Resistance to Trypanocidal drugs

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Tsetse distribution in Kenya showing tsetse belts and conservation areas

Kilometers

TSETSE CONFIRMED PRESENT IN 1996
- G. oxypertus
- G. pallidipes
- G. morsitans
- G. longipennis
- G. fuscipterus
- G. fuscipterae fuscipes
- G. brevipalpis
- G. auxeri

1. ASALs North of Mt. Kenya
2. Central Kenya belt
3 & 4. North and South Rift belts
5. Transmara-Narok-Kajiado belt
6. Western Kenya & L. Victoria belt
7. Coastal belt

Conservation areas
The disease and its Vector

- HAT (sleeping sickness) transmitted by the tsetse fly
- Two forms of HAT exist (acute – *T.b. rhodesiense* and chronic – *T.b. gambiense*) and two stages (early and late)

In livestock the disease is caused by *T. congolesiense*, *T. vivax* (cattle) and *T. evansi* (camels) – tsetse and non-tsetse transmitted

Trypanosomiasis in both humans and livestock is fatal but treatable
Trypanosoma brucei evansi


- Human trypanosomiasis caused by Trypanosoma evansi in India: the first case report.

Pathogen evolution???

*T.b. evansi*, the most widely distributed parasite (Asia, Africa, S. America)
Diseases of poverty

Sleeping sickness distribution

Cattle & tsetse distribution
Disease Control

- Vector control methods

- Parasite control methods
  - Trypanotolerant breeds
  - Disease tolerance vs productivity
  - Vaccination
    - None due to antigenic variation
    - Transmission blocking (genomics/genetics)
  - Chemotherapy and chemoprophylaxis
    - most important strategy for the control of trypanosomiasis in African livestock
Current treatments for HAT and associated problems

**Stage 1**
- Pentamidine (1940)
  - 10 day injections
- Suramin (1920)
  - Used primarily for rhodesiense SS

**Stage 2**
- Melarsoprol (1949)
  - Highly toxic, 5% treatment related mortality; increasing treatment failure up to 30%
- Eflornithine (1981)
  - Difficult to administer, requires 4 infusions per day for 14 days
- NECT (2009), combination therapy
Melarsoprol

Nifurtimox

Eflornithine

NECT = Nifurtimox Eflornithine Combination Therapy
### Commercial Animal trypanocides - AAT

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Main application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suramin</td>
<td>Naganol®</td>
<td><em>T. evansi</em> in camels</td>
</tr>
<tr>
<td>Diminizene aceturate</td>
<td>Berenil, Ganaseg, Trypazen, Veriben</td>
<td>Cattle and small ruminants</td>
</tr>
<tr>
<td>Homidium bromide</td>
<td>Ethidium</td>
<td>Cattle and small ruminants</td>
</tr>
<tr>
<td>Homidium chloride</td>
<td>Ethidium C, Novidium</td>
<td>Cattle and small ruminants</td>
</tr>
<tr>
<td>Quinapyramine methyl sulphate</td>
<td>Antrycide, Trypacide, Noroquin, Quintrycide</td>
<td><em>T. evansi</em> and <em>T. brucei</em> in camels and horses</td>
</tr>
<tr>
<td>Mel cy</td>
<td>Cymelarsan</td>
<td><em>T. evansi</em> in camels</td>
</tr>
<tr>
<td>Isometamidium chloride</td>
<td>Samorin, Trypamidium</td>
<td>Cattle, as a curative at lower rates, as a prophylactic at higher rates.</td>
</tr>
</tbody>
</table>

*Note: *T. evansi* and *T. brucei* refer to different species of trypanosomes that cause trypanosomiasis in animals.*
Drugs for treatment of trypanosomiasis in cattle and small ruminants

Diminazene di-aceturate (Berenil®, Veriben®)

Homidium bromide / chloride (Ethidium®, Novidium®)

Isometamidium chloride (Samorin®)
Drugs for treatment of trypanosomiasis in camels, donkeys and horses

Melarsenoxide cysteamine (Mel Cy)- 1985

Suramin (Germanin®); developed 1916, published 1924

Quinapyramine (Antrycide®)
Drug Use: Issues

- Poor diagnosis
- Poor estimation of weight
- Product Quality / counterfeits
- Access to quality products
  - Designated distribution points / private practice?
- Preparation (water quality) and administration E.g route
- Packaging – single vs multiple dosage
- Mixing of drugs (pastoral communities)
  - Antibiotics & trypanocides

- Role of immunosuppression
  - Using *T. evansi*, rapid development of high levels of resistance to Mel Cy, diminazene aceturate and isometamidium chloride through sub-curative treatments of infected immunosuppressed mice. Cross-resistance to pentamidine was also demonstrated. Normal immunocompetent mice infected with the same parent clones did not lead to the development of drug-resistance.
Lab: Development of drug resistance

- By repeated under-dosing and passage, drug resistance can be induced rapidly in drug-sensitive clones

- E.g.
    - Cross-resistance associated with development of resistance to isometamidium in a clone of *Trypanosoma congolense*. Derivative was 94-fold resistant to ISMM, 3.4-fold to diminazene, 33-fold to homidium, 4.2-fold to quinapyramine

  - Derivation and characterization of a quinapyramine-resistant clone of *Trypanosoma congolense*. Derivative 40-fold resistant to quinapyramine, 8-fold to ISMM, 28-fold to homidium and 5.5-fold to diminazene. The resistant clone was cyclically transmitted by *G.m. centrals*. Cross resistance was demonstrated
Field: Treatment failure

- Role of immunosuppression
  - Malnourished animals, poor body condition

- High Disease Challenge
How does drug resistance develop in the field?

- exposure of parasites to sub-therapeutic drug levels
  - under-dosing (Whiteside, 1960; 1962; Boyt, 1986)
  - Mass treatments of cattle and frequency; high drug pressure
  - Use of substandard products / counterfeits
Packed cell volume of Boran cattle infected with *Trypanosoma congolense* (Tc) and treated with homidium chloride at 1 mg/kg bwt.

![Graph showing packed cell volume changes over time for drug-sensitive and drug-resistant Tc infections.](image-url)
Serum drug profiles in cattle following treatment of *Trypanosoma congolense*-infected with homidium chloride at 1 mg/kg bwt

Drug resistant *T. Congolense* IL3330

Drug sensitive *T. congolense* IL1180
Plasma drug concentrations in Boran cattle following i.v. injection of $^{14}$C radio-labelled homidium and isometamidium.

Plasma drug concentrations in Boran cattle following i.m. injection of $^{14}$C radio-labelled homidium and isometamidium.
Plasma drug profiles in cattle following administration of $^{14}$C isometamidium at 1 mg/kg bwt
Tests for drug resistance

- In vitro
- In vivo – mice
- In vivo - cattle

Reference:

How to delay development of drug resistance

- use of the "sanative pair" of drugs
- Use correct dosage of quality drugs
- avoid exposure of trypanosomes to sub-therapeutic drug concentrations (Whiteside, 1960; Boyt, 1986).
- Improved formulations of existing drugs
- Ban use of quinapyramine in cattle
- In areas of high tsetse challenge:
  - use an integrated approach (control vector, reduce freq. of drug application (Fox et al., 1993; Peregrine et al., 1994).
  - use of trypanotolerant livestock and drugs (Diall et al., 1992).
- Evidence-based treatments
Acknowledgements

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