Investigations into the potency and resistance of the antimalarial drug combination dihydroartemisinin plus piperaquine (Artekin®)

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Introduction

- Dihydroartemisinin + piperaquine (Artekin®)
- ACT combination
- Widely used in many countries
- Excellent cure rate (94 to 100%)

Introduction

- Major draw back
- Basic PK/PD study
- Mechanism of action and resistance
- Artemisinin resistance

Objectives

- Investigate potency of this drugs combination
- Drug resistance mechanisms
- Pharmacokinetics study

Methods

- In vitro drug susceptibility test
- Clinical trial
- Plasma drug concentration measurement
- PK analysis

- Drugs vs. malaria parasites
- Drugs vs. human
- Drugs vs. malaria parasite in human

Clinical trial

- 28 patients with *P. falciparum* malaria
- Bangkok hospital for Tropical diseases
- Follow up for 42 days
- Safety and tolerability
- Cure rate, Parasite and fever clearance time

Drug measurement and PK analysis

- HPLC – UV for piperaquine measure
- HPLC – MS/MS for DHA measure
- AUC, C_{max}, T_{max}
- Day 7 piperaquine concentration
- Treatment failure vs completely cure

In vitro drugs test

- Radioactive hypoxanthine incorporation
- DHA and piperaquine
- Chloroquine sensitive and resistance
- Transfected and lab isolated *P. falciparum*
- IC 50 determination

Clinical result

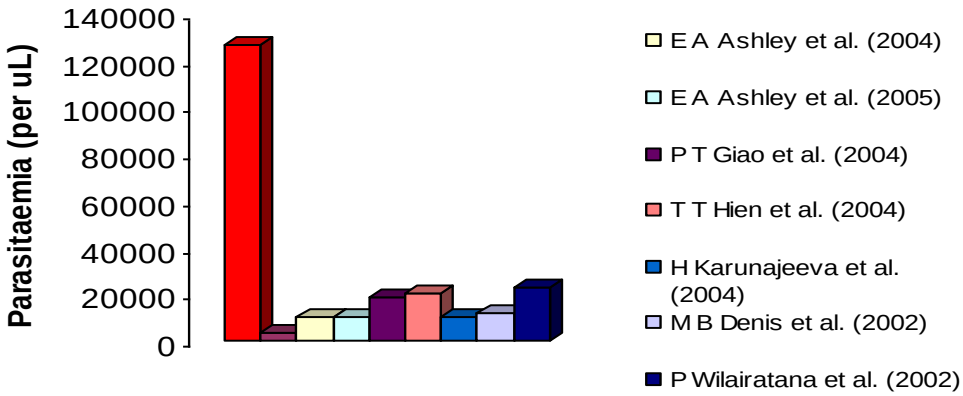
- **90% Complete 28 day follow up**

- **Parasite recrudescence at day**
- 17, 28, 23 and 21

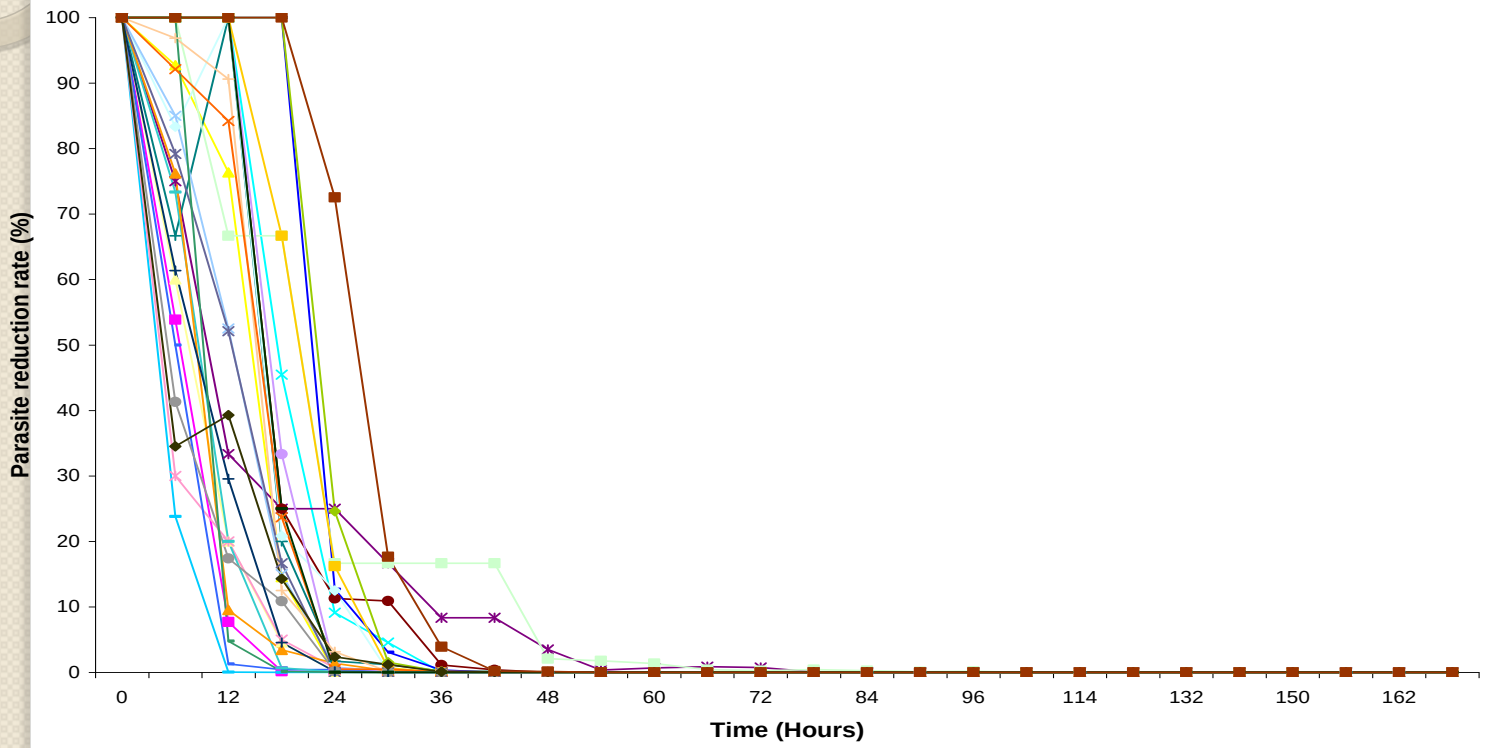
- **Mean starting parasiteia**
- 126372 (112 – 295750) per uL

Clinical result

- **28 day cure rate**
- 84% (21/25)
- **Parasite clearance time (Mean±SD)**
- 45.36 hours(±17.6)
- **Fever clearance time (Mean±SD)**
- 54.64 hours(±34.64)



Parasite reduction rate



Piperaquine PK profiles

CL/F (l h^{-1} kg^{-1})	0.9±0.8
Vd_{ss}/F (l kg^{-1})	424 ± 245
$t_{1/2,z}$ (h)	464±341
AUC $_{0\text{-}\infty\ h}$ (ng/mL h)	8.07 ±5.1
AUC $_{0\text{-}168\ h}$ (ng/mL h)	3.3 ± 2.1
T_{max} (h)	29 ±10
C_{max}(ng/mL)	60 ±20

DHA PK profiles

CL/F (l h^{-1} kg^{-1})	7.6 ±5.5
Vd_{ss}/F (l kg^{-1})	119±93
$t_{1/2,z}$ (h)	0.9±0.3
AUC $_{0\text{-}\infty\ h}$ (ng/mL h)	8.07 ±5.1
AUC $_{0\text{-}168\ h}$ (ng/mL h)	5.08±3.0
T_{max} (h)	8.0 ±9.0
C_{max}(ng/mL)	647 ±288

Piperaquine	Completely cured group	Recrudescent group	P value (95% CI)
AUC 0-168hrs (ng/mL h)	3.3	3.1	0.576 (-0.001 to 0.001)
Half life (days)	21.435	25.26	0.87 (-22.8 to 14.7)
T_{max} (hours)	29.8	31.5	0.50 (-21.99 to 22.01)
C_{max} (ug/ml)	0.60	0.061	0.97 (-0.034 to 0.039)

Dihydroartemisinin	Completely cured group	Recrudescent group	P value (95%CI)
AUC 0-168hrs (ng/mL h)	8.0	3.0	0.03**(0.001 to 0.008)
Half life (hours)	0.92	1.09	0.57 (-0.9 to 1.25)
T_{max} (hours)	8.0	7.6	0.53 (-18.1 to 7.2)
C_{max} (ng/ml)	648	410	0.15 (-95 to 582)

Day 7 plasma piperaquine

Day of recrudescent	**Plasma piperaquine concentrations (ng/ml)**
17	5.7
21	5.9
23	8.9
28	Below limit of detection(<5 ng/ml)
Day 7 mean piperaquine levels in treatment successes	8.45 ng/ml
Day 7 mean piperaquine levels in treatment failures	8.7 ng/ml

In vitro result

	Parasite line (standard laboratory)			
	CQ sensitive	CQ resistant		
	3D7	TM6	7G8	K1
Piperaquine (nM)	3.4±1.3	15.8±4	11.2±1.7	13.4±2.4
Dihydroartemisinin (nM)	0.6±1.1	1.0±0.2	1.3±0.3	1.0±0.1

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In vitro result

	Parasite line (Genetically modified)						
	pfcrt			*pfmdr1*			
	$C2^{GCO3}$	$C3^{DD2}$	$C6^{7G8}$	$D10^{D10}$	$D10^{7G8}$	$7G8^{7G8}$	$7G8^{D10}$
Piperaquine (nM)	3.9±0.4	11.5±1.8	6.6±1.58	8.1±1.3	10.4±1.1	9.1±1.3	12±3
Dihydroartemisinin (nM)	0.8±0.1	1±0.4	0.3±0.1	0.7±0.3	0.7±0.3	0.6±0.2	1.3±0.2

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Conclusion

- DHA + piperaquine are safe
- Good cure rate
- Recrudescent related to exposure of DHA
- In vitro testing shown cross resistance piperaquine to chloroquine

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THANK YOU