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CORRESPONDENCE

Inhaled oxitropium bromide is currently used as the first-line therapy of patients with chronic pulmonary disease in Japan

To the Editors:

With great interest, we read the article by CAZZOLA *et al.* [1] concerning the airway responses to salmeterol in combination with another bronchodilator in patients with chronic obstructive pulmonary disease (COPD). The authors concluded that "a pretreatment with a conventional dose of oxitropium bromide (OTB) did not preclude the possibility of inducing a further bronchodilation with salbutamol in patients suffering from partially reversible COPD". Because inhaled OTB is widely used in treatment of patients with COPD in Japan [2–5], the results are clinically very important.

We basically agree with the authors that further bronchodilating responses to salbutamol were not always investigated by pretreatment with OTB in patients with COPD. However, several possibilities still exist. The dose of OTB was not sufficient to prevent a further bronchodilation to salmeterol in the patients. Unfortunately the anthropometric data were not presented in the article, so it is difficult to evaluate whether a 200 μg of OTB was appropriate to elicit a maximal bronchodilation in the patients. It has been reported that OTB produces a dose-dependent increase of forced expiratory volume in one second (FEV_1) in patients with COPD [6]. The other possibility is that the participants enrolled in the current study were asthmatic rather than stable COPD patients. Although anticholinergic drugs usually produce a greater bronchodilating response than β_2-adrenergic drugs in stable COPD patients [7], the current study contradicted that β_2-adrenergic agonists produced a better bronchodilation than anticholinergic inhalation. Because COPD is strictly differentiated from bronchial asthma in association with hyperresponsiveness to β_2-adrenergic stimulants, patients having >20% reversibility on a β-adrenergic inhalational test were not determined as stable COPD patients. In the current study patients exhibited ~48% reversibility by a β-adrenergic inhalational drug. COPD also increases in frequency with age and is found more frequently in patients aged 70–80 yrs. Thus, age effect on the bronchodilator responses to the agents may be important. Bronchodilator responses to β_2-adrenergic and/or anticholinergic inhalational drugs between younger and older patients with asthma or obstructive lung disease have been reported [3, 8, 9]. Impaired bronchodilator response to salbuterol was implicated in the elderly [9]. The age of patients in the current study, which was not mentioned in the article, may effect the airway responses to the bronchodilators.

COPD is a slow but progressive disease. The main purposes of the treatment for COPD are considered to be prevention of exacerbation of the disease, and the production of a significant bronchodilating effect to maintain lung function, and subsequently achieving a standard level of quality of life (QoL). The β_2-adrenergic agonists used to be the first-line bronchodilators for treatment of COPD. Although the current study demonstrated that an anticholinergic inhalation, OTB, did not produce a further bronchodilation with salbutamol in patients with COPD, the effects of other β_2-adrenergic agonists on airway responses to OTB may be more important. Because the pathogenesis of COPD is closely related to the bronchomotor tone, which is based on the sympathetic and parasympathetic balance [7], inhaled OTB has already been used as the first line therapy of COPD in Japan. However, many elderly patients with COPD are often untreated despite some reversibility of airways obstruction in response to the drugs. As the inhaled anticholinergic drug may well be beneficial in these individuals in terms of reducing symptoms and improving the QoL [2–5, 10], older patients with chronic airflow limitation may be treated with the inhaled anticholinergic drug alone or its combination with β_2-adrenergic agents.

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REPLY

From the authors:

We thank S. Teramoto and Y. Ouchi for the interest they have taken in our work. Their letter raises some salient points that we would like to address.

The first point of S. Teramoto and Y. Ouchi is that the dose of oxitropium bromide (OTB) we used was not sufficient to produce a further than bronchodilation to salmeterol. We must stress that in our study [1] we did not evaluate the effects of salmeterol on airway responses to OTB, but rather the effects of OTB on airway responses to salbutamol. We agree that 200 μg OTB, which is its conventional dose, might be considered an insufficient dose. In fact, it has been demonstrated that forced expiratory volume in one second (FEV_1) reached a plateau only after administration of a cumulative dose of 600 μg OTB in patients with COPD [2]. Besides, we have shown that 400 μg, but not 200 μg, OTB would approximate 50 μg salmeterol in terms of mean peak response, but salmeterol has a longer duration of action than OTB [3]. In any case, we must highlight that recent data of our group (M. Cazzola, unpublished data) seem to suggest that the inhalation of 400–600 μg OTB may be required to achieve a further bronchodilation when inadequate relief is obtained after 50 μg salmeterol, but the use of 600 μg OTB alone might obviate the need for combination therapy. Therefore, we actually trust that adequate dosing with an inhaled β-agonist or an anticholinergic agent can result in the entire possible bronchodilation (as measured by FEV_1) and may obviate the need for combination therapy. In fact, addition of a second agent does not confer great additional benefit when the doses are increased to the top of the dose–response curve and this finding is independent of the class of bronchodilator used [4, 5]. In effect, the amount of smooth muscle relaxation that can be achieved in any particular patient is limited and independent of the mechanism that induces bronchodilation [6]. Precisely, in chronic obstructive pulmonary disease (COPD) there is parenchymal destruction, which will lead to a decrease in airways size. This effect might not be totally due to intrinsic airways disease but rather by a loss of the forces that keep them open.

Their second point is the possibility that the participants enrolled in our study were asthmatic rather than stable COPD patients. We are convinced that our patients were suffering from COPD because all fulfilled the criteria proposed by the American Thoracic Society [7]. The acute improvement in flow rates of airways obstruction following the short-term administration of an inhaled bronchodilation is often used in both the clinical and research setting for distinguishing between asthma and COPD. The opinion of many researchers is that the absence of an increase in FEV_1 of at least 15% from the initial value after an inhalation of a bronchodilator excludes the diagnosis of asthma, and the presence of such a change is specific, thereby ruling out other possibilities such as COPD. However, KESTEN and REBUCK [8] demonstrated that acute responses of FEV_1 and forced vital capacity (FVC) following a standard dose of inhaled bronchodilator are neither sufficiently sensitive nor sufficiently specific to differentiate asthma from COPD purely on spirometric grounds. Moreover, there are times when the patient with asthma may have entirely normal respiratory flow rates and times when obstruction does not respond dramatically to the short-term administration of a bronchodilator [9]. We believe that the classification of patients as reversible or irreversible probably leads to significant undertreatment of patients with COPD. In fact, the implication of having irreversible airflow obstruction is that therapy will not be useful. On the contrary, many patients will respond to therapy over a longer period of time or to therapy administered with a different agent [10]. Thus, patients with irreversible COPD defined by acute improvement in FEV_1 do not have fixed airflows and may be able to benefit from bronchodilator therapy. We highlight that recent British Thoracic Society guidelines [11] for management of COPD state that spirometric values should be measured before and after an adequate dose of inhaled β_2-agonist when testing airflow reversibility and, in fact, we have used a high cumulative dose of salbutamol. In any case, it is always important to bear in mind that there is difficulty in distinguishing, with certainty, the difference between subjects with COPD who may show a degree of reversibility and those older subjects with asthma whose reversibility airflow obstruction has become more fixed. There may also be mixtures of COPD and asthma which co-exist in any one patient.

Their third point is the need to treat the older patients with chronic airflow limitation with an inhaled anticholinergic drug or in combination with β_2-adrenergic agents. Our published data do not support the assumption that elderly patients suffering from COPD are less sensitive to action of β_2-agonists. In fact, we demonstrated that salmeterol was more potent than ipratropium bromide, although our study population was expressly chosen to include aged patients [12]. We must emphasize that it has been suggested that, whilst the function of β_2-receptors may become impaired with age, their responsiveness is nonetheless well preserved. This suggestion supports our opinion. All the recent findings with long-acting β_2-agonists raise the question of whether it is still correct to consider an anticholinergic drug as the bronchodilator

therapy of first choice in the treatment of stable COPD. We [13] believe that long-acting β_2-agonists should be considered an alternative first choice option in the algorithm supplied by FERGUSON and CHERNIACK [14]. However, since those patients suffering from COPD with pre-existing cardiac arrhythmias under treatment with long-acting β_2-agonists could be at special risk of developing new arrhythmias or of aggravating pre-existing ones [15], the use of anticholinergic drugs is preferable in all COPD patients suffering from pre-existing cardiac arrhythmias and hypoxaemia, regardless of their age.

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