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Longer-interval regimen of colistin reduces nephrotoxicity in kidney-on-a-chip

Anna Lee[1], **Kipyo Kim[1]**, Sung-Jin Kim[2], Sejoong Kim[1]
[1]Department of Internal Medicine-Nephrology, Seoul National University Bundang Hospital, Korea, Republic of
[2]Department of Mechanical Engineering, Konkuk University, Korea, Republic of

Objectives: Animal models have higher renal clearance than humans; kidney toxicity may be underestimated. In contrast, clinical trials for evaluating nephrotoxicity of antibiotics is still difficult. Previously we developed nephrotoxicity-monitoring system for different pharmacokinetic profiles of single drug using kidney-on-a-chip. We investigated whether bolus-mimicking regimens or continuous infused regimen of colistin may be safer in microfluidic kidney models.

Methods: We introduced colistin to the kidney epithelial cells on chips under physiological shear stress condition. The perfused chips were separated into two groups: bolus-mimicking regimen group and continuous infusion regimen group.

Results:

Two Bolus-like regimens mimicked pharmacokinetic profiles for bolus injection with starting cell exposure at 1138 ug/mL of colistin and reducing the dosage level by half every 9 h over a 36 h period (B1), and for double bolus injection with starting cell exposure at 2133 ug/ml of colistin and reducing the dosage level by half every 9 h over 45 h period (B2). Continuous Infusion regimen mimicked drug regimen infused at 400 ug/mL for 48 h (C). B1 and C groups are the same total colistin dose over 48 h period, and B2 group has 1.9 times higher than other two groups

B1 regimen injured 1.47 % and B2 regimen 1.61% out of total observed cells, whereas C regimen damaged 4.12% after 48-hour colistin exposed period. ($P < 0.05$). Bolus-mimicking regimens sustained low transmembrane permeability and tight cell-cell junctions, compared to the prolonged exposed regimen.

Conclusions: We found that a bolus mimicking regimen of colistin dramatically alleviates kidney injury, even at double high concentration, compared to the continuous infused regimen. Longer interval regimens may help to reduce nephrotoxicity in long-term colistin-using patients. In addition, the microfluidic cell culture methods may be useful for selecting safer pharmacokinetic regimens of toxicity-unknown drugs.

Figure 1. Schematic of study design

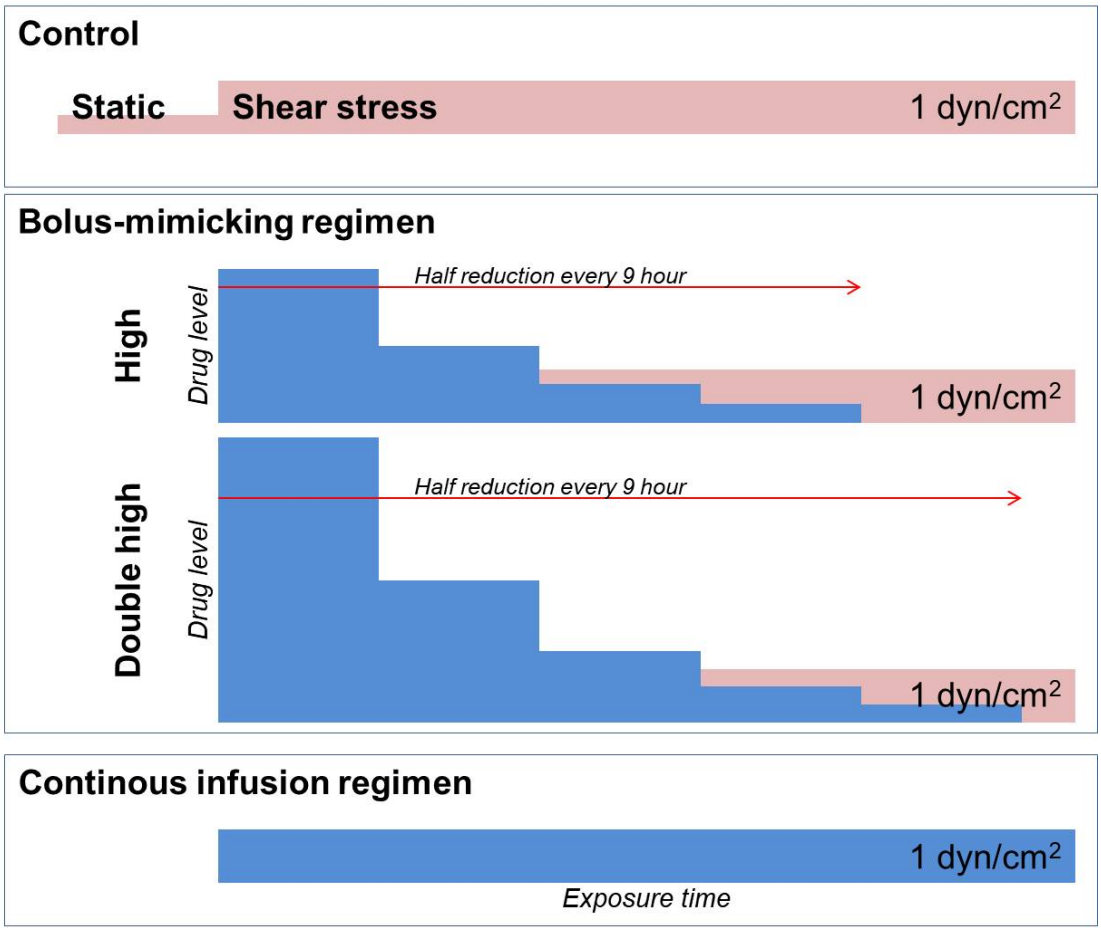


Figure 2. Live/dead stain of each group

