Swiss TPH
Swiss Tropical and Public Health Institute
Schweizerisches Tropen- und Public Health-Institut
Institut Tropical et de Santé Publique Suisse

Jürg Utzinger
Ecosystem Health Sciences

Tribendimidine against clonorchiasis: proof-of-concept study from China

Jürg Utzinger, Men-Bao Qian, Xiao-Nong Zhou & Jennifer Keiser

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Overview

- How it all started
- Tribendimidine: broad spectrum of activity
- Tribendimidine against clonorchiasis
  - Laboratory investigations, Switzerland
  - Clinical trial, China
- Summary and outlook

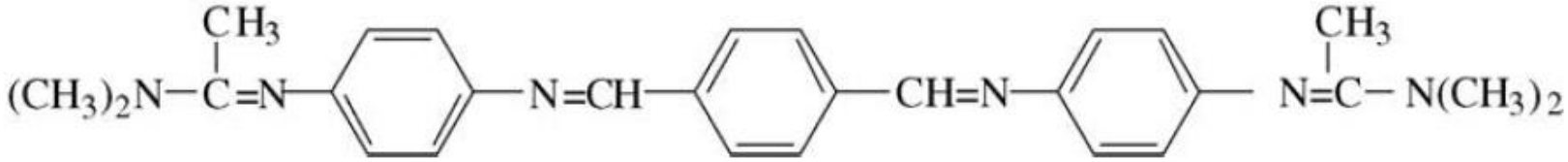
How it all started



- Visit and guest seminar at Princeton University, 18 April 2001
  1. Artemisinins against schistosomiasis
- E-mail exchange, 14 June 2003
  - Tribendimdine against helminthiases

Tribendimidine: going public

- Utzinger & Keiser, 2004, Expert Opinion on Pharmacotherapy



Parasites	Pretreatment		Treatment (mg)		Therapeutic efficacy	
	No. of patients infected	Infection intensity*	Tribendimidine	Albendazole	No. (%) of patients cured	Infection intensity (% reduction)*
A. lumbricoides	117	1496	1 × 300		115 (98.3)	65 (95.7)
	92	1632		1 × 400	91 (98.9)	85 (94.8)
T. trichiura	75	196	3 × 400		25 (33.3)	47 (76.0)
	41	223		3 × 400	23 (56.1)	48 (78.5)
Hookworms	36	1298	1 × 300		28 (77.8)	18 (98.6)
	94	1441	1 × 400		81 (86.2)	15 (99.0)
	89	1210		1 × 400	59 (66.3)	24 (98.0)

Tribendimidine: going public

- Xiao *et al.*, 2005, Acta Tropica

Parasite	**Rodent**	**Effect**
Nippostrongylus braziliensis	Rat	ED_{50}: 4.6 mg/kg
Necator americanus	Hamster	ED_{50}: 10.8 mg/kg
Syphacia mesocriceti	Mouse	ED_{50}: 61.3 mg/kg
Ancylostoma caninum	Dog	6-12 mg/kg: 90-100% worm burden reduction
Toxocara canis	Dog	12 mg/kg: 100% worm expelling rate
Echinostoma caproni	Mouse	125 mg/kg: 100% worm burden reduction

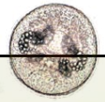
Helminth-rodent models at Swiss TPH

Nematode	Infection	Rodent
Ancylostoma ceylanicum	p.o.	
Necator americanus	s.c.	
Heligmosomoides bakeri	p.o.	
Trichuris muris	p.o.	
Ascaris suum	p.o.	
Strongyloides ratti	p.o.	
Trematode		
Schistosoma mansoni	s.c.	
Schistosoma haematobium	s.c.	
Fasciola hepatica	p.o.	
Clonorchis sinensis	**p.o.**	
Opistorchis viverrini	p.o.	
Echinostoma caproni	p.o.	



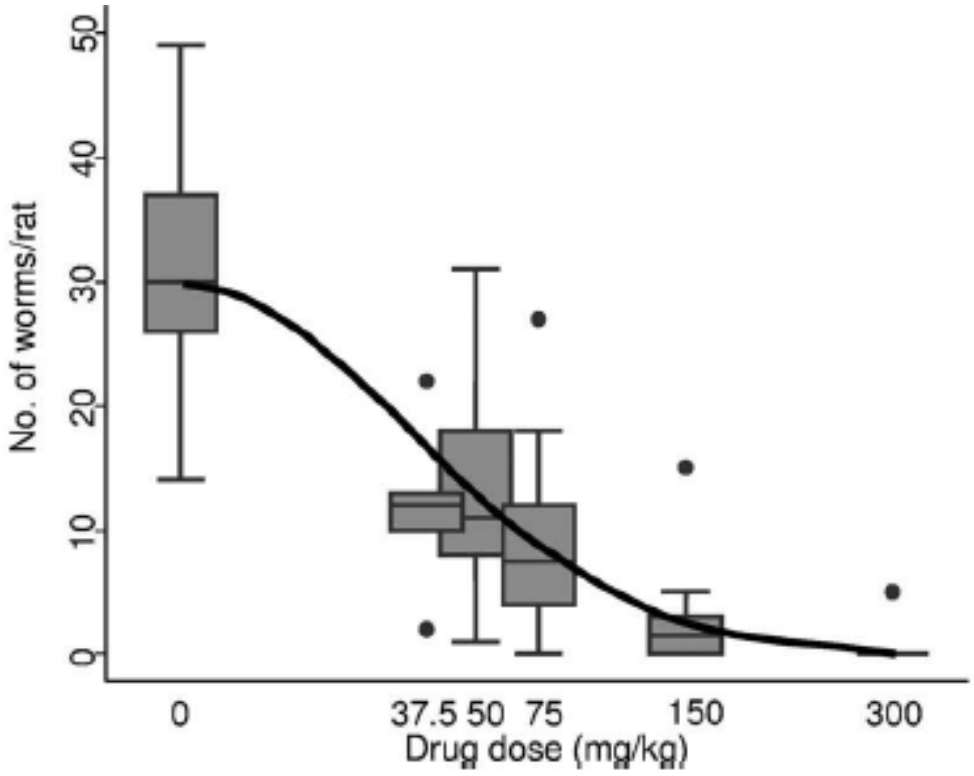




Tribendimidine against *C. sinensis*

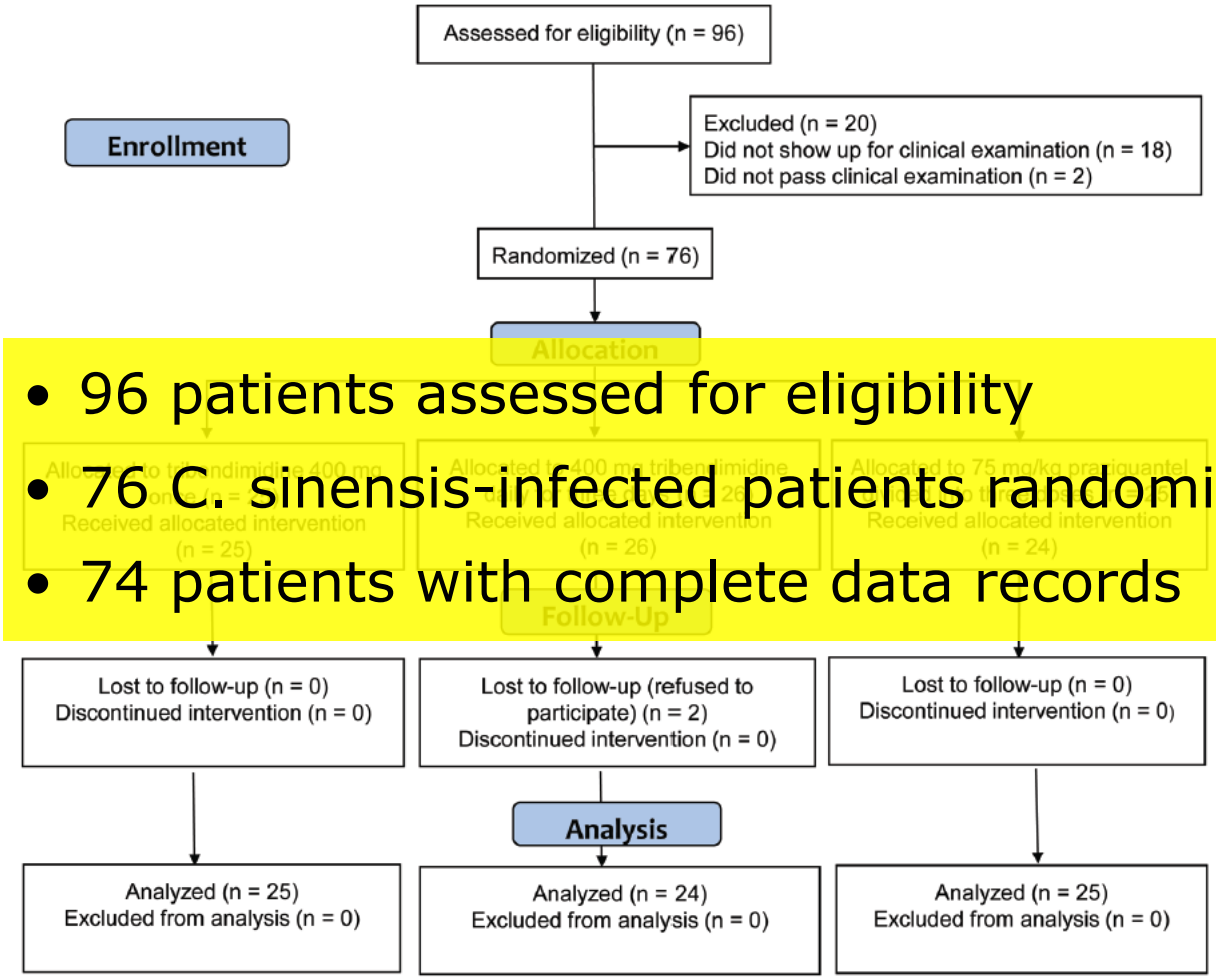
- Keiser *et al.*, 2009, Antimicrobial Agents and Chemotherapy



Trial design

- Randomised, open-label trial; Guangxi, China
- 76 parasitological-confirmed *C. sinensis* patients
- Treatment arms
  - Tribendimidine (400 mg), once
  - Tribendimidine (400 mg), daily for 3 days
  - Praziquantel (75 mg/kg), in 1 day divided into 3 doses
- Outcomes
  - Cure and egg reduction rates, 3 weeks post-treatment
  - Frequency and severity of adverse events

Trial flow diagram



- 96 patients assessed for eligibility
- 76 C. sinensis-infected patients randomised
- 74 patients with complete data records

Baseline characteristics

Parameter	Treatment Group		
	Tribendimidine 400 mg Once (n = 25)	Tribendimidine 400 mg Once Daily for 3 d (n = 24)	Praziquantel 75 mg/kg Divided in 3 Doses (n = 25)
Males/females (no.)	19/6	15/9	23/2
Mean (SD) age, years	51.2 (8.8)	49.9 (10.1)	50.5 (10.0)
Mean (SD) weight, kg	61.9 (10.8)	58.3 (7.6)	60.4 (12.3)
Mean (SD) height, cm	157 (6)	156 (8)	162 (8)
Overall GM fecal egg counts, EPG	3387	2816	4051
Fecal egg counts (range), EPG	(124–29 624)	(184–18 772)	(212–31 244)
No. of light infections (1–999 EPG)	5	4	4
No. of moderate infections (1000–9999 EPG)	11	17	13
No. of heavy infections (≥10 000 EPG)	9	3	8

- Similar baseline characteristics in the 3 treatment arms

Efficacy of tribendimidine

Parameter	Treatment Group		
	Tribendimidine 400 mg Once Daily for 1 d (n = 25)	Tribendimidine 400 mg Once Daily for 3 d (n = 24)	Praziquantel 75 mg/kg Divided in 3 Doses (n = 25)
No. of patients cured (%)	11 (44)	14 (58)	14 (56)
No. of patients cured of light infection (%)	4 (100)	4 (100)	4 (100)
No. of patients cured of moderate infection (%)	6 (54)	10 (59)	7 (54)
No. of patients cured of heavy infection (%)	1 (33)	0	3 (38)
C. sinensis infection intensity			
Overall GM fecal egg counts, EPG	96.9	38.1	50.0
Fecal egg counts (range), EPG	(0–3636)	(0–1296)	(0–1876)
Egg reduction rate (%) (95% CI)	97.6 (93.0–98.6)	98.8 (96.9–99.6)	98.8 (97.0–99.6)

- Cure rate
  1. 1x tribendimidine: 44%
  2. 3x tribendimidine: 58%
  3. Praziquantel: 56%
- Egg reduction rates (>97.5%)

Adverse events

Time Point	Treatment Group		
	Tribendimidine 400 mg Once	Tribendimidine 400 mg Once Daily for 3 d	Praziquantel 75 mg/kg Divided in 3 Doses
Related symptoms before treatment	3 (12)	1 (4)	4 (16)
No. of patients with adverse events (%)			
3 hours after first treatment	5 (20)[b]	9 (38)	12 (48)
24 hours after first treatment	7 (28)	10 (42)	NA
3 hours after second treatment	3 (12)	15 (63)	16 (64)
24 hours after second treatment	NA	4 (16)	NA
3 hours after third treatment	NA	3 (12.5)	NA[d]
24 hours after third treatment	NA	1 (4)[c]	17 (71)
Overall number of patients experiencing adverse events at any time point	11 (44)[b]	16 (67)[b]	23 (92)

- Single-dose tribendimidine best-tolerated treatment

Summary and outlook

- Tribendimidine exhibits a broad spectrum of activity
- *In vitro* investigations at Swiss TPH revealed *C. sinensis* activity
- Proof-of-concept trial of tribendimidine against clonorchiasis in China
  - Tribendimidine (1x 400 mg and 3x 400 mg) is safe
  - Similarly efficacious than praziquantel
- Phase III trials warranted, pending reprotoxicity data