A NOVEL METHOD FOR THE DETECTION OF DRUG INDUCED GASTROINTESTINAL IRRITANCY

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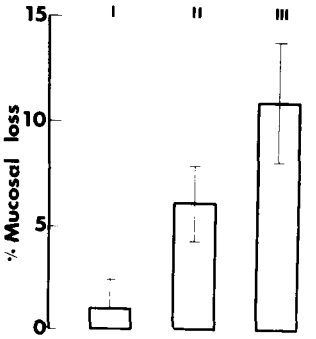
It is established that most, if not all, non-steroidal anti-inflammatory drugs (NSAID) induce gastrointestinal damage (Menguy 1972). The development of a simple in vitro method for quantifying this mucosal epithelial damage is described. The terminal ileum was removed from male Wistar rats (180-250 g.) and perfused through its lumen at 3 ml./min for 3 hours with Krebs solution at 37°C. bubbled with 5% CO_2 and O_2. Mucosal damage was determined by filtering the effluent from the ileum and weighing the residual mucosal cells. The drug under test was added to the reservoir prior to perfusion of the ileum and the result was compared with an adjacent section of tissue perfused with Krebs solution alone. All results are expressed as a percentage of the wet weight of the tissue. The mucosal damage induced by indomethacin, a known intestinal irritant (Fang et al 1976), was found to be dose dependent. (Fig. 1).

Fig. 1 : Mucosal epithelial loss due to indomethacin.

i. Indomethacin 7μM (n=9)
ii. Indomethacin 14μM (n=9)
iii. Indomethacin 28μM (n=6)



Aspirin (330μM) and phenylbutazone (129μM) also caused a significant mucosal loss of 3.8 ± 0.7% (n = 5, $p < 0.01$) and 6.2 ± 1.1% (n = 11, $p < 0.001$) respectively. However, neither paracetamol (660μM), a drug with minimal gastrointestinal irritancy, nor diclofenac (210μM), a new NSAID, caused any significant mucosal loss. Addition of prostaglandin E_2 (PGE_2) 1.4×10^{-12}M, to the perfusate in the presence of indomethacin (28μM), prevented the mucosal loss produced by indomethacin alone.

An explanation for the results is that inhibition of prostaglandin synthesis in the gastrointestinal tract may be the mechanism involved in mucosal loss, whilst the prevention of mucosal loss by PGE_2 is consistent with the known cyto-protective action of prostaglandins (Robert 1975). The correlation between the results of this study and the known intestinal irritancy of the drugs studied (Rainsford 1975; Yanagi et al 1978) indicates the validity of the method as a simple screen for gastrointestinal irritants.

R.W. is an S.R.C. student. We thank Dr. J. Pike (Upjohn Co.) for prostaglandins and Geigy for diclofenac ("Voltarol").

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