H3D Foundation and Ersilia Present

Bringing data science and AI/ML tools to infectious disease research

Session 3: ADME/PK Breakout activity

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Malaria team: Which compound would you choose to advance?

	A	B	C
In vitro antiplasmodial activity (nM)	11.2	2.8	3.9
LogD7.4	0.93	ND*	3.7
TPSA	31	25	46
Solubility pH 7.4 (µM)	>6250	<0.1	74
HLM $CL_{int, app}$ (µl/min/mg)	<7	<7	308
Permeability (A-B/ER)	16/1.4	ND*	90/0.7

- What issues might you expect in patients if any of the other compounds were advanced?

Malaria team: Compound descriptions

The compounds you have reviewed are all clinically used antimalarial drugs. Based on the discussions you have had in this workshop, why do you think these compounds were advanced to the clinic?

The descriptions below are from publications discussing aspects of the human pharmacokinetics and antimalarial efficacy of the drugs. Which description matches the drugs in the previous table?

1. **Lumefantrine is slowly and erratically absorbed….The low and variable bioavailability is the major factor contributing to the (high) interindividual variability in pharmacokinetics.**
2. **Oral amodiaquine undergoes rapid metabolism to its active metabolite *N*-desethylamodiaquine, which is the main contributor to antimalarial activity.**
3. **Oral absorption of chloroquine is nearly complete with an estimated bioavailability of 78% and 89% for the oral solution and tablet. After absorption, chloroquine extensively distributes across all tissues resulting in a very large volume of distrubutgion of 200 L/kg which, combined with a slow elimination, results in a terminal half life reported to vary between days and weeks depending on the sampling time used in the study**
4. **How will the team rank the following PK parameters (Bioavailability, Clearance and Volume of Distribution) from most to less important for development of a malaria drug?**

TB team: Which compound would you choose to advance?

	A	B	C
In vitro antimycobacterial activity (µM)	0.25	0.02	2
cLogP	7.7	3.7	1.7
TPSA	45	220	39
Solubility pH 7.4 (µM)	<11	2175	4210
HLM $CL_{int, app}$ (µl/min/mg)	<2	2.84	77.1
Permeability (A-B/ER)	0.17/1	1.5/12	57.3/0.5

- What issues might you expect in patients if any of the other compounds were advanced?

TB team: Compound descriptions

The compounds you have reviewed are all clinically used antiTB drugs. Based on the discussions you have had in this workshop, why do you think these compounds were advanced to the clinic?

The descriptions below are from publications discussing aspects of the human pharmacokinetics of the drugs. Which description matches the drugs in the previous table?

1. **Ethionamide is completely absorbed following oral administration with approximately 100% bioavailability. It is metabolized extensively by the liver with <1% excreted unchanged in urine, with the rest as inactive metabolites**
2. **Clofazimine is slowly absorbed, and the extent of absorption varies widely between individuals. Because of its lipophilicity, it is formulated as a microcrystalline suspension in an oil-wax base in order to improve absorption.**
3. **Rifampicin undergoes uptake into hepatocytes mediated by organic anion-transporting polypeptide 1B1 (OATP1B1) which is encoded by a polymorphic gene. Mutations in this gene are associated with variability in rifampicin pharmacokinetics.**

How will the team rank the following PK parameters (Bioavailability, Clearance and Volume of Distribution) from most to less important for development of a TB drug?