A randomized control trial on the effect of oral calcium carbonate to fecal levofloxacin concentration and microbiota diversity in healthy volunteers taking oral levofloxacin

Ophat Janphet[1],Kornthara Kawang[1], Weeraya Phaisal[2],Pajaree Chariyavilaskul[2], Naris Kueakulpattana[3], Tanittha Chatsuwan[3], Voraphoj Nilaratanakul[1]
[1] Division of Infectious Disease, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Thailand
[2] Department of Pharmacology, Faculty of Medicine, Chulalongkorn University, Thailand
[3] Department of Microbiology, Faculty of Medicine, Chulalongkorn University, Thailand

Background

Levofloxacin(LVX) is used in treatment against bacterial infections but also affect the intestinal microbiota. Calcium(Ca) can form complex with LVX and prevent its absorption. Taking them at least 2 hours apart does not affect LVX peak plasma concentration(C_{max}). Since, our *in vitro* study showed that Ca can increase LVX minimal inhibitory concentration (MIC) in some bacteria, we conducted a randomized control trial(RCT) to study whether oral $CaCO_3$ can lower fecal LVX concentration and preserve gut microbiota diversity in healthy volunteers.

Objective

1. To study whether oral calcium carbonate can lower fecal levofloxacin concentration in healthy volunteers taking levofloxacin.
2. To study whether oral calcium carbonate can protect gut microbiota diversity in healthy volunteers taking levofloxacin.

Methods

We conducted a RCT involving 20 healthy volunteers. All of them received a 5-day course of once-daily 500 mg LVX oral tablet at 8:00 AM. They were randomly assigned to treatment (taking 1,000 mg $CaCO_3$ oral tablet twice daily at 12:00 PM and 6:00 PM) and control group (no $CaCO_3$). The primary outcome was fecal LVX concentration by MIC and high-performance liquid chromatography (HPLC) on day 2 and 5 after taking LVX. The secondary outcomes were fecal microbiota diversity by Shannon index (H) by 16s rDNA analysis, LVX C_{max} by HPLC on day 1 and 5, and drug adverse events(AEs) in 4 weeks period.

Results

Each 10 volunteers were randomly assigned to treatment and control group. Mean fecal LVX concentration was higher in treatment than control group, 100.50 vs 53.21 µg/ml by MIC at day 5 (95% confidence interval [CI] 4.912, 89.73; p = 0.0242). There was no difference in mean fecal LVX concentrations by HPLC between treatment and control at day 2 and day 5. There was no difference in C_{max} LVX at day 1 and day5 in treatment and control. No difference of fecal H, but treatment group had significantly declined in H(p = 0.0019). No serious AE, mild AEs were reported (3 in treatment and 5 in control groups), including nausea and diarrhea.

Conclusion

In this study, $CaCO_3$ is significantly related to higher fecal LVX level by MIC but does not significantly affect the LVX C_{max}. However, rather than protecting gut microbiota from LVX, $CaCO_3$ may lower gut microbiota diversity in the presence of LVX. Therefore, co-prescription of LVX and $CaCO_3$ should be cautioned even without the concern about the absorption like when LVX is administered intravenously or when both drugs in oral forms are taken at different times.

Table 1 *in-vitro* data of drug interaction between levofloxacin and calcium gluconate on the MIC changes.

Tested agents	*E. coli* ATCC 25922 (MIC, mcg/ml)	*E. faecalis* ATCC (MIC, mcg/ml)
Levofloxacin	0.08	0.32
10% calcium gluconate	>9.28	>9.28
Levofloxacin+10%calcium gluconate 20 mcg: 4.64 mg/ml	Levofloxacin>41.8	Levofloxacin>41.8

Figure 1. demonstrates study methods

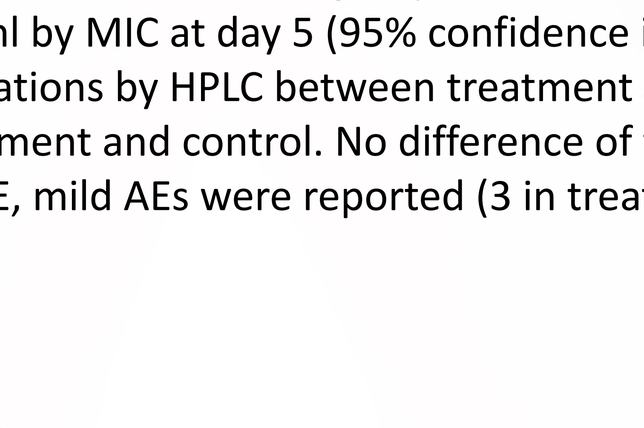

Table2. Baseline characteristic

Characteristic	Treatment group (N=10)	Control group (N=10)	Total (N=20)
Age (years)	34.60 ± 5.68	33.70 ± 5.37	34.15 ± 1.21
Sex			
Male	3 (30%)	4 (40%)	7 (35%)
Female	7 (70%)	6 (60%)	13 (65%)
Characteristic	Treatment group (N=10)	Control group (N=10)	Total (N=20)
BM (kg/m^2)	22.86 ± 3.30	22.30 ± 5.39	22.58 ± 0.97
Thai eGFR (ml/min/1.73m^2)	105.27 ± 12.93	100.71 ± 13.92	102.99 ± 2.96

Primary outcome

Table 3. Fecal levofloxacin concentration on day 0, 2, and 5

Outcome	Treatment group	Control group	Adjusted *p*-value 95% CI
Mean fecal functional levofloxacin concentration day 0 (mcg/ml) by MIC	< 1.56	< 1.56	> 0.99
Mean fecal functional levofloxacin concentration day 2 (mcg/ml) by MIC	41.50	30.26	0.87 (-29.00, 51.46)
Mean fecal functional levofloxacin concentration day 5 (mcg/ml) by MIC	100.50	53.21	0.0242 (4.91, 89.73)
Mean fecal levofloxacin concentration day 0 (mcg/ml) by HPLC	< 0.5	< 0.5	> 0.99
Mean fecal levofloxacin concentration day 2 by HPLC (mcg/ml)	55.90	34.23	0.645 (-28.52, 71.91)
Outcome	Treatment group	Control group	Adjusted *p*-value 95% CI
Mean fecal levofloxacin concentration day 5 by HPLC (mcg/ml)	108.23	60.75	0.069 (-2.73, 97.69)

Secondary outcome

Table 4. Shannon diversity index and peak plasma levofloxacin concentration

Outcome	Treatment group volunteers	Control group volunteers	*p*-value (95% CI)
Mean gut microbiota diversity Shannon index Day 0	3.86	3.73	0.923 (-0.28, 0.55)
Mean gut microbiota diversity Shannon index Day 2	3.58	3.84	0.426 (-0.68, 0.16)
Mean gut microbiota diversity Shannon index Day 5	3.30	3.62	0.237 (-0.75, 0.11)
Mean gut microbiota diversity Shannon index Day 14	4.17	4.02	0.912 (-0.29, 0.58)
Outcome	Treatment group volunteers	Control group volunteers	*p*-value (95% CI)
Mean gut microbiota diversity Shannon index Day 28	4.13	4.04	0.988 (-0.33, 0.51)
Mean plasma levofloxacin level day 1 (mcg/ml) by HPLC	3.66	3.25	0.88 (-1.17, 2.60)
Mean plasma levofloxacin level day 5 (mcg/ml) by HPLC	3.59	2.21	0.27 (-0.80, 3.56)

Figure 2. Shannon index diversity in treatment vs control group at each time points

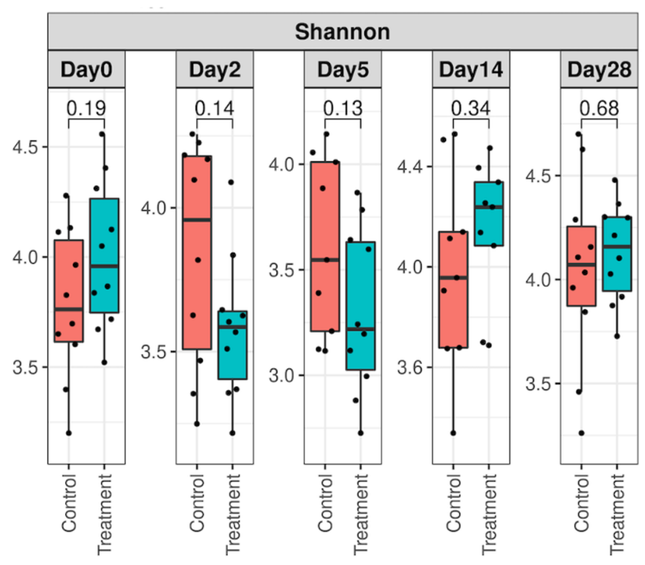

Table 6. Adverse events

Adverse effect	Treatment group volunteers (%) (N=10)	Control group volunteers (%) (N=10)	*p*-value
Any adverse event	3 (30%)	5 (50%)	0.388
nausea	0	2	0.168
dizziness	1	1	-
myalgia	0	1	0.343
diarrhea	1	1	-
belching	1	0	0.343
dyspepsia	0	1	0.343

Figure 3. Taxonomic profile