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EDITORIAL

Anti-inflammatory effects of macrolide antibiotics

P.N. Black

Several studies have demonstrated that macrolide antibiotics have anti-inflammatory actions. *In vitro*, macrolides have been shown to inhibit the proliferation of peripheral blood mononuclear cells [1], to reduce the formation of superoxide by neutrophils [2, 3] and to modify the release of cytokines [4]. Erythromycin inhibits the proliferation of peripheral blood mononuclear cells in response to phytohaemagglutinin and pokeweed mitogen [1] at concentrations of 1–100 $mg \cdot mL^{-1}$. The lower end of this range corresponds with concentrations obtained *in vivo*. Macrolides also inhibit the oxidative burst of neutrophils but these observations may not be clinically relevant. Some studies showed that roxithromycin inhibited the formation of superoxide at 10 $mg \cdot L^{-1}$ [2] whereas others only demonstrated effects at 50–100 $mg \cdot L^{-1}$ [3]. However, even the lower concentrations used in these studies exceed those found in plasma during treatment with conventional doses of roxithromycin. Treatment with roxithromycin in doses of 5 $mg \cdot kg^{-1}$ inhibits formation of interleukin-5 by mouse spleen cells [4], and these doses are comparable to those used in humans.

Animal models have been used to demonstrate anti-inflammatory effects of macrolides in the airways *in vivo*. In rat tracheal mucosa both erythromycin and roxithromycin inhibited microvascular leakage and neutrophil recruitment in response to intravenous lipopolysaccharide [5]. In mice, however, migration of neutrophils into the lung in response to aerosol inhalation with *Proteus mirabilis* was decreased by pretreatment with erythromycin [6]. Both of these studies used doses that are within the range used in humans. Macrolides have other actions which could also be potentially useful in the treatment of airway disease. Erythromycin inhibits the secretion of mucus from human airways in culture [7], and erythromycin, roxithromycin and clarithromycin have been shown to inhibit contraction of isolated human bronchial smooth muscle in response to electrical field stimulation [8].

The evidence that the anti-inflammatory actions of macrolides are useful in the treatment of asthma and other airway diseases is less well established. In 1959, KAPLAN and GOLDIN [9] reported that troleandomycin (TAO) was useful in the treatment of "infectious asthma" and led to a reduction in the amount of sputum and the requirement for medication including corticosteroids. ITKIN and MENZEL [10] also found that the use of TAO led to a marked reduction in the dose of oral corticosteroids. Similar effects were not observed with a variety of other antibiotics. They suggested that TAO could be acting by inhibiting the metabolism of corticosteroids and this was subsequently confirmed when TAO was shown to reduce the clearance of methylprednislone by 64% [11]. The unresolved question was whether or not the effects of TAO on corticosteroid metabolism accounted for all of the apparent steroid sparing effects of TAO. In uncontrolled studies, the reduction in the dose of methylprednislone with TAO was greater than would be anticipated from its effects on corticosteroid metabolism [12]. In contrast, in a double-blind controlled study, the reduction in the dose of methylprednislone at 1 year following treatment with TAO was only 39% of that seen with placebo [13].

Another way to address the question of whether or not the anti-inflammatory effects of macrolide are important in the treatment of asthma is to study patients who are not taking oral corticosteroids. Even so, there is still the possibility that macrolides such as TAO or erythromycin could exert effects by inhibiting the metabolism of inhaled corticosteroids through their effects on the CYP 3A4 (one of the cytochrome P450 enzymes). In contrast, newer macrolides such as roxithromycin and azithromycin have little or no effect on CYP 3A4 [14]. In a study with roxithromycin, treatment for 12 weeks was reported to decrease bronchial hyperresponsiveness in patients with asthma. This study, however, suffered from being opened and uncontrolled [15]. There are also anecdotal reports suggesting that roxithromycin could be useful in the treatment of asthma [16], but in the absence of double-blind, placebo controlled studies, which are not confounded by the effects of macrolides on steroid metabolism, it would be premature to assert that macrolides are useful in the treatment of asthma.

In this issue of the Journal, KOH and co-workers [17] report the effects of 12 weeks of treatment with roxithromycin in a group of children with bronchiectasis. In this double-blind, placebo controlled study they demonstrate a significant reduction in bronchial responsiveness, sputum purulence and leukocyte counts as a result of treatment with roxithromycin. Are the benefits of roxithromycin due to anti-inflammatory action? Certainly, airway inflammation is a characteristic feature of bronchiectasis. It is believed that there is a vicious cycle in bronchiectasis, where impaired clearance of mucus predisposes to infection which causes inflammation. The inflammation in turn could lead to damage to the lung and further impairment of mucociliary clearance.

Evidence for the benefit of anti-inflammatory agents in bronchiectasis comes from studies where alternate day prednisone inhibited the decline in lung function in cystic fibrosis [18]. Inhaled steroids have also been reported to reduce cough and sputum in patients with bronchiectasis [19]. The reduction in bronchial responsiveness observed by KOH and co-workers [17] may be

Dept of Medicine, University of Auckland, Private Bag 92019, Auckland, New Zealand.

a surrogate marker of an improvement in airway inflammation, but it is not clear whether these changes are due to the anti-inflammatory action of roxithromycin or an indirect consequence of its antimicrobial activity. Treatment of infection would also be expected to reduce inflammation in the airways. The findings of KOH and co-workers [17] are interesting but do not yet provide definite evidence that the anti-inflammatory effects of macrolides are important in the treatment of airways disease.

Although the study by KOH and co-workers [17] found growth of *Pseudomonas aeruginosa* in the sputum of only one patient, the effects of macrolides on *P. aeruginosa* may be of relevance in treatment of patients with bronchiectasis. Macrolides do not have direct antibacterial activity against *P. aeruginosa*, but erythromycin inhibits the release of elastase, protease, phospholipase C and exotoxin A by *P. aeruginosa* [20]. Macrolides may modify the virulence of *P. aeruginosa* and this could be useful in the treatment of patients with bronchiectasis infected with *P. aeruginosa*.

A discussion of the role of macrolides in the treatment of airways disease would not be complete without reference to the possibility that *Chlamydia pneumoniae* could have a role in the development of asthma. There are reports of individuals who developed asthma for the first time following acute infection with *C. pneumoniae* [21]. These observations have been followed by two uncontrolled studies where patients with asthma and evidence of infection with *C. pneumoniae* were treated with prolonged courses of macrolides. HAHN [22] treated 46 adults with serological evidence of infection with *C. pneumoniae* and a mean duration of symptoms of 5.5 years. Twenty five of the subjects were said to have a major improvement or complete resolution of symptoms. In another study, 12 children were treated with macrolides after they presented to the Emergency Department with acute wheezing and *C. pneumoniae* was isolated from their nasopharynx. Nine of the 12 (eight of whom had asthma prior to their acute presentation) had a marked improvement in symptoms following eradication treatment [23]. Larger controlled studies are awaited which will confirm or refute these preliminary observations.

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