FORMATION OF DNA-DAMAGING N-NITROSO COMPOUNDS FROM THE INTERACTION OF CALCIUM-CHANNEL BLOCKERS WITH NITRITE

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Cancer may be caused in humans by N-nitroso compounds (NOC) formed in the gastrointestinal tract from nitrite and nitrosatable compounds. A large number of drugs have been shown to react with nitrite to give genotoxic NOC (1), but a family of drugs that are still to be examined in this respect is that of calcium-channel blockers, which are all theoretically nitrosatable.

As a preliminary approach we examined seven calcium-channel blockers to determine, for each of them, the amount of NOC formed using the nitrosation assay procedure recommended by the WHO. Subsequently we measured the degree of DNA fragmentation in liver of rats given a single oral dose (½ LD50) of the test compound with 80 mg/kg of sodium nitrite. Rats were sacrificed 6 hr after treatment and liver DNA damage was evaluated with the alkaline Comet assay that provide two indexes, tail length (TL) and tail moment (TM), of the frequency of DNA single-strand breaks and alkali-labile sites.

The yields of NOC (% of the theoretical one) formed in the nitrosation assay procedure by nicardipine (37%), nifedipine (40%), nimodipine (45%) and nitrendipine (44%) were markedly higher than those formed by diltiazem (2.4%), gallopamil (4.8%) and verapamil (1.8%). The yield of N-nitroso-dimethylamine from dimethylamine-nitrite interaction, chosen as positive control, was 92%. In rats, the simultaneous oral administration of ½ LD50 of gallopamil, nifedipine, nimodipine and nitrendipine togheter with 80 mg/kg nitrite induced in the liver, as compared with the adminidtration of ½ LD50 of the drug alone, a statistically significant increase of both TL and TM indicative of the occurrence of DNA fragmentation, The ratio [TL of drug + $NaNO_2$/TL of drug alone] was 3.2 for nimodipine, 3.1 for gallopamil, 2.2 for nifedipine, and 2.1 for nitrendipine. In the same experimental conditions the increase in the degree of liver DNA fragmentation produced by the intragastric nitrosation of diltiazem, nicardipine and verapamil did not reach a statistical significance.