Update on Vascular Lesions

Pacific Dermatology Association 61st Annual Meeting

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Conflict Disclosure

- I have no paid consultancy agreements
- Do not sit on any paid advisory Boards or Speakers Bureau’s
- I do conduct Pediatric Clinical trials at OHSU
Hemangiomas and Vascular Malformations
- ISSVA -
• Classification (Mulliken)

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Vascular tumors

“Vascular birthmarks”
“Angiomas”
Vascular anomalies

Vascular tumors
Hemangiomas Others

Vascular malformations
Slow-flow
VMs

Fast-flow
LMs
CMs
AVMs
Hemangiomas Of Infancy

Rapid post natal growth
Over 3-12 months
Creates small or bulky lesion

Slow spontaneous involution
Over 2-10 yrs
Leaves normal skin or sequelae

Treatment of Hemangioma

For Non-Threatening lesions
Park Bench Approach

For Rapidly Enlarging or threatening lesions

1. Steroids (2-3 mg/kg)
   Must be maintained for 4-8 wks
   then slowly tapered over another 2-3 months until growth has ceased

2. -Interferon 2b
   3 Million U/m² sub cut. Daily

3. Vincristine (1-1.5 mg/m² weekly)
Steroid treatment of Hemangiomas

Dosage 2-3mgs/kg day
Maintain for 4-8 weeks and reduce
To 1 to 1.5 mgs/kg /day
Gradual taper to alternate days
Total length of treatment 3-6 months

Monitor growth and development
Monitor BP
Ranitidine
? PCP prophylaxis – We have had 2 pt’s

2wks prednisone
3mgs/kg

Stridor airway involved
4 weeks tracheostomy

4 weeks

Prednisone continued
Vincristine started
Vincristine
Weekly x 6
Biweekly x 6
Monthly x 3
Prednisone
Tapered over 9 months
Age 14 months

1 Day post 3rd PDL Rx
At 2 yrs 4 months of age
Early Surgery For Periocular Hemangiomas

18 PTS RX WITH Surgery after failure Of standard therapy PO or IL steroids Age 5 months to 3 yrs

PLASTIC AND RECONSTR SURGERY APRIL 2007 GEH JL. GEH.VS. JEMEC.B ET AL
Report of 11 pts treated with propranolol
Dosage 2-3 mgs/kg/day
Duration 2-10 months

Beta Blocking Agent for treatment Of Hemangioma

• Paper at ISSVA meeting Boston 2008
• Treated 4 infants with acebutolol
  • dosage 10 mgs /kg /day

• 3 out of 4 Continued on oral steroids for 3 months after acebutolol started

Bigorre M, Van Kien AK, Valette H.
Role of propranolol in the therapeutic strategy of infantile laryngotracheal hemangioma

Denoyelle F, Leboulanger N, Enjolras O. et al

Int. J of Ped Otorhinolaryngol 2009; 23:1168-72

2 patients with subglottic hemangiomas
Resistant to treatment with steroids/vincristine

Case 1: Spectacular response to Propranolol with improvement of stenosis from 80% to 10% after one month (3 mgs/kg/day)

Case 2: reduction from 50% stenosis To normal in second infant which allowed extubation and decreased steroid dose (2 mgs/kg/day)

Pt with PHACE Syndrome

Large Segmental Cervicofacial Hemangioma – Poor response to Prednisone 3mg/kg/day-

Started on IV Vincristine Hypertensive started on Labetalol
Initial response then
Late Proliferation At 1 yr of age
Restarted on Prednisone at 1 Yr for 3 months

At 2.5 yrs of age Off all treatment except Labetalol for hypertension
Pre Rx

2 wk

3 months

On 2mg/kg Prednisone For 6 weeks

Became Hypertensive
Steroids tapered

Propranolol started initially .5 mg/kg and increased to 1mg/kg over 2 weeks

March 2009  April 2009  June 2009
Propranolol for Hemangiomas of Infancy

- Starting dose 2 mg/kg/day
- 24 hours after initiation dramatic softening, with intense red to purple color change
- No regrowth after steroids stopped
- Hemangioma continued to improve until nearly flat with residual telangiectasia

Leaute-Labreze C, et al
NEJM 2008 358(24) 2649
The studies are just beginning…


Propranolol for Hemangiomas of Infancy

Mechanism of Action Unknown
But…..

Propranolol known to trigger apoptosis
In Endothelial cells

Down regulates MMP-9 (required for Endothelial cell migration and tube formation)

?decreased expression of VEGF & bFGF

Vasoconstrictive effect
MMP-9 expression at 92 Kd
Increased Expression of Urinary Matrix Metalloproteinases Parallels the extent and Activity of vascular Anomalies

Propranolol adrenergic blockade inhibits brain endothelial cells Tubulogenesis and matrix metalloproteinase-9 secretion
Annaabi B, Lachambre MP, Plouffe K et al. Pharmacological Research 2009 e-pub
Non-Selective B-blockers:
Propranolol, Timolol, Naldolol, Metipranolol, Oxprenolol, Penbutolol

B1 selective: Acebutolol
Mixed A1 B: Labutolol

Sir James Black
Won Nobel Prize in Medicine in 1988
For discovery of propranolol _1, _2 and _3. Adrenergic Receptors

_1-Adrenergic receptors
are located mainly in the heart and in the kidneys.

_2-Adrenergic receptors are located mainly
in the lungs, gastrointestinal tract, liver, uterus, vascular smooth muscle, and skeletal muscle.

_3-receptors are located in fat cells.

No data on expression of ß_1, ß_2, ß_3 in Hemangioma tissue
Propranolol: Potential side effects

- Typically mild and temporary
  - Bradycardia and hypotension
  - Dizziness, lethargy and fatigue
  - Diarrhea, nausea and vomiting
  - Bronchospasm
- Hypersensitivity rxn's are rare:
  - Rash (including EM, SJS and TEN)
  - Urticaria, fever, agranulocytosis and anaphylaxis
- Hypoglycemia

Propranolol: Potential side effects

- Hypoglycemia

  - Blunts sympathomimetic-mediated hepatic gluconeogenesis
  - Council parents that at risk times may be periods of fasting before a procedure, or with gastroenteritis with N/V and poor oral intake
  - May be useful to have oral rehydration solutions on hand (Pedialyte etc.)
Propranolol: Potential side effects

- Therapeutic levels (cardiac 30 – 100 ng/ml)
- Metabolized by CYP 450, 1A2, 2C18, 2C19, and 2D6 isoenzymes
- Concurrent barbiturates, indomethacin, and rifampin may cause decreased activity
- Concurrent cimetidine, hydralazine, and verapamil may cause increased activity

A Letter to the Editor...

- Discussion of safety regarding initiation and monitoring of propranolol in infants
- Highlighted risks: bradycardia, hypotension, masking of potential cardiac failure and/or hypoglycemia
- Developed treatment protocol to optimize safety: baseline echocardiogram, 48hr hospitalization or home nurse visits to monitor vital signs and glucose
- Dosed q8hrs; initial dose 0.16mg/kg, then gradually double to max 0.67 mg/kg (max daily dose 2mg/kg; gradually taper over 2wks
Propranolol Unanswered Questions

What is the Optimal dosage regimen?

What is Optimal monitoring for safety?

How long is Optimal treatment?

Is there synergism between B-Blockers and steroids?

Could topical B-Blockers be effective?

Do all Patients require echocardiograms?

Do all patients require admission?

Double Blind, Randomised, Placebo-Controlled Study of Propranolol in Infantile Capillary Hemangiomas

- University Hospital, Bordeaux (Léauté-Labrèze, Dumas)
- Oct 2008 - Sept 2009
- Expected N = 50
- Primary objective: determine efficiency of 1 month early treatment of propranolol in infants < 3mo with hemangioma without consequences on vital of functional structure, not justifying corticosteroids
- Primary outcome measure: Thickness, measured by U/S compared to basal state
- Compare placebo to 30 days propranolol (3mg/kg x 15 days + 4mg/kg x 15 days)
Complications of Large Slow Flow Malformations

1. Pulmonary thromboembolism especially with KTS

2. Localized intravascular coagulation syndrome resulting in thrombosis or hemorrhage (either large limb VM’s or combined VM/LM lesions)
   Arch. Dermatology 144;7:873-877 2007

140 pts with VM’s 42% had high D-dimer levels >1.0µg/ml (59 pt’s)
   6 pt’s had associated low fibrinogen levels

These patients often have local pain due to thrombosis and have a much higher risk of hemorrhage.
Low molecular weight heparin can be used to treat the pain caused by LIC
And prevent decompensation of severe LIC to DIC
D-Dimer 6796
N<499
Hgb 5 gms
RX with LMW Heparin
May be life saving

KTS with mixed venous lymphatic malformation
Gradual onset of fatigue and SOB over a period of several months
Multiple Pulmonary Emboli resulting in Heart failure and Pulmonary hypertension

Recovered after thoracotomy and Embolectomy

"By God, for a minute there it suddenly all made sense!"