Pharmacokinetics of 6-diazo-5-oxo-L-norleucine (DON) in Malawian healthy adults and adults with uncomplicated malaria

Evaluating Malaria's Impact on **DON Pharmacokinetics** for Effective Adjunctive Therapy in **Pediatric Cerebral Malaria**

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BACKGROUND:

Malaria / Cerebral Malaria (CM)

- In 2022, there were 249 million malaria cases with 608,000 deaths **worldwide**.
- CM is a severe and deadly neurological complication of malaria, primarily affecting children under 5 in endemic areas. Even with rapid and efficient anti-malarial parasite clearance, the mortality rate is 15-25%. Many survivors have short and long-term neurological impairments.

New pathophysiology pathway:

- Preclinical studies in mouse models indicate $CD8^+$ T cells are critical in CM pathophysiology, a mechanism not targeted in previous clinical trials for CM adjunctive therapies.

6-diazo-5-oxo-L-norleucine (DON):

- A structural analog of L-glutamine, inhibits $CD8^+$ T cell activation.
- Preclinical mouse experiments showed decreased mortality in advanced stages with brain swelling and blood-brain barrier dysfunction.
- Previously evaluated in US Phase I/II cancer clinical trials.

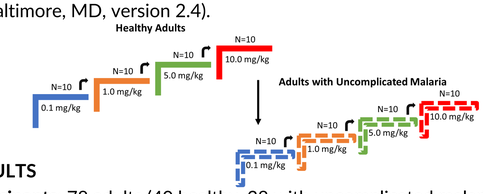
Current Study Objectives:

i. Characterize the PK of DON in healthy adults and adults with uncomplicated malaria.
ii. Evaluate the effect of malarial infection on the Pharmacokinetic (PK) characteristics of DON.
iii. Inform dosing in children with CM.

METHODS:

Study Design:

- Part of a Phase I/IIa clinical trial of adjunctive DON in children with CM.
- **Participants:** 8-10 in each dosing group for healthy
- **Dose**: Single-dose IV infusion, dose-escalation study with DON doses ranging from 0.1 mg/kg to 10.0 mg/kg.
- **Sampling**: 8 Blood samples collected at multiple time points up to 18 hours post-administration.
- **Data Analysis**: Non-compartmental analysis using Pumas (Pumas AI, Baltimore, MD, version 2.4).



RESULTS

Participants: 78 adults (40 healthy, 38 with uncomplicated malaria 10 in each dose group).

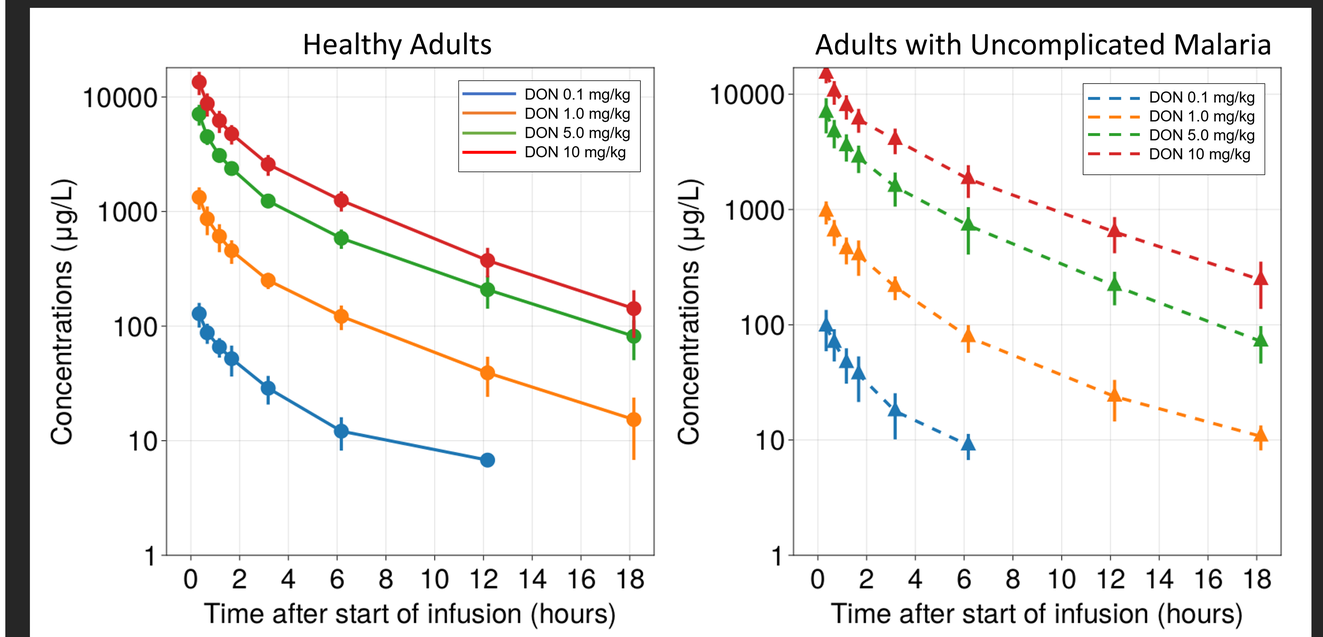
Dose Proportionality: Greater than dose-proportional relationship observed in adults with uncomplicated malaria but dose proportional for healthy adults.

DON Exposure (AUCinf):

- Lower in 0.1–1.0 mg/kg dose groups for adults with uncomplicated malaria (27–36% decrease) compared to healthy adults.
- Comparable or higher in 5.0–10.0 mg/kg dose groups for adults with uncomplicated malaria (13–38% increase).

CONCLUSIONS

- Differences in overall DON exposure between adults with and without uncomplicated malaria were within 30–40%, indicating no clinically meaningful effect on DON's PK properties.
- Rich PK sampling data from adults will aid in population PK analysis in children with CM, where sampling is designed to be sparse.

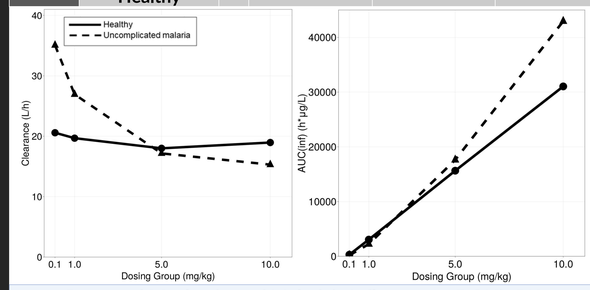


Dose proportionality assessment for healthy adults and adults with uncomplicated malaria DON 0.1–1.0 mg/kg

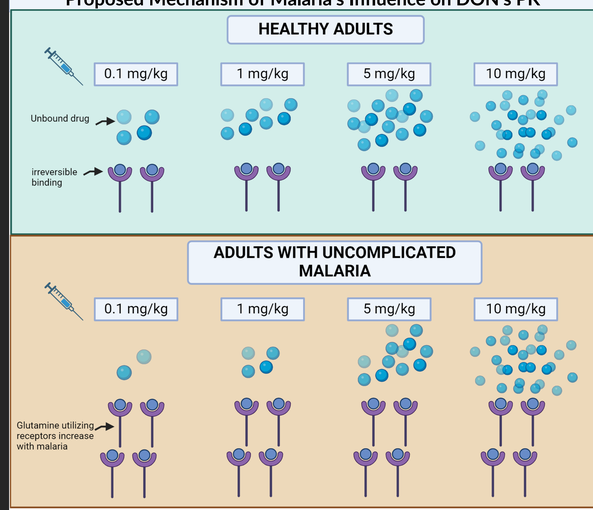
Parameter	Population	Slope Estimate	Lower CI 90%	Upper CI 90%
Healthy	Cmax	1.02	0.98	1.05
	AUCinf	1.02	0.99	1.05
Uncomplicated	Cmax	**1.09**	1.05	1.14
	AUCinf	**1.17**	1.12	1.22

DON Pharmacokinetic parameters for dose escalation cohorts

Dose	Population	N	C_{max} (µg/L)	AUC_{inf} (µg·h/L)	$T_{1/2}$ (h)
0.1 mg/kg	Healthy	10	131 (22.0)	296 (21.0)	2.36 (35.0)
	Uncomplicated	10	96.7 (39.0)	190 (42.0)	1.69 (21.0)
	% Change from Healthy	-	**-25.9%**	**-35.8%**	**-28.4%**
1.0 mg/kg	Healthy	10	1338.1 (21.0)	3052.0 (22.0)	3.85 (20.0)
	Uncomplicated	10	958.6 (23.0)	2238.0 (24.0)	2.98 (23.0)
	% Change from Healthy	-	**-28.4%**	**-26.7%**	**-22.6%**
5.0 mg/kg	Healthy	10	7078.0 (21.0)	15640.0 (16.0)	4.15 (19.0)
	Uncomplicated	10	6912.0 (34.0)	17620.0 (29.0)	3.7 (16.0)
	% Change from Healthy	-	**-2.3%**	**+12.7%**	**-10.8%**
10.0 mg/kg	Healthy	10	13478 (23.0)	31040 (19.0)	3.78 (18.0)
	Uncomplicated	8	15118 (18.0)	42950 (25.0)	3.94 (16.0)
	% Change from Healthy	-	**+12.2%**	**+38.4%**	**+4.2%**



Proposed Mechanism of Malaria's Influence on DON's PK



*Created with BioRender.com

Scan for supplemental material

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