Pharmacovigilance to inform policy in South Africa

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South African context
• Largest ARV treatment programme in the world
  – 3.7 million people on ART
• High rates of concomitant HIV and TB treatment
• Growing burden of non-communicable diseases

The need to for ongoing, locally relevant pharmacovigilance

Pharmacovigilance: “Detection, assessment, understanding and prevention of short and long term adverse effects of medicines”

• Clinical studies short
• Co-morbidities, concomitant medicines, genetic variability
• Risk versus benefit:
  – early treatment initiation
  – prevention
• Focus on serious adverse drug reactions (ADRs)
  – Resulting in hospitalisation and death
  – Treatment limiting ADRs - drug substitutions

Pharmacovigilance methods

• Hospital-based surveys
  • ADRs resulting in admission
  • ADRs resulting in death
  • ADRs presenting to emergency units
• Sentinel Cohorts
  • Spontaneous reporting
    • Targeted
    • ADR queries from HCW

Hospital-based ADR surveys

Hospital-based surveillance

• 4 South African hospitals in 2013
• 8.4% medical admissions in SA due to ADR (164/1951)
  (Worldwide 5.3% of admissions)
  – ART, TB treatment and/or co-trimoxazole implicated in 34%
  – 45% of ADRs were preventable
• In 16% of in-hospital deaths ADR implicated (56/357)
  – Most commonly implicated: tenofovir, rifampicin, co-trimoxazole
• ADR contributed to death of 2.9% of medical admissions
  (Europe, UK, USA 0.05 to 0.32% of admissions)

ADRs resulting in admission

<table>
<thead>
<tr>
<th>Renal impairment (n=24)</th>
<th>Hypoglycaemia (n=20)</th>
<th>Liver injury (n=20)</th>
<th>Haemorrhage (n=18)</th>
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<tbody>
<tr>
<td>Median age (yrs)</td>
<td>41</td>
<td>61</td>
<td>35</td>
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<tr>
<td>HIV infection</td>
<td>71%</td>
<td>5%</td>
<td>90%</td>
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<td>Commonly implicated drugs</td>
<td>tenofovir (46%)</td>
<td>insulin (64%)</td>
<td>TB drugs (60%)</td>
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<td>ACE-I (18%)</td>
<td>sulfamethoxas (50%)</td>
<td>efavirenz (20%)</td>
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<td>Mortality</td>
<td>46%</td>
<td>18%</td>
<td>35%</td>
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<tr>
<td>Median stay</td>
<td>9 days</td>
<td>6 days</td>
<td>10 days</td>
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<td>Preventable</td>
<td>46%</td>
<td>77%</td>
<td>15%</td>
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- ADRs in HIV patients: high mortality, prolonged admission
- Importance of looking at all drug exposures

Mouton et al Medicine 2016, 95 e3437

ADR-related adult admissions

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<tr>
<th>Drug</th>
<th>COX (95% CI)</th>
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Sentinel cohorts

- Valuable resource for ADR surveillance
  - Requires fewer resources than setting up cohorts solely for toxicity surveillance (Cohort event monitoring)
- Robust denominator data
  - Can determine incidence of treatment-limiting ADRs
  - Can identify risk factors

Data on stavudine toxicity from sentinel cohorts informed policy

- 2007: 30mg all weights, point of care lactate meters, avoidance in obesity, education HCW
- Dramatic decrease referral rates, severity at admission, mortality

Tenofovir and renal function

- Tenofovir (TDF): modest decline in eGFR over time
- Clinically significant kidney dysfunction uncommon:
  - higher risk with TDF compared to other ARVs
- 15156 adults commencing TDF-Thembel豪华和Khayelitsha
  - 34.5% commenced ART with CKD eGFR<90 mL/min

De Waal et al JIAS 2017

Boulle et al 2007 Antivir Ther 12:753; Schuz 2010 AIDS Ther, 7:13
Tenofovir and renal function

• 1.9% of patients develop eGFR<30mL/min

• Risk factors:
  • age, advanced disease (CD4<200), baseline eGFR<60 mL/min, weight<60 kg, protease inhibitor.

• Implication for guidelines:
  • Monitor patients with risk factors
  • Tenofovir cessation in acutely ill patients

De Waal et al JIAS 2017; 20: 1, De Waal et al SAMJ 2016 : 106(4) 369

ARV exposure and diabetes

Diabetes incidence: 13.24 per 1000 PYFU

Associations with diabetes:
• Older age
• Higher BMI
• Efavirenz, zidovudine and stavudine exposure
• Other diabetogenic meds

Karanthakud et al 2016 Endocrine 56(6) 2864

Spontaneous reporting

• Does not give prevalence/incidence
• Signal detection
  – e.g Interstitial nephritis lopinavir/r
• ADRs that trouble HCWs
  – Guide HCW training and clinical support
  – Nurse-driven services
• Need accessible and responsive systems
  – Telephonic and online reporting in addition to paper-based
  – Prompt, individualised feedback and clinical support


Western Cape ARV and TB pharmacovigilance programme

• Started in 2005, collaboration:
  – Western Cape Provincial Health Department
  – Medicines Information Centre (University of Cape Town)
• Targeted spontaneous reporting system
  – Serious ADR reporting form with case definitions for specific events
  – Follow up by pharmacist
  – Panel for causality assessment of deaths
• Goals:
  – Increase drug safety awareness
  – Identify signals
  – Inform policy and training
• Feedback
  – Information to reporter
  – Reports
  – newsletters

• SA National HIV & TB HCW hotline most frequent ADRs:
  – Rash (efavirenz)
  – Liver injury (tuberculosis treatment and efavirenz)
  – Kidney injury (tenofovir)
  – Gynaecomastia (efavirenz)
  – Neuropsychiatric (efavirenz)

Conclusions

- Pattern of serious ADRs in SA reflects colliding epidemics of infectious and non-communicable diseases
- Large burden of serious ADRs due to treatment of HIV and/or TB infection
  - ADRs due to ARVs AND concomitant medicines
- Resource limited settings
  - Create systems that can address multiple questions
- Repeated surveys to see changing patterns

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  - Andrew Boule
- IeDEA-SA data centre staff
- AfA
- Patients
- Health care workers who report

How can we help you?

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