DUAL EFFECTS OF TICLOPIDINE DURING FORMATION AND HEALING OF ETHANOL-INDUCED GASTRIC LESIONS IN THE RAT: COMPARISON WITH ASPIRIN

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It is well known that long-term acetyl-salicylic acid (ASA) therapy for the secondary prevention of heart attack and stroke is associated with the development of gastric ulcers and increased incidence of recurrent ulcer bleeding due to its inhibition of cyclooxygenase-derived prostaglandins in the gastrointestinal (GI) tract. An alternative to ASA in patients that are intolerant or resistant to ASA is the use of thienopiridynes (ticlopidine or clopidogrel), which inhibit platelet function by irreversibly antagonizing the platelet adenosine diphosphate receptor. Limited information is available about the GI toxicity of thienopiridynes, in clinical trials designed to evaluate their efficacy as antithrombotic drugs. Recently, it has been reported, in a multicentre population case-control study, that the risk of GI bleeding associated with the use of ticlopidine is similar to that of ASA and that clopidogrel increases the incidence of recurrent bleeding in patients with a previous peptic ulcer. The aims of the present study were: 1) to evaluate the effects of acute and long-term repeated oral ticlopidine administration in the rat on intact gastric mucosa or on gastric mucosa lesioned by 50% ethanol (EtOH, 1 ml/rat,os); 2) to examine the effects of ticlopidine on the time-course of the healing of EtOH-induced gastric lesions. All experiments included ASA as the control drug to assess the possible different GI toxicity between ticlopidine and ASA. Ticlopidine alone did not affect gastric mucosal integrity either after acute (100 and 300 mg/kg) or one-week (100 mg /kg, die) oral administration. Ticlopidine (30-300 mg/kg, os) administered 1 h before EtOH dose-dependently prevented the development of gastric hemorrhagic lesions. However when ticlopidine was administered 1 h after EtOH, it significantly ($P<0.05$) delaied gastric lesions healing. Acute ASA administration (50 and 100 mg/ kg, os) caused a mild irritant activity that faded after one week of oral ASA administration (50 mg/kg,/die). In condition of mucosal damage, ASA did not modify either the induction or the healing of EtOH-induced gastric lesions.

These results indicate that ticlopidine exerts dual effects whether in the development or in the healing processes of gastric lesions induced by EtOH. The evidence that ticlopidine delayed the healing of pre-existing ulcers, suggests caution in the use of ticlopidine in patients with a prior history of peptic ulcer.