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Differential effects of inhibitors of cyclooxygenase (cyclooxygenase 1 and cyclooxygenase 2) in acute inflammation

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Abstract

The anti-inflammatory activity of drugs more selective for cyclooxgenase isoform inhibition (cyclooxygenase 1, cyclooxygenase 2), were compared in rat carrageenin-induced pleurisy. Suppression of inflammation by cyclooxygenase 2-selective inhibitors, NS-398 (*N*-[-2-cyclohexyloxy]-4-nitrophenyl methanesulphonamide) and nimesulide (4-nitro-2-phenoxy-methanesulfonanilide), and by piroxicam and aspirin, more selective for cyclooxygenase 1, was measured. Piroxicam and aspirin significantly inhibited inflammatory cell influx, exudate and prostaglandin E_2 formation, 6 h after carrageenin injection. Cyclooxygenase 2 inhibitors had little effect on these parameters with NS-398 alone reducing prostaglandin E_2 levels, but increasing levels of leukotriene B_4. In contrast, at 3 h after carrageenin injection, cyclooxygenase 2 inhibitors significantly inhibited all inflammatory parameters however suppression with piroxicam and aspirin was greater, and more pronounced than at 6 h. NS-398 and nimesulide dosing did not reduce thromboxane B_2 production from platelets isolated from rats with carrageenin-induced pleurisy, demonstrating that at the doses used, cyclooxygenase 2 inhibitors did not inhibit cyclooxygenase 1, as platelets contain only this isoform. Therefore, in the rat carrageenin-induced pleurisy, drugs more selective for the inhibition of cyclooxygenase 1 attenuate inflammation over a wider time frame than cyclooxygenase 2-selective drugs, suggesting a significant role for cyclooxygenase 1 in this model. Inhibition of cyclooxygenase 2 by NS-398 however, resulted in an increase in the potent chemoattractant leukotriene B_4.

Keywords: Acute inflammation; Cyclooxygenase 1; Cyclooxygenase 2; NS-398; Nimesulide; Aspirin; Piroxicam; Leukotriene B_4

1. Introduction

Prostanoid research was given added impetus in the early 1990s with the discovery of a second isoform of the enzyme cyclooxygenase (Xie et al., 1991; Kujubu and Herschman, 1992). It is now established that the constitutive isoform cyclooxygenase 1 elaborates prostaglandins involved in cytoprotection, whilst cyclooxygenase 2 is induced at the site of inflammation (Vane, 1994). Non-steroidal anti-inflammatory drugs inhibit prostaglandin formation and in vitro studies showed that drugs in common clinical use at that time were either more selective for the inhibition of cyclooxygenase 1 or cyclooxygenase 1/cyclooxygenase 2 dual inhibitors (Meade et al., 1993; Battistini et al., 1994). The ability of a drug to preferentially inhibit cyclooxygenase 1 was related to the removal of cytoprotection and damaging side effects (Bateman, 1994), suggesting that selective inhibition of cyclooxygenase 2 may be a better therapy in inflammation. A number of selective cyclooxygenase 2 inhibitors were developed that did not cause gastric lesions at doses several fold higher than required for anti-inflammatory activity in animal models (Futaki et al., 1993a; Masferrer et al., 1994). This implied that such drugs did not inhibit cyclooxygenase 1 as this isoform had been suggested to produce gastro-protective prostaglandins. Whilst these inhibitors have been carried through into clinical trials, the benefit of preferential inhibition of cyclooxygenase 2 over cyclooxygenase 1 in inflammatory states is not fully proven.

The rat carrageenin-induced pleurisy is a well tried model of acute inflammation in which conventional non-steroidal anti-inflammatory drugs have been shown over many years to reduce a wide variety of inflammatory parameters (Willoughby, 1975). The basis of the present

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study was to compare the efficacy of conventional nonsteroidal anti-inflammatory drugs more selective for cyclooxygenase 1 and known to be anti-inflammatory in this model, with selective cyclooxygenase 2 inhibitors.

In a previous publication on this pleural model, we reported that cyclooxygenase activity was maximal at 2–6 h depending upon the metabolite measured; cyclooxygenase 2 protein was present in inflammatory cells in the pleural cavity from 2 to 24 h; cyclooxygenase 2 protein was maximal at 2 h in most animals, but at 6 h in others; cyclooxygenase 1 protein was present at low levels in inflammatory cell exudates at all times, but appeared not to be altered throughout the time course (Tomlinson et al., 1994).

Six hours after intrapleural injection of carrageenin is the customary time point for evaluation of the anti-inflammatory activity of conventional nonsteroidal anti-inflammatory drugs in this model. We compared the effects of prophylactic dosing of aspirin and piroxicam, more selective for the inhibition of cyclooxygenase 1 (Mitchell et al., 1993), with *N*-[-2-cyclohexyloxy]-4-nitrophenyl methanesulphonamide (NS-398) and nimesulide, more selective for the inhibition of cyclooxygenase 2 (Futaki et al., 1994; Grossman et al., 1995), on exudate volume, inflammatory cell number and levels of prostaglandin E_2 in inflammatory exudates.

Aspirin and piroxicam significantly inhibited all three parameters, whereas the sole effect with the cyclooxygenase 2 inhibitors was the suppression of prostaglandin E_2 levels by NS-398. Protein levels of cyclooxygenase 2, as assessed by Western blotting, were shown previously to be marginally higher at 3 h than at 6 h (Tomlinson et al., 1994). Therefore, the effects of the drugs were investigated at this earlier time point.

Reduction of prostaglandin E_2 by NS-398 at 6 h after carrageenin injection did not prevent inflammatory cell trafficking and exudate formation in the pleural cavity, suggesting that the inflammation was maintained in the absence of this prostaglandin. The presence of potential alternative mediators of inflammation was investigated.

The possibility was examined, that cyclooxygenase 2 inhibitors at the doses used in this study, were inhibiting cyclooxygenase 1. Platelets contain only one isoform of cyclooxygenase, cyclooxygenase 1, therefore thromboxane B_2 production was measured in platelets isolated from animals dosed with cyclooxygenase 2 inhibitors.

2. Materials and methods

2.1. Induction of pleurisy and assessment of inflammation

Pleurisy was induced according to Velo et al. (1973), by intrapleural injection of carrageenin (0.15 ml of 1% solution in saline, Marine Colloids, WI, USA) into anaesthetised male Wistar rats (160–180 g, Tuck and Sons, Essex, UK). Inflammatory exudates were collected at 3 h and 6 h after carrageenin injection, from the pleural cavity of control and drug-treated animals ($n = 10$ per group). Exudate volumes were measured, inflammatory cells counted (Coulter counter, Coulter Electronics, Luton, UK) and aliquots of cell-free exudate were snap frozen in liquid nitrogen for determination of prostaglandin E_2 by radioimmunoassay and leukotriene B_4 by enzyme immunoassay kit (Amersham, UK).

2.2. Drugs

NS-398 (*N*-[-2-cyclohexyloxy]-4-nitrophenyl methanesulphonamide, 0.1, 1, 10 mg/kg, Alexis, Nottingham, UK); nimesulide (4-nitro-2-phenoxy-methanesulfonanilide, 0.5, 3, 5 mg/kg); aspirin (10, 100, 200 mg/kg) and piroxicam (0.1, 1, 10 mg/kg) were dosed orally in phosphate buffered saline containing 1% Tween-80, 1 h before carrageenin injection.

2.3. Preparation of platelet-rich plasma

Peripheral blood was collected by cardiac puncture, with trisodium citrate (3.15% in saline) used as an anticoagulant, from rats with carrageenin-induced pleurisy, either untreated controls or pre-dosed 1 h before car-

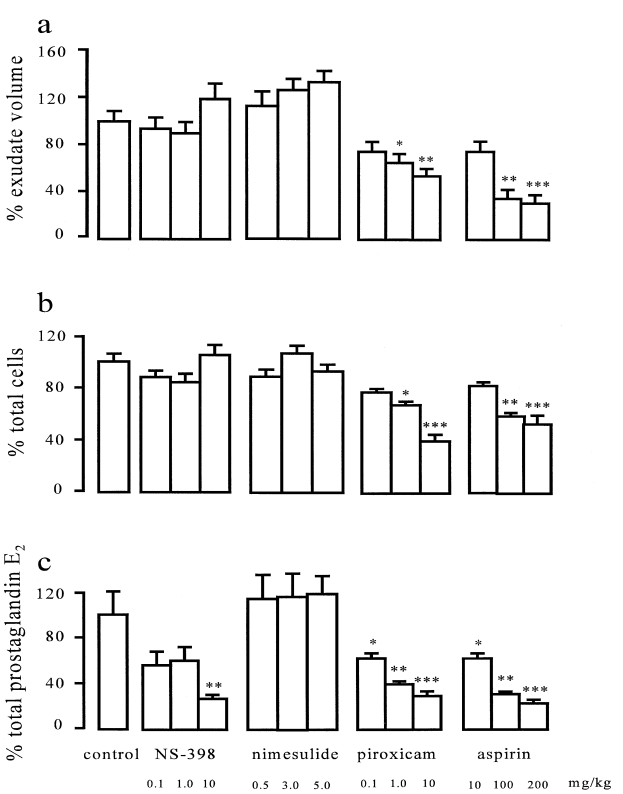

Fig. 1. The effects of piroxicam and aspirin and NS-398 and nimesulide on (a) exudate volume, (b) inflammatory cell influx and (c) prostaglandin E_2 levels in the rat carrageenin-induced pleurisy, 6 h after carrageenin injection. All drugs were dosed orally, 1 h before carrageenin injection. $n = 10$. $*\ P < 0.05$, $**\ P < 0.01$ and $***\ P < 0.001$.

rageenin injection with NS-398, nimesulide or aspirin at the doses given above ($n = 6$ per group). Samples were taken at 3 h and 6 h after injection of carrageenin, centrifuged ($180 \times g$, 10 min, 37°C), the top layer of platelet rich-plasma removed and incubated with 10 μM arachidonic acid as substrate (30 min, 37°C). The reaction was terminated by boiling (5 min) and the samples centrifuged ($10\,000 \times g$, 10 min). Supernatant levels of thromboxane B_2 were determined by radioimmunoassay.

2.4. Statistics

Statistical significance was assessed using analysis of variance and a Mann–Whitney U test with a P value of < 0.05 considered significant.

2.5. Suppliers

All supplies except where stated otherwise were obtained from Sigma (UK).

3. Results

3.1. Effects of cyclooxygenase inhibitors at 6 h after carrageenin injection

The volume of exudate and the number of inflammatory cells harvested from the pleural cavity at 6 h were significantly suppressed by both piroxicam (1, 10 mg/kg) and aspirin (100, 200 mg/kg) in comparison with controls (Fig. 1a,b).

Piroxicam and aspirin reduced exudate volumes by 31, 48% and 65, 69%, and cell numbers by 32, 60% and 41 and 47%, respectively. The lowest dose of either drug was without effect.

In contrast, NS-398 and nimesulide did not significantly alter these two parameters of inflammation at any of the doses used.

Piroxicam (0.1, 1, 10 mg/kg) significantly reduced levels of prostaglandin E_2 in cell-free exudates by 38, 62 and 71%, respectively (Fig. 1c, see Table 1 for absolute values). Prostaglandin E_2 levels were also significantly reduced by aspirin treatment; 38, 69 and 77% at 01, 100, and 200 mg/kg.

Of the two drugs with greater selectivity for cyclooxygenase 2, NS-398 significantly lowered prostaglandin E_2 levels, but only at the highest dose ($P < 0.01$), whilst nimesulide treatment had no effect on this prostaglandin.

NS-398 dosed at 30 mg/kg gave similar values to those observed with 10 mg/kg for all three inflammatory parameters, thus eliminating the possibility that a sufficiently high dose had not been used (data not shown).

3.2. Effects of cyclooxygenase inhibitors at 3 h after carrageenin injection

When the experiment detailed above was repeated at the earlier time point of 3 h, significant suppression of the inflammatory response was achieved with all the drugs.

Table 1
The effects of piroxicam and aspirin, and NS-398 and nimesulide, in the rat carrageenin-induced pleurisy, at 3 h and 6 h after carrageenin injection

	3 h			6 h		
	Total prostaglandin E_2 (ng)	Exudate volume (ml)	Total cell number ($\times 10^6$)	Total prostaglandin E_2 (ng)	Exudate volume (ml)	Total cell number ($\times 10^6$)
Control	10 ± 1.80	0.62 ± 0.05	50 ± 5.5	4.4 ± 0.90	1.27 ± 0.11	119 ± 7.0
Nimesulide						
0.5 mg/kg	3.0 ± 0.48	0.46 ± 0.07	26 ± 3.9	5.1 ± 0.90	1.42 ± 0.11	105 ± 5.2
3.0 mg/kg	2.1 ± 0.52	0.38 ± 0.05	21 ± 2.9	5.1 ± 0.96	1.59 ± 0.09	127 ± 5.5
5.0 mg/kg	1.5 ± 0.23	0.30 ± 0.05	13 ± 1.9	5.3 ± 0.70	1.68 ± 0.10	111 ± 5.2
Aspirin						
10 mg/kg	3.5 ± 0.60	0.31 ± 0.08	3.5 ± 0.6	2.8 ± 0.20	0.96 ± 0.10	98 ± 3.5
100 mg/kg	Not detected	Not detected	Not detected	1.5 ± 0.20	0.45 ± 0.10	70 ± 3.1
200 mg/kg	Not detected	Not detected	Not detected	1.0 ± 0.15	0.39 ± 0.09	63 ± 2.6
Control	9.5 ± 1.30	0.7 ± 0.15	55 ± 4.6	4.0 ± 0.85	1.30 ± 0.90	110 ± 5.5
NS-398						
0.1 mg/kg	4.7 ± 0.60	0.48 ± 0.05	23 ± 2.8	2.3 ± 0.05	1.20 ± 1.14	105 ± 6.0
1.0 mg/kg	3.1 ± 0.39	0.39 ± 0.07	17 ± 4.0	2.7 ± 0.05	1.14 ± 0.12	100 ± 8.0
10 mg/kg	1.7 ± 0.54	0.32 ± 0.06	15 ± 2.4	1.2 ± 0.15	1.51 ± 0.17	126 ± 9.0
Piroxicam						
Control	14.3 ± 1.3	0.85 ± 0.05	56 ± 0.8	6.6 ± 0.80	1.16 ± 0.03	107 ± 5.9
0.1 mg/kg	5.0 ± 0.70	0.68 ± 0.04	32 ± 5.0	4.1 ± 0.61	0.90 ± 0.04	85 ± 6.0
1.0 mg/kg	2.0 ± 0.14	0.43 ± 0.02	16 ± 1.4	2.5 ± 0.33	0.80 ± 0.05	73 ± 5.7
10 mg/kg	1.0 ± 0.08	0.13 ± 0.15	2.6 ± 0.6	1.9 ± 0.41	0.60 ± 0.05	43 ± 4.0

All drugs were dosed orally, 1 h before the injection of carrageenin. Absolute values presented as the mean of $n = 10 \pm$ standard error of the mean. Not detected = total inhibition of inflammatory parameters.

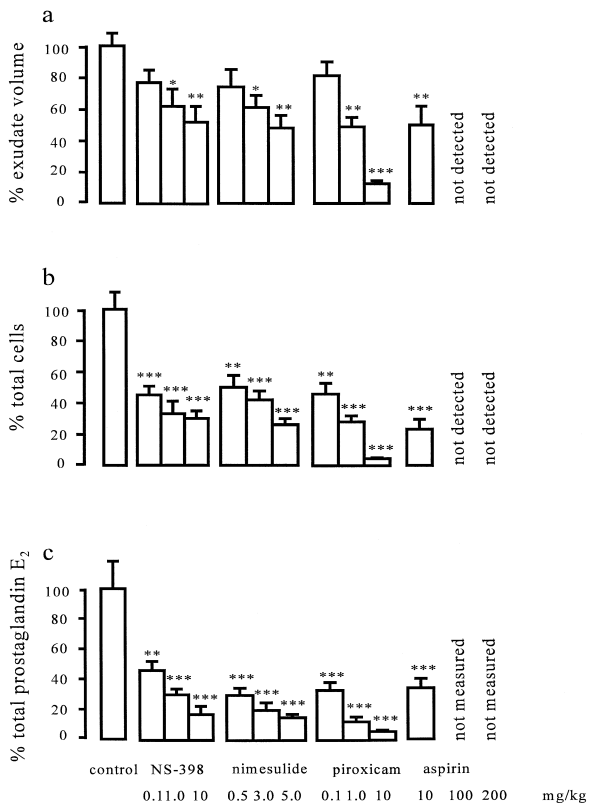

Fig. 2. The effects of piroxicam and aspirin and NS-398 and nimesulide on (a) exudate volume, (b) inflammatory cell influx and (c) prostaglandin E_2 levels, in the rat carrageenin-induced pleurisy, 3 h after carrageenin injection. All drugs were dosed orally, 1 h before carrageenin injection. Not detected indicates that the drug totally inhibited exudate formation and cell influx, thus as a result prostaglandin E_2 was not measured. $n = 10$. $* P < 0.05$, $** P < 0.01$ and $*** P < 0.001$.

NS-398 and nimesulide dose-dependently reduced exudate volume, inflammatory cell influx and levels of prostaglandin E_2. NS-398 (1, 10 mg/kg) reduced exudates by 38 and 48% and total cell numbers at all doses (Fig. 2a,b). An almost identical pattern was observed with nimesulide treatment. The cyclooxygenase 2 inhibitors also dose-dependently reduced levels of prostaglandin E_2 in pleural exudates in comparison to controls (Fig. 2c); NS-398 $P < 0.01$, 0.001, 0.001; nimesulide $P < 0.001$ at all doses.

Pleural exudates were not retrievable after aspirin treatment at 100 and 200 mg/kg, and in contrast to the 6 h time point, the lowest dose significantly inhibited exudate volume, cell number and prostaglandin levels ($P < 0.01$, 0.001, 0.001, respectively, Fig. 2a–c). Piroxicam also dose-dependently suppressed the inflammation more effectively than at the later time point (Fig. 2a–c, see Table 1 for absolute data).

3.3. Potential inflammatory mediators produced by cyclooxygenase 2 inhibition

Six hours after the induction of carrageenin pleurisy, prostaglandin E_2 levels in cell-free exudates from animals dosed with NS-398 (10 mg/kg), were significantly attenuated. However, this reduction was not accompanied by a reduction in exudate production or cell trafficking (Fig. 1a–c). Assays were performed to determine an increase in alternative mediators capable of sustaining the inflammation in the absence of prostaglandin E_2. Measurements of

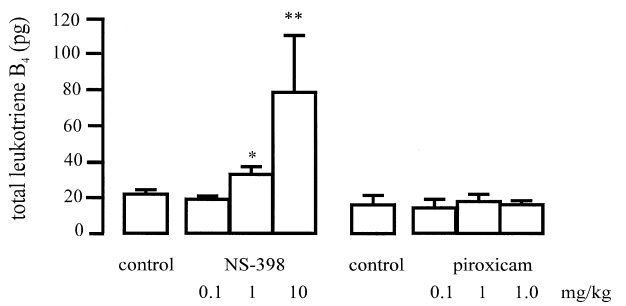

Fig. 3. The effects of piroxicam and NS-398 on leukotriene B_4 levels in the cell-free inflammatory exudate of the rat carrageenin-induced pleurisy, 6 h after carrageenin injection. All drugs were dosed orally, 1 h before carrageenin injection. $n = 10$. $* P < 0.05$ and $** P < 0.01$.

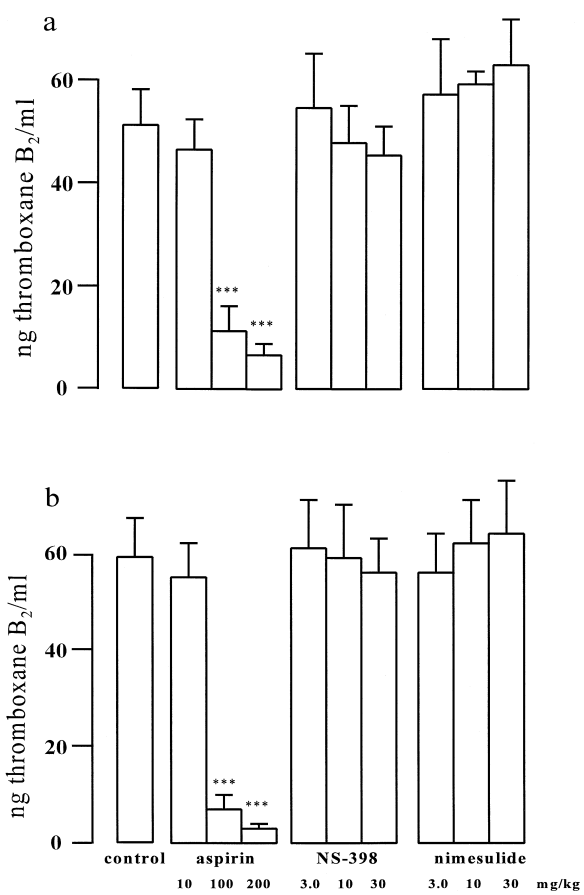

Fig. 4. The effects of aspirin, NS-398 and nimesulide on thromboxane B_2 release from platelets isolated from rats with carrageenin-induced pleurisy (a) 3 h and (b) 6 h after carrageenin injection. All drugs were dosed orally, 1 h before carrageenin injection. $n = 6$. $*** P < 0.001$.

the inducible isoform of nitric oxide synthase were unchanged by NS-398 at 6 h (data not shown). However, leukotriene production, as measured by leukotriene B_4, was dose-dependently and significantly increased after dosing with NS-398 (1, 10 mg/kg) to 30 ± 4 pg and 72 ± 29 pg respectively ($P < 0.05$, 0.01) in comparison to vehicle controls (20 ± 2 pg, Fig. 3). Piroxicam (0.1, 1.0 and 10 mg/kg) had no effect on levels of leukotriene B_4 at this time point.

3.4. Effects of cyclooxygenase inhibitors on platelet thromboxane B_2 production

Thromboxane B_2 production by platelets isolated from peripheral blood, 3 h after intrapleural injection of carrageenin, was significantly inhibited by dosing with aspirin (100, 200 mg/kg) (10 ± 4, 5 ± 2 ng/ml respectively) when compared to control samples (51 ± 6 ng/ml, Fig. 4a). A lower dose of 10 mg/kg had a minimal effect on thromboxane B_2 production (46 ± 9 ng/ml). In comparison, the cyclooxygenase 2 inhibitors NS-398 and nimesulide (3, 10, 30 mg/kg) had no effect.

A similar pattern was observed at 6 h after carrageenin injection. Aspirin (100, 200 mg/kg), reduced thromboxane B_2 production to 7 ± 3 and 3 ± 1 ng/ml respectively (Fig. 4b). In accordance with the results obtained at 3 h neither NS-398 nor nimesulide had any effect on thromboxane B_2 production.

4. Discussion

Data presented here show that in carrageenin-induced pleurisy in the Wistar rat, drugs shown in vitro to be more selective for cyclooxygenase 1, attenuate inflammation over a wider time frame than when cyclooxygenase 2 selective drugs are administered. The results of thromboxane B_2 production by platelets show that at the doses used in this study, NS-398 and nimesulide did not inhibit cyclooxygenase 1, therefore their activity may be attributable to cyclooxygenase 2 inhibition. This study also indicates that NS-398 has the capacity to significantly increase production of leukotriene B_4 in this model of acute inflammation.

The dosing levels of NS-398 used in this study are equivalent to those reported to have anti-inflammatory activity in the rat 6 day carrageenin air pouch (Masferrer et al., 1994) and in rat carrageenin-induced pleurisy (Harada et al., 1996). The doses of nimesulide chosen were reported to have anti-inflammatory activity in the rat carrageenin-induced paw edema (Magni, 1993) and in rat carrageenin-induced pleurisy (Harada et al., 1996).

In the present study, the cyclooxygenase 2 inhibitors showed little anti-inflammatory activity at 6 h. In a separate set of experiments (data not shown) NS-398 was dosed at 30 mg/kg 1 h before carrageenin injection, a 3-fold higher level than the highest dose used in this report. Additionally, both cyclooxygenase 2 inhibitors were administered 1 h before and 1 h after carrageenin injection at dosing levels used here. Both experimental regimes had no effect on exudate formation or inflammatory cell infiltrate at 6 h. NS-398 is an irreversible cyclooxygenase 2 inhibitor (Quellet and Percival, 1995) and its half life in rats dosed orally at 2 mg/kg is approximately 4 h (personal communication from Taisho Pharmaceutical, Japan). It may be argued that if an nonsteroidal anti-inflammatory drug is an irreversible cyclooxygenase 2 inhibitor, it will continue to inactivate the enzyme long after its plasma levels have reduced. Certainly, in the carrageenin induced pleurisy at 6 h, NS-398 reduced prostaglandin E_2 and increased leukotriene B_4 levels thus indicating that the drug was pharmacologically active at this time point. It was also demonstrated at this time that, at the doses used, the cyclooxygenase 2 inhibitors did not inhibit cyclooxygenase 1. Drugs shown to be more selective for cyclooxygenase 1 inhibition however did have significant anti-inflammatory activity, therefore, indicating a pro-inflammatory role for cyclooxygenase 1 at this time.

This anti-inflammatory activity of piroxicam and aspirin however, may not be attributed solely to the inhibition of cyclooxygenase 1. These drugs almost certainly have additional activity other than the inhibition of prostaglandins. Alternatively, at the doses used, they may be also inhibiting cyclooxygenase 2. Unfortunately, at present an unequivocal in vivo demonstration of cyclooxygenase 2 inhibition, comparable to thromboxane B_2 production from platelets as a measure of cyclooxygenase 1 activity, does not exist.

A number of publications have convincingly demonstrated the anti-inflammatory activity of cyclooxygenase 2 inhibitors in various animal models, but often at a single time point (Futaki et al., 1993b; Masferrer et al., 1994). However, using dexamethasone to prevent the induction of cyclooxygenase 2 in stimulated peritoneal macrophages, Wilborn et al. (1995) showed little reduction in the cellular production of prostaglandins, and concluded that cyclooxygenase 1 could account for the majority of prostaglandin release. Furthermore, investigations in cyclooxygenase 1 and cyclooxygenase 2 knockout mice, showed that topical application of triphorbol myristate acetate and arachidonic acid-induced inflammation in the rat ear, did not require cyclooxygenase 2 for these inflammatory reactions. A significant role for cyclooxygenase 1 was proposed in these models (Morham et al., 1995).

A recent publication also supporting these findings (Puignero and Queralt, 1997) reported that topical application of cyclooxygenase 2-selective inhibitors in the same two models, showed lower activity than indomethacin, a dual cyclooxygenase inhibitor.

The accumulation of data indicate, that whilst cyclooxygenase 2 inhibitors attenuate the side effects of nonsteroidal anti-inflammatory drug therapy, they may not be the panacea for inflammation, and perhaps a dual cyclo-

oxygenase 1/cyclooxygenase 2 inhibitor with improved gastric tolerance is preferable.

Nonsteroidal anti-inflammatory drug-induced asthma occurs in approximately 10% of asthmatics and one possible mechanism proposed for this phenomenon is the shunting of arachidonic acid, from the inhibited cyclooxygenase pathway, down the lipoxygenase pathway to give rise to bronchoconstrictive leukotrienes (Lee et al., 1986; Dworski et al., 1989). Leukotriene B_4, a product of the lipoxygenase pathway, is one of the most potent endogenous chemotactic factors known (Ford-Hutchinson et al., 1980; Goetzl, 1980), and leukotriene C_4 and leukotriene D_4, the peptidoleukotrienes, cause plasma exudation (Williams and Piper, 1980; Peck et al., 1981; Sugio et al., 1981).

NS-398 significantly increased levels of leukotriene B_4 in cell-free exudates 6 h after carrageenin injection whilst inhibiting prostaglandin E_2. These findings are consistent with results obtained in the cyclooxygenase 2 knockout mouse, where elevated levels of leukotriene B_4 were measured in the inflammatory exudate from a carrageenin-induced air pouch (Langenbach et al., 1996). Flosulide (CGP 28238) and L-745,337, both selective inhibitors of cyclooxygenase 2, have recently been shown to potentiate leukotriene B_4 in the triphorbol myristate acetate-induced ear inflammation in mice, but not in ear inflammation induced by arachidonic acid (Puignero and Queralt, 1997).

Thus, in this model leukotriene B_4 may be a candidate for the maintenance of inflammation in the absence of prostaglandin E_2. However, there are some reports which suggest that leukotriene B_4 is poorly chemoattractant for rat neutrophils (Zarif et al., 1996). Nevertheless, the overwhelming opinion is to the contrary as demonstrated by in vitro assays (Ford-Hutchinson, 1983) and studies using leukotriene B_4 receptor antagonists in rat inflammatory models (Fretland et al., 1990). Whether products of the 5-lipoxygenase pathway play a role in this model as a consequence of NS-398 treatment at the later time point requires further investigation.

In the present study, as nimesulide had no effect on the inflammatory parameters at 6 h, the capacity to produce leukotriene B_4 was not investigated. However conversely, nimesulide is reported to reduce leukotriene C_4 release from human basophils and mast cells isolated from lung parenchyma (Casolaro et al., 1993), and to reduce leukotriene B_4 production by polymorphonuclear neutrophils (Tool and Verhoeven, 1995). One explanation for this inconsistency is that nimesulide may also inhibit phospholipase A_2 activity and hence arachidonic acid release, thereby limiting substrate availability to the 5-lipoxygenase pathway (Fonteh et al., 1993).

Cyclooxygenase 2 inhibitors undoubtably have anti-inflammatory actions, however limited clinical trials data seems to suggest that their greatest effects are associated with pain relief and the symptoms of osteoarthritis (Hubbard et al., 1996). In addition, cyclooxygenase 1 protein is present in explanted synovial tissues and synoviocytes from patients with rheumatoid arthritis (Crofford et al., 1994). These findings, taken together with evidence from animal models of inflammation suggests that a role for the inhibition of the cyclooxygenase 1 isoform cannot be ruled out.

In summary, evidence is presented in the present study for an inflammatory role for cyclooxygenase 1 in the rat carrageenin-induced pleural model of acute inflammation. Whilst cyclooxygenase 2 inhibitors have anti-inflammatory activity in this model, drugs more selective for the inhibition of cyclooxygenase 1 attenuate inflammation over a wider time frame.

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