A new study resurrects the concept of potentially repurposing clinically available compounds such as AZT as adjunctive therapy against MDR pathogens. The investigators examined the pharmacodynamic interaction of AZT with colistin in vitro via checkerboard and time kill assays, and in vivo utilizing a murine peritonitis model.

By itself, AZT activity by minimum inhibitory concentration (MIC) was not particularly impressive, with minimum inhibitory concentration 50% (MIC<sub>50</sub>) of 4 to 8 mg/L against tested isolates. Checkerboards demonstrated synergy between AZT and colistin against 87% (27/31) of extended-spectrum beta-lactamase (ESBL)–producing Klebsiella pneumoniae, 61% (14/23) of ESBL-E. coli, 100% (7/7) of New Delhi metallo-beta-lactamase–producing strains, and 92% (12/13) of mcr-1 (a mediator of colistin resistance) E. coli. The remaining isolates showed no interaction between the AZT and colistin. Time kill assays against NDM-1–producing K. pneumoniae with 1–2 mg/L colistin plus 1–4 mg/L AZT showed killing to below detection level at 24 hours, whereas each agent alone showed stasis. Results were similar against mcr-1 positive colistin-resistant E. coli. In the peritonitis model, only AZT plus colistin achieved killing at 6 hours (2.72 log<sub>10</sub>) against NDM-1–producing K. pneumoniae. Against mcr-1 E.coli, higher doses of colistin were used in the murine peritonitis model and the AZT-colistin combination achieved 2.96 log<sub>10</sub> kill at 6 hours.

The activity of many compounds like AZT may be underappreciated using simple MIC testing methods compared with synergy testing or in vivo assays. Although the concentrations of AZT used in the time kill assays are not achievable with standard oral dosing, with more careful pharmacokinetic considerations AZT may have a future role in this space, particularly in urinary tract infections where concentrations of AZT may exceed MIC of common pathogens. Whereas AZT demonstrated myelotoxicity with long-term use associated with HIV maintenance in the past, this may be less of a problem with shorter durations of treatment, allowing for higher dosing.

CITATION(S):