DAPSONE

STEVEN MAYS, M.D.
ASSOCIATE PROFESSOR
DEPARTMENT OF DERMATOLOGY
UT/MCGOVERN MEDICAL SCHOOL – HOUSTON
I HAVE NO RELEVANT DISCLOSURES
METABOLISM

• >80% ABSORPTION FROM SMALL INTESTINE
• PEAK SERUM CONCENTRATION IN 2 – 8 HOURS
• HEPATIC METABOLISM
Dapsone can undergo hepatic acetylation and hydroxylation. The acetylated form, monoacetyl-dapsone, is more responsible for therapeutic effects, while the hydroxylated form, dapsone hydroxylamine, is more responsible for adverse effects.
METABOLISM

- RENAL EXCRETION
- HALF-LIFE IS 24 – 36 HOURS
METABOLISM

• Dapsone crosses the placenta and is detectable in breast milk
• Not known to cause teratogenicity in humans (category C)
• May cause hemolytic anemia in the fetus and the breast-feeding baby
MECHANISM OF ANTIBACTERIAL EFFECTS

• SULPHONE ANTIBIOTIC, CHEMICALLY RELATED TO SULFONAMIDES
• DAPSONE COMPETES WITH PABA → INHIBITS BACTERIAL DPT SYNTHETASE → BLOCKS BACTERIAL FOLIC ACID SYNTHESIS
• THERAPY FOR LEPROSY
• FOR PREVENTION AND THERAPY OF PCP PNEUMONIA
MECHANISM OF ANTI-INFLAMMATORY EFFECT

• INHIBITS MYELOPEROXIDASE IN NEUTROPHILS → DECREASES NEUTROPHIL-MEDIATED INFLAMMATION
• NO CONCLUSIVE EVIDENCE THAT DAPSONE INHIBITS NEUTROPHIL CHEMOTAXIS
• INHIBITS MPO IN EOSINOPHILS AS WELL
• ROLE IN NEUTROPHILIC AND EOSINOPHILIC SKIN DISEASES
DOSING

• 25 MG TABLET AND 100 MG TABLET

• THIRTY 100 MG TABS: $31 AT WALMART (GOODRX, FEBRUARY 2019)

• COMPOUNDING PHARMACIES MAY PREPARE DAPSONE ORAL SUSPENSION 2 MG/ML FOR PEDIATRIC PATIENTS

• TAKE WITH FOOD
DOSING

• FOR CHILDREN WITH LEPROSY: 2 MG/KG DAILY
• FOR ADULTS WITH LEPROSY: 100 MG DAILY
• FOR CHILDREN WITH DERMATOLOGIC DISORDERS: 0.5 – 2 MG/KG DAILY
• FOR ADULTS WITH DERMATOLOGIC DISORDERS: USUALLY 100 MG DAILY; DOSING MAY VARY FROM 25 MG/DAY TO 300 MG/DAY DEPENDING ON CLINICAL RESPONSE
INDICATIONS

• FDA-APPROVED FOR LEPROSY AND DH

• CONSISTENT EFFICACY FOR:
  • LINEAR IGA DISEASE (ADULT AND PEDI)
  • EED
  • BULLOUS ERUPTION OF SLE

WOLVERTON SE. COMPREHENSIVE DERMATOLOGIC DRUG THERAPY. SAUNDERS; 2013. P. 232
INDICATIONS

• VARIABLE EFFICACY FOR:
  • SUBCORNEAL PUSTULAR DERMATOSIS
  • LCV, UV
  • SWEET’S, PG, BEHCET’S
  • INFLAMMATORY ROSACEA, ACNE CONGLOBATA, ACNE FULMINANS
  • GA
  • BP, PV, PF, CP
BULLOUS DISORDERS

- “IN ONE DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL EVALUATING THE USE OF DAPSONE FOR PV … 19 PATIENTS RECEIVING SYSTEMIC IMMUNOSUPPRESSIVE THERAPY FOR PV WERE RANDOMIZED TO TWO GROUPS TREATED WITH THE ADDITION OF EITHER DAPSONE OR PLACEBO. SUCCESS WAS … THE ABILITY TO TAPER SYSTEMIC GLUCOCORTICOIDs TO AT LEAST 7.5 MG/DAY WITHIN 1 [ONE] YEAR OF REACHING THE MAXIMUM DOSE OF DAPsONE … ALTHOUGH THE DIFFERENCE BETWEEN GROUPS WAS NOT SIGNIFICANT, THE TREND FAVORED THE DAPsONE-TREATED GROUP.”

PIETTE EW, WERTH VP. DAPsONE IN THE MANAGEMENT OF AUTOIMMUNE BULLOUS DISEASEs. IMMUNOL ALLERGY CLIN N AM 32(2012):317 - 322
BULLOUS DISORDERS

• “[THERE ARE NO] RANDOMIZED CONTROLLED TRIALS EVALUATING DAPSONE AS A THERAPY FOR BP. THE 2009 REVIEW BY GURCAN AND AHMED … CONCLUDED THAT THERE ARE AT LEAST SIX PUBLISHED STUDIES ENCOMPASSING 170 PATIENTS WITH BP WHO RECEIVED DAPSONE. OF THESE PATIENTS, 139 (81%) SHOWED CLINICAL IMPROVEMENT WITH 50 TO 300 MG OF DAPSONE ALONE OR IN COMBINATION WITH IMMUNOSUPPRESSIVES.”

PIETTE EW ET AL.
SIDE EFFECTS

• EXPECTED SIDE EFFECTS:
  • METHEMOGLOBINEMIA
  • HEMOLYTIC ANEMIA

• IDIOSYNCRATIC SIDE EFFECTS:
  • DRESS
  • MOTOR NEUROPATHY
  • DERMATOLOGIC SIDE EFFECTS
HEMOLYTIC ANEMIA

• AN **EXPECTED** SIDE EFFECT
• OCCURS IN ALL PATIENTS TAKING >50 MG/DAY
• DOES NOT USUALLY CAUSE SYMPTOMS
• DOSE-DEPENDENT
HEMOLYTIC ANEMIA

• ONE HUNDRED LEPROSY PATIENTS TREATED WITH DAPSONE AT 100 MG DAILY
• 80% DROPPED HB > 1 GM/DL
• 50% DROPPED HB > 2 GM/DL

BYRD SR, GELBER RH. EFFECT OF DAPSONE ON HEMOGLOBIN CONCENTRATION IN PATIENTS WITH LEPROSY. LEPR REV 1991; 62:171 - 178
HEMOLYTIC ANEMIA

• G6PD deficiency → increased red blood cell sensitivity to oxidative stress
• Dapsone hydroxylamine → decreased lifespan of red blood cells
• More severe hemolytic anemia occurs in G6PD(-) patients who are treated with dapsone
ASYMPTOMATIC HEMATOLYTIC ANEMIA

• MONITOR THE PATIENT; OR DECREASE THE DAPSONE DOSE; OR DISCONTINUE DAPSONE
• MONITOR CBC MORE FREQUENTLY
SYMPTOMATIC HEMATOLYTIC ANEMIA

• HEADACHE, FATIGUE, DIZZINESS
• DARK URINE, JAUNDICE
SEVERE HEMATOLYTIC ANEMIA - THERAPY

- DISCONTINUE DAPSONE
- RED CELL TRANSFUSION
- SUPPLEMENTAL OXYGEN
- IV FLUIDS TO MAINTAIN URINARY EXCRETION OF DAPSONE
METHEMOGLOBINEMIA
HEMOGLOBIN

Dapsone

Hydroxylamine

HEMOGLOBIN

METH-HEMOGLOBIN

Total Hemoglobin Level Unchanged

Does not bind oxygen
METHEMOGLOBINEMIA

- MOST PATIENTS WHO TAKE DAPSONE HAVE SOME DEGREE OF METHEMOGLOBINEMIA … BUT ALMOST ALL ARE ASYMPTOMATIC. METHEMOGLOBIN LEVELS IN ASYMPTOMATIC PATIENTS ARE USUALLY <5%.

- WHETHER THESE PATIENTS BECOME SYMPTOMATIC DEPENDS ON TWO FACTORS:
  - THE METHEMOGLOBIN LEVEL
  - THE PRESENCE OF OTHER DISEASES THAT PREDISPOSE TO HYPOXIA, SUCH AS COPD, PNEUMONIA, OR PRE-EXISTING ANEMIA
SYMPTOMATIC METHEMOGLOBINEMIA

- Headache, Fatigue, Dizziness
- Shortness of Breath, Cyanosis, Tachypnea
METHEMOGLOBINEMIA: DIAGNOSIS

- (1) CLINICAL SIGNS
- (2) MET HB LEVEL
- (3) LACK OF IMPROVEMENT WITH SUPPLEMENTAL O₂
- (4) CHOCOLATE-BROWN BLOOD

- PULSE OX WILL SHOW HYPOXIA, BUT CANNOT ACCURATELY DETERMINE THE FUNCTIONAL O₂ SATURATION

- ABG: PaO₂ IS USUALLY NORMAL
METHEMOGLOBINEMIA: THERAPY

• DISCONTINUE DAPSONE
• SUPPLEMENTAL O₂ HAS LITTLE BENEFIT
• IV METHYLENE BLUE – CONVERTS MET HB BACK TO HB
• ?CIMETIDINE
METHEMOGLOBINEMIA

- **EXPECTED** SIDE EFFECT OF DAPSONE, BUT RARE TO BE SYMPTOMATIC
- UNRELATED TO G6PD STATUS
OTHER SIDE EFFECTS

- AGRANULOCYTOSIS
  - 0.3% OF TREATED PATIENTS
  - USUALLY OCCURS WITHIN FIRST THREE MONTHS

- PERIPHERAL MOTOR NEUROPATHY
  - WEAKNESS OF HANDS AND LOWER LEGS, WASTING OF HAND MUSCLES
  - USUALLY REVERSIBLE

- DRUG-INDUCED HEPATITIS
OTHER SIDE EFFECTS

- DRESS
  - MR IN ONE SERIES (N = 336) WAS 10%
  - IN THAT SERIES, ONSET WAS ALWAYS WITHIN THE FIRST THREE MONTHS
- MORBILLIFORM ERUPTION, TEN

PRE-THERAPY EVALUATIONS

• PAST MEDICAL HISTORY
  • ESPECIALLY PRE-EXISTING PULMONARY DISEASE AND SEVERE ANEMIA
  • ALSO PRIOR RENAL, HEPATIC, AND NEUROLOGIC DISEASE

• INITIAL LABS
  • G6PD
  • CBC
  • COMPREHENSIVE METABOLIC PANEL (FOR HEPATIC AND RENAL FUNCTIONS)
FOLLOWUP

- Peripheral Motor Neuro Exam
- CBC every 2 weeks for 3 months, then every 3 months
- LFT's and Renal Function every 3 months
SELECT DRUG INTERACTIONS

• HEMOLYSIS: METHOTREXATE, BACTRIM, PROBENECID

• METHEMOGLOBINEMIA: BENZOCAINE SPRAY (USED FOR BRONCHOSCOPY, LARYNGOSCOPY, UPPER GI)

• PERIPHERAL MOTOR NEUROPATHY: PLAQUENIL, ZICALCITABINE
SULFA ALLERGY

- APPROXIMATELY 20% CROSS-REACTIVITY BETWEEN DAPSONE AND BACTRIM
- PATIENTS WITH A MILD REACTION TO BACTRIM USUALLY HAVE A MILD (OR NO) REACTION TO DAPSONE
- FOR THOSE WITH A PRIOR SEVERE REACTION TO BACTRIM … AVOID THE USE OF DAPSONE

HOLTZER CD ET AL. CROSS-REACTIVITY IN HIV-INFECTED PATIENTS SWITCHED FROM TRIMETHOPRIM-SULFAMETHOZOLE TO DAPSONE. PHARMACOTHERAPY 1998; 18(4):831-835
QUESTIONS

• ALL OF THE FOLLOWING ARE SUGGESTIVE OF SYMPTOMATIC METHEMOGLOBINEMIA EXCEPT:

A) ELEVATED METHEMOGLOBIN LEVEL
B) SHORTNESS OF BREATH
C) SIGNIFICANTLY-DECREASED HEMOGLOBIN LEVEL
D) LACK OF IMPROVEMENT WITH SUPPLEMENTAL OXYGEN
E) CYANOSIS
QUESTIONS

• WITH RESPECT TO DAPSONE-INDUCED HEMOLYTIC ANEMIA, WHICH OF THE FOLLOWING IS FALSE?

A) ONE SHOULD CONSIDER DELAYING DAPSONE THERAPY IN PATIENTS WITH SIGNIFICANT PRE-EXISTING ANEMIA

B) THE DEGREE OF DAPSONE-INDUCED HEMOLYSIS TENDS TO BE MORE SEVERE IN PATIENTS WITH SEVERE G6PD DEFICIENCY THAN IN THOSE WITH Milder DEFICIENCY

C) IN GENERAL, DAPSONE-INDUCED HEMOLYSIS IS MOST SEVERE AT 3 – 4 MONTHS AFTER INITIATING THERAPY

D) DAPSONE-INDUCED HEMOLYSIS IS AN UNEXPECTED SIDE EFFECT IN PATIENTS WITH A NORMAL G6PD LEVEL
QUESTIONS

• EACH OF THE FOLLOWING HAS A WELL-ESTABLISHED INTERACTION WITH DAPSONE EXCEPT:

A) BACTRIM
B) PROBENECID
C) CYCLOSPORINE
D) BENZOCAINE SPRAY