Esterification of acidic anti-inflammatory drugs suppresses their gastrotoxicity without adversely affecting their anti-inflammatory activity in rats

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The potentially deleterious effects of acidic non-steroid anti-inflammatory (NSAI) drugs on the stomach, especially the glandular mucosa, are well-known (Jennings 1965; Rainsford 1975a; Whitehouse & Rainsford 1977; Pemberton & Strand 1979). While some of the newer NSAI drugs may have somewhat lower ulcerogenic activity than the traditional agents (e.g. indomethacin, aspirin), they are often expensive alternatives. In some cases it is also doubtful if they are really appreciably less ulcerogenic or as effective as their predecessors (Whitehouse & Rainsford 1977).

We have previously shown the methyl ester of aspirin to be almost devoid of the gastric ulcerogenic activity of aspirin itself (Rainsford & Whitehouse 1976). We now show that the procedure of methyl ester formation is effective in markedly reducing the ulcerogenic activity of some potent acidic NSAI drugs although these esters appear to maintain the full therapeutic efficacy of the parent acids.

For the preparation of the methyl esters of diclofenac and tolmetin both of the sodium salts were dissolved in water, acidified with HCl and the acids subsequently filtered, washed and dried. Methyl esters were prepared from these and other NSAID acids by treatment with methanolic HCl or diazomethane in ether. Flufenamic acid was treated with methanol and conc. H_2SO_4 on a steam bath for 16 h. The oily product was freed of acid after extraction into ether and washing with aqueous Na_2CO_3. The purity of all products was determined by t.l.c. on silica gel using the solvent systems: benzene–diethyl ether–acetic acid–methanol (120:60:18:v/v) or light petroleum (b.p. 40–60)–propionic acid (10:1 v/v) and confirmed by elemental analysis.

The parent acid and derived esters were assayed after oral administration for: (i) gastric ulceration in fasted and stressed Wistar rats (Rainsford 1975b; Rainsford & Whitehouse 1977), (ii) anti-inflammatory activity against carrageenan paw oedema in both non-fasted and fasted Wistar rats (Rainsford & Whitehouse 1977) and (iii) anti-arthritic activity determined by dosing female Hooded rats once daily on the 12th–15th days inclusive after inoculating *Mycobacterium tuberculosis* in squalane and measuring changes in signs of established polyarthritis (Whitehouse & Walker 1978). The drugs were all prepared as fine aqueous suspensions in distilled water (Rainsford & Whitehouse 1977) except for the carrageenan oedema assays in unstarved rats where the compounds were administered as dispersions in 0·1% aqueous Tween 20.

Table 1 shows that the methyl esters of 4 benzoic acids and 3 arylacetic acids were each far less ulcerogenic than the respective acids in the stress-sensitized ulcer assay in rats. In normal (i.e. unstressed) rats the esters were more than 80% as potent as the acids in controlling elicited paw oedema; the principal exception being indomethacin methyl ester (IME). The potency of IME in this assay was increased by extending the time of predosing (up to 4 h) before treatment with the carrageenan inflammagen.

The safety margin of IME relative to indomethacin in Wistar rats was also shown by the effects of repeated oral dosing. With indomethacin all rats died at cumulative doses of 10 mg kg^{-1} day^{-1} d for 4 days, but with IME, 8/8 rats survived cumulative doses of 30 mg kg^{-1} day^{-1} over the same period.

In the anti-arthritic assay the three phenylacetate esters were effective drugs being almost equipotent with

Table 1. Comparison of some NSAI acidic drugs with their methyl esters for gastric ulcerogenic and anti-inflammatory activities in rats.

Compounds	Gastric ulcer activity dose (mg kg^{-1})	Lesion Index*	Anti-oedemic activity ED50** (mg kg^{-1})
Benzoates			
Salicylic acid	100	16	150
Methyl salicylate		0	170
Diflunisal, DF	50	13	110
DF methyl ester		0	125
Cinchophen, CN (m.p. 213 °C)	100	25	100
CN methyl ester (m.p. 58 °C)		4	120
Flufenamic acid (FFA)	100	39	40
FFA methyl ester ***		9	50
Arylacetates			
Indomethacin, IM	5	8	4
IM methyl ester		0†	7
Tolmetin (TM), Na salt	100	49	70
TM methyl ester (m.p. 157 °C)		4	85
TM acid (m.p. 191 °C)		31	70
Diclofenac (DCF), Na salt	50	38	N.D.
DCF methyl ester (m.p. 100 °C)		0	10
DCF acid (m.p. 175 °C)		55	13

* For lesion index, see Rainsford & Whitehouse (1977).
** Dose inhibiting 2 h paw oedema by 45–55%, given 1 h before injecting 0·1 ml 0·9% NaCl containing carrageenan (1 mg) in each rear paw. Gastric ulcer activity in fasted and cold-stressed rats (n = 5). Anti-inflammatory activity in replete rats (n = 4).
*** Oil, contaminated with less than 3% FFA as determined by t.l.c. and titration.
†ED50 significantly reduced when given at −2 h (instead of −1 h).

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the corresponding acids at the daily doses indicated: diclofenac (1–10 mg kg^{-1}); indomethacin (2 mg kg^{-1}); tolmetin (60 mg kg^{-1}). These acetate esters showed impressive stability in aqueous dispersions, with very little hydrolysis under neutral conditions (5 days, 20 °C, pH 6·0) as indicated by t.l.c. analysis.

Esters of acidic NSAI drugs may not always be fully effective anti-inflammatory agents compared with their parent acids e.g. benorylate (Brooks & Buchanan 1976; Rainsford & Whitehouse 1977) or the triglyceride ester of aspirin (Kumar & Billimora 1978). Thus the principle of esterification of acidic NSAI drugs to reduce gastric ulcerogenic activity (and still retain full therapeutic effectiveness inherent in the parent acids) will depend on the capacity of the particular ester to release the active drug after absorption through the gastric mucosa. Relatively rapid hydrolysis occurs after absorption of aspirin methyl ester (Rainsford & Whitehouse 1976; Rainsford et al 1980) and the carbonate esters of aspirin (Dittert et al 1968). Rapid metabolic hydrolysis would likewise be expected to occur with the methyl esters of the benzoates and arylacetates studied here. The principle of blocking the acidic moiety of NSAI drugs with such moderately labile groups or formation of cyclic (Edelson et al 1975; Sofia et al 1975) or other derivatives (Sinkula 1975) to produce latent forms (pro-drugs) appears a most effective means of reducing interaction of the irritant NSAI acids in the acidic millieu of the stomach with drug sensitive mucosal (Rainsford 1975a) and parietal cells (Rainsford & Brune 1976; Brune et al 1977). While the methyl esters of acidic NSAI drugs have still to be fully evaluated for intrinsic toxicity (e.g. from formation of one-carbon metabolites of the methyl moiety) it has been found that the methyl ester of aspirin is less toxic than aspirin after long-term oral administration to rats and pigs (Rainsford & Whitehouse 1980).

May 30, 1980

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On the accuracy of displacement measurements by instrumented single-punch machines

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The physical phenomena of the compression process have been much studied over the last three decades. Brake (1951) introduced equipment for measurement of compressional forces in tableting. Higuchi and his co-workers also developed equipment for the same purpose (Higuchi et al 1952, 1953). For the first time in pharmacy they introduced a system for measuring displacement of the punch during the compression process (Higuchi et al 1954). This was achieved by means of an inductive displacement transducer mounted onto the upper punch system. This kind of connection has been shown to be useful in routine observation of the tableting process.

De Blaey & Polderman (1970) introduced another kind of displacement measuring system. In this equipment the displacement transducer unit was linked to the machine part holding the upper punch, but the essential inductive part was firmly linked to the lower punch. Thus, this equipment takes into account the change of the distance between the punches due to the movement of the lower punch. From the technical point of view this system is more difficult to construct than the system

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