A comparison of the effect of flurbiprofen on prostaglandin synthetase from human rheumatoid synovium and enzymatically active animal tissues

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Flurbiprofen (2-(2-fluoro-4-biphenylyl) propionic acid, Froben, Boots), is a potent new non-steroidal anti-inflammatory compound which has shown early promise as an antirheumatic drug (Chalmers, Cathcart & others, 1972). In view of the now widely accepted theory (Vane, 1971) that such compounds exert their anti-inflammatory properties by inhibition of prostaglandin biosynthesis, we have investigated the *in vitro* effect of low doses of this new compound on PG synthetase preparations, and compared its potency with that of two well-studied inhibitors, aspirin and indomethacin. Vane (1972) postulated the existence of isoenzymes of PG synthetase that may show different sensitivities to inhibition by the 'aspirin-like' drugs, and gave hope to the possibility of developing drugs aimed specifically at target tissues. We, therefore, have compared the action of flurbiprofen on enzyme systems derived from two active animal sources, namely bovine seminal vesicles and rabbit renal medulla (Christ & van Dorp, 1972), with the enzyme prepared from human rheumatoid synovium; the former are now commonly used as *in vitro* preparations for the screening of new compounds for potential anti-inflammatory activity, and the latter is an appropriate target tissue for drug action in the treatment of rheumatoid disease.

Table 1. *Relative molar potencies of aspirin, indomethacin and flurbiprofen on different preparations of PG synthetase.*

Preparation	Human rheumatoid synovium	Bovine seminal vesicles	Rabbit renal medulla	
pH of incubation	8·0	8·3	7·0	
Prostaglandin(s) synthesized	E_2	E_2	$F_{2\alpha}$	E_2
Aspirin	1(93)*	1(476)	1(104)	1(90)
Indomethacin	257(0·36)	830(0·6)	173(0·6)	300(0·3)
Flurbiprofen	5610(0·17)	2760(0·017)	260(0·4)	300(0·3)

* Figures in parentheses are the concentrations (μM) of each drug causing 50% inhibition of prostaglandin biosynthesis.

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The various preparations of prostaglandin synthetase used have been described elsewhere (Rose & Collins, 1974; Crook & Collins, 1975). Enriched microsomal suspensions of bovine seminal vesicles and human rheumatoid synovium, and a cell-free homogenate of rabbit renal medulla, were assayed for prostaglandin synthetase activity by measuring the formation of [^{14}C]prostaglandins from [^{14}C]arachidonic acid precursor. Ether extracts of the acidified incubates were subjected to thin-layer chromatography (0·25 mm silica gel G containing 5% silver nitrate; solvent system benzene–dioxan–acetic acid (20:20:1). Formed [^{14}C]-prostaglandins and unconverted [^{14}C]arachidonic acid were located by radioactive scanning and by reference to authentic markers, scraped from the plate and measured by liquid scintillation counting.

Flurbiprofen inhibited the three different PG synthetase preparations in a dose-related manner, as did aspirin and indomethacin. The concentrations of drug necessary to produce 50% inhibition of prostaglandin biosynthesis (IC50) and their potencies expressed on a molar basis relative to aspirin are shown in Table 1. The variation observed in the relative molar potencies of the drugs between the three different PG synthetase preparations studied is in accord with the concept of synthetase isoenzymes in different tissues. Thus, whilst flurbiprofen was 300 times more active than aspirin and equipotent with indomethacin in the rabbit renal medulla preparation, it was found to be 2760 and 5600 times more potent than aspirin on bovine seminal vesicle microsomes and human rheumatoid synovial microsomes respectively—about 3 and 20 times more potent than indomethacin.

Although it would be unwise to expect the inhibition of prostaglandin biosynthesis *in vitro* to closely parallel anti-inflammatory activity *in vivo*, the finding that flurbiprofen is an extremely potent inhibitor of prostaglandin biosynthesis *in vitro* in all three preparations studied is consistent with its known anti-inflammatory activity in animal models and rheumatoid disease.

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