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Fitness cost of resistance for lumefantrine and piperaquine-resistant *Plasmodium berghei* in a mouse model

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Abstract

Background: The evolution of drug-resistant parasites is a major hindrance to malaria control, and thus understanding the behaviour of drug-resistant mutants is of clinical relevance. The study aimed to investigate how resistance against lumefantrine (LU) and piperaquine (PQ), anti-malarials used as partner drugs in artemisinin-based combination therapy (ACT), impacts parasite fitness. This is important since resistance to ACT, the first-line anti-malarial regimen is increasingly being reported.

Methods: The stability of *Plasmodium berghei* ANKA strain that was previously selected for LU and PQ resistance was evaluated using the 4-day assay and established infection test in mice. Fitness cost of resistance was determined by comparing parasites proliferation rates in absence of drug pressure for the drug-exposed parasites between day 4 and 7 post-infection (pi), relative to the wild-type. Statistical analysis of data to compare mean parasitaemia and growth rates of respective parasite lines was carried out using student's *t*-test and one-way analysis of variance, with significance level set at $p<0.05$.

Results: During serial passaging in the absence of the drug, the PQ-resistant parasite maintained low growth rates at day 7 pi (mean parasitaemia, 5.6% ± 2.3) relative to the wild-type (28.4% ± 6.6), translating into a fitness cost of resistance of 80.3%. Whilst resistance phenotype for PQ was stable, that of LU was transient since after several serial passages in the absence of drug, the LU-exposed line assumed the growth patterns of the wild-type.

Conclusions: The contrasting behaviour of PQ- and LU-resistance phenotypes support similar findings which indicate that even for drugs within the same chemical class, resistance-conferred traits may vary on how they influence parasite fitness and virulence. Resistance-mediating polymorphisms have been associated with less fit malaria parasites. In the absence of drug pressure in the field, it is therefore likely that the wild-type parasite will out-compete the mutant form. This implies the possibility of reintroducing a drug previously lost to resistance, after a period of suspended use. Considering the recent reports of high failure rates associated with ACT, high fitness cost of resistance to PQ is therefore of clinical relevance as the drug is a partner in ACT.

Keywords: Fitness cost, Drug resistance, Piperaquine, Lumefantrine, Malaria

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