

## Leading article

# Inflammatory mediators in the oesophagus

Prostaglandins, especially PGE<sub>2</sub> and PGI<sub>2</sub>, protect the gastric mucosa. They help support the normal defence mechanisms by maintaining submucosal blood flow, stimulating bicarbonate secretion, and enhancing gastric mucus production.<sup>1</sup>

Non-steroidal anti-inflammatory drugs (NSAIDs) cause irritation, ulceration, and bleeding in the stomach,<sup>2</sup> predominantly, it is believed, by inhibiting endogenous prostaglandin synthesis. Misoprostil, a PGE<sub>1</sub> analogue, will effectively prevent NSAID damage to the gastric mucosa.<sup>3</sup>

In the oesophagus the converse is true, NSAIDs protect and prostaglandins are harmful. Several independent studies have shown that NSAIDs such as indomethacin are effective in preventing and reversing established oesophageal mucosal inflammation. This effect has been described in the cat,<sup>4-7</sup> opossum,<sup>8-10</sup> monkey,<sup>11</sup> man,<sup>12-13</sup> rabbit,<sup>14-15</sup> and mouse<sup>16</sup> where the oesophagus has been exposed to insult in the form of acid,<sup>4-7</sup> radiation,<sup>8-12</sup> or proteolytic digestion.<sup>15</sup> These studies show a twin beneficial effect of NSAIDs in the oesophagus – there is an initial enhancement of tissue resistance to noxious stimuli followed by an anti-inflammatory effect. These observations can be explained biochemically.

Healthy oesophageal mucosa of the rabbit<sup>17-19</sup> and man<sup>20</sup> metabolise arachidonic acid predominantly via the 12-lipoxygenase pathway (Figure) to form the leukotriene 12-hydroxyeicosatetraenoic acid (12-HETE), also known as oesophagus derived lipoxygenase material (EDLM).<sup>15</sup> In an *in vivo* acid-pepsin induced model of oesophagitis in rabbits, Stein *et al*<sup>15</sup> suggested that EDLM constitutes a protective factor in the oesophageal mucosa, since its inhibition resulted in severe damage and increased permeability as measured by proton back diffusion. In the same model, indomethacin simultaneously raised mucosal resistance and EDLM activities. The enhancement of oesophageal mucosal resistance by NSAIDs therefore seems to be related to their ability to augment levels of protective EDLM, an effect resulting from the diversion of the arachidonic acid cascade away from the cyclo-oxygenase pathway and into lipoxygenase metabolism.

Healthy oesophageal mucosa contains low concentrations of prostaglandins.<sup>17-20</sup> However, very large tissue amounts of PGE<sub>2</sub> have been observed in human biopsy tissues from inflamed oesophageal mucosa.<sup>20-24</sup> In addition, prostaglandins have no protective properties in the oesophageal mucosa as shown in the rabbit,<sup>25</sup> cat,<sup>7</sup> opossum,<sup>9</sup> and man.<sup>27</sup> In the opossum model, Northway *et al*<sup>9</sup> showed that administration of a prostaglandin analogue before oesophageal insult accelerated the resultant inflammation. These observations implicate prostaglandins as inflammatory mediators in the oesophageal mucosa, a view shared by others.<sup>28-34</sup>

NSAIDs have other effects in the oesophagus. Indomethacin significantly raises lower oesophageal sphincter (LOS) pressure in dogs<sup>35</sup> and man.<sup>36-37</sup> This effect is almost certainly a result of the inhibition of oesophageal prostaglandins since PGE<sub>2</sub> induces sphincter hypotension in the opossum,<sup>38</sup> baboon,<sup>39</sup> and man.<sup>40</sup>

A competent LOS is a vital oesophageal function<sup>41</sup> since it helps prevent reflux. Patients with reflux disease and oesophagitis suffer from LOS dysfunction,<sup>42</sup> a factor largely responsible for the increased reflux episodes. Inflammation may, however, contribute to LOS incompetence. Experimental oesophagitis will adversely affect a previously

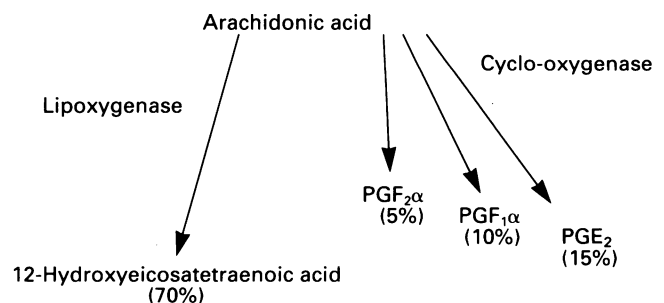
competent sphincter,<sup>42-46</sup> while inactivation of the LOS will result in severe oesophagitis.<sup>47-48</sup> These observations have clinical implications. Once oesophageal inflammation is established, the cyclic process of inflammation, diminished LOS pressure, recurrent gastroesophageal reflux, and further inflammation may continue, and prostaglandins drive this vicious circle. PGE<sub>2</sub>, which is released in high concentrations during inflammation, may act locally to reduce the LOS and thus propagate further reflux. The studies of Castell *et al*<sup>45</sup> support this hypothesis since indomethacin simultaneously restored LOS competence and removed inflammation in their experimental cat model.

Taha *et al*<sup>13</sup> conducted a large scale histological study of patients with rheumatological disorders given a variety of NSAIDs. The incidences of basal cell hyperplasia and papillary elongation were 18% and 29% respectively in 45 control subjects but 4% and 7% respectively in 53 patients given NSAIDs. Basal cell hyperplasia and papillary elongation are histological markers of oesophageal inflammation.<sup>49-50</sup> NSAID ingestion therefore seems to reduce the incidence of oesophageal mucosal inflammation. This study raises the intriguing suggestion that NSAIDs can protect the oesophagus from damage by a threefold mechanism – firstly stimulation of the LOS pressure, secondly enhancement of mucosal resistance, and thirdly an anti-inflammatory effect.

Anecdotal evidence suggests that NSAIDs damage rather than protect the oesophageal mucosa but reports of NSAID damage to the oesophagus in individual patients are uncommon<sup>51</sup> and are balanced by large studies which suggest that NSAIDs have no damaging effects.<sup>52</sup> It is very unlikely that NSAIDs do damage the oesophagus by a systemic mechanism, and any toxic effects are the result of local irritation. Factors that predispose to this include impaired peristalsis and insufficient fluid chaser or body position while swallowing.<sup>53-55</sup> Simple measures such as encouraging the patient to drink plenty of water should largely prevent this local pill induced damage.

There are therapeutic implications if NSAIDs do indeed protect the oesophageal mucosa. Low dose NSAID therapy may be helpful in severe reflux disease and in maintenance treatment. Radiation oesophagitis could be prevented by low dose indomethacin<sup>12</sup> and this treatment may be of benefit in acute caustic oesophagitis.

In summary, in contrast to the conclusive evidence that prostaglandins protect and NSAIDs damage the gastric mucosa, there is good evidence that the reverse is true in the



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oesophagus. Further, the oesophageal mucosa seems to be protected by the leukotriene 12-hydroxyeicosatetraenoic acid. The clinical use of NSAIDs in treating patients with oesophageal inflammation resulting from reflux, radiation, or caustic ingestion, could be explored further.

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