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A pilot study of novel liposomal colistin sulphate versus colistin sulphate in rats; plasma concentration and safety profile

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Background: Colistin, prepared in the form of colistinmetate sodium (CMS), was using worldwide as the rescue antibiotic to combat with multidrug resistant Gram-negative bacteria (MDR GNB). CMS was used with renal toxicity as the worst complication. Another form of colistin, colistin sulphate, was reported to treatment in few patients with low renal adverse. However, colsitin sulphate has not been well studied. Moreover, the nanotechnology may assist to established liposomal form of colistin sulphate for the purpose of reducing renal toxicity. The present study aimed to determine plasma concentration and safety of colistin sulphate (CS) and novel form of CS, liposomal colistin sulphate (LCS), injection (subcutaneous) in rats.

Material/methods: A pilot study was conducted using CS and LCS which was prepared using CS under nanotechnology development by National Science and Technology Development Agency. CS, 2mg/kg of colistin-based activity (CBA) and LCS, 3mg/kg of CBA, were subcutaneously injected to 18l rats every 24h. All rats were categorized into 6 groups to collect plasma at 0.5, 1, 2, 4h after CS and LCS injection on Day1. The rest of studied rats were injected with both drugs for 14 days for renal toxicity monitoring. Plasma CBA concentrations were measured using UPLC. Plasma creatinine and kidney histopathology were examined on Day14.

Results: Peak concentration (mg/L) of plasma CBA concentration in CS and LCS were 4.96 and 6.67, respectively and time of peak CBA concentration (Tmax) of CS and LCS group were 0.5 and 1 hour, respectively, figure 1. All rats' plasma creatinine was in normal range. Kidney histopathology reviewed some changes such as tubular dilatation, pigmentation, and lymphocyte & basophil infiltration in both CS and LCS groups. No rats died due to drugs toxicity.

Conclusions: All animals were well tolerated to both CS and LCS despite of higher dose in LCS group. However, the Tmax in LCS was slower than CS. The CBA concentration at steady state needed to be monitor in further study if higher dose of LCS can be established for higher CBA concentration with lower nephrotoxicity thus the novel form of colistin sulphate may be the answer to combat with MDR GNB. Further study of CS and LCS for bridging to use in human, both dosage and safety, need to be studied.

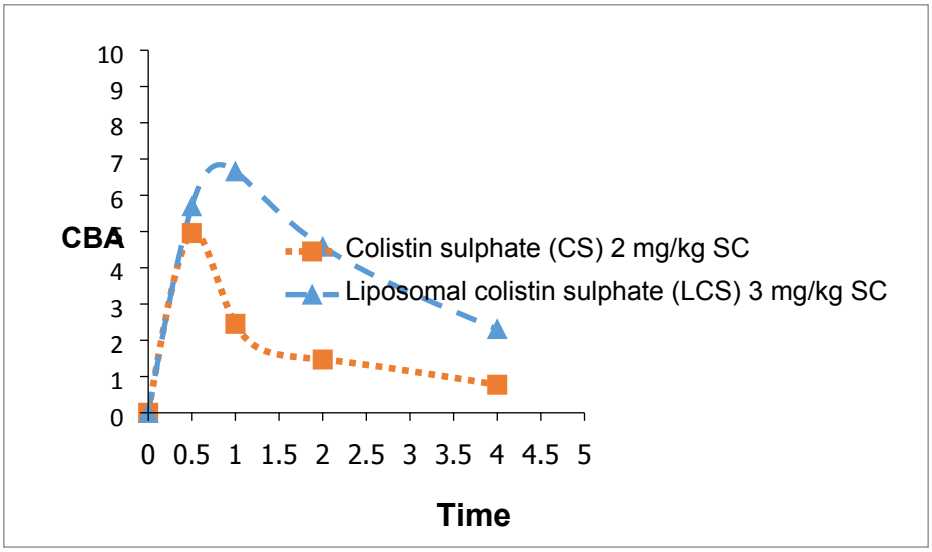

Figure 1. Colistin-based activity (CBA) concentration in colistin sulphate (CS) and liposomal colistin sulphate (LCS) group