Adverse effects of existing second-line and novel antituberculosis drugs in children with multidrug-resistant tuberculosis

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Every breath counts

Overview

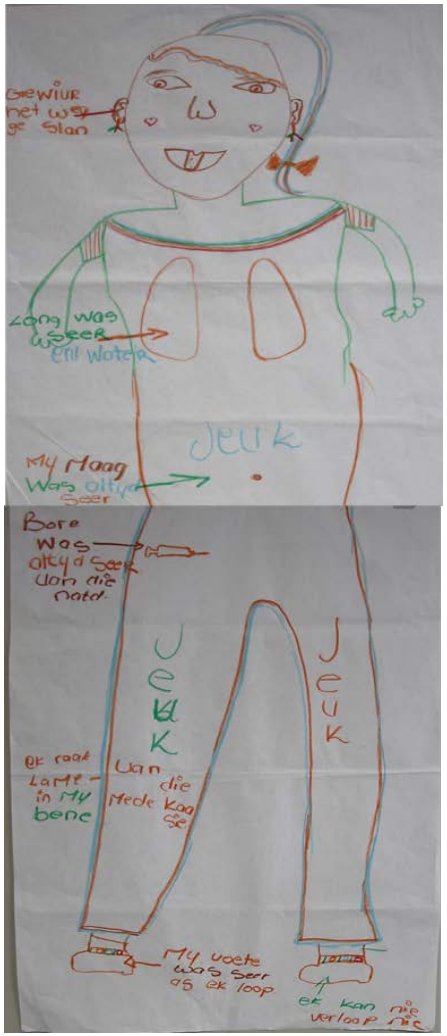
- General considerations for AE assessment in children
- Common and important AEs of 2nd-line TB drugs by drug class
- Delamanid and bedaquiline AEs

General considerations (1)

- Why important?
  - Complex multidrug-regimens
  - Clinical management
  - Assessment of attribution in context of trial
  - PHOENiX sites??
- Fewer adverse effects in children vs adults
  - Actually tolerate better?
  - Lower drug exposures
  - Difficulty in assessing subjective effects, under-reporting (??)

General considerations (2)

- “My ore het toegeslaan” – My ears were blocked
- “Long was seer en water” - Lung was sore and water (in my lung)
- “Jeuk” - Itch
- “My maag was altyd seer” - My stomach always pained
- “Bene was altyd seer van die naald” - Legs always pained from the needle (injection)
- “Ek raak lam in my bene van die medikasie” - I become weak in my legs from the medication
- Ek kan nie ver loop nie” - I cannot walk far
- My voete was seer as ek loop”- My feet were hurting when I walk



Resources

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REVIEW

Adverse effects of oral second-line antituberculosis drugs in children

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REVIEW

The safety and tolerability of the second-line injectable antituberculosis drugs in children

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WHO Revised grouping of MDR-TB medications

A. Flouroquinolones	Levofloxacin Moxifloxacin Gatifloxacin
B. Second-line injectables	Amikacin Capreomycin Kanamycin
C. Other core second-line agents	Ethionamide/prothionamide Cycloserine/terizidone Linezolid Clofazimine
D. Add-on agents	D1: Pyranzmide Ethambutol High-dose isoniaizd
	D2: Bedaquiline Delamanid
	D3: PAS Imipenem-cilastin Meropenem-amoxicillin-clavunate

Flouroquinolones (1)

- Musculoskeletal
  - Arthropathy, achilles tendon rupture
  - Animal data
  - Clinical experience in children
    - Minimal, non-severe, self-limited
    - No reported cases of achilles tendon rupture
- Cardiac
  - QT interval prolongation
  - Mfx > Lfx
  - Limited experience in children

Flouroquinolones (2)

- Central nervous system
  - Caffeine-like effects – sleep disturbance, hyperactivity
  - Nightmares, hallucinations
  - Intracranial hypertension
- Others
  - Dermatologic
  - GI disturbance
  - Ophthalmologic

PROBABLE LEVOFLOXACIN-ASSOCIATED SECONDARY INTRACRANIAL HYPERTENSION IN A CHILD WITH MULTIDRUG-RESISTANT TUBERCULOSIS

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*and Anthony J. Garcia-Prats, MD**

MDRPK1: Baseline characteristics (n=70)

	N (%)
Median age in years (range)	2.1 (0.4-7.3)
Age at enrolment	
0 to <2 years	31 (44%)
2 to <6 years	35 (50%)
6 to <15 years	4 (6%)
Male sex	38 (54%)
HIV-infected	12 (17%)
Weight-for-age Z-score < -2	16 (23%)
Person-years of observation	
Total, in years	68.5
Median, in months (IQR)	11.6 (9.2-14.7)

Results (1): All adverse events

Adverse Event	# of patients with event	Adverse event by grade				total # of events	Event Rate (per person-yrs)
		Grade 1	Grade 2	Grade 3	Grade 4		
Arthralgia	3	3	0	0	0	3	0.044
Arthritis	0	0	0	0	0	0	--
Pain other than traumatic injury	11	11	0	0	0	11	0.161
Headache	4	4	0	1	0	5	0.073
Neurosensory alteration	1	1	0	0	0	1	0.015
Insomnia	1	0	1	0	0	1	0.015
Fatigue/malaise	1	1	0	0	0	1	0.015
Nausea	12	13	0	0	0	13	0.190
Vomiting	19	23	1	0	0	24	0.351
Anorexia	11	8	5	0	0	13	0.190
Cutaneous reaction	12	8	6	0	0	14	0.204
Pruritus	13	16	1	0	0	17	0.248
Acute systemic allergic reaction	0	0	0	0	0	0	--
ALT	22	17	3	2	5	27	0.394
Bilirubin	0	0	0	0	0	0	--

# of events may exceed # of patients with event, as patients may have had more than one event

Results (2): Adverse effects at least possibly related to levofloxacin

Adverse Event	Adverse effects possibly, probably, definitely attributed to levofloxacin						
	# of patients with event	Grade 1	Grade 2	Grade 3	Grade 4	total # of events	Event Rate (per person-yrs)
Arthralgia	2	2	0	0	0	2	0.029
Arthritis	0	0	0	0	0	0	--
Pain other than traumatic injury	4	4	0	0	0	4	0.058
Headache	2	1	0	1	0	2	0.029
Neurosensory alteration	0	0	0	0	0	0	--
Insomnia	1	0	1	0	0	1	0.015
Fatigue/malaise	0	0	0	0	0	0	--
Nausea	8	9	0	0	0	9	0.131
Vomiting	14	16	0	0	0	16	0.234
Anorexia	7	4	3	0	0	7	0.102
Cutaneous reaction	7	3	4	0	0	7	0.102
Pruritus	7	7	1	0	0	8	0.117
Acute systemic allergic reaction	0	0	0	0	0	0	--
ALT	16	16	2	0	0	18	0.263
Bilirubin	0	0	0	0	0	0	--

# of events may exceed # of patients with event, as patients may have had more than one event

Second-line injectables (1)

- Nephrotoxicity
  - Renal tubular dysfunction, oliguric renal failure
  - Adults - <1 – 9.8%
  - Children – unusual
  - Capreomycin – may pose higher risk
- Electrolyte abnormalities
  - Hypokalemia, hypomagnesemia
  - Capreomycin
  - Adults – up to 35%, cohort in Peru
  - Children - unusual

Second-line injectables (2)

- Ototoxicity
  - Up to 25% in children*
  - Permanent sensorineural
  - High frequency hearing loss most common
  - HL may continue after stopping the drug
  - Risks
    - Cumulative drug exposure
    - Genetics
    - Agent (??)

Second-line injectables (3)

- Ototoxicity (cont).
- How to assess
  - Pure tone audiometry
  - Otoacoustic Emission (OAE)
    - Ensure can test high frequencies

- Assess middle ear via tympanometry or otoscopy (conductive hearing loss)
  - Interpret OAE/pure tone in light of these results.
- Routinely screen for hearing abnormality
  - Cannot rely on subjective report of hearing loss or gross evidence of hearing loss
  - Baseline, then monthly
  - If abnormal then more frequent
  - Management

Second-line injectables (4)

- Injection site adverse effects
  - Local irritation/redness
  - Subcutaneous and muscles abscesses
  - Infection
  - Neurovascular injury
  - Fibrosis
- Injection pain
  - Co-administration with lignocaine

Ethionamide/prothionamide (1)

- GIT disturbances
  - Poor palatability - metallic taste
  - Nausea, vomiting
    - May need to split dose or start with lower dose, but usually stops within 1-2 weeks
- Hepatotoxicity
- Other less common:
  - Convulsions
  - Peripheral neuropathy – pyridoxine responsive
  - Gynaecomastia

Ethionamide/prothionamide (2)

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SHORT COMMUNICATION

Abnormal thyroid function tests in children on ethionamide treatment

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SUMMARY

- Retrospective cohort, 137 children on a regimen containing ethionamide:
- Abnormal TFTs - 79 of 137 (58%) Elevated serum TSH and suppressed fT4 in 30 (22%)
- Risk of hypothyroidism higher with treatment with PAS and in HIV-infected children.

Ethionamide/prothionamide (3)

- Screening
  - Symptomatic hypothyroidism uncommon
  - Interpret with caution in first 1-2 months of treatment - acute illness may affect TFTs
- Management
  - If primary hypothyroidism (elevated TSH, low fT4), supplement with levothyroxine (50 mcg OD)
  - Reversible - stop levothyroxine once ETO/PAS stopped

Cycloserine/terizidone

- Neurological system AEs:
  - Dose-related
  - Dizziness, insomnia, headache, tremor, anxiety, confusion, depression, psychosis, convulsions
  - Adults – 9.1%
  - Children – infrequent (??)
- Pyridoxine supplementation should be prescribed
- Management
  - Reduce the dose or stop the drug if CNS AEs occur
  - Treatment of psychiatric events

Linezolid (1)

- General
  - Adult SR-MA (n=107)
    - 59% experienced linezolid-related AE
    - 69% of these required dose reduction or discontinuation
  - Dose and duration dependent
  - Many related to inhibition of mitochondrial protein synthesis

Linezolid (2)

- Neurologic
  - Peripheral neuropathy (47%)
  - Optic neuropathy (13%)
- Haematologic
  - Anaemia (38%)
  - Thrombocytopaenia (12%)
- Other – lactic acidosis, pancreatitis, rhabdomyolosis
- Children – less frequent, but still problematic
- Management
  - Dose reduction or discontinuation

Clofazimine

- Gastrointestinal – nausea, vomiting, pain
- Dermatologic
  - Skin discoloration
    - Reddish, black, orange
    - Resolves slowly over time
  - Icthyosis
    - Thickened, dry, scaly skin
    - Up to 25%, but highly variable in reports
- Cardiac
  - QT interval prolongation

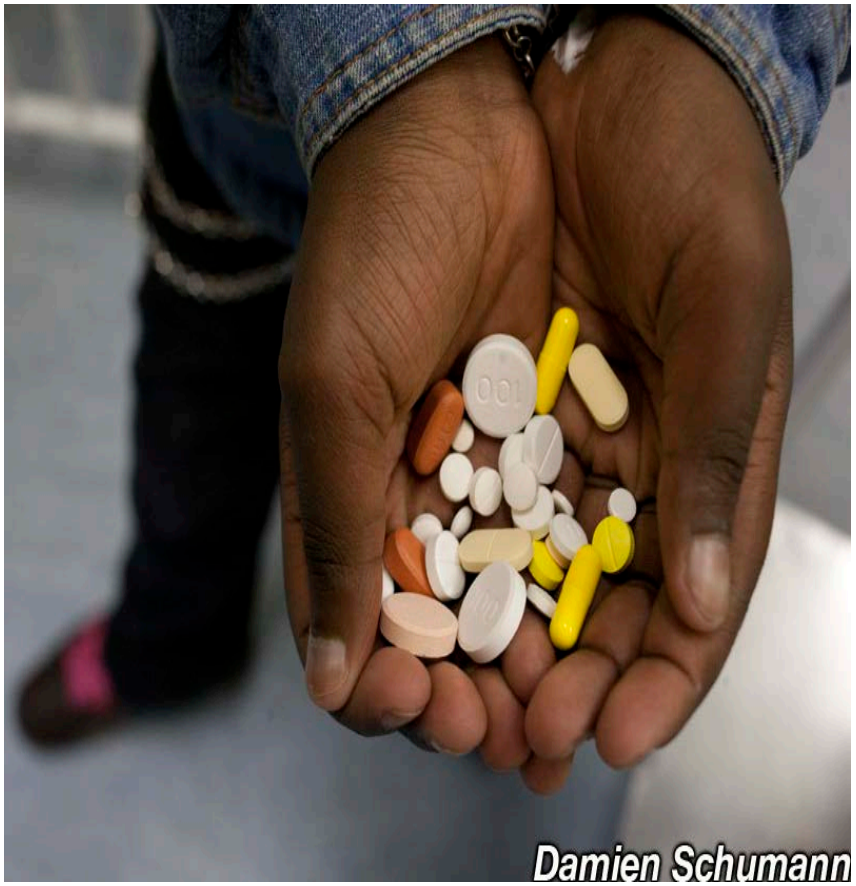
Para-aminosalicylic acid (PAS)

- GIT disturbances
  - Anorexia, diarrhoea, nausea
  - Relatively well tolerated in our experience
- Hypothyroidism
  - Risk quite high (79% in one small study)
  - Increased risk with ethionamide co-treatment
- Hepatotoxicity

Isoniazid

- Mild transaminase elevation
  - 10-20%
  - Mild, self-limited, asymptomatic
- Severe hepatitis
  - <1%
  - Signs of hepatitis, jaundice – hold INH
- Neuropathy
  - Supplement with B6

Palatability and acceptability



Delamanid (1)

- QT prolongation
  - Phase 2 study (Gler, et al. NEJM 2012.)
    - DLM 100 mg – 9.9%
    - DLM 200 mg - 13.1%
    - Control arm – 3.8%
  - No known arrhythmias reported to date
- Risk factors
  - Associated with DM-6705 concentration
    - Plateau at 8 weeks
  - Hypoalbuminaemia, CYP3A4
  - Electrolyte abnormalities
  - Other QT prolonging meds
- Other AEs??

Delamanid (2): Otsuka 232/233

Table 1. Incidence of QT elevation		
Category	**Cut-off (ms)**	**Group 1 n (%)**
New onset QTcF	>450	3 (42.9)
	>480	0
	>500	0
Change in QTcF from baseline	≥30 and ≤60	5 (71.4)
	> 60	1 (14.3)

Table 2. Mean [SD] QTcF by study day	
Day	Group 1
Baseline	407.0 [19.2]
28	423.4 [11.9]
56	417.1 [16.0]
84	427.9 [17.1]
126	428.6 [13.7]
154	423.6 [15.2]
182	420. 8 [16.8]
210	414.2 [8.0]

Presented at Union Meeting 2015 (Cape Town, SA), Jeff Hafkin, Otsuka Pharmaceuticals

*Adolescent with MDR-TB on CU DLM had QTcF >500ms, hypokalemia; interrupted and resolved (Tadolini M, et al. ERJ 2016).

Bedaquiline (1)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SIRTURO™ safely and effectively. See full prescribing information for SIRTURO.

SIRTURO™ (bedaquiline) Tablets

Initial U.S. Approval – 2012

WARNINGS:

See Full Prescribing Information for complete boxed warning.

- **An increased risk of death was seen in the SIRTURO treatment group (9/79, 11.4%) compared to the placebo treatment group (2/81, 2.5%) in one placebo-controlled trial. Only use SIRTURO when an effective treatment regimen cannot otherwise be provided.**
- **QT prolongation can occur with SIRTURO. Use with drugs that prolong the QT interval may cause additive QT prolongation.**

Bedaquiline (2)

- Most common AEs
  - Nausea
  - Arthralgia
  - Headache
- Liver abnormalities
  - Increased risk with BDQ vs placebo
    - ALT >3x ULN – BDQ 10.8% vs placebo 5.7%
  - Mostly mild, self-limited

Bedaquiline (3)

- Cardiac - QT prolongation
  - Correlate with drug exposure – peak 16-18 weeks
  - Study 1 - QTcF change from baseline
    - 15.7ms (BDQ) vs 6.2ms (PLB) – week 18
  - Study 3 – QTcF change from baseline
    - No other QT prolonging drugs – 23.8ms, 0 > 480ms
    - 2 other QT prolonging drugs – 30.7ms, 1 > 500ms
  - No Torsade de Pointes
  - Risk factors – electrolyte abnormalities, hypothyroidism

Toxicity management (1)

APPENDIX V: SUPPLEMENTAL TOXICITY TABLE FOR GRADING ELECTROCARDIOGRAM CHANGES AND POSSIBLE SYMPTOMS RELATED TO CARDIAC CONDUCTION ABNORMALITIES

	Grade 1	Grade 2	Grade 3	Grade 4
ECG Criteria: corrected QTc interval Note: QT corrected based on Frederica method (QTc=QT/cubed root of RR interval).	QTc ≥460msec, but <480msec	QTc >=480msec, but <500msec	QTc ≥500msec OR QT > 60 msec greater than baseline AND QT>=480 ms	Life-threatening consequences (Torsades de pointes, other serious ventricular dysrhythmias)
Cardiac Clinical Criteria	Any one of the following clinical symptoms (one event, without clear evidence of non-cardiac etiology): ⇒ syncope ⇒ chest pain ⇒ palpitations ⇒ dizziness	Recurrence/ongoing clinical symptoms (without clear evidence of non-cardiac etiology): ⇒ syncope ⇒ chest pain ⇒ palpitations ⇒ dizziness	Recurrence/ongoing clinical symptoms - *with evidence of ventricular tachycardia** ⇒ syncope ⇒ chest pain ⇒ palpitations ⇒ dizziness * Note that this presence of Ventricular Tachycardia (VT) *is the adverse outcome* to be avoided/identified; the symptoms are surrogates for "possible" VT, but if VT is demonstrated, then BDQ is permanently discontinued irrespective of QTc or symptoms.	

Toxicity management (2)

APPENDIX VI: TOXICITY MANAGEMENT OF SPECIFIC TOXICITIES
ECG-Determined or Clinical Cardiac Toxicity

ECG-determined or clinical cardiac toxicity		
SEVERITY	**STUDY DRUG USE**	**FOLLOW-UP AND MANAGEMENT**
Grade 1	Continue BDQ	Repeat ECG and clinical evaluation of symptoms within 72 hours
Grade 2	Continue BDQ	Repeat ECG and clinical evaluation of symptoms within 48 hours
Grade 3 (ECG)	Hold Fluoroquinolone (FQ) and BDQ	If repeat ECG and clinical evaluation of symptoms within 72 hours continues to show Grade 3, hold the FQ and hold study drug (= Grade 4). Check K+, Mg +2 and Ca +2 (corrected for albumin) and correct as necessary Contact the study team and indicate in the participant line: "Grade 3 ECG."
Grade 3/4 (*Cardiac Clinical Criteria*)	Hold FQ and Permanently discontinue BDQ if not other explanation; e.g., lab abnormality Note: STUDY DRUG USE for *Cardiac Clinical Criteria* meeting Grade 3 or Grade 4 are equivalent – that is *permanently discontinue BDQ*	Check K+, Mg +2 and Ca +2 (corrected for albumin) and correct as necessary Contact the study team and indicate in the participant line: "Grade 3/4 Cardiac." Discuss with the team the permanent discontinuation of study drug.
Grade 4 (ECG)	Hold FQ and Permanently discontinue BDQ if not other explanation; e.g., lab abnormality	Check K+, Mg +2 and Ca +2 (corrected for albumin) and correct as necessary Contact the study team and indicate in the participant line: "Grade 4 ECG." Discuss with the team the permanent discontinuation of study drug.

Conclusion

- Questions or comments?
- Acknowledgements – Simon Schaaf