Is the pharmacology of corticosteroids in the lung modified by age?

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ABSTRACT

What we need to know

- Is the lung in older patients with asthma less responsive to inhaled and systemic corticosteroids? (While anecdotal observations suggest this may be the case, no well conducted studies document the phenomenon.)

What we need to do

- Carefully plan a clinical study to compare corticosteroid responsiveness between older people with asthma and their younger counterparts.
- Select sensitive and clinically relevant outcome variables for this study.

MJA 2005; 183: S47–S48

Anecdotal clinical observations suggest that older patients with asthma have less beneficial responses to corticosteroids than their younger counterparts. This apparent reduced sensitivity may be because of longer duration of disease, and resultant structural changes, such as remodelling, which reduce steroid responsiveness. Indeed, one study found that patients treated with a β-agonist alone for 2 years appeared to have less response to inhaled corticosteroids than patients who had begun corticosteroid therapy 2 years earlier.[1] This suggests that delayed initiation of inhaled corticosteroid treatment — often the case in older patients — decreases corticosteroid responsiveness. If reduced responsiveness to corticosteroids is indeed a function of age, it may be caused by pharmacokinetic or pharmacodynamic mechanisms.

A 1988 study found pharmacokinetic changes in response to prednisolone in 12 older people (aged 65–89 years) compared with 19 younger participants (aged 23–34 years).[2] After receiving intravenous and oral prednisolone, older participants had greater total exposure to the drug, because of diminished clearance.[2] From this study, it is possible that the systemic clearance of systemically absorbed inhaled corticosteroids may be diminished in older people, although it cannot be assumed that the clearance pathways for all corticosteroids are similarly affected. There are no published studies on the intrapulmonary deposition pharmacokinetics and systemic bioavailability of inhaled corticosteroids in older people.

There is also evidence of age-dependent pharmacodynamic changes in corticosteroid action. Rat studies comparing expression of serotonin-transporter mRNA in the midbrain between young and old rats found that dexamethasone significantly decreased mRNA expression in both age groups, but that its effect was more marked in the older rats.[3] Rat studies have also suggested age-dependent loss of hippocampal adrenocorticoid receptors, indicated by an increased basal level of circulating corticosteroids and reduced sensitivity to the dexamethasone suppression test in older rats.[4] Similarly, reduced sensitivity of the hypothalamus to corticosteroids has been found in older humans; cortisol infusion caused significantly greater feedback inhibition of adrenocorticotropic hormone in 22 healthy young individuals (aged 20–35 years), compared with 21 older individuals (aged over 65 years).[5] While the evidence for diminished responsiveness to corticosteroids at the hypothalamic level with increasing age is consistent in both rats and humans, there are no data on steroid responsiveness of receptors in other parts of the body, such as the lung.

Diminished steroid responsiveness could be due to a number of mechanisms, including a decreased number of steroid receptors, decreased affinity of steroids for their receptors, and downstream effects, such as diminished binding of the steroid-receptor complex to nuclear glucocorticoid response elements. Indeed, a study of the glucocorticoid-receptor binding affinity of peripheral blood mononuclear cells in older people found that it was lower in those with asthma than in those without asthma.[6] It was also lower in the patients with asthma who had less response to corticosteroids, compared with those with greater response.

However, it is not known whether the steroid-binding characteristics of peripheral blood mononuclear cells reflect those of target cells in the lungs. In-vitro studies of asthmatic smooth muscle cells have shown that their proliferation is not inhibited by corticosteroids.[7] This steroid insensitivity is associated with the absence of a transcription factor, the α-isoform of the cytosine-nucleotide enhancer binding protein (C/α), but it is not known whether this deficiency is related to age.

What we need to know

We need to know whether the response to corticosteroids, both inhaled and given systemically, is reduced in older patients with asthma compared with their younger counterparts. If this is shown to be the case, we need to know whether it is due to altered intrapulmonary distribution of the inhaled drug, diminished uptake into target cells within the lungs, or relative "resistance" of the target cell.

While there is convincing evidence that corticosteroid receptors in the hypothalamus become less responsive with increasing age, it is unknown whether the same occurs in steroid receptors elsewhere in the body, such as inflammatory cells and other target cells in the lung. When considering inhaled corticosteroids, it is important to know whether the systemic bioavailability is greater in older people. If this is the case, it has implications for systemic consequences, such as risk factors for osteoporosis and subscapular ocular cataracts.

What we need to do

A well planned clinical study of older people with asthma is required to determine whether they have less response to corticosteroids than their younger counterparts. The selection of

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clinically relevant endpoints (eg, measurement of airway hyperresponsiveness and expired nitric oxide) is important in such clinical trials. We also need to investigate the systemic bioavailability of inhaled corticosteroids in older people, given their age-related predisposition to osteoporosis.

Finally, we should investigate the extent to which the reduced corticosteroid responsiveness of receptors in the hypothalamus is present in other relevant cells of the body, such as bone (for propensity to side effects) and inflammatory cells in the lung (with respect to efficacy).

Competing interests

The Clinical Trials Unit of the Woolcock Institute of Medical Research, of which J Paul Seale is the head, conducts clinical trials which are funded by GlaxoSmithKline, AstraZeneca, ALTANA, Amgen, Pfizer, and Accrux. He has received honoraria for educational activities from AstraZeneca, Boehringer Ingelheim, and ALTANA Pharma. He has served on advisory boards for Boehringer Ingelheim, GlaxoSmithKline, and ALTANA. He has acted as a consultant to Novartis.

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