COMPARISON OF SEVELAMER, SEVELAMER CARBONATE AND LANTHANIUM CARBONATE *IN VITRO* AND *IN VIVO*

Lucisano Silvia[1], Coppolino Giuseppe[1], Villari Antonino [2], Lionello Giovanna[3], Donato Valentina[1], Fazio Maria Rosaria[1], Cernaro Valeria[1], Lupica Rosaria[1], Trimboli Domenico[1],Aloisi Carmela[1], Buemi Michele[1].

[1] Unit of Nephrology, Department of Internal Medicine, Messina, Italy.
[2] Department of Inorganic and Analytical Physics, Messina, Italy.
[3] Unit of Gastro-intestinal surgery, Department of General Surgery Messina, Italy.

OBJECTIVES

Hyperphosphatemia is common in patients with chronic renal failure (CKD), particularly in advanced stages. The chelators of the phosphate group [sevelamer (S), sevelamer carbonate (SC) and lanthanum carbonate (LC)] are the drugs most commonly used to reduce the serum concentration of phosphorus (P). They are, however, associated with gastrointestinal intolerance.(1)
We studied *in vitro* the different dissolution, the ability to uptake P and the amount of carbon dioxide (CO_2) produced by these drugs. In addition, we evaluated gastric pH changes *in vivo,* with and without administration of phosphate binders (PB) .

METHODS

one tablet of SC 800 mg, one of S 800 mg and a tablet of LC 750 mg were dissolved in solutions at pH2 corresponding to stomach-pH, following the USP dissolution II paddle method at a rotation speed of 50 rev/min in 900 ml of dissolution medium at a stable temperature of 37 0.01 C, maintained by a Haake cryostat. [Figure 1]
The dissolution profile was obtained before and after addition of trehalose , a disaccharide used to stabilize pharmaceutical products for his effect on H-binding structures. The pH variations were graphically reproduced using software TableCurve 2D ®.
To calculate the amount of phosphoric acid stoichiometrically engaged by each single tablet, we followed the variation of pH of a phosphoric acid solution 4.00 X 10^{-9} Mol . We also calculated the amount of CO_2 produced from each tablet and evaluated gastric-pH *in vivo* using 24-h esophago-gastric pH measurement with and without administration of Phosphate Binders and Proton pump inhibitor (PPis) in CKD patients and in a control group. A electrode was positioned at the esophago-gastric juncture and another in the stomach.

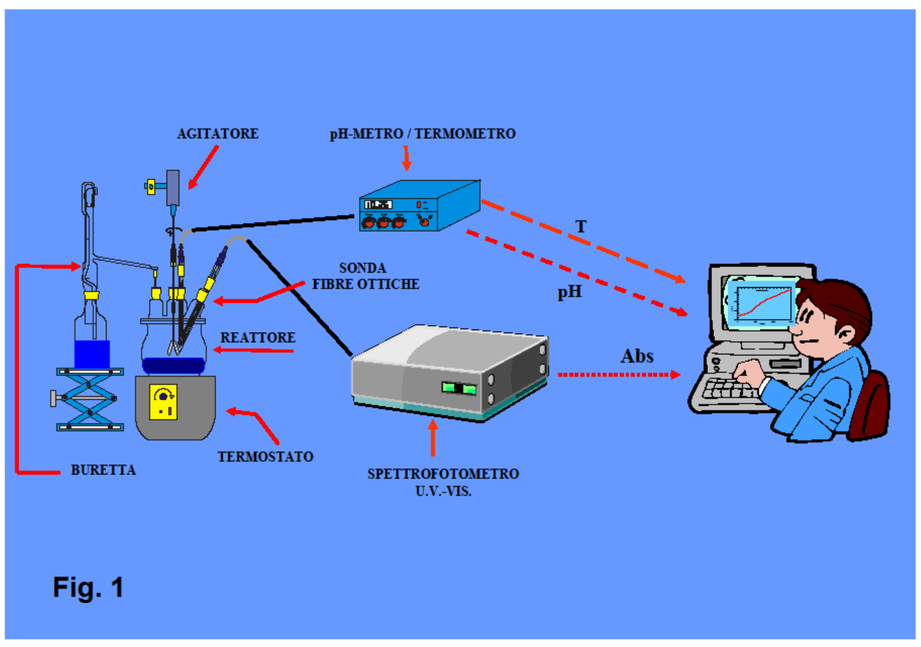

Fig. 1

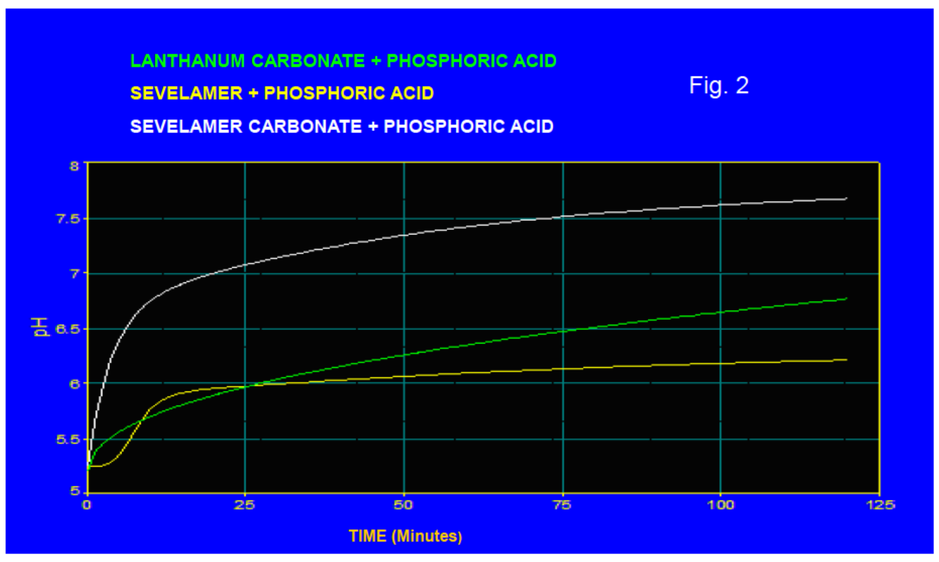

Fig. 2

RESULTS

The complete solubilization of a tablet of Lanthanum Carbonate occurs in 60 min, while that of Sevelamer and Sevelamer Carbonate in 10 min. [Figure 3-A]
The dissolution of PB increases the pH of solution ($p<0.0001$), this action is linked to the ability of these drugs to bind protons. The addition of trehalose increases the density of medium, but not generate any significant variation in the profile of drugs solubility.
Engaged by the amount of phosphoric acid there was a net best action of Sevelamer Carbonate (a tablet of S undertakes 4.00 X 10-9 mol /L, one of LC 3.99 X 10-9 mol / L and a tablet of S 3.95 X 10-9 mol / L). [Figure 2]
The amount of CO_2 produced by Lanthanum Carbonate is 56 ml, that of Sevelamer Carbonate is 30 ml; S does not produce CO_2. [Figure 3-B]
The pHmeter shown that gastric-pH increases significantly after administration of the tablets, especially with Sevelamer Carbonate ($p<0.0001$). The pH increases even more after administration of Proton pump inhibitor. [Figure 3-C]

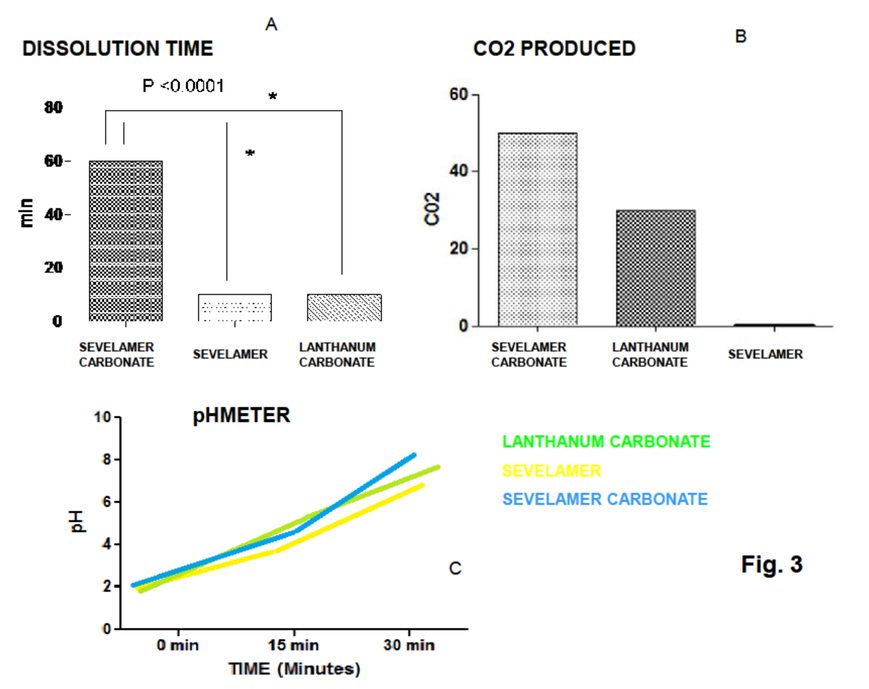

Fig. 3

CONCLUSIONS

The action of PB is linked to their ability to uptake protons, so is preferable to take them after meal and especially after Proton pump inhibitor; reducing the stomach acidity the protons detected are those of phosphoric acid. Sevelamer Carbonate has a greater capacity and rapidity to uptake phosphorus, Sevelamer is the most tolerated because it doesn't produce CO_2, while Lanthanum Carbonate is the less soluble.

REFERENCES:

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