Effect of nebulized albuterol on circulating leukocyte counts in normal subjects


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Nebulized β2-receptor agonists may cause neutrophil demargination and result in misleading total circulating leukocyte counts (WBCs) in patients with acute bronchospasm. Varying underlying adrenergic stimulation in these patients also makes interpretation of these data difficult. This study examined the direct effect of these agents on the measured WBCs of healthy adults without evidence of bronchospasm or illness.

A prospective, blinded, randomized study of 30 healthy volunteers (aged 18-50 years) was performed in a controlled environment. Subjects were excluded if they were pregnant, had a known underlying medical disorder or have had a prior reaction to albuterol or similar medications. Participants in the study were given either a nebulized albuterol treatment or nebulized normal saline (control group). Leukocyte counts were then obtained before and after treatments. Paired data were analysed using a one-tailed t-test while considering an increase of 40% in WBCs to be significant, P=0.05, and β=0.10.

Mean leukocyte counts were 5.9 (±1.2) before treatment as compared to 6.0 (±1.3) after albuterol nebulization. Using the coefficient of variance of WBCs in normal humans as c. 50% (6000 ± 3000 cells mm⁻³) we were unable to demonstrate a significant difference in variation in post-nebulized leukocyte counts between the control group and the nebulized albuterol group.

While there is concern that the treatment of patients experiencing acute bronchospasm with β2 agonists may result in factitious elevations in peripheral leukocyte counts, we found no direct effect of these agents on measured counts in normal subjects.

Introduction

Infectious processes can precipitate an acute exacerbation of bronchospasm in patients with chronic pulmonary diseases and asthma. Therefore, it is important to identify those patients with an underlying infection in order to speed recovery and prevent re-occurrence. Many physicians continue to rely heavily on measured total circulating leukocyte counts (WBCs) as a basis for clinical decision-making (e.g. admission, further laboratory analysis, antibiotic therapy, etc.) despite evidence indicating a limited clinical usefulness of this test (1-4). Measurements of WBCs in patients with acute bronchospasm are often difficult to interpret due to the underlying adrenergic stimulation. The situation can be further complicated by the use of β2-receptor agonist (e.g. epinephrine) which cause an increase in WBCs via a demarginating effect on neutrophils and lymphocytes (5,6,7). Enberg et al. found that normal adult controls had a significantly greater increase in WBCs after treatment with epinephrine when compared to those patients with an acute asthma exacerbation treated with epinephrine (40% vs. 14%, respectively), mainly due to increased lymphocytes (8).

The use of β2-receptor agonists has revolutionized the treatment of acute airway disease via inhalation of a nebulized solution. The most widely used β2-receptor agonist, albuterol, is commonly used in the acute treatment of bronchospasm because it is efficacious and has minimal clinical systemic effects. There is concern that nebulized β2-receptor agonists may also cause neutrophil demargination and result in misleading WBC determinations. Prior studies have demonstrated varying effects of these agents on leukocyte counts in patients with bronchospasm. Shah et al. found a 3-7% increase (above pretreatment baseline) in WBCs (due mainly to neutrophils) in asthmatics presenting with acute exacerbations and treated with nebulized albuterol (9). Most recently, Vetto and Moore found no difference in WBCs before and after albuterol nebulization treatment in adults presenting with bronchospasms secondary to asthma or COPD (10). They postulated that the lack of an increase in WBCs correlates with the minimal...
The results of the current study examined the direct effect of nebulized albuterol on the measured WBCs of healthy adults without bronchospasm and under controlled conditions. If albuterol does affect measured circulating leukocyte counts this would indicate that WBCs are of limited use in clinical decision-making in patients receiving these agents (1-3). Otherwise, a negative result would support the contention that systemic absorption of inhaled albuterol using normal pharmacological doses is minimal. This would confirm the apparent lack of significant systemic effects (heart rate and blood pressure changes) associated with albuterol use, unlike those seen with many other sympathomimetic agents (8-10).

### Methods

A prospective, double-blind, randomized study of 30 healthy recruited volunteers (18-50 years old) was performed in a controlled environment. Subjects were excluded if they were pregnant, had a known underlying cardiac, pulmonary, renal, allergic, immunological, neurological or haematological disorder, or have had a prior reaction to albuterol or similar medications. In 30 study participants who meet the above criteria, a complete baseline blood count (CBC) was collected by phlebotomy (5 ml antecubitaly) immediately prior to administration of a nebulized solution. The volunteers were then randomized into treatment and control groups of 15 patients each. The treatment group received nebulized albuterol solution (2.5 mg in 3 ml of normal saline). The control group received nebulized normal saline (3 ml) only. Twenty minutes after the completion of the nebulized solution, a second CBC was collected (5 ml antecubitaly). The CBCs were sent to the clinical laboratory for routine analysis (including differentials), and the results were compared descriptively and subjected to statistical analysis. Using the coefficient of variance of WBCs in normal humans as c. 50% (6000 ± 3000 cells mm\(^{-1}\)) paired data were analysed using a one-tailed \(t\)-test while considering an increase of 40% in WBCs to be significant, \(P=0.05\), and \(\beta=0.10\).

### Results

The results of the CBC analyses for all 30 subjects are listed in Table 1. In the 15 volunteers who received albuterol, the leukocyte counts averaged 5.9 (± 1.2) cells mm\(^{-1}\) before treatment as compared to 6.0 (± 1.3) cells mm\(^{-1}\) after the nebulized therapy. In the 15 volunteers who received saline only, the leukocyte counts averaged 7.4 (± 1.5) cells mm\(^{-1}\) before treatment as compared to 7.3 (± 1.4) cells mm\(^{-1}\) after the nebulization. Statistical analysis failed to demonstrate a significant difference in the variation between the control group and the nebulized albuterol group in postnebulized leukocyte counts or their differentials.

### Conclusion

While there is concern that the treatment of patients experiencing acute bronchospasm with \(\beta_2\) agonists may result in factitious elevations in peripheral leukocyte counts, we found no direct effect of these agents on the measured WBCs or their differentials under controlled conditions.
conditions. As noted before this finding supports the contention that the systemic absorption of inhaled albuterol using normal pharmacological doses is minimal. However, adrenergic stimulation during acute bronchospasm may still result in artificially high leukocyte counts and should be considered in any clinical decision-making process.

There are several minor limitations of the study worth noting. It is uncertain if the use of the 20-min waiting period after nebulization before drawing the blood samples is optimal for determining the effect. However, the time-frame of 20 min post-nebulization should 'catch' the demarginated neutrophils and lymphocytes, as this effect is almost immediate, and is probably maximal at about 20 min (11–14).

The artificial setting of the study prohibits examining the possible synergistic effects of the albuterol with the conditions of adrenergic stimulation and haemodynamic hyperactivity. While we do not know if such a synergism actually exists, previously published clinical studies suggest that this is not an important consideration (10). Furthermore, our study was designed to dissect out the selective action of albuterol on demargination of leukocytes independent of other controlling variables.

References