and erythema; treatment response; percentage treatment success (patients with $\geq 50\%$ improvement); and time to initial success. Efficacy was equivalent on target lesion sites (trunk or limbs and knees or elbows) and overall. A sustained therapeutic effect was observed for 12 weeks after treatment. Tazarotene gel was cosmetically acceptable. There was low systemic absorption, limiting toxicity to local irritation.

Conclusion: Once-daily tazarotene was effective and safe as a topical monotherapy for plaque psoriasis, providing rapid reduction of signs and symptoms. (*J Am Acad Dermatol* 1997;37:85-92.)

Although the pathogenesis of psoriasis is complex and incompletely understood, there appear to be at least three major factors: keratinocyte hyperproliferation, abnormal keratinocyte differ-

entiation, and infiltration of inflammatory cells.

Retinoids mediate cell differentiation and proliferation, and the systemic retinoid etretinate has proved effective in the treatment of severe recalcitrant psoriasis.¹ Etretinate is particularly effective for pustular and erythrodermic psoriasis. However, the use of etretinate is restricted because of a high incidence of adverse effects, such as mucocutaneous toxicity, skeletal changes, serum lipid elevations, and hair loss.¹ Although topical retinoids should circumvent many of the toxicity problems associated with systemic retinoid therapy of psoriasis, they have generally been either marginally effective or too irritating.^{2,7}

Tazarotene (AGN 190168) is a member of a novel class of retinoids, the acetylenic retinoids. Pharmacology studies suggest that tazarotene

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Supported by Allergan, Inc.

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Tazarotene cream in the treatment of psoriasis: Two multicenter, double-blind, randomized, vehicle-controlled studies of the safety and efficacy of tazarotene creams 0.05% and 0.1% applied once daily for 12 weeks

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San Francisco, Santa Monica, and Irvine, California; Salt Lake City, Utah; New York, New York; and Dallas, Texas

Background: Tazarotene in a gel formulation is widely used in the treatment of psoriasis.

Objective: To determine the efficacy and safety of tazarotene 0.1% and 0.05% creams in the treatment of psoriasis.

Methods: A total of 1303 patients participated in 2 clinical trials. Patients applied tazarotene creams 0.1% and 0.05% or vehicle once daily to all psoriatic lesions for 12 weeks followed by a 12-week posttreatment period.

Results: Both creams were significantly more effective than vehicle on the basis of an overall assessment of psoriasis, a global response to treatment, and reduction in plaque elevation and scaling. Therapeutic effect was maintained during the posttreatment period. Common adverse events included signs and symptoms of skin irritation.

Conclusion: Tazarotene creams were associated with significant reductions in the severity of the clinical signs of psoriasis and were found to be safe with acceptable tolerability. Tazarotene cream 0.1% was generally more effective, although slightly less well tolerated, than the 0.05% cream. (*J Am Acad Dermatol* 2003;48:760-7.)

Tazarotene is the first receptor-selective retinoid for the topical treatment of plaque psoriasis.¹ On application, tazarotene is rapidly hydrolyzed to its main metabolite, tazarotenic acid, which binds to retinoic acid receptors (RARs) in the nucleus.² Tazarotenic acid selectively binds to RARs β and γ and exhibits little affinity for retinoid X receptors.³ The predominant type of RAR expressed in the human epidermis is RAR γ , indicating that it

may be an important mediator of retinoid action in skin.^{3,4} By regulating gene transcription, tazarotene normalizes abnormal keratinocyte differentiation, reduces epidermal hyperproliferation, and decreases inflammation, the 3 pathogenic factors in psoriasis, thereby producing a more normal expression of skin differentiation in psoriatic lesions.⁵

Tazarotene gels 0.05% and 0.1% applied once daily for 3 months were found to be safe and effective.

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Disclosure: Drs Weinstein and Lowe are currently paid consultants to Allergan. Drs Koo, Krueger, Lebwohl, and Menter have at various times received honoraria for their participation as ad hoc consultants

to Allergan and have received payments for their participation as investigators in clinical studies funded by Allergan. Drs Lew-Kaya, Sefton, Walker, and Gibson are Allergan employees. *Members of the Tazarotene Cream Clinical Study Group are listed at the end of the article.

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Interactions between tazarotene and ultraviolet light

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Tazarotene in combination with phototherapy is being used clinically for the treatment of plaque psoriasis. This study investigates the dose of UVB light required to induce minimal erythema and the dose of UVA light required to induce immediate pigment darkening, with and without pretreatment with tazarotene 0.1% gel. The photostability of tazarotene is also assessed. Pretreatment with tazarotene 0.1% gel 3 times per week for 2 weeks before phototherapy significantly reduced the mean minimal erythema dose (MED) for UVB from 56.25 to 42.50 mJ/cm² ($P < .01$), and significantly reduced the mean UVA exposure required to induce immediate pigment darkening from 20.18 to 18.50 J/cm² ($P < .05$). A thin application of tazarotene gel immediately before phototherapy had no significant effect on the mean MED for UVB, whereas a thick application of the gel increased the MED slightly, from 56.25 to 62.50 mJ/cm² ($P = .3$). Tazarotene remained chemically stable when used in conjunction with UVB or UVA phototherapy. To reduce the patient's potential to burn or tan, we recommend initiating UVB phototherapy at 50% to 75% of the MED when it is used in combination with tazarotene. We also recommend initiating PUVA therapy at slightly lower doses than usual. Lower total doses of UVA or UVB may be needed when patients with psoriasis are treated concomitantly with tazarotene. (*J Am Acad Dermatol* 1999;41:927-30.)

Tazarotene is a new topical retinoid preparation and a member of a novel class of retinoids, the acetylenic retinoids.¹ Like other retinoids, tazarotene mediates cell differentiation and proliferation and is now being used in the treatment of plaque-type psoriasis both as monotherapy and in combination with various other therapies including ultraviolet light. The enhanced efficacy of combining acitretin or etretinate (oral retinoids) with phototherapy is well known.^{2,3} Although the potential clinical advantages of adding tazarotene to phototherapy have not been examined extensively, one study has shown that the addition of tazarotene to UVB phototherapy significantly reduces the cumulative UVB exposure required to achieve initial treatment success (approximately 50% or greater improvement in psoriasis).⁴ Although an enhanced erythemogenic effect of oral retinoids when combined with ultraviolet light has been observed,⁵ to our knowledge there is no controlled study showing that application of a topical retinoid increases a

patient's ability to burn when exposed to ultraviolet light. According to the package insert for tazarotene, "photosensitivity has not been noticed in 3 months of treatment with tazarotene gel." However, when tazarotene gel was added to the regimen of patients treated with UVB, there were anecdotal reports of burns.

The purpose of this study was two-fold: (1) to examine in vivo the effects of ultraviolet light when combined with tazarotene gel and (2) to measure the chemical stability of tazarotene gel when exposed to ultraviolet light.

METHODS

This protocol was approved by an institutional review board, and informed consent was obtained from participants. Twelve volunteers (8 men, 4 women; age range, 26-54 years; mean age, 33 years) with normal skin were recruited for the first phase of the study. One side of the back of each patient was pretreated with 2 g 0.1% tazarotene gel applied 3 times per week for a 2-week period. Minimal erythema dose (MED) testing for UVB was performed, and the minimal dose required for immediate pigment darkening for UVA was measured.

Patients had Fitzpatrick skin types I to IV (4 with type I, 4 with type II, 3 with type III, 1 with type IV). MEDs were determined by irradiating columns of skin on the back with Light Sources FS72 T12-UVB-HO bulbs. Subjects were irradiated with 15 to 90 mJ/cm² at 15 mJ/cm² increments. The minimal dose required for UVA-

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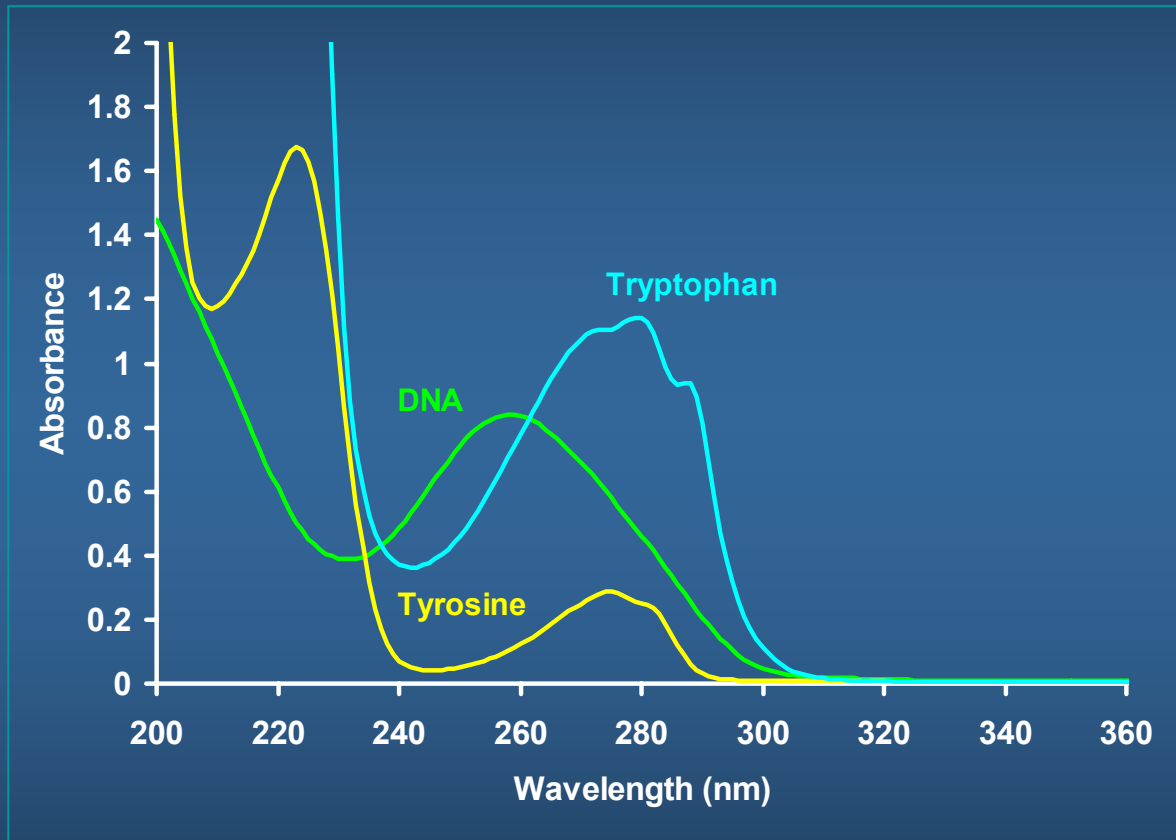
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Medicamentos tradicionales en psoriasis

Sistémicos:

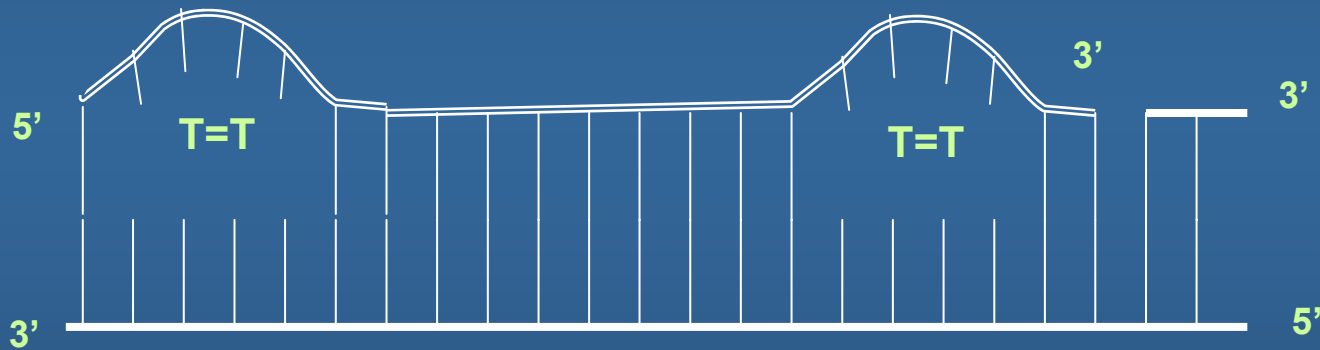
- Fototerapia (LUV A o B) y fotoquimioterapia (psoraleno tópico u oral + UVA)
- Retinoides orales solos o con LUV
- Metotrexato en contados casos, otros antimetabolitos como ciclofosfamida
- Ciclosporina u otros reguladores inmunes como mofetil micofenolato

Principales cromóforos de UVB: QT y CL

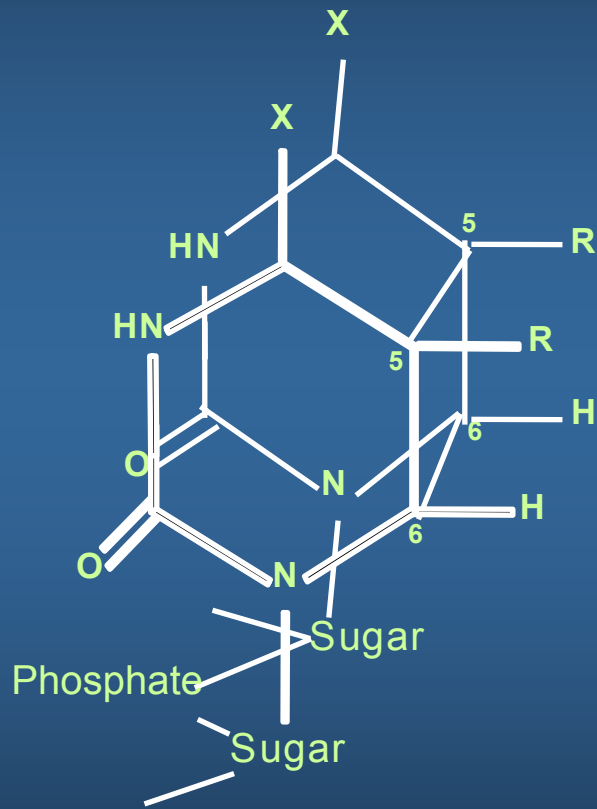


- 260nm; peak de abs de DNA, efecto del estrato corneo → >>eficiencia de daño 313nm

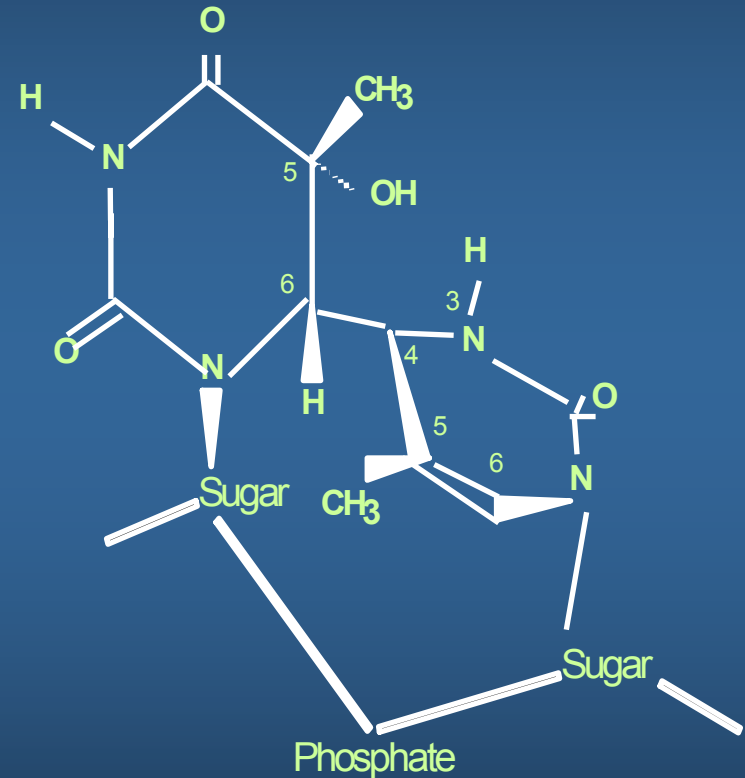
Formación de lesiones de dipiridiminos



Fotoproductos de las lesiones del DNA



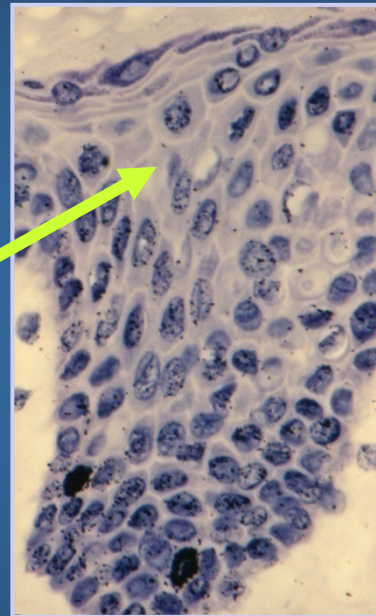
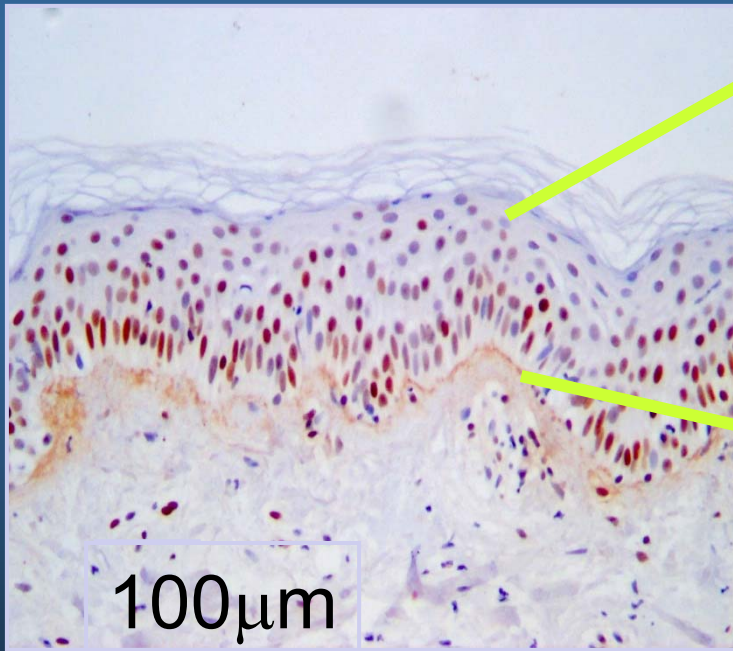
Cyclobutane pyrimidine dimer (CPD)



6-4 Photoproduct

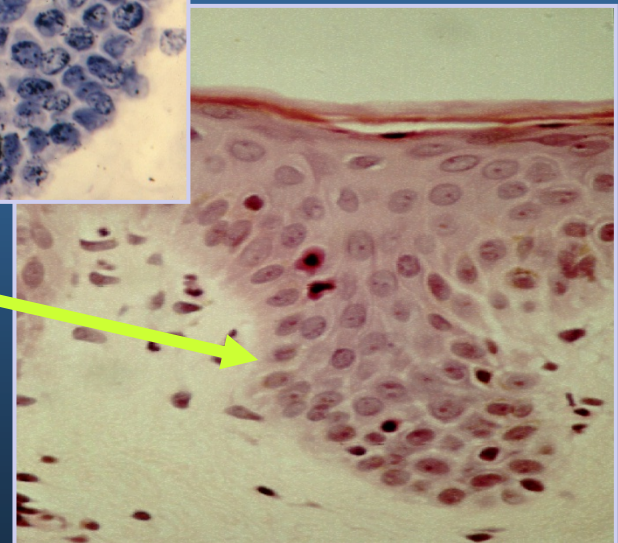
Respuesta del DNA al fotodaño

Expresión de p53

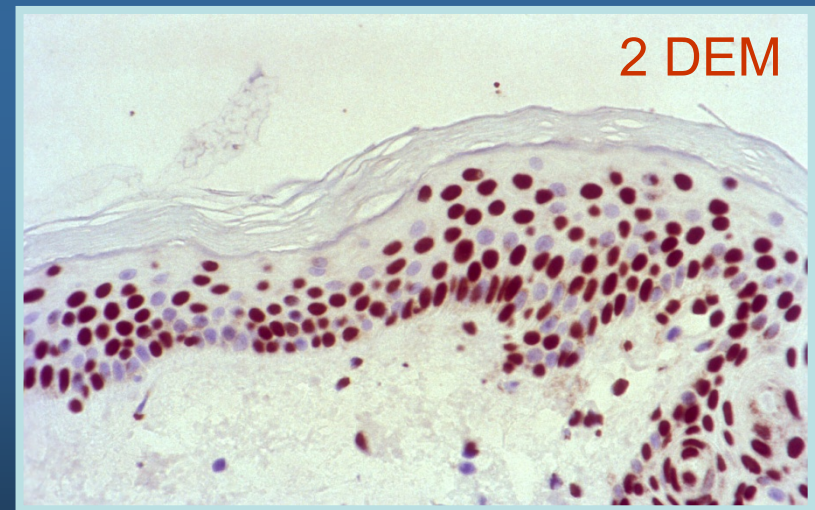
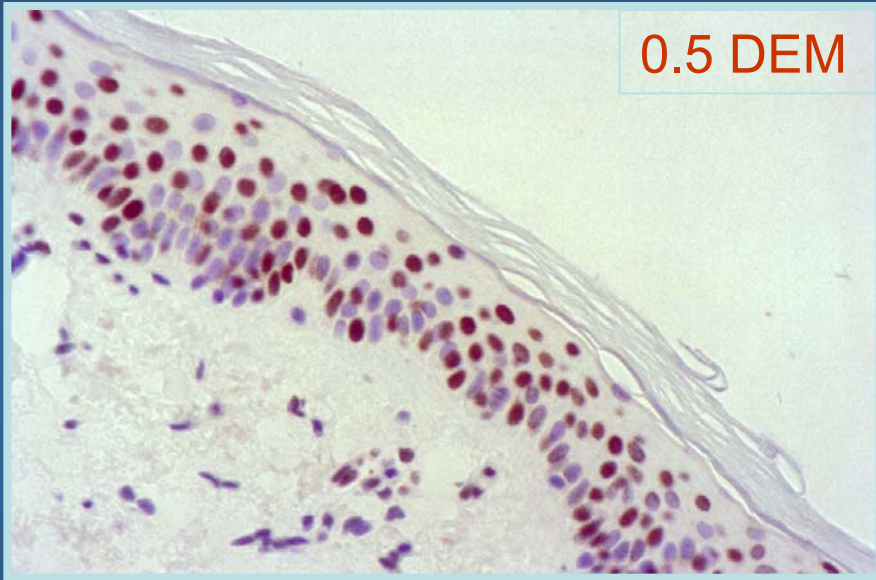


Reparación del DNA

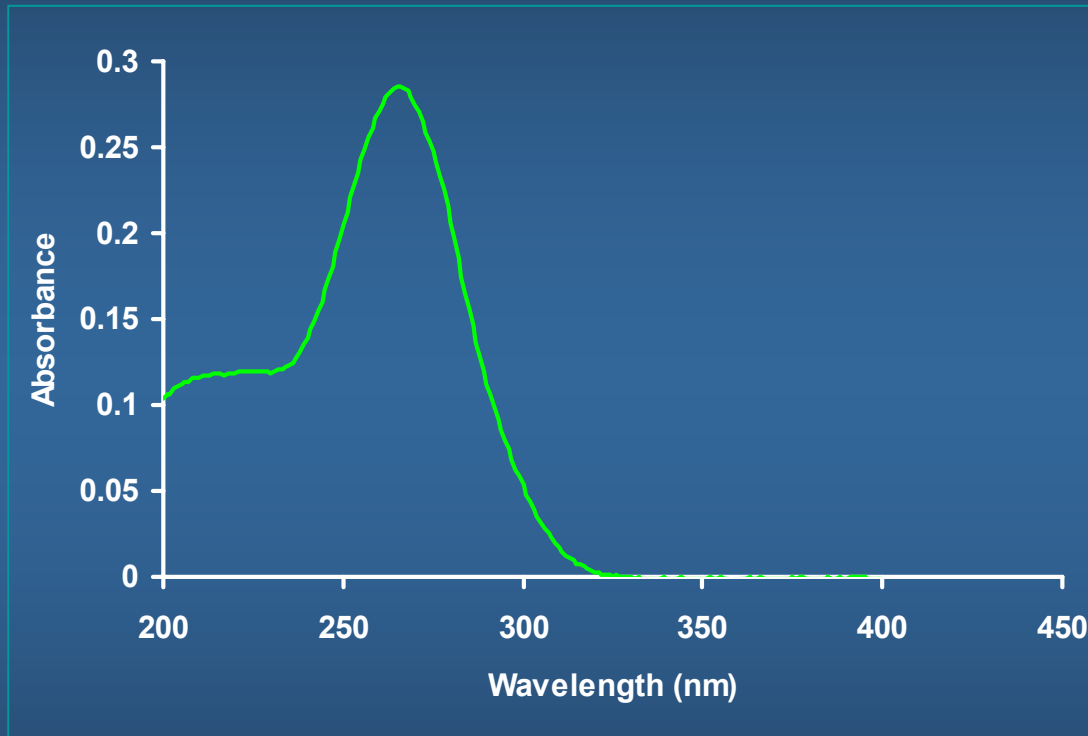
Apoptosis



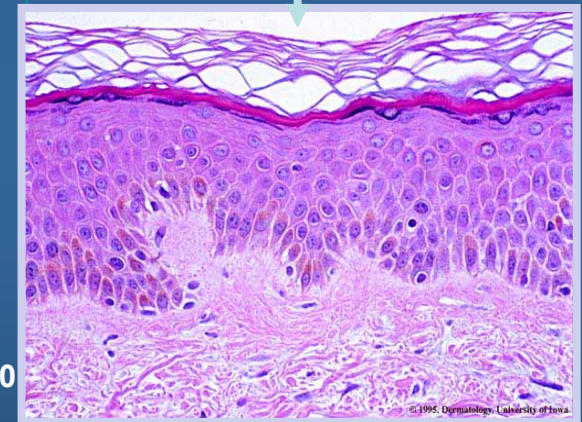
Expresión de p53 luego de LUVB 300mn



Espectro de absorción del ac urocánico a pH5.7 (cis a trans)



AUC en estrato córneo



- 290-340nm isomerización → cambio expresión de citoquinas → infiltrados Th2 y no Th1

Mecanismo de mutación de UVA

(Rüniger, Kappes PPP2008)

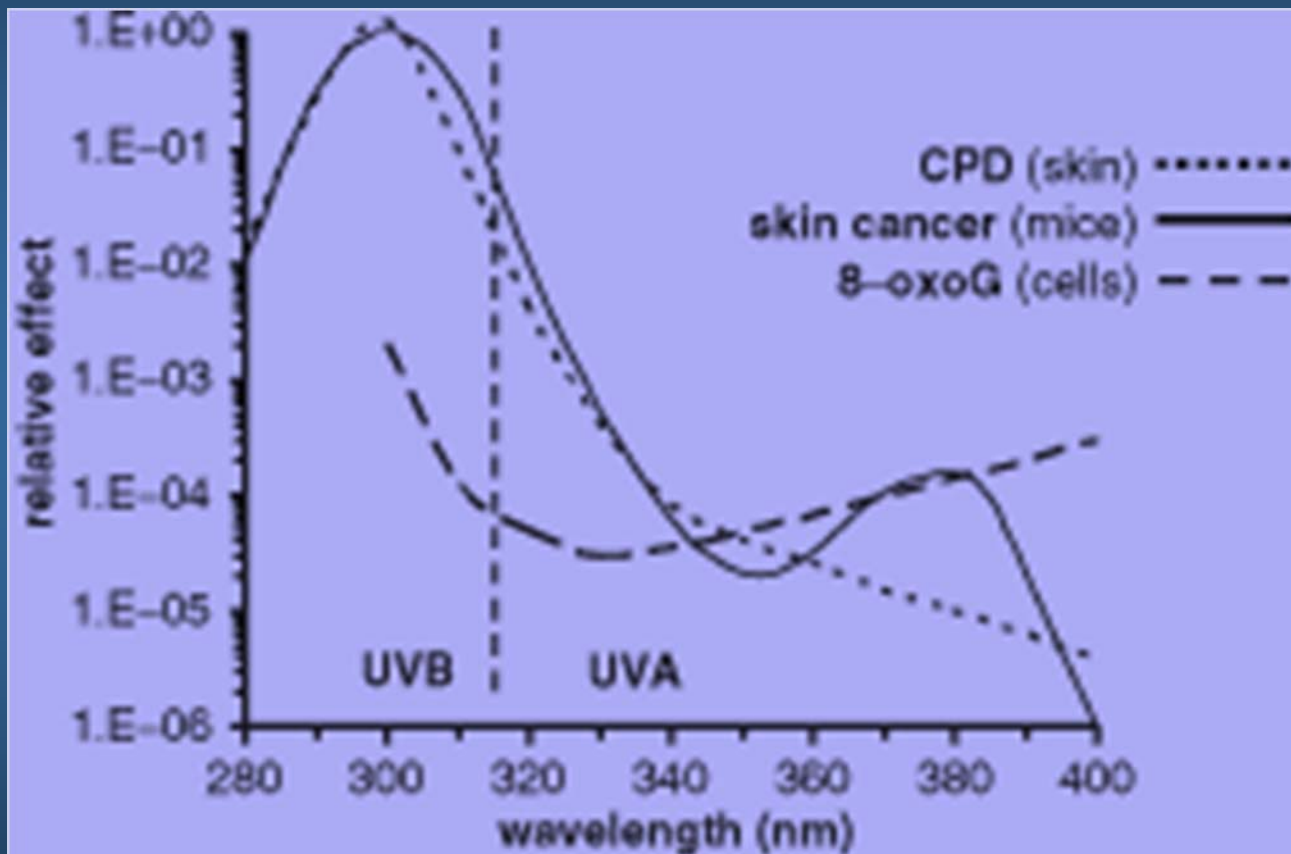
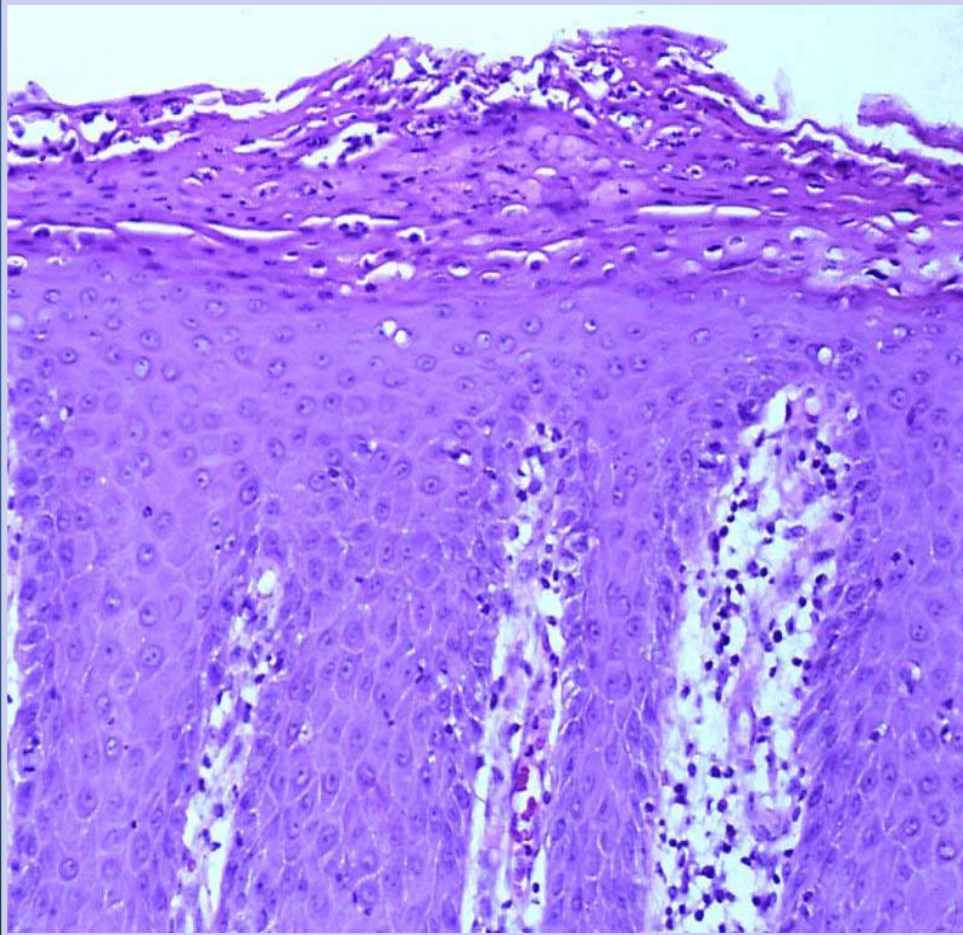


Fig. 1. Action spectra of DNA damage and skin cancer formation. Redrawn after data from (17, 34, 36, 70); CPD, cyclopyrimidine dimers.

Fototerapia en psoriasis



- ↓ multiplicación celular exagerada; detención en G1y G2
- ↑ apoptosis de infiltrados; via directa o por daño DNA
- ↓ llegada y migración de nuevas células inflamatorias: ↑ PG E2 → → inh reclutam linf y por ↓ expresión de ICAM-1 en QT

Luz ultravioleta B y nb UVB

Efectos adversos agudos:

- Eritema (>12hrs) Quemadura
- Descamación y xerosis
- Prurito
- Aparición de ampollas en placas

Efectos adversos crónicos:

- No se ha demostrado ↑ riesgo de CEC ni Mm sólo discreta > frec CBC (Br.J.Dermatol. 2005. 4aseg)

Luz ultravioleta B y nb UVB

Interacciones medicación tópica:

- **Emolientes:** petrolato y cremas alcalinas previo a UVB, bloquean penetración. No así la glicerina ni el aceite de oliva (en placas gruesas)
- **Queratolíticos:** no usar previo a LUV es fotoabsorbente
- **8 MOP 0.1% cr. nbUVB** (Amorpiyokeit P.P.P.2006) 10pac

Uso combinado: corticoides, alquitranes y antralina, calcipotriol, retinoides tópicos e inhibidores de la calcineurina

Luz ultravioleta B y nb UVB

Interacciones con terapia sistémica:

Muchos son IS → ajustar dosis + >fotoprot.

- **Retinoides sistémicos** (Iest, Br.J.Dermatol 1989)
- **Metotrexate** (Paul, Monitaz J.A.Acad.Dermatol 1982)
- **Ciclosporina** (Koo, Bandow therapy of Ps 2003)
para mantener el efecto
- **Biológicos** especialmente nbUVB en
terapia rotativa

Puvaterapia, indicaciones

- Psoriasis vulgar extensa > 20% sup. Corporal
- Psoriasis que no responde a otras terapias
- Psoriasis palmoplantar
- Psoriasis pustulosa
- Persona sana

PUVA, contraindicaciones

Absolutas: Xeroderma Pigmentoso
Albinismo
Lactancia
Incapacidad de seguir el tratamiento

Relativas: Falla hepática o renal
Edad
LES
Embarazo
Pénfigo y Penfigoide
Historia familiar y personal de Ca
Inmunosupresión
Cataratas
Uso de drogas fotosensibilizantes

PUVA , efectos adversos agudos:

Por psoraleno: gastrointestinales

nerviosismo, insomnio

<<frec bronco constricción fiebre

por droga y exantema

Por fototoxicidad: eritema (72hrs) y prurito incluso edema discreto, foto-onicolisis y Koebner

No por fototoxicidad: Pigmentación exagerada, hipertrichosis, herpes simple

PUVA , efectos adversos a largo plazo

- **CEC:** >200 ses. o >2000J/cm acumulados ↑14v. riesgo c/r a los con < dosis (Stern, Arch Dermatol 98) sigue ↑ por10a (Stern, Cancer 94)
- **CBC:** No existe ↑ del riesgo (Stern, Cancer 94)
- **MM:** 1380pac por 20^a, 9 con MM (Stern, Nichols N.Engl.J.Med 97) esos a lo menos 250ses.
- **Otras malignidades:** 286v>frec Ca pene escroto (Stern, Vakeva, J.Invest.Dermatol 97)

PUVA, Otros efectos adversos crónicos:

- **Lentigines: > frec.**
(Rhodes J.Invest.Dermatol 1983)
- **Degeneración actínica:**
queratosis actínicas
(Stern J.Invest.Dermatol 85)
- **Poroqueratosis**
superficial actínica:
(Hazen J.A.A.Dermatol 85)
- **Cataratas por**
fotoproductos de
psoralenos: (Woo Arch
Dermatol 85)

Puvaterapia

Interacciones:

- Medicamentos tópicos
- Orales: Drogas fotosensibilizantes (antibióticos, hipoglicemiantes...)
inmunosupresores ↑ riesgo de Ca

Combinaciones

- Biológicos no depletadores de Lintocitos ya que PUVA ↓ CD3
- Otros tópicos y orales

Fototerapia tasa de efectos agudos

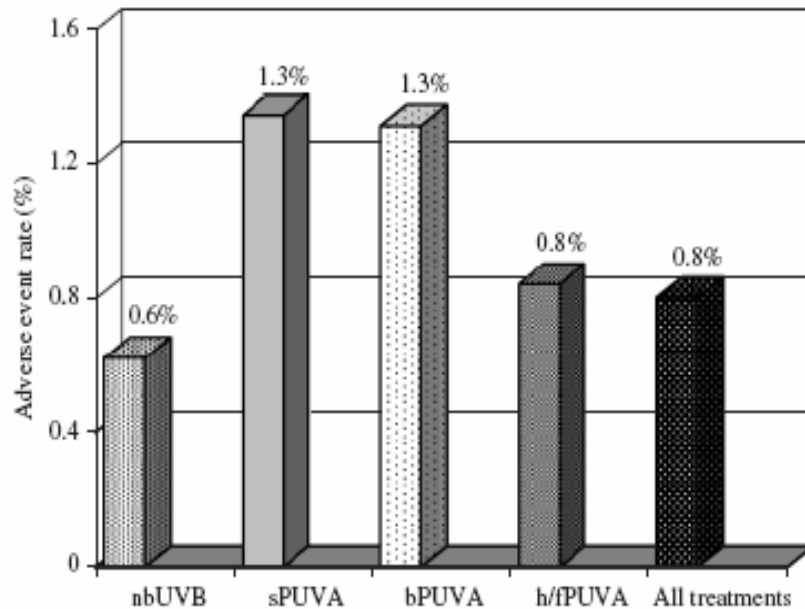


Fig. 2. Adverse event rate per treatment modality (%).

Rate of acute adverse events for narrow-band UVB and Psoralen-UVA phototherapy

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Background: Ultraviolet (UV) radiation therapies are commonly used to treat a wide range of dermatological conditions. However, no published data exist regarding the rate of acute adverse events occurring within the different UV therapy modalities.

Aim: The aim of this study was to determine the rate of acute adverse events experienced by patients receiving narrow-band UVB or photochemotherapy in 3 neighboring dermatology units.

Method: Standardized adverse event forms from all 3 units were retrospectively analysed over a 12-month period between October 2003 and September 2004. The treatments included were narrow-band UVB and systemic, bath and hand/foot PUVA.

Results: A total of 8784 treatments were given over the study period. The total number of acute adverse events recorded for all phototherapy treatments was 70 (0.8%). The rates of acute adverse events for each

treatment modality were 0.6% for narrow-band UVB, 1.3% for systemic PUVA, 1.3% for bath PUVA and 0.8% for hand/foot PUVA. Adverse events were due to patient non-compliance with standard operating procedures in 15 cases (21%) and operator error in 2 (3%). Only 4 of the acute adverse events were considered to be severe, accounting for 0.05% of all treatments.

Conclusions: The rates of acute adverse events with phototherapy in this analysis were low, in particular the rate of severe adverse events. The highest rate was seen with both systemic and bath PUVA. The number of adverse events resulting from operator error was low. These published rates for adverse events associated with narrow-band UVB and PUVA may help other units when analyzing their own rate of adverse events.

Key words: adverse events; phototherapy; UVA, UVB.

Phototherapy with narrow-band UVB (nbUVB) and also photochemotherapy with psoralen and UVA (PUVA) is frequently used in the treatment of psoriasis. Both modalities are established therapies for a range of other skin conditions including polymorphic light eruption, atopic dermatitis, vitiligo and mycosis fungoides. Acute adverse events may occur either at the time or shortly after UV therapy treatment. Published guidelines for phototherapy aim to optimize the efficacy and safety of treatment and advise monitoring of patients for adverse events (1-4). In particular, the use of specifically trained phototherapy staff working closely with a dermatologist is highlighted as being key to optimizing the safety of a phototherapy service (1-4).

Despite these guidelines, there is wide variation in the delivery of phototherapy treatment throughout the UK. Improvement in the efficacy and safety of

phototherapy can be achieved through regular clinical audit based on recognized best practice. However, no audits concerning the rates of acute adverse events occurring within a phototherapy service have been published to date.

The aim of this study was to identify the frequency of acute adverse events occurring during phototherapy treatment in 3 units in South East Wales in order to establish a benchmark for future audit of this topic.

Method

Three neighboring dermatology units in South East Wales with facilities for UV therapies were included in the study. These units serve a population of approximately 1.1 million people. The service in each center is nurse-led under the supervision of the same consultant dermatologist. All phototherapy nurses receive train-

3 centros de fototerapia 8784 pacientes durante un año. 0.005% severo

Retinoides sistémicos Isotretinoína:

Aprobado como monoterapia en acné de diferente grado y psoriasis pustulosa.

Contraindicado

- absoluta: Embarazo, lactancia, insuficiencia renal o hepática, hipervitaminosis A
- relativa: hiperlipidemias

Interacciones: fenitoina,

tetraciclina obs. Pseudotumor cerebri.

Efectos adversos: teratogénico, irritación y xerosis cutánea, fotosensibilidad y rara vez ↓ visión nocturna, depresión y síntomas psicóticos <<<frec. pancreatitis por hipertrigliceridemia

Retinoides sistémicos Isotretinoína

Contraindicado en embarazo y lactancia y durante los durante el año siguiente

Categoría X, etanol ↑ conversión a etretinato.
No alcohol durante ni 2m después de dejarlo

Retinoides sistémicos Acitretin

Aprobado en psoriasis vulgar extensa, refractaria o grave

Efectos adversos (Gupta J.A.A.Dermatol 89): bien tolerado a dosis <de 50mg/día

- **Queilitis** más frecuente, > 75%
- **Caída cabello** (50-75%);
- **Alteraciones ungueales, xerosis y prurito** (25-50%),
- **Sequedad ocular y bucal** (10%)
- **Alteración de pruebas hepáticas y lípidos circulantes,**
- **Pseudotumor cerebri y las alt. Musculoesqueléticas;** calcificaciones ligamentosas y osteoporosis <<frec.

Retinoides sistémicos Acitretin

Contraindicado en embarazo y lactancia y durante los 3 años siguientes

Categoría X, etanol ↑ conversión a etretinato.
No alcohol durante ni 2m después de dejarlo

Uso con precaución en niños y adolescentes < 17a

Retinoides sistémicos Acitretin

Interacciones:

- **Fenitoina:** ↑ concentración sanguínea
- **Vitamina A:** efecto aditivo a dosis >de 25000UI hipervitaminosis

Uso combinado UVA y UVB (Cons J.A.A.Dermatol 2001)

Indicado en Ps. crónica severa o moderada

Mejora la tolerancia, efectividad, dosis total y disminuyen los efectos adversos a largo plazo c/r a fototerapia sola.

Debe regularse dosis por fotosens. y según exs.

Consensus conference: Acitretin in combination with UVB or PUVA in the treatment of psoriasis

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Although adhesive treatment with retinoids in concert with either psoralen-ultraviolet A (PUVA) or ultraviolet B (UVB) phototherapy has been a treatment option for chronic, moderate to severe plaque psoriasis for nearly two decades, acitretin-UV therapy is an underutilized therapeutic modality. According to a recent member survey by the National Psoriasis Foundation, many psoriasis patients are frustrated with available treatment options, which they perceive as ineffective, inconvenient, and/or excessively conservative. Treatment of psoriasis with acitretin in concert with UVB or PUVA is emerging as a viable clinical strategy. Compared with either acitretin or UV light monotherapy alone, the combination regimen enhances efficacy and limits treatment frequency, duration, and cumulative doses. These effects translate into care that is more effective, better tolerated, more convenient, less costly and, perhaps, safer during long-term treatment than phototherapy alone. Drawing from an extensive literature search and the expertise of its participants, this consensus conference advances clinical recommendations as well as "clinical pearls" for health providers who treat patients with chronic, moderate to severe plaque psoriasis and suggests avenues for future research. (J Am Acad Dermatol 2001;45:544-55.)

RATIONALE AND OBJECTIVES

According to a recent National Psoriasis Foundation survey¹ involving nearly 18,000 respondents, approximately 40% of all patients with psoriasis and 85% of those with severe disease are frustrated with the ineffectiveness, cost, and/or inconvenience of their current therapies. A total of 32% of respondents with severe psoriasis viewed their therapy as insufficiently aggressive, and 65% of respondents

reported that their physicians had discussed either psoralen-ultraviolet A (PUVA) or ultraviolet B (UVB) phototherapy as a possible treatment strategy. However, only 25% of patients had ever received phototherapy.

Also termed photochemotherapy, PUVA utilizes long-wavelength (~320-400 nm) UV radiation in combination with a psoralen such as 8-methoxypsoralen (8-MOP). On the other hand, UVB uses shorter wavelength (~290-320 nm) radiation. Recent studies²⁻⁴ suggest that narrow-band UVB, which uses radiation at a wavelength of 311 to 313 nm, is associated with more effective clearing of psoriasis compared with broad-band UVB. However, at the time of this consensus conference, no studies had been reported concerning the safety and efficacy of narrow-band UVB plus acitretin.

The combination of this retinoid with phototherapy—a strategy broadly termed ReUVB or RePUVA—enhances the efficacy of phototherapy while sharply reducing the cumulative UV dose as well as the total number, frequency, and duration of therapy needed to treat chronic, moderate to severe plaque psoriasis. Conversely, phototherapy exerts a retinoid dose-sparing effect, potentially diminishing the acute side effects of acitretin.

Phototherapy (UVB) with adjunctive acitretin (ie, ReUVB) may be underutilized partly because of gaps

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PUVA +10mg Acitretin
21ses

Metotrexato en psoriasis

Indicado en psoriasis en placa que no responde, Ps eritrodermica y pustulosa localizada o generalizada y artritis psoriática

Containdicado en

- Insuficiencia renal o hepática (enf hepatica hereditaria)
- Embarazo y lactancia
- Deseo de procreación
- Infección viral aguda
- Anemia o leucopenia
- Úlcera péptica

Methotrexate in psoriasis: Consensus conference

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Gerald Weinstein, MD,^d and Mark Lebwohl, MD^e *Chicago, Illinois, New York, New York, and
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Because methotrexate was the first effective systemic drug for psoriasis and remains in clinical use today, it is the standard systemic therapy for psoriasis.

The initial use of antimetabolic drugs for cancer ushered in a new era in the treatment of psoriasis. In 1951 Gubner¹ noted the rapid clearing of psoriatic skin lesions in several patients with psoriatic arthritis treated with aminopterin. Clinical experience developed with aminopterin,² but this drug was later replaced by a more stable derivative, methotrexate.³

PUVA therapy and systemic retinoids have challenged methotrexate as the best systemic treatments for psoriasis. Although methotrexate was widely used for treatment of psoriasis in the 1960s, it was not approved by the Food and Drug Administration (FDA) for this indication. The first guidelines on methotrexate therapy for psoriasis⁴⁻⁶ published initially in 1972 were followed by FDA approval. The most recent guidelines were published in 1988.⁷ We have summarized the current literature and the increased use of methotrexate in rheumatoid arthritis in a recent review⁸ and editorial.⁹

Methotrexate was approved for treatment of rheumatoid arthritis in 1988 and guidelines published by the American College of Physicians (1987) differed from dermatology guidelines by not requiring a liver biopsy before methotrexate treatment. Recent revised guidelines by rheumatologists¹⁰ also differ in recommendations on monitoring possible liver toxicity from methotrexate. On the 26th anniversary of the psoriasis guidelines for methotrexate, this article reviews available data

to recommend new updated guidelines on the use of methotrexate in the treatment of psoriasis.

INDICATIONS

Moderate to severe psoriasis, variably defined as patients with 20% or more involvement of body surface area or patients unresponsive to topical therapy, can be treated with several modalities including phototherapy, photochemotherapy (PUVA), retinoids, or methotrexate. This population comprises approximately 20% of patients with psoriasis in the United States.¹¹ These guidelines are directed to the use of methotrexate in treatment of psoriasis. To minimize the toxicity of systemic therapy, combination or rotational therapy should be considered in the management of psoriasis.

The decision to administer methotrexate for the treatment of psoriasis should be individualized. Each patient should be evaluated with reference to disease severity, discomfort, incapacity, and general medical and psychologic status. Methotrexate is indicated in the symptomatic control of recalcitrant psoriasis not responsive to topical therapy or other systemic therapies such as PUVA or retinoids. The diagnosis of psoriasis and the need for methotrexate therapy should be established by dermatologic consultation. In general, these patients should have severe psoriasis that may be life-ruining physically, emotionally, or economically. Examples of candidates for methotrexate therapy are patients with moderate to severe psoriasis, defined as follows as those patients with:

- Psoriatic erythroderma
- Psoriatic arthritis, moderate to severe
- Acute pustular psoriasis, von Zumbusch type
- More than 20% involvement of body surface
- Localized pustular psoriasis
- Psoriasis that affects certain areas of body so that normal function and employment are prevented
- Lack of response to phototherapy, PUVA, and retinoids

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Metotrexato en psoriasis efectos adversos:

Más frecuentes:

Gastrointestinales

Astenia cefalea

Hematológicos < con ácido fólico

Mucocutáneos; erosiones orales, alopecia,
fototoxicidad

Menos frecuentes: mareos ↓ líbido y la
memoria, urticaria o rash

Metotrexato en psoriasis; Daño hepático

Hepatotóxico → fibrosis hepática

- A misma dosis semanal, pac. Ps > riesgo que pac. reumatológico
- Ingesta de alcohol ↑ riesgo de daño

Biopsia hepática con

- factores de riesgo a los 2-4 meses luego cada 1.5gr acumulados
- Sin factores de riesgo a los 1.5gr cada ↑ en 1.5gr

Metotrexato en psoriasis Daño hepático

Boffa Eur. Acad. Dermatol. Venereol. 2005,19:196-202

Cuestionario enviado a 150 dermatólogos de 32 países UE 69 respondió

- Enormes variaciones en dosificación y tiempo de uso
- Ninguno Bp inicial
- De cada 10 pac. Estimaban que sólo a 2
- 20% usaba de rutina PINP (peptido aminoterminal de procolageno III)

Metotrexato en psoriasis; Daño hepático

Indicación de Bp

- Con PIIINP > 8mcg/l
- Aumento del rango en 1.7-4.2mcg/l 3 veces durante el último año
- Aumento >8.0mcg/l en 2 mediciones consecutivas

Sauspender

- Aumento a 10mcg/l en 43 mediciones consecutivas en el año

Metotrexato interacciones

Por ↓ excreción renal:

- Slicilatos
- Sulfonamidas
- Fenilbutazona
- Probenecid
- Penicilina
- Colchicina
- AINE ibuprofeno, naproxeno
- Nefrotóxicos ej. Ciclosporina

Por toxicidad aditiva sinérgica

- Sulfatrimetroprin con cotrimoxazol
- Alcohol y retinoides

Metotrexato interacciones

Por desplazamiento desde proteínas transport.

- Salicicos
- Probenecid
- Barbituricos
- Fenitoina
- Retinoides
- Sulfonamidas
- Sulfonilurea
- Tetraciclina

Por acumulación intracelular

- Dipyridamol

Ciclosporina

Indicaciones

- Psoriasis grave, extensa y que no responde a otras terapias

Contraindicaciones

- Insuficiencia renal y hepática
- Hipertensión
- Infección crónica

Uso con precaución en embarazo y niños

Ciclosporina

Efectos adversos:

- Nefrotoxicidad < a dosis de 5mg/kg/d y si \uparrow creatinina no > a 130% del original Controlar tb K
- Aumento de Br, colesterol y TG
- Artralgias mialgias
- Nauseas, vómitos
- Hiperplasia gingival
- Hipertricosis
- Alteración tolerancia a glu
- Infecciones
- Tumores (CSC, Ly)

Ciclosporina

Interacciones:

- Baja en K aumenta riesgo de hipocalcemia
- Baja en absorción: jugo de naranjas y algunas hierbas
- Drogas que afectan el metabolismo hepático por CYP450 ; >toxicidad eritromicina, itraconazol, verapamilo > toxicidad carbamazepina, fenitoina y rifampicina
- Estatinas > riesgo de miositis