

# TOP Journal Club

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## Effect of cilostazol on the ventricular escape rate and neurohumoral factors in patients with third-degree atrioventricular block.

Reference: Chest 2003 Apr;123(4):1161-9

**STUDY OBJECTIVE:**s: This study assessed whether the antiplatelet agent cilostazol, which has potent cyclic nucleotide phosphodiesterase type-3 inhibitory activity, affects the ventricular escape rate and neurohumoral factors in patients with third-degree atrioventricular block.

**DESIGN:** Prospective, but nonrandomized, study.  
**SETTING:** Cardiology division of an acute care hospital.

**PATIENTS:** We studied 12 patients with third-degree intra-His or infra-His atrioventricular block who were in functional class II or III of the New York Heart Association classification. None of the patients had experienced Adams-Stokes attacks.

**INTERVENTIONS:** These patients were given cilostazol orally at a dose of 200 mg daily for at least 1 week. Measurements and results: Before and after treatment with cilostazol, continuous 24-h ECG monitoring and measurement of plasma natriuretic peptide concentrations were performed. Cilostazol significantly increased the mean ( $\pm$  SEM) total 24-h QRS count from 57,300  $\pm$  2,800 to 74,400  $\pm$  3,200 beats ( $p = 0.001$ ) and significantly decreased the maximum geometric mean R-R interval over a 24-h period from 1,900 ms (95% confidence interval [CI], 1,700 to 2,100 ms) to 1,600 ms (95% CI, 1,400 to 1,900 ms;  $p = 0.02$ ), although none of the patients showed the abolishment of the atrioventricular conduction abnormalities. The total 24-h count of premature ventricular beats was not different before treatment (15 beats; 95% CI, 5 to 44 beats) and after treatment (12 beats; 95% CI, 5 to 30 beats;  $p = 0.57$ ). Treatment with cilostazol significantly decreased the concentration of plasma atrial natriuretic peptide from 88 pg/mL (95% CI, 49 to 160 pg/mL) to 51 pg/mL (95% CI, 32 to 80 pg/mL;  $p = 0.007$ ) and of brain natriuretic peptide from 166 pg/mL (95% CI, 71 to 389 pg/mL) to 77 pg/mL (95% CI, 30 to 178 pg/mL;  $p = 0.02$ ).  
**CONCLUSIONS:** Cilostazol significantly increased the ventricular escape rate and significantly decreased the

level of circulating natriuretic peptides. Thus, cilostazol could be safely given to selected patients over the short term with third-degree atrioventricular block.

## A Paclitaxel-eluting stent for the prevention of coronary restenosis.

Reference: N Engl J Med 2003 Apr 17;348(16):1537-45

**BACKGROUND:** Intimal hyperplasia and resulting restenosis limit the efficacy of coronary stenting. We studied a coronary stent coated with the antiproliferative agent paclitaxel as a means of preventing restenosis.

**METHODS:** We conducted a multicenter, randomized, controlled, triple-blind study to evaluate the ability of a paclitaxel-eluting stent to inhibit restenosis. At three centers, 177 patients with discrete coronary lesions ( $<15$  mm in length, 2.25 to 3.5 mm in diameter) underwent implantation of paclitaxel-eluting stents (low dose, 1.3 microg per square millimeter, or high dose, 3.1 microg per square millimeter) or control stents. Antiplatelet therapies included aspirin with ticlopidine (120 patients), clopidogrel (18 patients), or cilostazol (37 patients). Clinical follow-up was performed at one month and four to six months, and angiographic follow-up at four to six months.

**RESULTS:** Technical success was achieved in 99 percent of the patients (176 of 177). At follow-up, the high-dose group, as compared with the control group, had significantly better result for the degree of stenosis (mean [ $\pm$ SD], 14 $\pm$ 21 percent vs. 39 $\pm$ 27 percent;  $P < 0.001$ ), late loss of luminal diameter (0.29 $\pm$ 0.72 mm vs. 1.04 $\pm$ 0.83 mm,  $P < 0.001$ ), and restenosis of more than 50 percent (4 percent vs. 27 percent,  $P < 0.001$ ). Intravascular ultrasound analysis demonstrated a dose-dependent reduction in the volume of intimal hyperplasia (31, 18, and 13 mm<sup>3</sup>, in the high-dose, low-dose, and control groups, respectively). There was a higher rate of major cardiac events in patients receiving cilostazol than in those receiving ticlopidine or clopidogrel. Among patients receiving ticlopidine or clopidogrel, event-free survival was 98 percent and 100 percent in the high-dose and control groups, respectively, at one month, and 96 percent in both at four to six months.

**CONCLUSIONS:** Paclitaxel-eluting stents used with conventional antiplatelet therapy effectively inhibit restenosis and neointimal hyperplasia, with a safety profile similar to that of standard stents.

## **Combinatorial use of sodium laurate with taurine or L-glutamine enhances colonic absorption of rebamipide, poorly absorbable antiulcer drug, without any serious histopathological mucosal damages.**

Reference: J Pharm Sci 2003 Apr;92(4):911-921

We previously reported that the combinatorial use of sodium laurate (C12) with several amino acids such as taurine (Tau) and L-glutamine (L-Gln) enhanced the colonic absorption of phenol red with attenuating the local toxicity caused by C12. However, even these amino acids could not protect epithelial cells from being damaged if the mucosal damage got worse to the coagulation necrosis by an excessive dose of C12. Comparing C12 with sodium caprate (C10), used in drug products marketed, 100 µmol C10 was needed to exert the similar absorption-enhancement of rebamipide, a poorly absorbable antiulcer drug, to that by 10 µmol C12, and 100 µmol C10 was obviously more toxic to the mucosa than 10 µmol C12. The combinatorial use of C12 with Tau or L-Gln enhanced the colonic absorption of rebamipide four to nine times larger in AUC than the control. Histopathologic studies clearly showed that Tau and L-Gln exerted the cytoprotective action on epithelial cells suffering from slight damages such as shrinkage and exfoliation, more articulately at 6 h than at 1.5 h after dosing. In conclusion, the combinatorial use of C12 with Tau or L-Gln could lead to a novel formulation improving the bioavailability of poorly absorbable drugs without any serious local damages.

## **Effect of rebamipide on acetic acid-induced gastric ulcer in rats: involvement of hepatocyte growth factor.**

Reference: Scand J Gastroenterol 2003 Feb;38(2):141-6

**BACKGROUND:** Rebamipide is used clinically as an anti-ulcer agent, especially in Japan. The major mechanisms of rebamipide include prostaglandin induction and free radical scavenging. Since prostaglandins are inducers of hepatocyte growth factor (HGF), we examined the effect of rebamipide on the expression of HGF, c-met, cyclooxygenase-2 (Cox-2) and subtype of the prostaglandin E2 receptor (EP2) in

acetic acid-induced gastric ulcer, a model of human ulcer.

**METHODS:** Ninety-six male Fisher rats were used in the experiments. Gastric ulcers were produced by injecting 50 µl of 20% acetic acid into subserosa of the border between the fundic and antral gland areas. The rats of the rebamipide group were fed a diet containing 60 mg kg<sup>-1</sup> day<sup>-1</sup> rebamipide and killed on days 10, 30, 60, 90, 120 and 150 after ulceration. Reverse transcription polymerase chain reaction of HGF, c-met, Cox-2 and EP2 gene and immunohistochemistry of proliferating cell nuclear antigen (PCNA) were performed.

**RESULTS:** In the rebamipide group, gastric ulcer index was significantly smaller than in the control group at each time-point except at 10 days (P < 0.05, each); up regulation of HGF, c-met, Cox-2 and EP2 mRNA was also observed. The mRNA level of HGF was significantly correlated with that of Cox-2 and EP2 (P < 0.05, each). The PCNA-labelled epithelial cells in the rebamipide group were also greater than in the control group on days 10, 30, 90 and 120 (P < 0.05, each).

**CONCLUSION:** The study suggests that rebamipide has anti-ulcerative effects on gastric mucosal cells via up-regulation of HGF, c-met, Cox-2 and EP2.

## **The effects of the formula of amino acids enriched BCAA on nutritional support in traumatic patients.**

The formula of amino acid enriched BCAA may normalize the levels of serum amino acids, reduce the proteolysis, increase the synthesis of protein, improve the nutritional status of traumatic patients after operation.

*World J Gastroenterol 2003 Mar;9(3):599-602*

**Coming next month.....**

## **Cilostazol: An "Intermittent Claudication" Remedy for the Management of Third-Degree AV Block.**

<http://www.thai-otsuka.co.th/pxnews/index.html> Opinions and suggestions are welcomed Dr. Shwe Win, [shwewin@thai-otsuka.co.th](mailto:shwewin@thai-otsuka.co.th)