

Indomethacin and other NSAIDs do indeed modulate IgE-dependent late phase oedema in human skin

To the Editor,

The pathogenesis and pharmacotherapy of late phase reactions (LPR) was recently reviewed in Allergy (1). It was concluded that IgE-dependent mast cell degranulation can initiate a dual reaction, i.e. an immediate wheal and flare response (WFR) followed by an LPR-erythema and -oedema. The anti-LPR action of various compounds was listed in Table 2 and commented on in the text. Here indomethacin, given topically (cream), did not alter the late oedema formation but only reduced the intensity of the erythema up to 5 h post allergen challenge in asthmatics. It is of note that we reported a 35% inhibition of the late oedema induced by anti-human IgE over a 24 h observation period in a placebo-controlled study in healthy volunteers (6). Here, indomethacin was given as a therapeutic oral regimen 50 mg t.i.d. during and 48 h prior to skin testing. Thus, it seems that the peroral route is superior to topical administration of the drug as to anti-LPR-oedema action. This concept was further supported by our observation in the same trial of a marginal suppression of the 1-6 h induration by intradermally (i.d.) injected indomethacin.

Interestingly, enhancing effects were observed on the LPR-oedema to various dilutions of anti-IgE in 30% of the individuals. Naproxen, another non-steroid anti-inflammatory drug (NSAID), exhibited a more clear-cut anti-LPR-oedema action. Both drugs attenuated the size of the preceding flare, but not that of the wheal response. We have later reproduced the data on indomethacin and, since it seemed that NSAIDs shared the anti-LPR action in common, we extended the study to include

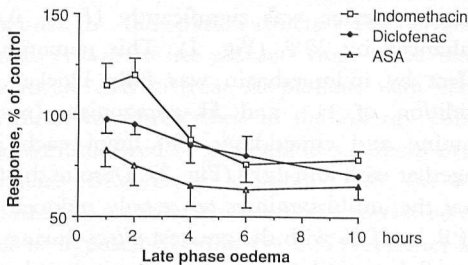


Fig. 1. Effect, (expressed as % of control, mean $\pm$ SEM) on late phase oedema induced by intradermal challenge with rabbit Fc-specific anti-IgE 1/200 v/v in human volunteers, by indomethacin (Indomec®) 50 mg $\times$ 4 (n = 18), diclofenac sodium (Voltaren®) 50 mg $\times$ 4 (n = 6) and acetylsalicylic acid (ASA) (Bamyl®) 0.5 g $\times$ 6 (n = 8). The NSAIDs were given during and 48 h prior to skin testing performed on the volar aspects of the forearms. Comparison of responses during control vs drug trials was made for unpaired observations via Student's sample test. The magnitude of the LPR-oedema during the control trials, given as the mean arithmetic diameter, was 45 mm (35-65) at 6 h and the coefficient of variation 15% at 1-24 h.

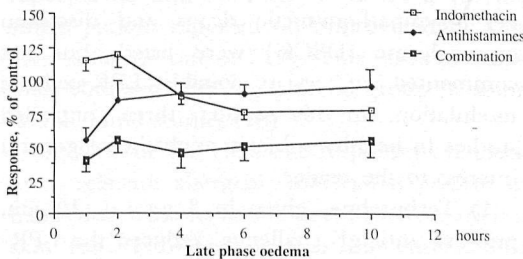


Fig. 2. Effect, expressed as % of control (means $\pm$ SEM, n = 7), of indomethacin, histamine antagonists and of the combination on late phase oedema to intradermal (i.d.) challenge with anti-IgE in volunteers. Indomethacin, 50 mg $\times$ 4, was given 48 h prior to skin testing and maintained during the experimental day. Histamine antagonists comprised mepyramine and cimetidine, in 100 nmol each i.d. injected simultaneously with anti-IgE.

diclofenac sodium and acetylsalicylic acid (ASA) (3, 4). Therapeutic regimens of these three NSAIDs carried, in analogy with our first study (6), a minor anti-flare effect (not shown) but caused an overall reduction ($P < 0.01$) of the LPR-oedema to anti-IgE over 1–10 h by 20 % (indomethacin), 30 % (diclofenac) and by 35 % (ASA) (Fig. 1). Whereas ASA and diclofenac sodium caused a uniform suppression of the LPR-oedema, indomethacin had a biphasic effect. Namely, the induration at 1–2 h after challenge was significantly ($P < 0.05$) enhanced by 20 % (Fig. 1). This potentiating effect by indomethacin was fully blocked by addition of H_1 - and H_2 -antagonists (mepyramine and cimetidine, 100 nmol each i.d. together with anti-IgE) (Fig. 2). Despite the fact that the antihistaminics *per se* only reduced the LPR by 20 % with the greatest effect during the first 2 h period the combination induced synergism. The data support an indomethacin initiated enhanced release of histamine subsequently to the initial mast cell degranulation process.

The three NSAIDs included in our experiments are cyclooxygenase inhibitors of arachidonic acid metabolism with, in the doses used, documented capacity to block *in vivo* formation of prostaglandins and thromboxanes (2). In view of this fact, our data strongly implicate that cyclooxygenase products contribute to the evolution of IgE-dependent LPR-oedema.

Finally, in Table 2 in the review by Dorsch (1) β -sympathomimetic drugs and disodium cromoglycate (DSCG) were listed, but not commented on, as to possible LPR-oedema modulation. In this context, three controlled studies in healthy subjects might be of general interest to the reader.

1) Terbutaline, given in 3 μ g i.d. 10 min prior to anti-IgE challenge, reduced the LPR-oedema up to 6 h by 20 % preceded by a 50 % suppression of the wheal response (5).

2) Further, we have just finished a similarly designed trial on formoterol, which is a novel β_2 -agonist (8) with higher potency and prolonged duration as to bronchodilation when

compared with terbutaline and salbutamol. Formoterol, injected i.d. in 20 ng 5 min before anti-IgE, reduced the early whealing and the 1–24 h LPR-oedema by 30 % (10–65) ($P < 0.001$, $n = 9$) (Grönneberg, R. & Zetterström, O., manuscript in preparation).

3) DSCG, given in 250 μ g i.d. together with anti-IgE, attenuated the 1–24 h induration by 15 % but lacked anti-WFR action (7).

Thus, provided that β -agonists and DSCG are administered in high local doses, they modulate the LPR-oedema.

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