DAPSONE

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I HAVE NO RELEVANT DISCLOSURES
METABOLISM

- >80% ABSORPTION FROM SMALL INTESTINE
- PEAK SERUM CONCENTRATION IN 2 – 8 HOURS
- HEPATIC METABOLISM
DAPSONE

- Hepatic acetylation
- Hydroxylation (Cyt P450)

MONOACETYL-DAPSONE

DAPSONE HYDROXYLAMINE

(1) Most responsible for therapeutic effects
(2) Most responsible for adverse effects
METABOLISM

• Dapsone crosses the blood-brain barrier and the placenta; it is detectable in breast milk
• Renal excretion
• Half-life is 24 – 36 hours
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
- PROPHYLAXIS FOR MALARIA AND PCP PNEUMONIA
MECHANISM OF ANTI-INFLAMMATORY EFFECT

- INHIBITS MYELOPEROXIDASE IN NEUTROPHILS $\rightarrow$ DECREASES NEUTROPHIL ACTIVITY $\rightarrow$ 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: $30 AT CVS (GOODRX, FEBRUARY 2017)

• COMPOUNDING PHARMACIES MAY PREPARE DAPSONE ORAL SUSPENSION 2 MG/ML FOR PEDIATRIC PATIENTS
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; 2007. P. 244
INDICATIONS

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

WOLVERTON SE
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.”

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

• OTHER SIDE EFFECTS:
  • DRESS
  • MOTOR NEUROPATHY
  • DERMATOLOGIC SIDE EFFECTS
HEMOGLOBIN

\[ \text{dapsone} \rightarrow \text{ METH-HEMOGLOBIN } \]

does not bind oxygen

total hemoglobin level unchanged
• 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
METHEMOglobinem ia

• 20% METHEMOGLOBIN

• NON-ANEMIC PATIENT WITH HEMOGLOBIN = 15 \( \rightarrow \) FUNCTIONAL HEMOGLOBIN = 12 ... UNLIKELY TO BE SYMPTOMATIC

• ANEMIC PATIENT WITH HEMOGLOBIN = 10 \( \rightarrow \) FUNCTIONAL HEMOGLOBIN = 8 ... LIKELY TO BECOME SYMPTOMATIC
SYMPTOMATIC METHEMOGLOBINEMIA

• HEADACHE, FATIGUE, DIZZINESS
• SHORTNESS OF BREATH, CYANOSIS, TACHYPNEA
• ARRHYTHMIAS, SEIZURES, COMA
METHEMOGLOBINEMIA: DIAGNOSIS

• (1) CLINICAL SIGNS  (2) MET HB LEVEL  (3) LACK OF IMPROVEMENT WITH SUPPLEMENTAL O\textsubscript{2}  
  (4) CHOCOLATE-BROWN BLOOD  
• PULSE O\textsubscript{X} WILL SHOW HYPOXIA, BUT CANNOT ACCURATELY DETERMINE THE FUNCTIONAL O\textsubscript{2}  
  SATURATION
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
HEMOLYTIC ANEMIA

• AN EXPECTED SIDE EFFECT

• AFFECTS ALL PATIENTS WHO TAKE DAPSONE, BUT DOES NOT USUALLY CAUSE SYMPTOMS

• PATIENTS WITH NORMAL G6PD FUNCTION USUALLY DROP THE HEMOGLOBIN LEVEL BY 1 – 2 POINTS
HEMOLYTIC ANEMIA

• IN ONE STUDY OF DAPSONE-TREATED LEPROSY PATIENTS (N = 100), THE HEMOGLOBIN NADIR OCCURRED AT 4 MONTHS. IN 83% OF THOSE PATIENTS, THE DECREASE IN HB AT 4 MONTHS WAS >1 G/DL.

• BONE MARROW COMPENSATION MAY OCCUR SUBSEQUENTLY, SO THAT THE FINAL HEMOGLOBIN LEVEL MAY BE HIGHER THAN THE NADIR.

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

• **SYMPTOMATIC** HEMOLYTIC ANEMIA IS MORE LIKELY TO OCCUR IN G6PD-DEFICIENT PATIENTS, BUT MAY ALSO OCCUR IN THOSE WITH NORMAL G6PD FUNCTION

• CHECK G6PD LEVEL PRIOR TO STARTING DAPSONE, AS HA IN G6PD-DEFICIENT PATIENTS MAY BE SEVERE

• SHOULD ALSO CONSIDER DELAYING DAPSONE THERAPY IN PATIENTS WITH BASELINE ANEMIA (IRON/B12/FOLATE DEFICIENCY, ETC)
OTHER SIDE EFFECTS

• AGRANULO CYTOSIS
  • 0.3% OF TREATED PATIENTS
  • USUALLY OCCURS WITHIN FIRST THREE MONTHS

• PERIPHERAL MOTOR NEUROPATHY
  • WEAKNESS OF HANDS AND LOWER LEGS, WASTING OF HAND MUSCLES
  • MAY OCCUR WITH HIGH DOSE/SHORT-TERM DOSING, OR WITH CHRONIC NORMAL DOSING
  • USUALLY REVERSIBLE

• DRUG-INDUCED HEPATITIS
OTHER SIDE EFFECTS

• DRESS
  • MR IN ONE SERIES (N = 336) WAS 10%
  • IN THAT SERIES, THE ONSET OF DRESS 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 FUNCTION)
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 ENDOSCOPY)
- PERIPHERAL NEUROPATHY: PLAQUENIL, ZICALCITABINE