NSAIDs

Can NSAIDs and prostaglandin analogues be combined?

A Alm

This study illustrates the difficulty of sorting out basic mechanisms of action with clinical techniques

When the prostaglandin analogues were introduced a frequently asked question was would the use of an oral non-steroid anti-inflammatory drug (NSAID) blunt the effect of prostaglandin analogues on intraocular pressure (IOP)? Prostaglandins act directly on the prostanoïd receptor, and NSAIDs exert their effect through inhibiting production/release of prostaglandins in the tissue, one would not expect an interaction between the two drugs. Thus, combining prostaglandin analogues and an oral NSAID has never been considered a problem. Still, in this issue of *BJO*, Chiba and co-workers (p 314) report that adding a topical NSAID (bromfenac) to eyes already treated with latanoprost induces a small increase in IOP, suggesting that NSAIDs after all blunt some of the effect of latanoprost on IOP. The authors do not suggest an interaction between the two drugs, but they put forward the idea that the explanation is that part of the effect of latanoprost on IOP is mediated by a release of naturally occurring prostaglandins. Thus, the effect on IOP of latanoprost, and presumably of the other PGF_{2α} analogues, should be a combination of two effects. One is a direct effect on the FP receptor mediated by the drug and not affected by NSAIDs. The other effect is the result of the release of naturally occurring prostaglandins presumably acting on some other prostanoïd receptor. One could then expect that NSAIDs could abolish the latter part of the response. The authors conclude that the effect of NSAIDs is small and probably of little clinical significance, but that the results may provide information on the mechanism of action of latanoprost.

Obviously, the knowledge that prostaglandins have marked effects on IOP raised the question about a possible physiological role of endogenous prostaglandins in aqueous humour dynamics. They do not seem to be involved in the normal regulation of IOP. Levels of PGF_{2α} and PGE₂ in aqueous are very low¹ and systemic

administration of indomethacin or acetyl salicylic acid has no effect on IOP in normal or glaucomatous eyes.^{2,3} It is quite possible that the major role of endogenous prostaglandins is a pathophysiological one rather than a physiological one. In eyes with inflammatory changes in the trabecular meshwork increased uveoscleral flow may become an important outflow route, ridding the eye of excess proteins and maintaining the IOP.⁴

This is a hypothesis that has to be tested in further studies before it can be accepted

The current understanding of the mechanism of action of PGF_{2α} and its analogues is based on a large number of studies in vitro and in vivo. Most, if not all, of the effect on IOP is mediated by the prostanoïd FP receptor and is caused by an increase in uveoscleral flow.⁵⁻⁷ Early studies on human eyes were performed with PGF_{2α} isopropylester.⁸ This drug was abandoned because the side effects were too pronounced. Thus, the development of latanoprost was to a large extent a search for an FP receptor agonist that was more selective than the endogenous prostaglandins, including PGF_{2α}.⁹ Obviously, that advantage would be lost if there is a substantial release of endogenous prostaglandins. In fact, the modification of the molecule seems to have been remarkably effective in terms of receptor selectivity. While topical application of PGF_{2α} causes increased vascular permeability in the anterior segment of the primate eye no such effect was observed with latanoprost,¹⁰ and neither acute nor chronic use of latanoprost induces a measurable flare in normal human eyes.¹¹⁻¹³ The FP receptor is not involved in these ocular side effects. Thus, ocular irritation, hyperaemia, and increased vascular permeability were all seen with the non-selective prostaglandin agonist PGF_{2α} isopropylester but not with the FP selective agonist latanoprost.⁹ The lack of any observable effect on the eye,

outside the effect on IOP, in the study of Chiba *et al* is surprising considering the lack of receptor specificity of the endogenous prostaglandins. The study illustrates the difficulty of sorting out basic mechanisms of action with clinical techniques. The mechanism proposed by the authors would certainly have a stronger support if they could demonstrate reasonable levels of endogenous prostaglandins in the aqueous of human eyes after application of latanoprost. Flare measurements might have revealed a small change in vascular permeability to support the possibility of endogenous prostaglandin activity. Other possible explanations should be considered. A possible effect of bromfenac on IOP must be ruled out. As pointed out above, oral NSAIDs have not been found to affect IOP but bromfenac is a potent compound and topical administration may reveal effects not obvious with oral administration. Also, the possibility of a pharmacokinetic interaction between bromfenac and latanoprost eye drops should be considered. Finally, the effect on IOP of adding topical NSAIDs to latanoprost is not entirely predictable. Kashiwagi and Tsukahara reported similar results as seen in the study in this issue, in a previous study on normal eyes,¹⁴ while Costagliola *et al* recently reported that combining a topical NSAID and latanoprost induced a more marked IOP reduction than latanoprost alone.¹⁵

The mechanism of action at a cellular level of PGF_{2α} analogues has been investigated in a series of studies by Lindsey and Weinreb.⁵⁻⁷ They have convincingly demonstrated an increase in matrix metalloproteinase enzyme release from human ciliary smooth muscle in vitro. Obviously, additional mechanisms of action cannot be ruled out and clinical studies can add important clues. It has in fact been questioned if FP receptor agonists exploit the full potential of PGs as ocular hypotensive agents. Chiba and co-workers have made a serious attempt to shed more light on this possibility. They conclude that there is a small effect on IOP, besides the accepted FP mediated effect on the ciliary muscle extracellular matrix. This is, however, a hypothesis that has to be tested in further studies before it can be accepted. As they point out, the effect on IOP they observed is small and clinically unimportant. The results do not argue against the concomitant use of oral NSAID and topical prostaglandin analogues.

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