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Gastric ulcerogenicity of non-steroidal anti-inflammatory drugs in mice with mucosa sensitized by cholinomimetic treatment

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Corrigendum

The names for the drugs in Figs 1a–c and 2a–c were omitted and Fig. 4 was misplaced in the printing of this text. Amended figures and the legend for Figs 1a–c and 2a–c are as follows.

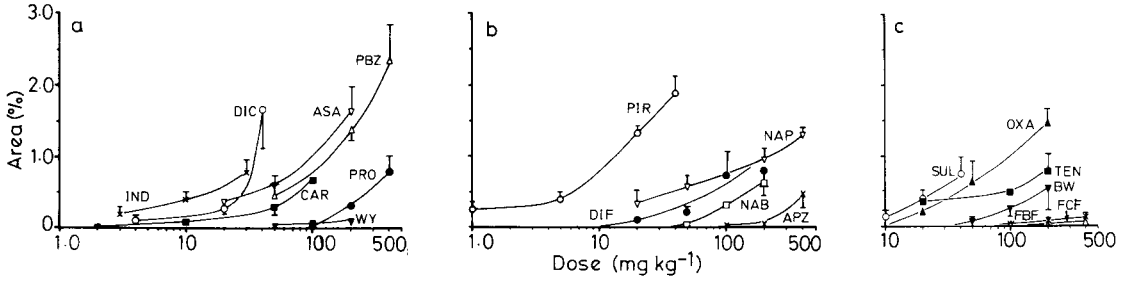

FIG. 1a–c. Dose-response curves of the per cent area of lesions for a range of NSAI drugs assayed in the bethanechol (5 mg kg^{-1} i.p.) treated mouse model as described herein. No data are shown for chloroquine phosphate since it failed to produce any detectable haemorrhagic lesions when given orally in doses up to 400 mg kg^{-1}. Likewise no damage was observed when this drug was given in equivalent doses of the base or the HCl salt. Tilomisole (Wy 18,251) was also non-irritant when given in oral doses up to 200 mg kg^{-1}. The histologic appearance of the haemorrhagic lesions observed in formalin-fixed, haematoxylin and eosin stained tissues from animals given bethanechol chloride with aspirin (200 mg kg^{-1} p.o.) or indomethacin 10 mg kg^{-1} p.o., while more severe, was identical to that in animals not given this cholinomimetic. Abbreviations: APZ azapropazone, ASA aspirin (acetylsalicylic acid), BW BW755c, CAR carprofen, DIC diclofenac, DIF diflunisal, FBF fenbufen, FCF fenclofenac, IND indomethacin, NAB nabumetone, NAP naproxen, OXA oxaprozin, PBZ phenylbutazone, PIR piroxicam, PRO proquazone, SUL sulindac, TEN tenoxicam, WY Wy 41,770.

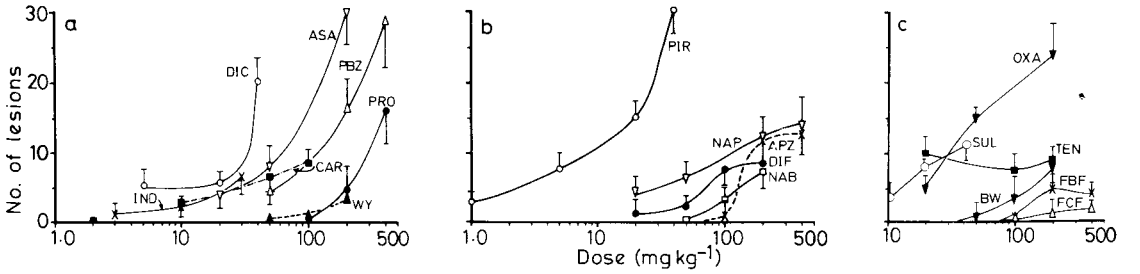

FIG. 2a–c. Dose-response curves for numbers of lesions recorded for the same doses of drugs as shown in Fig. 1a–c.

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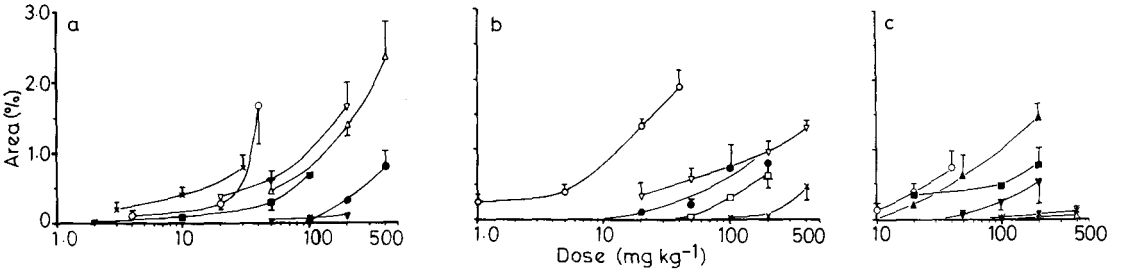

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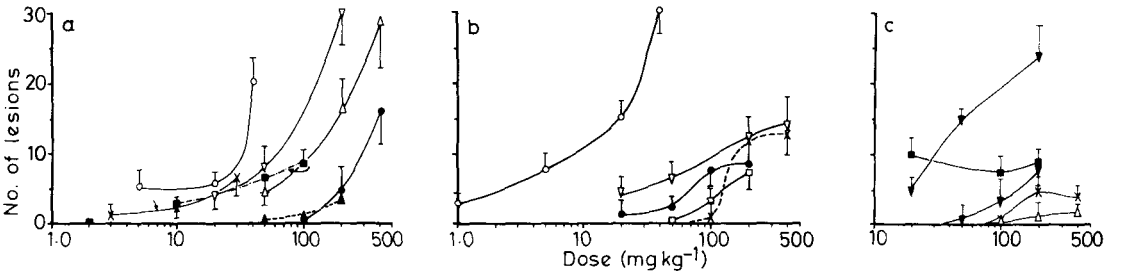

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Results and discussion

The per cent area of haemorrhagic lesions and the lesion numbers for a range of NSAI drugs studied are shown in Figs 1a–c and 2a–c, respectively. From these data a statistically significant correlation was found between the per cent area of lesions and number of gastric lesions (Fig. 3). While the lesion numbers were well correlated,

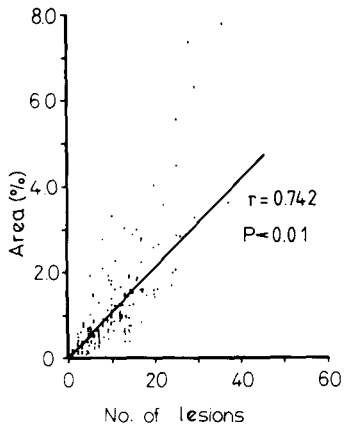

FIG. 3. Correlation of per cent area of lesions with lesion numbers using data derived from Figs 1a–c and 2a–c.

some variation may reflect the fact that these are only a partial measurement of gastric injury. Measurements of the area of mucosal damage probably constitute the best measure of mucosal injury.

Since differences exist in the gastric ulcerogenicity of NSAIDs relative to their anti-inflammatory activity, drugs were ranked from low to high relative gastric irritancy or ulcerogenicity. The *relative* gastric irritancy was assessed by comparing data on the gastric irritancy of the NSAID, as the ED0·5% (a value chosen for the area of lesions being 0·5% of total area) relative to the anti-inflammatory activity in carrageenan paw oedema (Fig. 4) and in the established adjuvant polyarthritis in rats, from data previously reported (Atkinson & Leach 1976; Cashin et al 1977; Rainsford 1981, 1985b; Boyle et al 1982; Blackham et al 1985; Gilman et al 1985). Comparison of data for anti-inflammatory activity by NSAIDs in mice with those in rats is justified on the grounds that published data on the acute anti-inflammatory and analgesic effects of the drugs in various models in mice (Carlson et al 1985; Pong et al 1985; Calhoun et al 1987), rank well with their acute anti-inflammatory activities in the carrageenan paw oedema model in rats (Cashin et al 1977; Rainsford 1981, 1985a, b; Boyle et al 1982; Blackham et al 1985). Thus, by dividing the ED0·5% values for areas of gastric lesions in Fig. 1a–c by their published ED values for both acute and chronic

anti-inflammatory effects in rats, it is seen that carprofen, diclofenac, fenbufen, tenoxicam and tilomisole (Wy 18,251) have ratios greater than 10 and so can be considered of low relative gastric irritancy, i.e. by comparison with other NSAIDs. Other drugs (e.g. fenclofenac, nabumetone) show lower relative gastric irritancy when the gastric lesion areas were compared with data on acute anti-inflammatory activities alone, whereas others (e.g. naproxen, sulindac) show lower relative gastric irritancy when the data were compared with their chronic anti-inflammatory effects. These findings are in good agreement with previously published reports on the gastric irritant effects of those drugs in relation to their anti-inflammatory activities in rats (Atkinson & Leach 1976; Takesue et al 1976; Cashin et al 1977; Shriver et al 1977; Rainsford 1982, 1985b, 1987b; Boyle et al 1982; Dearden & Nicholson 1984; Gilman et al 1985) and in man (Rainsford 1982, 1984, 1985b).

The absence of any appreciable gastric irritancy by chloroquine (given as the phosphate or hydrochloride salts or the base; Fig. 1a–c) may be related to its inhibitory effects on phospholipase A_2 (Matsuzawa & Hostetler 1980) which would be expected to achieve a balanced reduction of products from the prostaglandin cyclo-oxygenase (CO) and lipoxygenase (LO) pathways. While the basic properties of chloroquine might be responsible for poorer gastric absorption compared with acidic NSAIDs, this drug has been found to reduce gastric mucosal PGE_2 levels when orally administered to rats (Rainsford 1987a) so it is obviously absorbed quite well.

Likewise, the dual CO/LO inhibitor, BW755c (also a base), had an ED0·5% of approximately 200 mg kg^{-1} so compared with its anti-inflammatory activity (Blackham et al 1985), this drug appears to have relatively low ulcerogenicity, which is in agreement with previous results in less sensitive rat gastric ulcer models (Whittle et al 1980). Thus, as with chloroquine, the relatively low irritancy of BW755c appears to be related to its dual CO/LO activity, as suggested by Whittle et al (1980) as well as to its basic properties which contrast with irritancy attributed to the acidic properties of most NSAIDs (Rainsford 1987a).

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Not added in press.

Enhancement of gastric mucosal sensitivity towards the irritant actions of NSAIDs has also been obtained by concurrent administration of reserpine (5 mg kg^{-1} i.p. or s.c.) in both rats and mice, thus affording another pharmacological method for mimicking stress effects so as to sensitize the gastric mucosa towards the ulcerogenic effects of NSAIDs.

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