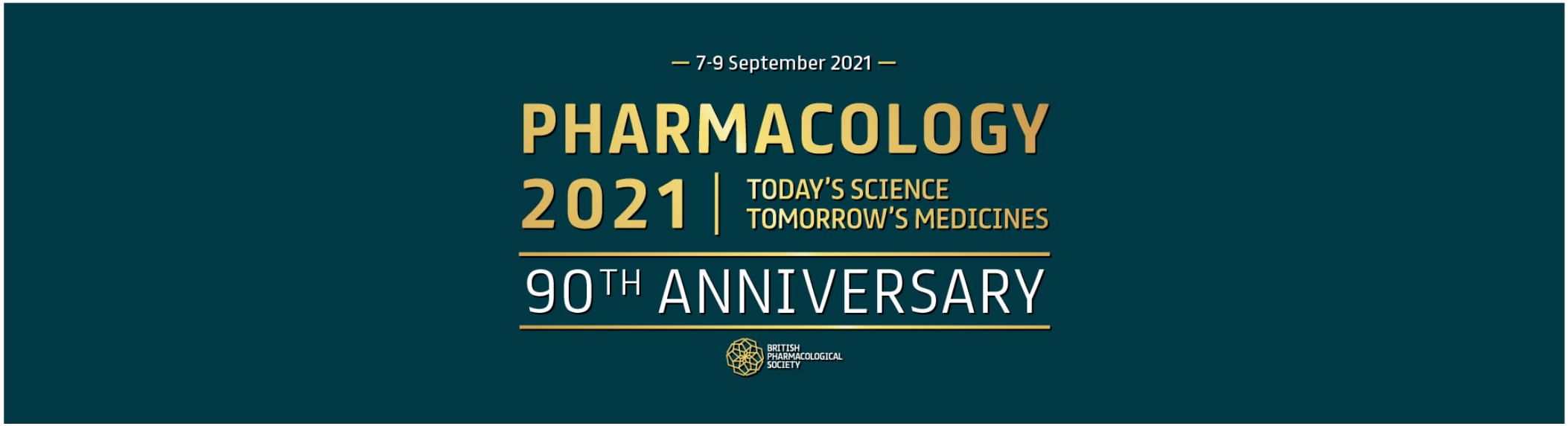
BRITISH PHARMACOLOGICAL SOCIETY



Abstract Details

Title: Clinical trial design optimisation and dose rationale for the treatment of Buruli Ulcer antibiotic combination therapy

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Introduction/Background & aims

The recommended treatment for Buruli Ulcer (BU) consists in the combination of rifampicin (10 mg/kg o.d.) and clarithromycin (7.5 mg/kg b.i.d.) for 8 weeks. The addition of other antibiotics to the combination has been considered as an opportunity to reduce treatment duration. Various candidate combinations have shown enhanced antibacterial activity in vitro. However, the translation of such findings into suitable dosing regimens into the clinic has been empirical, without careful consideration of pharmacokinetic (PK) and pharmacodynamic variability. The aims of this investigation were 1) to identify the optimal dose and dosing regimen for BU using rifampicin in combination with amoxicillin/clavulanic acid and/or clarithromycin, and 2) to explore the effect of covariate factors on drug exposure in paediatric patients.

Method/Summary of work

Clinical trial simulations (CTS) were performed to identify suitable doses and dosing regimens that maximise the time above the minimum inhibitory concentration (T>MIC) for amoxicillin and the probability of target attainment (PTA) for combination regimens. Using a virtual population of 1000 subjects (5-

69 years) sampled from the National Health and Nutrition Examination Survey (NHANES) data set, the pharmacokinetic profiles of rifampicin, amoxicillin and clarithromycin were simulated based on published population PK models [1-3]. Dosing scenarios included combinations of rifampicin, amoxicillin/clavulanic acid and/or clarithromycin at varying doses and dosing intervals. MIC values were obtained from in vitro experiments using clinical isolates. All simulations were performed using NONMEM 7.3.

Results/Discussion

Our results show that the best performing treatment including standard of care drugs consists of 10 mg/kg b.i.d. rifampicin, 7.5 mg/kg b.i.d. clarithromycin and 22.5 mg/kg / 1000 mg amoxicillin/clavulanic acid b.i.d. In addition, our analysis strongly suggests that the removal of clarithromycin does not affect the overall treatment performance.

Conclusion(s)

Our analysis shows how CTS provides insight into the overall performance of combination therapy taking into account the effect of interindividual variability. These results show that optimisation of BU treatment is feasible, possibly without clarithromycin, providing the basis for the evaluation of alternative regimens in a prospective clinical trial, where it can be demonstrated whether comparable efficacy rates can be achieved with a shorter (4-week) therapy.

Reference(s)

[1] Muliaditan M, Della Pasqua O. How long will treatment guidelines for TB continue to overlook variability in drug exposure?. J Antimicrob Chemother. 2019;74(11):3274-3280. doi:10.1093/jac/dkz319
[2] Carlier M, Noë M, De Waele JJ, et al. Population pharmacokinetics and dosing simulations of amoxicillin/clavulanic acid in critically ill patients. J Antimicrob Chemother. 2013;68(11):2600-2608. doi:10.1093/jac/dkt240
[3] Abduljalil K, Kinzig M, Bulitta J, et al. Modeling the autoinhibition of clarithromycin metabolism during repeated oral administration. Antimicrob Agents Chemother. 2009;53(7):2892-2901. doi:10.1128/AAC.01193-08

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