

Clarke, Mode

COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 10-040510- -00015-0000

Fecha: 2013-10-31 14:59:41 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 412 REPOSPRESRECU Folios: 32

P-2521

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. S. D.

Re: Expediente No. **10-040.510**
Solicitud de patente a nombre de **UNIVERSITÉ VICTOR
SEGALEN-BORDEAUX 2**

Yo, SILVANA MARIA LOPEZ DÍAZ, actuando como apoderada sustituta de acuerdo con la sustitución adjunta e identificada como aparece al pie de mi firma, domiciliada en la carrera 11 A No. 86-53, piso 6, de la sociedad **UNIVERSITÉ VICTOR SEGALEN-BORDEAUX 2**, domiciliada en Francia, solicitante de la patente de la referencia, *interpongo recurso de reposición* contra la resolución No. **55546** emitida el 18 de septiembre de 2013 por el Superintendente de Industria y Comercio, por medio de la cual se niega el privilegio de patente de invención para la solicitud contenida en el expediente de la referencia.

1. FUNDAMENTOS DEL RECURSO

Con fundamento en la facultad que confiere el artículo 34 de la Decisión 486 al solicitante para modificar la solicitud de patente en cualquier momento del trámite, presento junto con este memorial un nuevo capítulo reivindicatorio, el cual consta de 15 reivindicaciones y reemplaza completamente el capítulo presentado anteriormente.

En cuanto a estas modificaciones, me permito decir que las mismas no amplían de ninguna manera la materia objeto de la presente solicitud y se realizaron con el ánimo de superar las objeciones planteadas por el examinador en su concepto técnico.

Así las cosas, cabe aclarar que el nuevo capítulo reivindicatorio que consta de 15 reivindicaciones y la materia contenida en dichas reivindicaciones corresponde a la misma materia de las reivindicaciones allegadas junto con el memorial de respuesta al oficio No. 675 notificado por fijación en lista el 22 de enero de 2013, con la diferencia que se ha añadido la nueva reivindicación 11 y se han modificado las antiguas reivindicaciones 3, 10, 13 y 14 con el fin de corregir algunos errores de claridad y superar las objeciones indicadas por el examinador.

A este respecto, se desea aclarar que las características esenciales incluidas en la nueva reivindicación 11, están soportadas en el capítulo descriptivo (ver página 14, líneas 21-25).

Adicionalmente, es deseo del solicitante indicar que la nueva reivindicación 15 (antigua reivindicación 14) se refiere a una característica propia del medicamento reivindicado. De esta forma, el rango mencionado en dicha reivindicación (entre 1 y 5mg/kg) se refiere a la concentración del principio activo que contiene dicho medicamento y no a la dosis para ser administrada.

1/32

1.1 La indebida interpretación del artículo 16 de la Decisión 486/00

En relación con los argumentos presentados por ese despacho en la resolución impugnada No. 55546 emitida el 18 de septiembre de 2013, es necesario señalar que carecen de un enfoque adecuado de conformidad con las normas, jurisprudencia y reglas técnicas que existen para evaluar la novedad de una invención.

Considerando lo anterior, es deseo del solicitante presentar argumentos contra las declaraciones de ese Despacho indicando como primera medida que el examinador no realizó una adecuada interpretación del artículo 16 de la Decisión 486/00 y parte de premisas erradas, en cuanto a la supuesta anticipación de la materia objeto de la presente invención, y realiza un equivocado análisis del requisito en cuestión, para finalmente negar sin justificación la patente para la solicitud en comento.

El solicitante desea se tengan en cuenta los siguientes argumentos así como los argumentos inicialmente presentados en respuesta al oficio No. 675 notificado por fijación en lista el 22 de enero de 2013, los cuales dan soporte a los dichos siguientes argumentos y demuestran que la solicitud de la referencia cumple con los requisitos de novedad.

El examinador objeta la novedad de la reivindicación 1 respecto a los documentos citados D1 y D2. Según el examinador, D1 divulga compuestos con efecto agonista adrenérgico beta3 para la preparación de un medicamento que comprende un betabloqueante elegido de entre varios como los descritos en la presente solicitud, entre ellos propranolol.

A este respecto, el solicitante muy respetuosamente indica estar en desacuerdo con el examinador, ya que, aunque D1 describe el uso de compuestos con efecto agonista adrenérgico beta3 preferiblemente combinado con un compuesto con efecto antagonista de adrenoreceptor beta1/beta2 (ver página 4, párrafo 0003) para la estimulación de neo-angiogénesis y tratamiento de enfermedades relacionadas (ver página 16, párrafo 0004), **la estimulación de neo-angiogénesis descrita en D1 es el efecto contrario del conseguido por la composición de la presente invención**, donde se utiliza bloqueantes de receptores beta.

Por otra parte, el examinador indica que D2 describe una composición que contiene al menos un agente para el tratamiento de pacientes con neoplasia, entre los que describe el carvedilol. Sin embargo, el solicitante manifiesta que D2 no afecta la novedad de la composición de la presente invención, ya que **D2 no describe la dosis efectiva para tratar dichos hemangiomas**. Adicionalmente, se resalta que un hemangioma es un tumor benigno que solo se presenta en niños y es además potencialmente agresivo, lo cual junto con su origen lo distingue absolutamente del comportamiento y fisiología de los tumores cancerígenos tratados mediante la composición descrita en D2.

De esta manera, no hay nada en los documentos D1 y D2 que afecte la novedad de un medicamento como el revelado en la presente invención.

↩

Con respecto al argumento del examinador mediante el cual indica que el capítulo reivindicatorio radicado *“no corresponde de manera específica a un medicamento con componentes claros y no limita el alcance de la solicitud, porque abarca todos los medicamentos betabloqueantes conocidos y que pueden desarrollarse en el futuro”*, el solicitante desea muy respetuosamente manifestar su desacuerdo, teniendo en cuenta los siguientes argumentos:

- Los compuestos de la presente invención sólo se pueden definir con el término utilizado, o de otra forma se entraría en una restricción impropia hasta llegar a considerar los compuestos individuales. No existe ningún componente estructural o de composición que sirva para caracterizar los compuestos de la invención, de forma que el uso del término “betabloqueante” se revela como la única alternativa válida.
- El resultado de los componentes de la familia definida por los betabloqueantes puede ser verificado por ensayos convenientemente especificados en el capítulo descriptivo, o bien son conocidos e implementados por el experto medio con una experimentación abordable. El término utilizado es entendido de forma positiva por el experto en la materia como caracterizante de un grupo de compuestos concreto.

Como complemento a lo anteriormente expuesto, el solicitante desea anexar al presente recurso de reposición, los siguientes documentos posteriores a la fecha de prioridad de la presente solicitud, que muestran cómo distintos betabloqueantes son efectivos para el tratamiento de hemangiomas, lo cual redundaría en la única caracterización posible de todos ellos de acuerdo al término funcional.

- Blanchet et al. “Management of infantile subglottic hemangioma: Acebutolol or propranolol?” Int. Jour. of Pediatric Otorhinolaryngology 74 (2010) 959-961.
- Khunger et al. “Dramatic response to a large hemifacial infantile hemangioma associated with PHACE syndrome to topical timolol lotion”, British Journal of Dermatology (2010).
- Pope et al. “Topical Timolol Gel for Infantile Hemangiomas: A Pilot Study. Arch. Dermatol, 146, 5 (2010) 564-565.
- Ensayo clínico NCT01147601.
- Ensayo clínico NCT01010308.

En consecuencia, teniendo en cuenta los anteriores argumentos, es claro que las reivindicaciones de la presente invención cumplen a cabalidad con los requisitos de claridad y patentabilidad según la Decisión 486/00, es decir, novedad, nivel inventivo y aplicabilidad industrial.

Teniendo en cuenta lo dicho anteriormente, solicito a usted lo siguiente:

- a) Que de conformidad con lo previsto por los artículos 3 (inciso 3); 35 (inciso 2) y 59 (inciso 2) del Código Contencioso Administrativo se consideren y se resuelvan TODOS los argumentos y TODAS las cuestiones planteadas así como las que aparezcan con motivo de este recurso.

7

b) Que se revoque la resolución No. 55546 emitida el 18 de septiembre de 2013 expedida por el Superintendente de Industria y Comercio, se declare infundada la oposición presentada por LAFRANCOL S.A., y se proceda a conceder el privilegio de patente de invención a la solicitud de mi mandante

Señor Superintendente,



SILVANA MARIA LÓPEZ DÍAZ
C.C. 22468787 de Barranquilla
T.P 147463 del CSJ
notificaciones@clarkemodet.com.co

P-2521

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

Re: Expediente No. **10-040.510**

Solicitud de patente a nombre de **UNIVERSITÉ VICTOR SEGALEN-BORDEAUX 2**

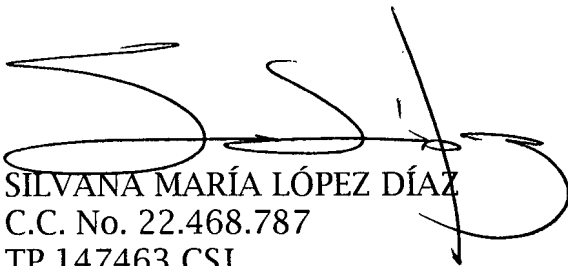
Yo, **DILIA RODRÍGUEZ D´ALEMAN**, identificada como aparece al pie de mi firma, domiciliada en Bogotá, Colombia, atentamente informo a usted que sustituyo el poder con que obro a la doctora **SILVANA MARÍA LÓPEZ DÍAZ**, domiciliada en Bogotá, identificada con la Cédula de Ciudadanía No. 22.468.787 y portadora de la tarjeta profesional No. 147.463 del CSJ, con las mismas facultades con que me fueron conferidas para este caso.

Señor Superintendente,



DILIA RODRÍGUEZ D´ALEMAN
C.C. 41.654.882 de Bogotá
TP 20824 CSJ

Acepto sustitución



SILVANA MARÍA LÓPEZ DÍAZ
C.C. No. 22.468.787
TP 147463 CSJ

PRESENTACION PERSONAL

El anterior escrito fue presentado ante el
NOTARIO ONCE (11) DEL CIRCULO DE BOGOTA, D.C.
personalmente por **LILIANA RODRIGUEZ**

D'ARMA
quien exhibió la c.c. **41654882** **BOGOTA**
y Tarjeta Profesional No. **20824** C.S.J.

Firma

Fecha

20 SEP 2013

Nelson J. Sánchez García
NOTARIO (E)



DIRECCIÓN DE NUEVAS CREACIONES
MODIFICACIONES Y/O CORRECCIONES

1. Identificación del Trámite

- ☐ Error material ☒ Modificación a una Solicitud en trámite
- ☒ Patente de Invención
☐ Patente de Modelo de Utilidad
☐ Registro de Diseño Industrial
☐ Esquema de Trazado de Circuitos Integrados

2. Datos del solicitante

Persona Natural ☐ Persona Jurídica ☒

UNIVERSITÉ VICTOR SEGALEN-BORDEAUX 2

Nombre o denominación / Nombre o razón social completa

Nombre representante legal

Tipo de empresa Micro Pequeña Mediana Otra

Documento de identificación: ☐ C.E. ☐ NIT ☐ Otro ☐hero ☐

Nacionalidad/País de constitución	Dirección y domicilio del titular	Ciudad
FRANCIA	146 rue Léo Saignat, F-33076 Bordeaux Cedex	Bordeaux Cedex
Dirección electrónica		No. Fax
		Número telefónico

☐ Autorizo expresamente a la Superintendencia de Industria y Comercio para que todas las comunicaciones sean enviadas a través de la dirección de correo electrónico

3. Datos del apoderado:

SILVANA MARIA LÓPEZ DÍAZ

C.C. 22.468.787

147463 CSJ

Apellidos y Nombre

Documento de identificación

Tarjeta profesional

Dirección y domicilio	Ciudad
Carrera 11 No. 86-53, Piso 6, Bogotá D.C., Colombia	Bogotá D.C.
Dirección electrónica	No. Fax
<u>notificaciones@clarkemodet.com.co</u>	6350824
	Número telefónico
	6181088

En caso de haber presentado poder general para asuntos que se adelanten ante la Delegatura de Propiedad Industrial, sírvase indicar el número de su radicación o protocolo de poder general

4. Datos del trámite

Corrección:

Expediente No. 14-040.510

Aparece _____

Debe ser _____

Modificación:

☒ Presentación Solicitud Divisional.

Modificación al capítulo descriptivo.

Presento junto con este memorial nuevo capítulo reivindicatorio, el cual consta de 15 reivindicaciones y reemplaza completamente el capítulo presentado anteriormente.

☐ _____

Modificación al capítulo Reivindicatorio

☐ _____

Modificación al resumen.

☐ _____

Modificación a los dibujos.

5. Anexos

☒ Comprobante de pago de la tasa para la presentación de la corrección y/o modificación

☐ Poder, si fuere el caso.

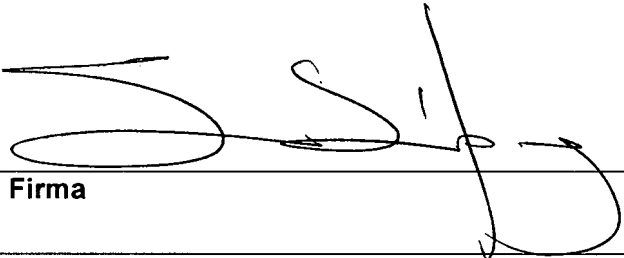
☒ Documento que contiene las modificaciones o correcciones.

☐ Copia de la solicitud y sus anexos en formato magnético.

6. Firma

SILVANA MARIA LÓPEZ DÍAZ

Nombre y apellidos



Firma

C.C. 22.468.787

Tarjeta Profesional T.P. 147463 CSJ

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -



RECIBO DE CAJA

No. 13 - 0099782

Bogotá D.C., Octubre 03 de 2013 - 16:51:22

RECIBIDO DE : CLARKE MODET

NI 830.008.643

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	560783226	02/10/2013	71.325.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr. UNIDITARIO	Vr. CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICACIONES CAMBIO SOLICITANTE POR CESION	125.000.00	125.000.00
				\$125.000.00

SON: **CIENTO VEINTICINCO MIL PESOS MONEDA CORRIENTE**

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia

Web: www.sic.gov.co e-mai: info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 6513240

, Octubre 3 de 2013 - 16:51:32

7

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -



RECIBO DE CAJA

No. 13 - 0051176

Bogotá D.C., Mayo 28 de 2013 - 09:53:06

RECIBIDO DE : CLARKE MODET

NI 830.008.643

R

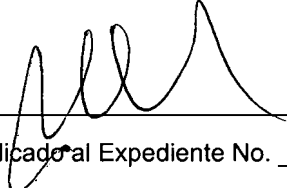
*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
EFFECTIVO	999999999	40917	30/04/2013		530.000.00
EFFECTIVO	999999999	40918	30/04/2013		530.000.00
EFFECTIVO	999999999	40919	30/04/2013		530.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD INDUSTRIAL	54 INFORMACION DETALLADA DE UN TRAMITE /ANTECEDENTES	30.000.00	30.000.00
				\$30.000.00

SON: **TREINTA MIL PESOS MONEDA CORRIENTE***

Responsable: 

Recibo de Caja Aplicado al Expediente No. _____

Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia

Web: www.sic.gov.co e-mai: info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 6513240

Mayo 28 de 2013 - 09:53:07

ANEXOS

- Blanchet et al. "Management of infantile subglottic hemangioma: Acebutolol or propranolol?" Int. Jour. of Pediatric Otorhinolaryngology 74 (2010) 959-961.
- Khunger et al. "Dramatic response to a large hemifacial infantile hemangioma associated with PHACE syndrome to topical timolol lotion", British Journal of Dermatology (2010).
- Pope et al. "Topical Timolol Gel for Infantile Hemangiomas: A Pilot Study. Arch. Dermatol, 146, 5 (2010) 564-565.
- Ensayo clínico NCT01147601.
- Ensayo clínico NCT01010308.

REIVINDICACIONES

1. Medicamento para el tratamiento de los hemangiomas, el cual comprende un beta bloqueante que se selecciona del grupo que comprende un beta bloqueante no selectivo, un beta bloqueante selectivo beta 1, una mezcla de antagonistas adrenérgicos alfa-1/beta, un beta bloqueante selectivo beta 2 y una mezcla de dos o más beta bloqueantes.
2. Un medicamento de acuerdo con la reivindicación 1, en donde el beta bloqueante es un beta bloqueante no selectivo.
3. Un medicamento de acuerdo con la reivindicación 2, en donde el beta bloqueante no selectivo se selecciona del grupo que comprende alprenolol, bucindolol, carteolol, carvedilol, labetalol, levobunolol, medroxalol, mepindolol, metipranolol, nadolol, oxprenolol, penbutolol, pindolol, propafenona, propranolol, sotalol, timolol, sus sales aceptables para uso farmacéutico y sus mezclas.
4. Un medicamento de acuerdo con la reivindicación 1, en donde el beta bloqueante es un beta bloqueante selectivo beta 1.
5. Un medicamento de acuerdo con la reivindicación 4, en donde el beta bloqueante selectivo beta 1 se selecciona por ejemplo del grupo que comprende acebutolol, atenolol, betaxolol, bisoprolol, celiprolol, esmolol, metoprolol, nebivolol.

6. Un medicamento de acuerdo con la reivindicación 1, en donde el beta bloqueante tiene una actividad simpaticomimética intrínseca.

7. Un medicamento de acuerdo con la reivindicación 6, en donde el beta bloqueante se selecciona del grupo que comprende acebutolol, betaxolol, carteolol, carvedilol, labetalol, oxprenolol, penbutolol, pindolol, propranolol.

8. Un medicamento de acuerdo con la reivindicación 1, en donde dicho beta bloqueante es propranolol o una de sus sales farmacéuticas.

9. Un medicamento de acuerdo con la reivindicación 8, en donde el beta bloqueante comprende una mezcla de L y D-propanolol en una proporción entre 0:1 y 1:0.

10. Un medicamento de acuerdo a cualquiera de las reivindicaciones 1-9, en donde el medicamento es un jarabe o una solución inyectable.

11. Un medicamento de acuerdo a la reivindicación 10, en que dicho jarabe o solución inyectable es apto para niños.

12. El medicamento de cualquiera de las reivindicaciones 1-9, en donde el medicamento es un medicamento para administración oral seleccionado del grupo que comprende una formulación líquida, una forma de dosis oral efervescente, un polvo oral, un sistema de múltiples partículas, una forma de dosis bucodispersable.

13. El medicamento de acuerdo con la reivindicación 12, en donde el medicamento para administración oral es una formulación líquida seleccionado del grupo que comprende un solución, un jarabe, una suspensión, una emulsión y gotas orales.

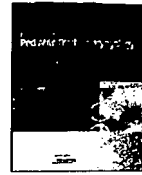
14. Un medicamento de acuerdo a cualquiera de las reivindicaciones 1-9, para las vías bucal y sublingual.

15. Un medicamento de acuerdo a cualquiera de las reivindicaciones precedentes, en donde el medicamento comprende una dosis de beta bloqueante de 1 mg/kg de peso corporal a 5 mg/kg de peso corporal.



Contents lists available at ScienceDirect

International Journal of Pediatric Otorhinolaryngology

journal homepage: www.elsevier.com/locate/ijporl

Case report

Management of infantile subglottic hemangioma: Acebutolol or propranolol?

Catherine Blanchet^a, Richard Nicollas^b, Michèle Bigorre^c, Pascal Amedro^d, Michel Mondain^{a,*}^a ENT Department, CHU Montpellier, France^b ENT Department, CHU Timone, Marseille, France^c Pediatric Plastic Surgery Department, CHU Montpellier, France^d Pediatric Cardiology Department, CHU Montpellier, France

ARTICLE INFO

Article history:

Received 9 March 2010

Received in revised form 6 May 2010

Accepted 9 May 2010

Keywords:

Acebutolol, Beta-blocker, Subglottic hemangioma, Propranolol

ABSTRACT

The successful management of subglottic hemangioma with propranolol has been reported. We report three cases of subglottic hemangioma treated with the cardioselective beta-blocker acebutolol, 8 mg/kg/day. Treatment was efficient in two cases while an open procedure was necessary in the third child. In our experience, acebutolol could be easily administered in oral form twice-a-day only with a dose that was adaptable according to the growth of the child and showed no side effects.

We also report a case of rebound growth after beta-mimetic drug use and the efficiency of propranolol treatment in such a recurrence.

Considering the lack of side effects and the advantages in terms of administration, we suggest acebutolol as a first-line treatment of subglottic hemangiomas for which intervention is required.

© 2010 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Congenital subglottic hemangioma is the most common neoplasm of the airway in children and is potentially life-threatening during the proliferative phase (occurring below the age of 6–12 months), necessitating medical or surgical intervention. This may consist of a tracheotomy, general or local treatment with steroids, interferon or vincristine therapy, LASER treatment, or open surgery with laryngo-tracheal reconstruction, all of which carry a risk of adverse effects. Spontaneous regression typically occurs after 18–24 months of age.

Recent reports have been made of the effective treatment of cutaneous [1–3] and subglottic hemangiomas [4–6] with propranolol, a non-cardioselective beta-adrenoceptor blocking agent. This drug does however carry some potential side effects including bronchoconstriction, bradycardia, hypotension, and reduced physiological responses to hypoglycemia, as well as the drawback of needing administering three times daily. Another beta-adrenoceptor blocking agent, acebutolol, is not only cardioselective, but possesses both partial agonist (intrinsic sympathomimetic) and membrane stabilizing activity, can be administered twice daily, and has significantly fewer side effects on resting heart rate than propranolol, metoprolol and atenolol [7]. It seems therefore that acebutolol may prove more useful in treating subglottic hemangiomas.

Here we report our experience in four infants of treating subglottic hemangioma with either propranolol or acebutolol.

2. Case reports

2.1. Clinical presentation

Four female infants were referred to our department for respiratory distress relating to a subglottic hemangioma with a laryngeal stenosis ranging from 70 to 90% with microlaryngoscopy and bronchoscopy (MLB) examination. Age at presentation ranged from 1.5 to 3 months. The subglottic hemangioma was associated with cutaneous hemangioma in cases 2 and 4 (neither had PHACES syndrome). Case 4 presented with an interventricular septal defect with right ventricular stenosis. The location of each subglottic hemangioma is presented in Table 1.

2.2. Treatment and results (Table 2)

All infants were firstly treated with high doses of steroids (prednisolone, 2 mg/kg/day) and a proton pump inhibitor (lansoprazole, 1 mg/kg/day). All were steroid-dependent apart from case 1 who showed steroid resistance. Beta-blocker treatment was initiated after full cardiovascular and respiratory review, under the supervision of a pediatric cardiologist as described by Siegfried [8].

In all cases, beta-blockers were introduced in the pediatric cardiology department. Echocardiography was systematically performed prior to treatment initiation to ensure the absence of ventricular dysfunction due to increased systemic flow. An

* Corresponding author. Tel.: +33 467336804.

E-mail address: michel.mondain@free.fr (M. Mondain).

Table 1
Clinical presentation at referral.

Case	Age at referral (months)	Sex	Associated disease	Cutaneous hemangioma presence	Laryngeal stenosis % (MLD) at referral	Subglottic hemangioma topography	Clinical presentation
1	1.5	F	None	No	90%	Circumferential subglottic hemangioma	Respiratory distress
2	1.5	F	None	Buttock cutaneous hemangioma	70%	Lateral hemangioma (right side–subglottic and first tracheal ring level)	Respiratory distress
3	2	F	None	No	90%	Lateral subglottic hemangioma (left side)	Respiratory distress
4	3	F	Interventricular communication	Cervical cutaneous hemangioma	90%	Circumferential subglottic hemangioma (and first tracheal ring level)	Respiratory distress

Table 2
Management and results (LTR: laryngo-tracheal reconstruction).

Case	Steroid therapy before beta-blockers treatment	Steroid efficiency (prednisolone)	Age at beta-blocker treatment initiation (months)	Beta-blocker: molecule used and dose	Beta-blocker efficiency	Laryngeal stenosis during beta-blocker treatment (%)	Additional treatment needed
1	Yes	Steroid-resistant (2 mg/kg/day)	1.5	Acebutolol 8 mg/kg/day	Failure	90	LTR
2	Yes	Steroid-dependent (1 mg/kg/day)	2	Acebutolol 8 mg/kg/day	Success	10	None
3	Yes	Steroid-dependent (1 mg/kg/day)	2	Acebutolol 8 mg/kg/day	Success	5	None
4	Yes	Steroid-dependent (1.5 mg/kg/day)	3	Propranolol 3 mg/kg/day	Success	5	None

electrocardiogram (ECG) was also performed to eliminate atrio-ventricular block. Once treatment was initiated, the blood sugar levels and blood pressure were monitored regularly during the first 48 h. Acebutolol (Sectral) was initiated at a dose of 2 mg/kg twice-a-day for 48 h and if well tolerated was increased to 4 mg/kg twice-a-day after a second ECG was performed. A dose of 8 mg/kg/day was reached in cases 1–3; case 4 was given propranolol (Syprol) 3 mg/kg/day (three times daily).

Regression of cutaneous hemangioma was observed in cases 2 (acebutolol treatment) and 4 (propranolol treatment).

Case 1 did not respond to acebutolol treatment and a control MLB revealed a 90% reduction in diameter of the laryngeal lumen leading to open-excision. Extubation was achieved on day 7 with no significant problems. Steroid therapy was slowly stopped and MLB revealed a normal anatomy 1 month after surgery.

Acebutolol treatment led to a spectacular regression of stridor in cases 2 and 3 which did not recur after steroid treatment was stopped. MLB performed at 1 month showed a reduction in the size of the subglottic hemangioma, now causing less than 10% obstruction. Both infants are still receiving treatment with beta-blockers (now 6 and 8 months old).

Case 4 responded well to beta-blocker therapy (propranolol). Steroid treatment was stopped and the girl was discharged after 1 month. A reduction in size of both the subglottic hemangioma and cutaneous neck hemangioma was observed on MLB. The girl was kept on propranolol therapy for 6 months before the dose was gradually decreased. She was referred for surgical repair of the interventricular septal defect and right ventricular stenosis at the age of 12 months at which time she was receiving 0.5 mg/kg/day of propranolol. During cardiac surgery, beta-mimetic drugs were used. Post-cardiac surgery extubation failed in ICU and MLB revealed a huge increase in size of the laryngeal hemangioma causing a 95% lumen reduction. A tracheotomy was therefore performed and the propranolol treatment dose increased to 2 mg/kg/day. MLB 1 month later showed a reduction in the size of the subglottic hemangioma, now causing less than 5% obstruction. The

child was decanulated with no problem. Propranolol treatment has been progressively reduced (now 0.5 mg/kg/day) without any stridor recurrence.

In all cases, the tolerance of the beta-blocker treatment was good with no obvious cardiological or bronchial side effects.

3. Discussion

In order to prevent potentially life-threatening complications associated with subglottic hemangioma during the proliferative phase (below the age of 6 months), medical or surgical intervention is necessary. Nevertheless, all treatment options to date themselves expose the child to potentially severe complications. Recently, the use of propranolol or acebutolol has been described in children with cutaneous hemangiomas [1–3] with success in almost all cases.

In this paper, we report three clinical cases illustrating that both acebutolol and propranolol can be powerful beta-blockers used in the management of subglottic and tracheal localized hemangiomas. While our results look promising, due to the small number of children presented in this study, we cannot definitively conclude whether acebutolol is as effective as propranolol for treating hemangiomas.

It does however seem to present advantages for use in treating subglottic hemangiomas including the fact that it is β 1-selective and already commonly used in pediatrics for treating hypertension and arrhythmia. In France, many pediatric cardiologists and nephrologists use the oral solution of Sectral (40 mg/ml) since it is the only beta-blocker with market authorization and with a recommended dose range for children. We decided to use Sectral for two reasons: first we postulated that the positive effect of beta-blockers on hemangioma is likely to be not limited to propranolol and secondly that acebutolol was easier to administer considering its dose range adaptability with an oral solution in accordance with the infant's growth and its recommended two administrations daily only (compared to three administrations/day for propranolol).

14

Previous authors have compared the side effects of acebutolol and propranolol in adults and a trend in favor of the acebutolol was described [9,10]. While we have reported the failure of acebutolol to reduce hemangioma size in one out of four infants (case 1), we believe that it may be useful as a first-line treatment of subglottic hemangiomas requiring intervention. It would however be necessary to thoroughly evaluate acebutolol therapy in a larger series.

We believe that surgical therapy (LASER vaporization of lateral hemangiomas and as an external approach for the removal of circumferential or extensive hemangiomas) should only be considered in the event of acebutolol therapy failure. We propose that steroid therapy only be given to infants in respiratory distress and quickly stopped after acebutolol treatment initiation since the latter does not interfere with the healing process if surgery is needed and is safer than long-term steroid therapy. In small unilateral subglottic hemangiomas, the benefit–risk ratio of acebutolol versus LASER should be evaluated before any definitive decision is made.

Concerning the length of treatment, Denoyelle et al. [5] suggested that propranolol therapy could be stopped before the age of spontaneous regression of the hemangiomas, however further studies are necessary to confirm the validity of this approach. Cases 2 and 3 described here, now 6 and 8 months old, are still receiving 10 mg/kg/day of acebutolol.

Case 4 is particularly informative, showing that the effect of propranolol can be reversed using beta-mimetic drugs, leading to a huge increase in hemangioma volume. The use of beta-mimetic drugs should therefore be carefully evaluated and perhaps avoided in such children in whom the risk of rebound growth is large. Interestingly however, even when used after the proliferative phase, propranolol was still efficient at controlling the hemangioma volume.

4. Conclusion

Treatment of subglottic hemangiomas with acebutolol was efficient at controlling hemangioma volume. It was well tolerated in our patients with no reported side effects, and was easier to administer compared to propranolol. Once diagnosis has been confirmed, we propose the immediate initiation of acebutolol. The equal efficiencies of acebutolol and propranolol need to be demonstrated in a randomized controlled study which we are now working towards. Steroids should be used only in cases of respiratory distress. The potential risk of rebound growth using beta-mimetic drugs observed in this population should be stressed.

References

- [1] C. Leaute-Labreze, et al., Propranolol for severe hemangiomas of infancy, *N. Engl. J. Med.* 358 (24) (2008) 2649–2651.
- [2] C. Leaute-Labreze, A. Taieb, Efficacy of beta-blockers in infantile capillary haemangiomas: the physiopathological significance and therapeutic consequences, *Ann. Dermatol. Venereol.* 135 (12) (2008) 860–862.
- [3] M. Bigorre, A.K. Van Kien, H. Valette, Beta-blocking agent for treatment of infantile hemangioma, *Plast. Reconstr. Surg.* 123 (6) (2009) 195e–196e.
- [4] L. Buckmiller, U. Dyamenahalli, G.T. Richter, Propranolol for airway hemangiomas: case report of novel treatment, *Laryngoscope* 119 (10) (2009) 2051–2054.
- [5] F. Denoyelle, et al., Role of propranolol in the therapeutic strategy of infantile laryngotracheal hemangioma, *Int. J. Pediatr. Otorhinolaryngol.* 73 (8) (2009) 1168–1172.
- [6] C.G. Jephson, et al., Successful treatment of isolated subglottic haemangioma with propranolol alone, *Int. J. Pediatr. Otorhinolaryngol.* 73 (12) (2009) 1821–1823.
- [7] B.N. Singh, W.R. Thoden, A. Ward, Acebutolol. A review of its pharmacological properties and therapeutic efficacy in hypertension, angina pectoris and arrhythmia, *Drugs* 29 (6) (1985) 531–569.
- [8] E.C. Siegfried, W.J. Keenan, S. Al-Jureidini, More on propranolol for hemangiomas of infancy, *N. Engl. J. Med.* 359 (26) (2008) 2846, author reply 2846–7.
- [9] M. Davidov, Acebutolol in essential hypertension: results of two multicenter studies against placebo and propranolol, *Am. Heart J.* 109 (5 Pt 2) (1985) 1158–1167.
- [10] H.R. Lubis, M. Silalahi, Yushar, A comparative study of two beta-blocker–diuretic combinations in the treatment of hypertension, *Curr. Med. Res. Opin.* 10 (4) (1986) 221–227.

(5)

A2

These articles have been accepted for publication in the British Journal of Dermatology and are currently being edited and typeset. Readers should note that articles published below have been fully refereed, but have not been through the copy-editing and proof correction process. Wiley-Blackwell and the British Association of Dermatologists cannot be held responsible for errors or consequences arising from the use of information contained in these articles; nor do the views and opinions expressed necessarily reflect those of Wiley-Blackwell or the British Association of Dermatologists

Accepted Date : 07-Dec-2010

Article type : Item of Correspondence

Dramatic response of a large hemifacial infantile hemangioma associated with PHACE syndrome to topical timolol lotion

Madam,

The PHACE syndrome is an uncommon condition seen in a subgroup of children, particularly associated with large segmental facial hemangiomas. It is an acronym coined by Frieden et al¹ for the association of Posterior fossa defects, Hemangiomas, Arterial anomalies, Cardiac defects and Coarctation of the aorta, and Eye anomalies. "S" signifies associated Sternal clefting and/or Supraumbilical raphe. The hemangiomas associated with PHACE syndrome are typically large, prone to ulceration and generally require treatment. Traditional treatment options for hemangiomas include observation, systemic and intralesional corticosteroids, interferon alpha 2a, vascular lasers, sclerotherapy, embolization, immunomodulators and surgery²⁻⁴. The first use of a beta blocker, oral propranolol for infantile hemangiomas was reported in 2008⁵. However, systemic propranolol carries a risk of serious adverse effects including bradycardia, arrhythmias, hypotension and hypoglycemia⁶. Children with PHACES syndrome may have cerebrovascular anomalies and oral propranolol can be a contraindication in these patients owing to the risk of cerebral ischemia⁶. The use of another beta blocker, topical timolol was reported in the treatment of a thin eyelid hemangioma⁷. To the best of our knowledge, this therapy has not been previously reported in the treatment of a large ulcerating hemangioma with PHACE syndrome.

An 18 months old female child, born as a full term normal delivery, presented with a large, ulcerated hemangioma on the right side of the face. The onset was from the third day of birth, rapidly growing in size with history of repeated ulcerations and bleeding. There was inability to open the right eye and hoarseness of voice, but no difficulty in breathing. There were no systemic complaints, including neurological symptoms. Previous treatment with oral and systemic antibiotics and systemic steroids at a dose of 1.5 mg/kg body weight for 3 weeks, were without significant improvement.

On examination, there was a large raised edematous erythematous plaque covering the entire right cheek, with a segmental distribution of the trigeminal nerve and loss of hair over the scalp and eyebrows. (Figure 1). There was severe distortion of the right ear and closure of the right eye leading to complete palpebral occlusion. Hemangiomas were absent at other sites including the subglottic region. No sternal pits, clefting or supraumbilical raphe were observed. Ophthalmological examination, showed palpebral closure, nanophthalmia and a corneal opacity. Fundoscopy was within normal limits. A neurological examination was normal and examination of other systems was unremarkable. Hematological investigations revealed anemia. The coagulation profile, thyroid profile, liver and kidney function tests & blood sugar levels were normal. Chest radiograph, ECG, Echocardiography including Doppler study of subclavian arteries showed no abnormalities. MRI Brain done using dedicated coil with following sequences, axial T1 CE T2 and coronal T1 T2 STIR revealed the presence of hypoplasia of right cerebellar hemisphere with Dandy Walker variant with dilation of the right CSF cisterns; and a mild dilatation of IVth ventricle, suggestive of hypoplasia of right cerebellar hemisphere, which have been observed with PHACE syndrome (Figure 1). Rest of brain parenchyma was normal. Heterogenous area was seen in subcutaneous tissue on right side involving the entire cheek and extending into the parapharyngeal spaces with flow voids suggestive of hemangiomas.

Treatment was started with topical timolol ophthalmic solution 0.5% (lotim® FDC, India) applied twice a day, over the hemangiomas, 10 drops per dose. The drops were gently applied on the lesion using a gloved finger tip. No other medication, topical or systemic was given. Response was observed from the third day onwards, with reduction in erythema. At the end of one week, a dramatic response was noted with a 50% reduction in the size and flattening of the lesion. The opening of the eye and deformity of the ear also improved significantly. Treatment was continued till complete resolution of the lesion was seen at the end of 8 weeks (Figure 2). The

pulse rate, blood pressure and blood glucose were monitored every four hours on the first day, then twice a day for the next six days and thereafter weekly till the duration of treatment. These were within normal limits at all times. The only adverse effect reported after application of timolol was mild pruritus over the lesion, after 4 weeks of application. This resulted in excoriations and erosions, which was managed with topical antibiotic, sodium fusidate (Figure 2). Topical application of timolol was stopped at 12 weeks and the child is now under observation, without any recurrence of the lesion at least one month after stopping treatment. Unfortunately, due to lack of facilities the serum levels of timolol could not be monitored.

The treatment of large ulcerating facial hemangiomas associated with PHACE syndrome is a challenge. Timolol has been previously used for small uncomplicated hemangiomas. A pilot study of small uncomplicated infantile hemangiomas in 6 patients showed improvement with 0.5% timolol maleate gel, applied for an average duration of 3.33 months⁸

Early effects of beta blockers that occur within 1–3 days after start of therapy are due to vasoconstriction, intermediate effects are due to the blocking of proangiogenic signals, including vascular endothelial growth factor, basic fibroblast growth factor, matrix metalloproteinase that result in growth arrest and long-term effects are due to induction of apoptosis in proliferating endothelial cells, resulting in tumour regression^{9,10}. Hence timolol is potentially useful in reducing progression and hastening resolution of progressive or non-involuting hemangiomas.

Our patient showed a dramatic response to topical timolol 0.5% ophthalmic lotion applied over the hemangiomas. There was decrease in redness within three days and almost complete resolution of the hemangiomas by 8 weeks. Pruritus was the only side effect observed after 4 weeks of application. Close clinical monitoring did not show adverse effects suggestive of systemic absorption of a beta blocker.

The systemic bioavailability of ocular timolol in healthy volunteers is about 50%, while systemic absorption following topical application has not been studied. It will depend on the thickness and size of the hemangioma and hence should be used with close monitoring of systemic side effects. Adverse reactions reported with ocular timolol for pediatric glaucoma include drowsiness, bradycardia, itching sensation in the eyes, Cheyne-Stokes breathing, apneic spells and multiple severe asthma exacerbations¹¹. Hence it should be used with caution in children with cardiorespiratory disorders.

Thus topical application of timolol is a safe and highly cost effective technique for the management of infantile hemangiomas and can be particularly useful in children with PHACES syndrome, where oral propranolol may be contraindicated. The availability of topical formulations, that are effective with minimal systemic absorption will make the topical application of timolol a first-line therapy and treatment of choice for the management of hemangiomas in the future.

N. Khunger, M. Pahwa

VM Medical College and Safdarjang Hospital, Department of Dermatology and STD, New Delhi, India

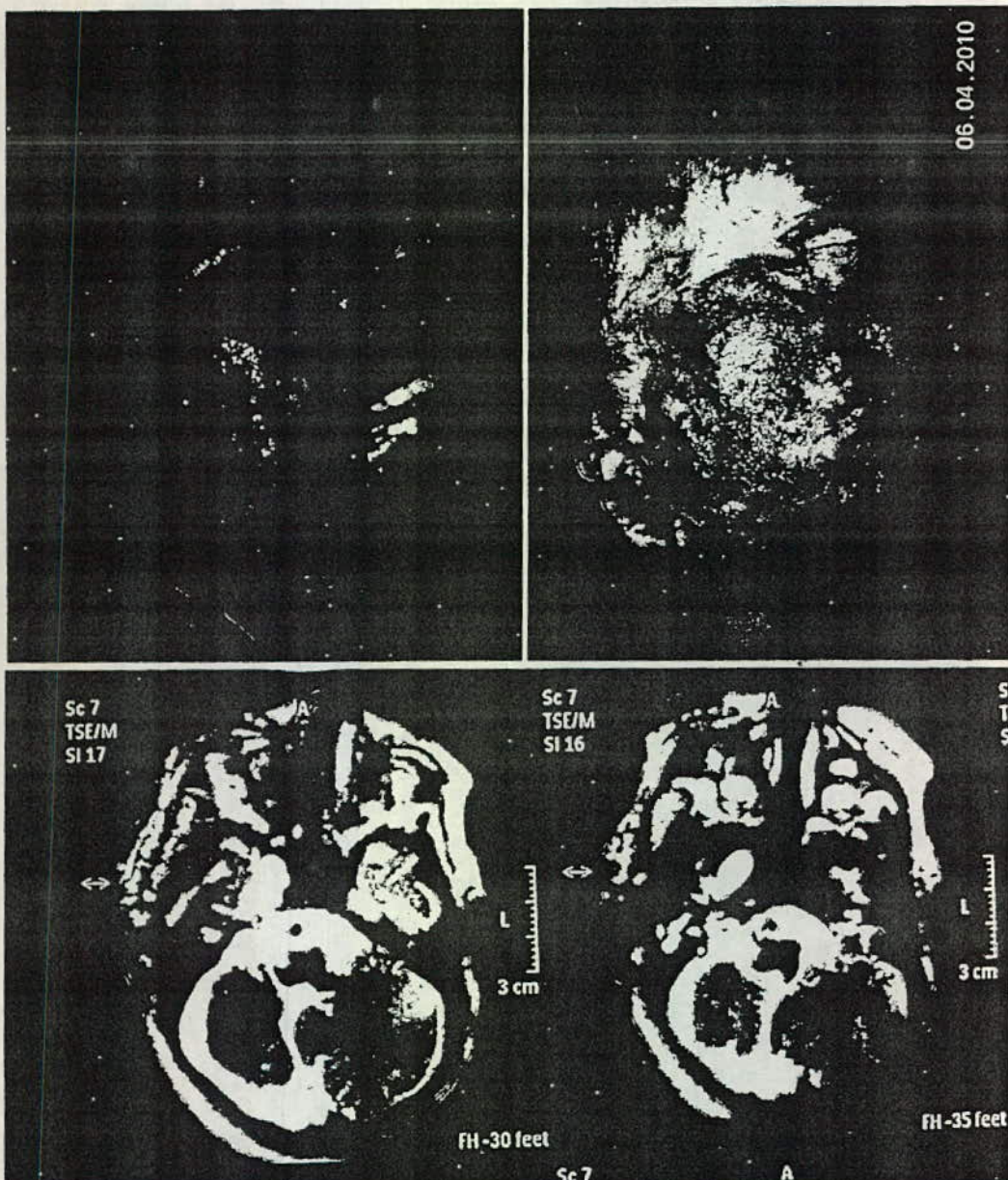
Correspondence: Niti Khunger

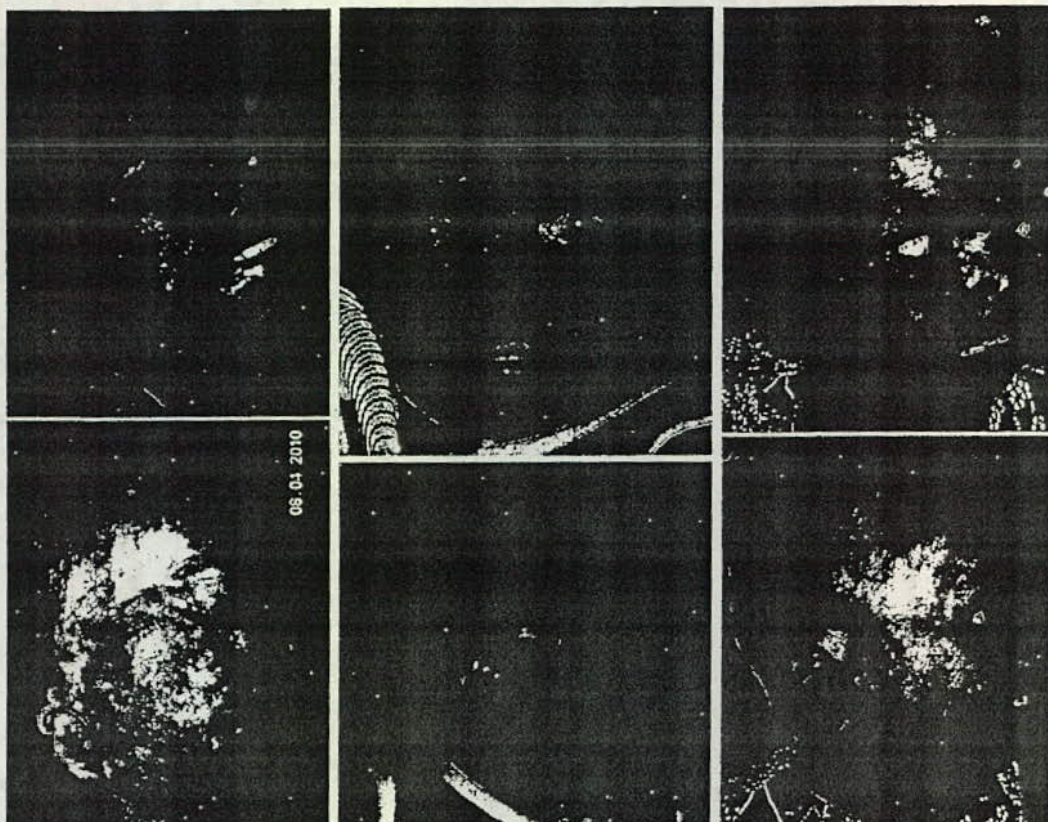
E-mail: drniti@rediffmail.com

References

1. Frieden IJ, Reese V, Cohen D. PHACE syndrome: the association of posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects and eye abnormalities. *Arch Dermatol* 1996;132:307-311.
2. Khunger N. Vascular anomalies in the neonate: Dilemmas in management. *J Neonatol* 2008;22:41-48.
3. Williams EF 3rd, Stanislaw P, Dupree M, et al. Hemangiomas in infants and children. An algorithm for intervention. *Arch Facial Plast Surg* 2000, 2:103-111.
4. Dinehart SM, Kincannon J, Geronemus R. Hemangiomas: evaluation and treatment. *Dermatol Surg* 2001, 27:475-485.
5. Le´aute´-Labre`ze C, Dumas de la Roque E, et al. Propranolol for severe hemangiomas of infancy. *N Engl J Med*. 2008;358:2649-2651.
6. Manunza F, Syed S, Laguda B, et al. Propranolol for complicated infantile haemangiomas: a case series of 30 infants. *Br J Dermatol*. 2010;162:466-468.

7. Guo S, Ni N. Topical treatment for capillary hemangioma of the eyelid using β -blocker solution. Arch Ophthalmol 2010; 128:255.
8. Pope E, Chakkittakandiyil. Topical timolol gel for infantile hemangiomas: A Pilot study. Arch Dermatol. 2010;146:564-565.
9. D'Angelo G, Lee H, Weiner RI. cAMP-dependent protein kinase inhibits the mitogenic action of vascular endothelial growth factor and fibroblast growth factor in capillary endothelial cells by blocking Raf activation. J Cell Biochem 1997;67:353-66.
10. Storch CH, Hoeger PH. Propranolol for infantile haemangiomas - insights into the molecular mechanisms of action. Br J Dermatol 2010;163:269-274.
11. Zimmerman TJ, Kooner KS, Morgan KS. Safety and efficacy of timolol in pediatric glaucoma. Surv Ophthalmol. 1983;28:262-264.





06.04.2010

RESEARCH LETTERS

Topical Timolol Gel for Infantile Hemangiomas: A Pilot Study

Infantile hemangiomas (IHs) affect approximately 5% to 10% of white children.¹⁻³ Most IHs undergo spontaneous involution, with only a small proportion requiring systemic intervention. For these, pro-

pranolol, a nonselective β -blocker, has emerged as an alternative systemic treatment to corticosteroids. The proposed therapeutic effects of propranolol on IHs are vasoconstriction; decreased expression of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) genes through downregulation of the RAF/mitogen-activated protein kinase pathway^{4,5}; and apoptosis of capillary endothelial cells.⁴

Superficial IHs, particularly facial IHs, are associated with substantial parental distress, and we currently have a limited therapeutic repertoire. Timolol, a nonselective β -blocker similar to propranolol, is available in a topical gel formulation for treatment of glaucoma. We describe herein a series of 6 patients with superficial head and neck IHs treated with timolol maleate, 0.5%, gel.

Methods. A retrospective medical chart review analysis was performed of 6 patients with uncomplicated IHs in the head and neck area who were treated with timolol maleate, 0.5%, gel after informed consent. Timolol maleate, 0.5%, gel was applied topically twice daily to the IHs. Two investigators independently analyzed the response to treatment by comparing digital photographs at baseline vs at 4 weeks, 8 weeks, and final visits using a global score (-4 to +4) representing the difference in the size and/or extent and color of IHs (-2 [much worse], -1 [worse], 0 [same], +1 [better], and +2 [much better]) and a visual analog scale (VAS) (a 100-mm scale where -100 indicates that the hemangioma is twice as big; 0, no change;

Table. Summary of Patient Characteristics and Treatment Outcomes

Characteristic	Value ^a
Patient age, mean (SD) (range), mo	11.7 (14.71) (1-36)
Younger than 6 mo, No.	3
Older than 6 mo, No.	3
Girls, No. (%)	6 (100)
Duration of treatment, mo	3.33 (1.54)
Global score at last visit	2.58 (1.20)
VAS 1 at last follow-up	42.67 (23.45)
VAS 2 at last follow-up	45.00 (24.06)
Combined VAS	43.83 (23.28)
Correlation coefficient between VAS 1 and VAS 2	0.92
P value	.01

Abbreviations: VAS, visual analog score; VAS 1, VAS for investigator 1; VAS 2, VAS for investigator 2.

^aUnless otherwise indicated, data are reported as mean (SD) values.

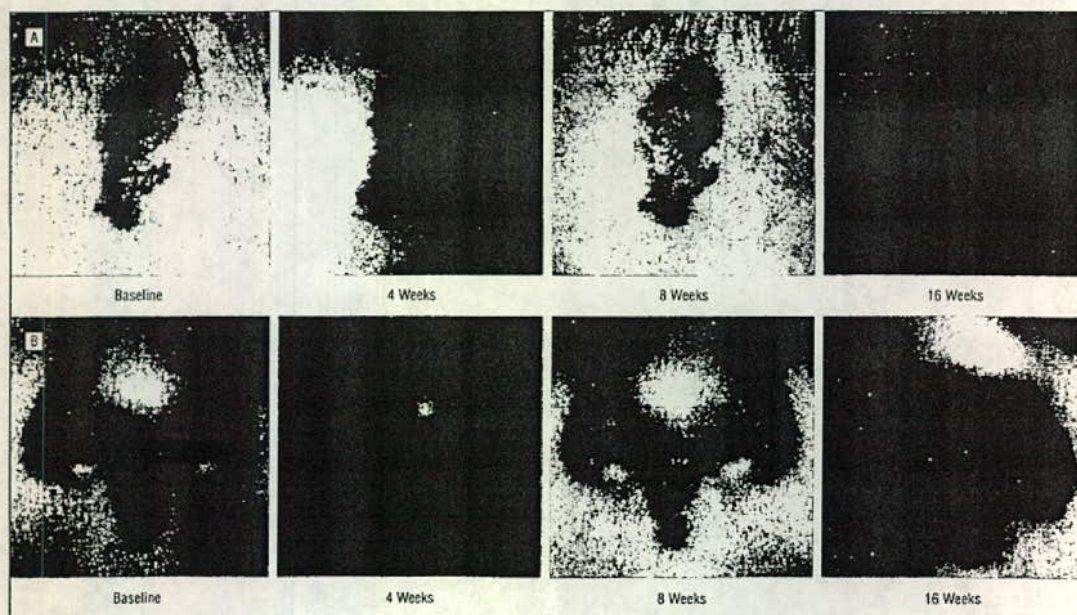


Figure 1. Regression of infantile hemangiomas over time in 2 patients. A, Four-month-old patient with a left forehead hemangioma. B, A 14-month-old patient with a philtrum hemangioma.

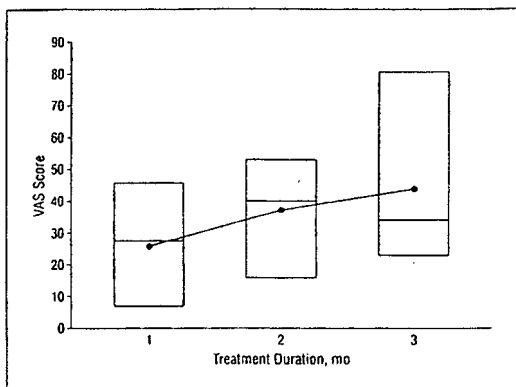


Figure 2. Change in mean combined visual analog scale score (VAS) (range, 0-100 mm) over the course of treatment with timolol maleate, 0.5%, gel.

and +100, complete shrinkage). Descriptive statistics and the observer intraclass correlation were performed.

Results. The **Table** lists patient characteristics and response data. Clinically, 3 patients had IHs still in the proliferative phase; 2 had IHs that were stable; and 1 had IHs in regression. The difference in appearance of IHs at the various stages of treatment is shown in **Figure 1**. The mean change in VAS over time is presented in **Figure 2**. None of the patients experienced any local or systemic adverse events.

Comment. This proof of concept study shows that timolol maleate, 0.5%, gel, a nonselective β -blocker in topical formulation, is effective and safe for the treatment of IHs. Patients with superficial IHs and those treated for longer periods showed better response to timolol. Early intervention during the rapid proliferative phase (age 1-6 months) may result in better and faster resolution of IHs. This preliminary work suggests that topical timolol maleate, 0.5%, gel is an alternative to systemic propranolol for treatment of superficial IHs. Further prospective studies are required to substantiate the safety and efficacy of timolol maleate, 0.5%, gel in the treatment of IHs.

Elena Pope, MD, FRCPC
Ajith Chakkittakandiyil, MD

Accepted for Publication: November 15, 2009.

Author Affiliations: Section of Dermatology (Dr Pope), Hospital for Sick Children (Dr Chakkittakandiyil), Toronto, Ontario, Canada.

Correspondence: Dr Pope, Section of Dermatology, 555 University Ave, Toronto, ON M5G 1X8, Canada (elena.pope@sickkids.ca).

Author Contributions: Both authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. **Study concept and design:** Pope. **Acquisition of data:** Pope and Chakkittakandiyil. **Analysis and interpretation of data:** Pope and Chakkittakandiyil. **Drafting of the manuscript:** Pope and Chakkittakandiyil. **Critical revision of the manuscript for important intellectual content:** Pope. **Statistical analysis:** Pope. **Administrative, technical, or material support:** Chakkittakandiyil.

Study supervision: Pope.

Financial Disclosure: None reported.

1. Drolet BA, Esterly NB, Frieden IJ. Hemangiomas in children. *N Engl J Med*. 1999;341(3):173-181.
2. Metry DW, Hebert AA. Benign cutaneous vascular tumors of infancy: when to worry, what to do. *Arch Dermatol*. 2000;136(7):905-914.
3. Kilcline C, Frieden IJ. Infantile hemangiomas: how common are they? a systematic review of the medical literature. *Pediatr Dermatol*. 2008;25(2):168-173.
4. Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, Boralevi F, Tambo JB, Taïeb A. Propranolol for severe hemangiomas of infancy. *N Engl J Med*. 2008;358(24):2649-2651.
5. D'Angelo G, Lee H, Weiner RI. cAMP-dependent protein kinase inhibits the mitogenic action of vascular endothelial growth factor and fibroblast growth factor in capillary endothelial cells by blocking Raf activation. *J Cell Biochem*. 1997;67(3):353-366.

Anetoderma of Prematurity: An Iatrogenic Consequence of Neonatal Intensive Care

Anetoderma of prematurity was described by Prizant et al¹ in very-low-birth-weight infants in neonatal intensive care units (NICUs). This recent description probably reflects improvement in care of premature neonates who were previously unable to survive. The mechanism for the development of anetoderma is unknown, but the role of monitoring leads has been suspected. To further delineate this clinical condition, we have studied 11 additional cases.

Methods. All cases of anetoderma of prematurity seen in a single NICU (University Hospital, Dijon, France) from 1999 to 2006 were retrospectively studied. Anetoderma was diagnosed clinically.

Results. Gestational age and birth weight ranged from 25 to 30 weeks and from 725 to 1250 g, respectively. All neonates had pulmonary diseases and required assisted ventilation. Ten developed bronchopulmonary dysplasia and received oral steroid treatment. Three had severe digestive tract complications (necrotizing enterocolitis or ileal perforation). Nine were treated with indomethacin for patent ductus arteriosus, and 4 of these needed surgical closure. The median duration of hospitalization in the NICU was 125.0 days vs 99.5 days in 30 control neonates matched for gestational age ($P = .001$).

Twin pregnancies occurred in 5 cases, but no co-twins were affected with anetoderma. In these twin pairs, the affected twin had the lower birth weight in 2 instances, and the higher in 3 instances. The incidence and severity of pulmonary or digestive tract diseases were similar in twins without anetoderma.

Localized, rounded flat, atrophic skin patches 5 to 20 mm in diameter were first noted between age 6 weeks and 5 months (**Figure 1B** and **Figure 2A**). Five infants had previously been examined for ecchymoses without atrophy or necrosis (**Figure 1A**) at the sites where monitoring leads had been applied. On follow-up, all ecchymoses turned into atrophic patches within a few days. Previous placement of monitoring leads at the site of atrophic patches was noted in 8 cases. All lesions were ventrally located: in the subclavicular areas on the chest in 8 cases (**Figure 1**) and in paraumbilical areas on the abdomen in 6 (**Figure 2**).

A4

Study 1 of 10 for search of: topical timolol 0.5%

[Previous Study](#) [Return to Search Results](#) [Next Study](#) ➔
[Full Text View](#)[Tabular View](#)[No Study Results Posted](#)[Related Studies](#)

Topical Timolol 0.5% Solution for Proliferating Infantile Hemangiomas

This study is currently recruiting participants.

Verified by Oregon Health and Science University, June 2010

First Received: June 14, 2010 Last Updated: June 18, 2010 [History of Changes](#)

Sponsor:	Oregon Health and Science University
Information provided by:	Oregon Health and Science University
ClinicalTrials.gov Identifier:	NCT01147601

► Purpose

The purpose of this study is to learn about a new potential use for **topical timolol 0.5%** aqueous solution that may help treat small uncomplicated infantile hemangiomas. This study would examine whether **topical timolol** could be a potential therapy.

Condition	Intervention	Phase
Hemangioma Infant	Drug: topical 0.5% Timolol Drug: Control (placebo) group	Phase 0

Study Type: Interventional
 Study Design: Allocation: Randomized
 Control: Placebo Control
 Endpoint Classification: Safety/Efficacy Study
 Intervention Model: Parallel Assignment
 Masking: Open Label
 Primary Purpose: Treatment

Official Title: **Topical Timolol 0.5% Solution for Proliferating Infantile Hemangiomas: A Prospective Double Blinded Placebo Controlled Study**

Resource links provided by NLM:

[MedlinePlus](#) related topics: [Birthmarks](#)

[Drug Information](#) available for: [Timolol](#) [Timolol maleate](#)

[U.S. FDA Resources](#)

Further study details as provided by Oregon Health and Science University:

Primary Outcome Measures:

- Proportion of subjects in treatment group compared to placebo group with at least 75% improvement in the extent of the hemangioma as compared to baseline photos.
 [Time Frame: at 6 months] [Designated as safety issue: Yes]

This will be generated by asking each of the assessors to score the improvement using a visual analog scale (VAS) assessing the decrease in size of hemangioma by comparing photographs at different times of treatment. The

assessors will score this improvement into one of the following categories: 0-24%, 25-49%, 50-74%, >75%.

Secondary Outcome Measures:

- Compare treatment group to control group improvement assessments [Time Frame: at 6 months] [Designated as safety issue: Yes]
 1. The proportion of subjects in the treatment group as compared to the placebo control group with at least 50% improvement in the extent of the hemangioma.
 2. The difference between the extent/size of the hemangioma as an outcome measure versus color changes.
 3. Frequency of adverse events (e.g. hypotension, behavioral changes, etc.), collected by the investigator and reported by the parents.

Estimated Enrollment: 75
 Study Start Date: March 2010
 Estimated Primary Completion Date: March 2011 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Topical 0.5% Timolol: Active Comparator Half of the enrolled subjects (intervention group) will receive topical 0.5% Timolol . Intervention: Drug: topical 0.5% Timolol	Drug: topical 0.5% Timolol topical 0.5% Timolol aqueous solution, 2-3 drops to cover the hemangioma, twice daily
Placebo: Placebo Comparator Aqueous placebo, 2-3 drops to cover the hemangioma, twice daily Intervention: Drug: Control (placebo) group	Drug: Control (placebo) group Control (placebo) group

Detailed Description:

At the first visit, subjects will fill out a questionnaire that asks about the child's history and the hemangioma. Photographs and measurements will be taken at this and each subsequent visit. At the first visit, subjects will have a physical exam, including vital signs, height and weight. An EKG will also be done. Study drug will be dispensed and instructions given. Half of the subjects will receive a placebo. This is a blinded randomized study. Follow-up visits will be weekly for the first two weeks (three visits total including the first visit), then monthly until the study is over. Photographs and measurements will again be taken at each visit. Subjects will be asked to evaluate the size and the color of the hemangioma against the first photographs and fill out forms regarding any changes in behavior and asked about any side effects.

► Eligibility

Ages Eligible for Study: 1 Month to 8 Months
 Genders Eligible for Study: Both
 Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

Infants 1 month to 8 months of age with infantile hemangioma (IH) that are 3 cm or less on the scalp, trunk, or extremities.

Exclusion Criteria:

1. Subjects with facial, genital, perianal, hand, finger, feet, or toe IH
2. Subjects with PHACES syndrome (proven) or suspected PHACES (plaque-like hemangioma on the face awaiting imaging).
3. Subjects with IH measuring more than 3cm in size or ulcerated.
4. Children with a history of hypersensitivity to beta blockers.
5. Children with a personal history of asthma.

6. Children with known renal impairment.
7. Children with known cardiac conditions that may predispose to heart block
8. Personal history of hypoglycemia
9. Children on medications that may interact with beta blockers

► Contacts and Locations

Please refer to this study by its ClinicalTrials.gov identifier: NCT01147601

Contacts

Contact: Alfons L. Krol, M.D. 503 494 9333 krola@ohsu.edu
 Contact: Lindsay K. Severson, B.S., CCRC 503 494 6009 seversol@ohsu.edu

Locations

United States, Oregon

Oregon Health & Science University **Recruiting**
 Portland, Oregon, United States, 97239-4501
 Contact: Alfons L. Krol, M.D. 503-494-9993 krola@ohsu.edu
 Contact: Lindsay K. Severson, B.A., CCRC 503 494 6009 seversol@ohsu.edu
 Principal Investigator: Alfons L. Krol, M.D.

Sponsors and Collaborators

Oregon Health and Science University

Investigators

Principal Investigator: Alfons L. Krol, M.D. Oregon Health and Science University

► More Information

No publications provided

Responsible Party: Oregon Health & Science University (Alfons L. Krol, M.D.)
 ClinicalTrials.gov Identifier: [NCT01147601](#) [History of Changes](#)
 Other Study ID Numbers: 6114
 Study First Received: June 14, 2010
 Last Updated: June 18, 2010
 Health Authority: United States: Institutional Review Board

Keywords provided by Oregon Health and Science University:

topical 0.5% Timolol
 infantile hemangioma (IH)

Additional relevant MeSH terms:

Timolol	Neurotransmitter Agents
Hemangioma	Molecular Mechanisms of Pharmacological Action
Hemangioma, Capillary	Pharmacologic Actions
Neoplasms, Vascular Tissue	Physiological Effects of Drugs
Neoplasms by Histologic Type	Anti-Arrhythmia Agents
Neoplasms	Cardiovascular Agents
Adrenergic beta-Antagonists	Therapeutic Uses
Adrenergic Antagonists	Antihypertensive Agents
Adrenergic Agents	

ClinicalTrials.gov processed this record on February 02, 2011

[Contact Help Desk](#)
[Lister Hill National Center for Biomedical Communications](#), [U.S. National Library of Medicine](#),
[U.S. National Institutes of Health](#), [U.S. Department of Health & Human Services](#),
[USA.gov](#), [Copyright](#), [Privacy](#), [Accessibility](#), [Freedom of Information Act](#)



A5

Study 3 of 15 for search of: Nadolol

Previous Study

Return to Search Results

Next Study

Full Text View

Tabular View

No Study Results Posted

Related Studies

Nadolol for Proliferating Infantile Hemangiomas

This study is currently recruiting participants.
Verified by The Hospital for Sick Children, January 2010

First Received: November 8, 2009 Last Updated: January 27, 2010 [History of Changes](#)

Sponsor:	The Hospital for Sick Children
Information provided by:	The Hospital for Sick Children
ClinicalTrials.gov Identifier:	NCT01010308

► Purpose

The purpose of this study is to explore the efficacy and safety of **Nadolol** in hemangiomas of infancy.
The secondary objective is to assess the feasibility of conducting a randomized controlled trial comparing **nadolol** with corticosteroids and propranolol.

Condition	Intervention	Phase
Infantile Hemangioma	Drug: Nadolol	Phase II

Study Type: Interventional
Study Design: Allocation: Non-Randomized
Control: Historical Control
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: **Nadolol** for Proliferating Infantile Hemangiomas: A Prospective Open Label Study With a Historical Control

Resource links provided by NLM:

[MedlinePlus](#) related topics: [Birthmarks](#)
[Drug Information](#) available for: [Nadolol](#)
[U.S. FDA Resources](#)

Further study details as provided by The Hospital for Sick Children:

- Primary Outcome Measures:
- Proportion of subjects with at least 75% improvement in the extent of the hemangioma [Time Frame: Baseline, 6months] [Designated as safety issue: No]
- Secondary Outcome Measures:
- The proportion of subjects with at least 50% improvement in the extent of the hemangiomas [Time Frame: Baseline and 6 months] [Designated as safety issue: No]

29

- The percentage of patients with >75% improvement in the **Nadolol** group compared to a historical cohort of patients receiving propranolol. [Time Frame: 6 months] [Designated as safety issue: No]
- The correlation between the changes in the levels of angiogenesis markers and clinical response to treatment. [Time Frame: 6 months] [Designated as safety issue: No]

Estimated Enrollment:30

Study Start Date:November 2009

Estimated Study Completion Date:February 2012

Estimated Primary Completion Date:February 2012 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Intervention Group:: Experimental The patients in this study are infants aged 1 month to 1 year of age with head and neck hemangiomas currently causing /or with impending function loss (e.g. vision, airway obstruction, feeding, etc), or hemangiomas currently causing/or with potential for facial disfigurement Infants aged 1 month to 1 year of age with head and neck hemangiomas that received treatment with systemic propranolol in the past 2 years as a control group Intervention: Drug: Nadolol	Drug: Nadolol Nadolol will be administered orally at home starting at 0.5 mg/kg/day divided into 2 doses. Weekly, if BP and heart rate are acceptable, the dose will be increased by 0.5 mg/kg/day up to 2 mg/kg/day.
Historical control group: No Intervention Ten infants (1-12 months of age) treated with propranolol will be identified from a Dermatology Database. Patients will be considered as controls if they were treated with propranolol before 1 year of age and had digital photography documentation of their hemangioma.	
Angiogenesis marker control group: No Intervention The angiogenesis marker control group will consist of 6 -10 patients seen in the Dermatology clinic for conditions other than IH and not receiving corticosteroids or beta blockers.	

Detailed Description:

Systemic corticosteroids are currently the most frequent used medication for treatment of problematic infantile hemangiomas (IH's). Since June 2008, systemic propranolol has been an important addition to the therapeutic options for problematic IH, allowing decreased dependence on the systemic corticosteroids. So far, we have found excellent response with propranolol with minimal short-term side effects. Studies, which compared nadolol and propranolol in children with other conditions, suggest that nadolol is safer and more efficacious than propranolol. In addition, it has better dosing schedules and less central nervous system (CNS) penetration, making it suitable even for patients with suspected or proven PHACES syndrome.

► **Eligibility**

Ages Eligible for Study:1 Month to 1 Year

Genders Eligible for Study:Both

Accepts Healthy Volunteers:No

Criteria

Inclusion Criteria:

Intervention Group

- Infants aged 1 month to 1 year of age with head and neck hemangiomas currently causing /or with impending function loss (e.g. vision, airway obstruction, feeding, etc), or hemangiomas currently causing/or with potential for facial disfigurement.

Historical Control Group

- Infants aged 1 month to 1 year of age with head and neck hemangiomas that received treatment with systemic propranolol in the past 2 years

Angiogenesis Marker Control Group

- Infants aged 1 month to 1 year attending dermatology clinic

Exclusion Criteria:**Intervention Group**

- Patients with PHACES syndrome (proven) or suspected PHACES (plaque like hemangioma awaiting imaging).
- Children with history of hypersensitivity to beta blockers
- Children with personal history or family history of a first degree relative with asthma
- Children with known renal impairment
- Children with known cardiac conditions which may predispose to heart blocks
- Personal history of hypoglycemia
- Children on medications that may interact with beta blockers

Historical Control Group:

- No digital photography available documenting IHs progression

Angiogenesis Marker Control Group:

- Children with IH
- Children on beta blocker or systemic corticosteroids

► Contacts and Locations

Please refer to this study by its ClinicalTrials.gov identifier: NCT01010308

Contacts

Contact: Ajith Chakkittakandil, MD (416) - 813 - 7835 Ajith.chakkittakandil@sickkids.ca

Locations**Canada, Ontario**

The Hospital for Sick Children **Recruiting**
Toronto, Ontario, Canada
Principal Investigator: Elena Pope, MD

Sponsors and Collaborators

The Hospital for Sick Children

Investigators

Principal Investigator: Elena Pope, MD The Hospital for Sick Children

► More Information

No publications provided

Responsible Party: The Hospital for Sick Children (Elena Pope, MD)
ClinicalTrials.gov Identifier: [NCT01010308](#) [History of Changes](#)
Other Study ID Numbers: 1000014079
Study First Received: November 8, 2009
Last Updated: January 27, 2010
Health Authority: Canada: Health Canada

Keywords provided by The Hospital for Sick Children:
infantile hemangioma
nadolol

Additional relevant MeSH terms:

Nadolol

Hemangioma
Hemangioma, Capillary
Neoplasms, Vascular Tissue
Neoplasms by Histologic Type
Neoplasms
Adrenergic beta-Antagonists
Adrenergic Antagonists
Adrenergic Agents
Neurotransmitter Agents

Molecular Mechanisms of Pharmacological
Action
Pharmacologic Actions
Physiological Effects of Drugs
Anti-Arrhythmia Agents
Cardiovascular Agents
Therapeutic Uses
Antihypertensive Agents
Sympatholytics
Autonomic Agents
Peripheral Nervous System Agents

ClinicalTrials.gov processed this record on February 02, 2011

[Contact Help Desk](#)

[Lister Hill National Center for Biomedical Communications](#), [U.S. National Library of Medicine](#),
[U.S. National Institutes of Health](#), [U.S. Department of Health & Human Services](#),
[USA.gov](#), [Copyright](#), [Privacy](#), [Accessibility](#), [Freedom of Information Act](#)

