REPURPOSING TO SPEED CHEMICAL AND BIOLOGICAL MEDICAL COUNTERMEASURE DISCOVERY AND DEVELOPMENT

Assessment Of Antibiotics Using The Hollow Fibre Infection Model To Identify Improved Melioidosis Therapeutics

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It is widely recognized that there is an urgency to develop new or improved antibiotics to combat the threat of multi-drug resistant nosocomial infections. Bacterial pathogens of interest to Defence are intrinsically highly virulent and can be difficult to treat. The possibility of such antibiotic resistances arising in highly virulent biothreat agents, either by natural or deliberate means, will greatly exacerbate this problem. While the development of entirely new antibiotics would be ideal, the timeline from compound identification to licensure can take more than a decade. Seeking approval for a therapeutic, be it novel or repurposed, to treat a biothreat agent is difficult. Most applications have to rely on in vitro data and animal models, as clinical trials are not feasible due to the rarity of natural infections and ethical considerations. While animal models are useful, treatment regimens derived from them may not translate well into humans due to differences in antibiotic pharmacokinetics. The in vitro Hollow Fibre Infection Model (HFIM) is able to bridge this gap, as it can precisely mimic human antibiotic pharmacokinetic parameters to assess a whole treatment regimens' effect on its target bacterial infection. Consequently the HFIM has a high correlation in being able to predict clinical outcomes, generating data that is accepted by both the FDA and EMA.

Burkholderia pseudomallei, the causative agent of melioidosis, is innately resistant to numerous antibiotics and can only be effectively treated with 'antibiotics of last resort'. Here, we use B. pseudomallei (K96243) in the HFIM to assess the efficacy of existing antibiotics to treat melioidosis. The fluoroquinolone, levofloxacin, given as an equivalent human 7-day dosing regimen of 750mg q24d iv, was unable to suppress the growth of B. pseudomallei despite an initial 3-log kill. These results suggest that levofloxacin, despite being approved as an anthrax and plague treatment, would not make for an effective melioidosis treatment. In contrast, the β-lactam/β-lactamase inhibitor combination of piperacillin/tazobactam, given as an equivalent human 7 day dosing regimen of 4000/500mg q8d iv, was able to give an initial 3-log kill, suppress the growth of B. pseudomallei and prevent the emergence of piperacillin/tazobactam resistance. These results suggest that piperacillin/tazobactam has the potential to be used as a future melioidosis treatment. Despite piperacillin/tazobactam being long theorized as a potential melioidosis treatment, there is no published information about its efficacy in animal models or human clinical trials. Here lies the strength of the HFIM, in being able to rapidly assess prescribed human dose regimens against a range of biothreat agents to generate efficacy data predictive of clinical outcomes in a dynamic in vitro setting. Furthermore, the HFIM has proven invaluable in human dosing regimen optimization and the assessment a therapeutics potential effectiveness, even when in early phase clinical trials where only the human pharmacokinetics are known, providing a technology that will accelerate the potential licensure of both new and existing antibiotics as treatments for biothreat agent infections.