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Original Article

# Standard dose of inhaled albuterol significantly increases QT dispersion compared to low dose of albuterol plus ipratropium bromide therapy in moderate to severe acute asthma attacks in children

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**Abstract**

***Background***: Beta-2 agonist therapy has previously shown to increase the QT dispersion (QTd) in asthmatic patients and increased QTd has been well documented in association with cardiac arrhythmias and sudden death. However, the data concerning the effect of low doses of beta-2 agonist therapy in combination with the anticholinergic agents to potentiate bronchodilatation on QTd in asthmatic children are limited. The objectives of this study was to investigate the changes on QTd during both the standard dose of nebulized albuterol therapy and low dose nebulized albuterol plus inhaled ipratropium therapyn to assess the potential arrhytmogenic risk of these two treatment strategies in children with acute asthmatic attacks.

***Methods***: Forty-three children with the diagnosis of moderate to severe acute asthma were enrolled in the study. Standard dose of nebulized albuterol therapy (0.15 mg/kg) were administered to 20 patients (group 1) and low dose of nebulized albuterol (0.075 mg/kg) plus nebulized ipratropium bromide therapy (250 μg/dose) were given to the remaining 23 patients (group 2). Respiratory distress score, peak expiratory flow rate, arterial blood pressure, $O_2$ saturation, serum potassium and urea nitrogen levels were studied and QT interval parameters were measured from the standard 12-lead electrocardiograms at baseline and after treatment.

***Results***: Significant improvement was achieved in respiratory distress score and peak expiratory flow rate after three dose inhalation. No significant difference was observed between the pre and post-treatment values of serum potassium, blood urea nitrogen, $O_2$ saturation and arterial blood pressure values. The evaluation of the corrected QTd (QTcd) showed that while there was no statistical difference in the pre and post-treatment values in group 2 ($30.4 \pm 3.1$ msn *vs* $32.1 \pm 3.9$ msn), QTcd was found to be significantly increased in group 1 after treatment ($29.0 \pm 3$ msn *vs* $40.6 \pm 5.1$ msn, $P < 0.0001$).

***Conclusion***: The data of the present study suggest that the increase of the QTd is more prominent with the use of a standard dose of albuterol compared to low dose albuterol plus ipratropium therapy. Therefore, it may be concluded that a low dose of albuterol plus ipratropium bromide therapy may be preferred to avoid rhythm disturbances in asthmatic children.

**Key words** albuterol, asthma, dispersion, electrocardiography, ipratropium-bromide.

It is well known that the incidence of cardiac arrhythmias was increased during the treatment of acute asthmatic attack by bronchodilators, such as albuterol or theophylline.[1] Several factors may be potentially arrhytmogenic in obstructive airway disease such as hypoxia, hypercapnia and acid-base disturbances or the use of beta-2 agonists.[2,3] Beta-2 adrenergic agonists are very effective and potential bronchodilator drugs widely used in the treatment of bronchospasm in acute asthmatic attack was shown to increase the repolarizing current.[4] In fact, in the sinus node, the beta-2 adrenoreceptor stimulation not only increases the slope of the slow diastolic depolarizing and maximum diastolic potential, but also accelerates repolarization.[5] Kiely *et al.* demonstrated that inhalation of fenoterol, a beta-2 stimulant, results in a significant increase in QT dispersion (QTd) and QTd has recently been proposed as being a more sensitive marker of repolarization abnormalities and shown to be a more specific index of arrhythmia risk.[6,7]

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Albuterol is a selective beta-2 agonist and provides bronchodilation by an inhalation route in the diagnosis and treatment of asthma.[8] In a previous study evaluating the cardiotoxic effects of continuous inhaled albuterol for bronchospasm in infants and children, Katz *et al*. reported that no significant evidence of cardiotoxicity was observed.[9] However, in another study, inhaled short acting beta-2 agonists were claimed to cause hyperexcitablity in the conduction system.[10] High dose continuous inhaled albuterol therapy was determined as a cause of tachycardia.[11] Also many studies have linked inhaled beta agonist usage with an increased risk of death from asthma.[12–14]

Ipratropium bromide is an anticholinergic aerosol used as a bronchodilator in the treatment of reversible airway disease.[15] When used concomitantly, it increases the effect and the duration for bronchodilation of albuterol.[16] Ipratropium bromide has no significant effect on cardiac vagal tone while producing an improvement on pulmonary function.[17]

As mentioned above, although beta-2 agonists therapy have previously shown to increase the QTd in asthmatic patients, the data regarding the effect of low doses of beta-2 agonist therapy or in combination of this therapy with the anticholinergic agents on QTd in asthmatic children are limited.[10,16] The aim of the present study is to investigate the changes on the corrected QTd (QTcd) both during the standard dose of nebulized albuterol therapy and low dose nebulized albuterol plus nebulized ipratropium bromide therapy to assess the potential arrhytmogenic risk of these two treatment strategies.

## Methods

### *Subjects*

Fourty-three children with moderate or severe acute asthma attacks were included in the study. The patients had been diagnosed as having asthma as they had experienced the following features: recurrent wheezing attack, positive family history for asthma or atopy, high serum IgE level, positive serum specific IgE results (Phadiatop CAP, Pharmacia, Uppsala, Sweden) and having an increase of 15% or higher on peak expiratory flow rate (PEF) value after nebulized albuterol.[8] Table 1 shows demographic and clinical characteristics of subjects.

### *Study design and protocol*

We conducted a blind, randomized and prospective study design in which the patient and physicians were masked to the treatment strategy. The protocol was approved by the Institutional Ethic Committee and informed consent was obtained from parents. The study was carried out at the pediatric emergency department.

**Table 1** Clinical characteristics of both groups of patients

| | Group 1 ($n$ = 20) | Group 2 ($n$ = 23) |
|---|---|---|
| Age (year) | 6.4 ± 2.5 | 7.6 ± 3.4 |
| Female/Male | 1.2 | 0.8 |
| Moderate AA | 17 | 19 |
| Severe AA | 3 | 4 |
| Positive FH | All | All |
| High serum IgE | All | All |
| Positive sp.-IgE | All | All |

Group 1, patients nebulized standard dose albuterol; Group 2, patients nebulized low dose albuterol plus nebulized ipratropium bromide; AA, acute asthma attack; FH, family history of asthma and/or atopy; IgE, immunoglobulin E; Sp-IgE, specific IgE.

At admission, the attacks of subjects were classified as moderate or severe due to consensus report depending on respiratory rate, heart rate, $O_2$ saturation and PEF value.[8] The patients were divided into two groups by using a simple randomization procedure. In this procedure, they had been numbered and enrolled into group 1 and group 2 sequentually. Standard dose nebulized albuterol (0.15 mg/kg, maximum 2.5 mg) was administered to group 1 and, then with an interval of 20 min 0.1 mg/kg albuterol was repeated twice. There were 20 children (nine male, 11 female; age range: 4–13, mean age: 6.4 ± 2.5) in group 1 and three of them had severe asthma. The remaining children in this group had moderate asthma. The combination of low dose nebulized albuterol (0.075 mg/kg, maximum 2.5 mg) and nebulized ipratropium bromide (250 μg) were given to group 2 and the doses were repeated as in group 1. In group 2, there were 23 children (13 male, 10 female; age range: 4–15, mean age: 7.6 ± 3.4), four with severe asthma and the remaining with moderate asthma.

Children with established cardiac and renal disease who had received treatment by a bronchodilator within the last 15 days or who were given systemic corticosteroids in the last 30 days were excluded from the study. The clinical characteristics of the cases were shown on Table 1. Heart rate, arterial blood pressure, standard 12-lead electrocardiogram (ECG), $O_2$ saturation, respiratory distress scoring and PEF were studied in all cases at baseline and also 15 min later after the third inhalation of albuterol. Children with acute asthma were followed by hospitalization.

### *QT interval measurements*

All the QT interval measurements were performed from the 12-lead standard ECG recorded at a paper speed of 50 mm/s. The QT intervals were measured from the beginning of the

**Table 2** Respiratory distress scores in acute asthma attack

| Finding | Score 0 | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| Cyanosis | Absent | Present | – | – | – | – |
| NF | Absent | Present | – | – | – | – |
| Retractions | Suprasternal | + low IC | + upper IC | – | – | – |
| Oscultation | Sibilans ST | + wheezing FO | + moderate EP | + severe EP | + decrease in RS | No RS |

NF, nasal flaring; ST, with steteschop; IC, intercostal; FO, from outside; EP, prolongation of expirium; RS, respiration sound.

inscription of the complex consisting of Q, R and S waves (QRS) to the point at which the repolarization of the ventricles (T wave) returned to the isoelectric line from the three consecutive beats. If an undulating deflection that follows the T wave (U wave) was present, the termination of the T wave was defined as the nadir between the T and U waves. Leads where the T wave ends or T wave morphology could not be clearly observed were excluded from analysis. The PR segment was taken as the baseline to solve the difficulty in identifying the end of the T wave in the presence of the segment between the end of the S wave and the beginning of the T wave (ST) abnormalities. A minimum of nine ECG leads (mean 10.2) was analyzed. The ECG's with fewer than eight measurable leads were excluded from the study.

The QTd was calculated as the difference between the longest (QTmax) and the shortest QT (QTmin) intervals recorded. The QT interval was corrected (QTc) for the heart rate by using Bazett's formula (QTc = QT/square root of R –R interval in seconds).[18] The QTcd was defined as the difference between the maximum and the minimum QTc for a given heart rate.

#### *Intraobserver variability in measurements of QTd*

Intraobserver variability in measurements of QTd was determined from blind, repeat interpretation of 15 randomly selected ECG. The mean difference between the first and second measurements of the same observer was 9.4 ± 4.2 msn and linear regression analysis yielded minimal intraobserver variation with a correlation coefficient of 0.92 ($P < 0.0005$).

#### *Oxygen saturation, respiratory distress scoring and PEF measurements*

The $O_2$ saturation was calculated at baseline conditions and at the follow-up period after the treatment by a pulse oxymeter (Nellcor NPB-195; Nellcor Puriton Bennet, Pleasanton, USA). Respiratory distress was scored at baseline and after the treatment according to the criteria as shown in Table 2. This score was adapted from Bierman *et al*. which has been previously used in childhood asthma.[19] The PEF values were also measured and calculated as the percentage of normal values recorded for every patient before by using a flowmeter (Mini-Wright, Clement Clerk, London, UK).

#### *Statistics*

Data are expressed as mean ± SD. The relation between the continuous variables was evaluated by using paired and unpaired Student's *t*-test. The SPSS statistical software package program (version 9.0) was used to perform all statistical calculations. A $P$-value $< 0.05$ was considered significant.

## Results

There was no statistically significant difference between two groups in terms of age, sex and severity of asthma (Table 1). Heart rate, arterial blood pressure, serum potassium and urea values were similar in the two groups before and after the treatment. At the end of the treatment, heart rates were increased in both groups, but the difference was not statistically significant (Table 3).

#### *$O_2$ saturation*

The mean $O_2$ saturation at baseline was similar in each group (93.6 ± 2.9% for group 1 and 92.9 ± 3.1% for group 2). At the end of the treatment, these values were increased to 97.6 ± 3.9% and 97.8 ± 2.9%, respectively, and the difference was not significant (Table 4).

#### *Distress scores and PEF*

Respiratory distress scores at baseline were 7.2 ± 2.8 for group 1 and 6.9 ± 2.1 for group 2. These values were measured 2.3 ± 0.5 and 2.8 ± 0.6 after the treatment, respectively, and the difference was not significant (Table 4). The PEF values of group 1 and group 2 were 68.1 ± 19.2 and 69.3 ± 18.9 before treatment and 89.23 ± 18 and 93.6 ± 17.5 after the treatment, respectively. No statistically significant

**Table 3** Blood pressure, heart rate, serum potassium and urea nitrogen levels and respiratory distress scores in patients within both groups

| | Group 1 | | | Group 2 | | |
|---|---|---|---|---|---|---|
| | BT | AT | *P*-value | BT | AT | *P*-value |
| Systolic blood pressure (mmHg) | 97.7 ± 13.7 | 95.2 ± 16 | NS | 100.7 ± 10.5 | 96.4 ± 11.2 | NS |
| Heart rate (beat/min) | 120 ± 30.6 | 134 ± 2.1 | NS | 129 ± 22.3 | 140 ± 23.6 | NS |
| Potassium (mg/dL) | 4.1 ± 0.6 | 3.8 ± 0.3 | NS | 4.2 ± 0.4 | 3.7 ± 0.3 | NS |
| RDS | 7.2 ± 2.8 | 2.3 ± 0.5 | < 0.05 | 6.9 ± 2.1 | 2.8 ± 0.6 | < 0.05 |
| Urea nitrogen (mg/dL) | 12.0 ± 3.4 | 10.2 ± 2.3 | NS | 13.2 ± 4.4 | 10.4 ± 2.3 | NS |

Group 1, patients nebulized standard dose albuterol; Group 2, patients nebulized low dose albuterol plus nebulized ipratropium bromide; AT, after treatment; BT, before treatment; NS, not significant; RDS, respiratory distress score.

**Table 4** Respiratory distress scores and percentage oxygen saturations in both groups

| | Group 1 | Group 2 | | Group 1 | Group 2 | |
|---|---|---|---|---|---|---|
| | BT | BT | *P*-value | AT | AT | *P*-value |
| RDS | 7.2 ± 2.8 | 6.9 ± 2.1 | NS | 2.3 ± 0.5 | 2,80,6 | NS |
| Oxygen saturation (%) | 93.6 ± 2.9 | 92.9 ± 3.1 | NS | 97.6 ± 3.9 | 97.8 ± 2.9 | NS |

Group 1, patients nebulized standard dose albuterol; Group 2, patients nebulized low dose albuterol plus nebulized ipratropium bromide; AT, after treatment; BT, before treatment; NS, not significant; RDS, respiratory distress score.

difference was found between groups (Table 4). However, a significant decrease in respiratory distress score and an increase in PEF values were observed in both groups after the treatment ($P < 0.05$) (Table 3).

### *QT interval measurements*

While no significant difference was observed between the pre and post-treatment values in QTc max, QTc min and QTcd values in group 2, QTc max and QTcd were found to be significantly increased in the standard dose albuterol group at the end of the treatment (from 367.5 ± 46.0 msn to 399.1 ± 36.3 msn, $P < 0.01$ and from 29.0 ± 4.3 msn to 40.6 ± 5.1 msn, $P < 0.0001$, respectively) (Table 5, Fig. 1).

## Discussion

It is well documented that due to their excitation effect on the cardiac conduction system, beta-2 agonist agents used in the treatment of acute asthmatic attacks frequently increase the incidence of cardiac arrhythmias.[9,10] Beta-2 agonists were also shown to cause hypoxaemia by decreasing $PaO_2$ by increasing blood through poorly ventilated areas of the lung and thereby increasing ventilation/perfusion mismatch.[20,21] The presence of hypoxaemia can also enhance the risk of rhythm disturbances.[22] In particular, patients with hypoxaemic patients may have a subclinical autonomic neuropathy that has been associated with a prolonged QTc interval and risk of ventricular arrhythmias and death.[23]

The QT interval reflects the total duration of depolarization and repolarization of ventricular muscle. The difference between the maximum and minimum QT interval measured from 12-lead ECG is called QTd. This term is used to describe the heterogeneity of ventricular repolarization and an increase in QTd has been shown to increase the risk of serious arrhythmias and sudden cardiac death.[7,24]

The effect of beta agonists on QTd in patients with chronic obstructive pulmonary disease (COPD) were investigated in a few studies. In one of them, Bremmer *et al.* observed a significant increase in QTc after inhalation of albuterol.[25] In another study reported by Kiely *et al*. it was shown that inhalation of fenoterol, a beta-2 stimulant, resulted in a significant increase in QTd.[6] They suggested that the increase in QTd might be relevant in the etiology of arrhythmias in patients with acute severe asthma where beta agonist therapy and hypoxaemia coexist. Castro *et al*. demonstrated a type of malign arrhythmia in a 27-year-old patient with severe acute asthmatic attack after inhalation of a few doses of albuterol, which resulted in cardiac arrest due to an increase in QTd.[26] In the light of these findings, beta-2 agonist therapy might not be considered completely safe in children especially with moderate or severe acute asthmatic attacks. New therapeutic regimens having a lower risk of

**Table 5** Cardiac output interval parameters (msn) in patients administered standard dose of nebulized albuterol (group 1) and low dose of nebulized albuterol plus nebulized ipratropium bromide (group 2) at baseline and at the end of treatment

| | | Pretreatment | Post-treatment | *P*-value |
|---|---|---|---|---|
| Group 1 | HR (beat/min) | 120 ± 30.6 | 134 ± 21.1 | NS |
| | QT max | 263.4 ± 32.5 | 292.2 ± 32.7 | 0.007 |
| | QT min | 235.1 ± 9.2 | 251.8 ± 26.4 | NS |
| | QTd | 30.2 ± 4 | 42.9 ± 5 | 0.0001 |
| | QTc max | 367.5 ± 46.0 | 399.1 ± 36.3 | 0.01 |
| | QTc min | 337.2 ± 43.1 | 360.4 ± 35.9 | NS |
| | QTcd | 29.0 ± 4.3 | 40.6 ± 5.1 | 0.0001 |
| Group 2 | HR (beat/min) | 129 ± 22.3 | 140 ± 23.6 | NS |
| | QT max | 266.2 ± 20.4 | 258.0 ± 18.3 | NS |
| | QT min | 242.4 ± 19.5 | 239.2 ± 19.1 | NS |
| | QTd | 23.8 ± 4.9 | 21.3 ± 3.2 | NS |
| | QTc max | 373.8 ± 21.5 | 377.1 ± 22.3 | NS |
| | QTc min | 338.2 ± 20.6 | 345.8 ± 21.5 | NS |
| | QTcd | 30.4 ± 3.1 | 32.1 ± 3.9 | NS |

HR, heart rate; NS, not significant; QTd, cardiac output (QT) dispersion; QTcd, corrected QT dispersion.

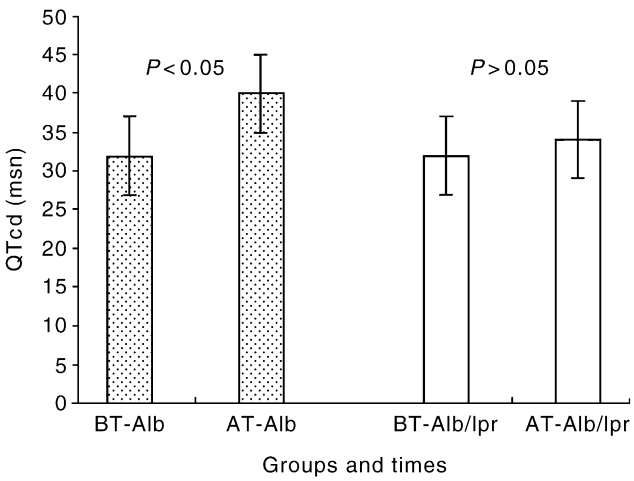


**Fig. 1** Comparison of the corrected QT dispersion (QTcd) values in both groups of before and after standard doses of albuterol versus before and after low-dose albuterol plus ipratropium therapy.

cardiac arrhythmia may be more safe. In some previous studies, it was suggested that a combination of anticholinergic with beta-2 agonist therapy could be beneficial in patients with bronchospasm and hypoxia.[27,28]

Braun *et al*. has proposed that ipratropium bromide may be useful in therapy when beta agonists are contradindicated.[29] In a study where the clinical efficacy of high doses of albuterol with low dose albuterol and ipratropium bromide in children were compared, similar improvement was observed with both therapies.[30] There was no finding in medical reviews that ipratropium bromide increases QTd.

To our knowledge this is probably the first study investigating the effect of low and standard doses of beta-2 agonist therapy in combination with an anticholinergic agent on QTcd in asthmatic children with an acute attack. With this study, we aimed to clarify the potential arrhytmogenic risk of these two treatment strategies. The main finding of our study is that while both of the treatment protocol showed similar clinical improvement in children with moderate to severe asthma, the increase of QTd was more evident in the standard dose of albuterol group. This finding is consistent with the finding of Bremmer *et al*. who also observed a significant increase in QTc after albuterol inhalation.[25] We also confirmed that ipratropium bromide has no effect on QTd in patients with moderate to severe asthma. Therefore, low doses of albuterol in combination with ipratropium bromide, to potentiate bronchodilatation and protect cardiac side-effects of albuterol, may be useful as much as standard or high doses of albuterol.

## Conclusion

The results of the present study pointed out that standard dose of nebulized albuterol therapy is associated with higher QTd compared to the low dose of nebulized albuterol plus ipratropium bromide therapy. In acute asthmatic patients with hypoxemia, inhaled therapies having less proarrhythmic risk could be chosen. For this reason, low dose of albuterol plus ipratropium bromide therapy may be preferred to avoid rhythm disturbances in acute asthmatic children.

## References

1 Sutherland DC, Wilson JD. Theophylline, beta agonist and fatal asthma. *Lancet* 1981; **2**: 988.

2 Sarubbi B, Esposito V, Duccesschi V *et al*. Effect of blood gas derangement on QTc dispersion in severe chronic obstructive pulmonary disease: evidence of an electropathy? *Int. J. Cardiol.* 1997; **58**: 287–92.
3 Conradson TB, Eklundh G, Olofsson B, Pahlm O, Persson G. Cardiac arrhythmias in patients with mild-to-moderate obstructive lung disease. Comparison of beta-agonist therapy alone and in combination with a xanthine derivative, enprofylline or theophylline. *Chest* 1985; **88**: 537–42.
4 Ben-Zvi Z, Lam C, Hoffman J, Teets-Grimn KC, Kattan M. An evaluation of initial treatment of acute asthma. *Pediatrics* 1982; **70**: 348–53.
5 Vaughan Williams EM. Cardiac electrophysiological effects of selective adrenoceptor stimulation and their possible roles in arrhythmias. *J. Cardiovasc. Pharmacol.* 1985; **7**: S61–4.
6 Kiely DG, Cargill RI, Grove A, Struthers AD, Lipworth BJ. Abnormal myocardial repolarisation in response to hypoxaemia and fenoterol. *Thorax* 1995; **50**: 1062–6.
7 Pye M, Quinn AC, Cobbe SM. QT interval dispersion: a non-invasive marker of susceptibility to arrhythmia in patients with sustained ventricular arrhythmias? *Br. Heart J.* 1994; **71**: 511–14.
8 National Asthma Education and Prevention Program. Expert Panel Report-2. Guidelines for the Diagnosis and Management of Asthma. US Department of Health and Human Service, Bethesda, 1997.
9 Katz RW, Kelly HW, Crowley MR, Grad R, McWilliams BC, Murphy SJ. Safety of continuous nebulized albuterol for bronchospasm in infants and children. *Pediatrics* 1993; **92**: 666–9.
10 Finn AF, Thompson CM, Banov CH, O'Connor BK, Case CL. Beta-2 agonist induced ventricular dysrhythmias secondary to hyperexcitable conduction system in the absence of a long OT syndrome. *Ann. Allergy Asthma Immunol.* 1997; **78**: 230–2.
11 Lin RY, Smith AJ, Hergenroeder P. High serum albuterol levels and tachycardia in adult asthmatics with high-dose continuously aerosolized albuterol. *Chest* 1993; **103**: 221–5.
12 Crane J, Pearce N, Flatt A *et al*. Prescribed fenoterol and death from asthma in New Zealand 1981–83: Case-control study. *Lancet* 1989; **1**: 917–22.
13 Pearce N, Grainger J, Atkinson M *et al*. Case-control study of prescribed fenoterol and death from asthma in New Zealand, 1977–81. *Thorax* 1990; **45**: 170–5.
14 Grainger J, Woodman K, Pearce N *et al*. Prescribed fenoterol and death from asthma in New Zealand 1981–87: A further case-control study. *Thorax* 1991; **46**: 105–11.
15 Davis A, Vickerson V, Worsley G, Mindorff C, Kazim F, Levison H. Determination of dose response relationship for nebulized ipratropium in asthmatic children. *J. Pediatr.* 1984; **105**: 1002–5.
16 Reisman J, Galdes-Sebalt M, Kazim F, Canny G, Levison H. Frequent administration by inhalation of salbutamol and ipratropium bromide in the initial management of severe acute asthma in children. *J. Allergy Clin. Immunol.* 1988; **81**: 16–20.
17 Lehrer PM, Hochron SM, Rausch L, Carr R. Effects of aerosol ipratropium bromide on cardiac vagal tone. *Chest* 1994; **105**: 1701–4.
18 Fei L, Statters DJ, Camm AJ. Q-T interval dispersion on 12 lead electrocardiogram in normal subjects. Its reproducibility and relation to the T wave. *Am. Heart J.* 1994; **127**: 1654–5.
19 Bierman CW, Pierson WE. The pharmacologic management of status asthmaticus in children. *Pediatrics* 1974; **54**: 245–7.
20 Jenne JW. Physiological actions of beta-adrenergic agonists. In: Leff AR (ed). *Pulmonary and Critical Care Pharmacology and Therapeutics*. McGraw-Hill, New York, 1996; 473–87.
21 Viegas CA, Ferrer A, Montserrat JM, Barbera JA, Roca J, Rodriguez-Roisin R. Ventilation-perfusion response after fenoterol in hypoxaemic patients with stable COPD. *Chest* 1996; **110**: 71–7.
22 Gorecka D. Cardiac arrhythmias in chronic obstructive pulmonary disease. *Monaldi Arch. Chest Dis.* 1997; **52**: 278–81.
23 Steward AG, Waterhouse JC, Howard T. The QTc interval, autonomic neuropathy and mortality in hypoxaemic COPD. *Respir. Med.* 1995; **89**: 79–84.
24 Higham PD, Campbell RW. QT dispersion. *Br. Heart J.* 1994; **71**: 508–10.
25 Bremner P, Woodman K, Burgess C *et al*. A comparison of the cardiovascular and metabolic effects of formoterol, salbutamol and fenoterol. *Eur. Respir. J.* 1993; **6**: 204–10.
26 Castro A, Pandozi C, Bianconi L, Toscano S, Santini M. Latent long QT syndrome: description of a clinical case. *G. Ital. Cardiol.* 1997; **27**: 374–9 (in Italian).
27 Hughes JA, Tobin MJ, Bellamy D, Hutchinson DC. Effects of ipratropium bromide and fenoterol aerosols in pulmonary emphysema. *Thorax* 1982; **37**: 667–70.
28 Leitch AG, Hopkin JM, Ellis DA, Merchant S, McHardy GJR. The effect of aerosol ipratropium bromide and salbutamol on exercise tolerance in chronic bronchitis. *Thorax* 1978; **33**: 711–13.
29 Braun SR, McKenzie WN, Copeland C, Knight L, Ellersieck M. A comparison of the effect of ipratropium and albuterol in the treatment of chronic obstructive airway disease. *Arch. Intern. Med.* 1989; **149**: 544–7.
30 Ducharme FM, Davis GM. Randomized controlled trial of ipratropium bromide and frequent low doses of salbutamol in the management of mild and moderate acute pediatric asthma. *J. Pediatr.* 1998; **133**: 479–85.