Concor AM Therapy in Patients with Chronic Obstructive Pulmonary Disease and Concomitant Arterial Hypertension

Nikitin VA, Gosteva EV, Mishina YV* and Vasilieva LV
Voronezh State Medical University, Russia

Abstract

Context: To date, there are very few studies regarding the eruption status of third molars in South Indian population. This study aims to analyse the eruption status of third molars and also the reasons behind their impactions.

Aim: To study the prevalence of eruption status of third molars in South Indian population.

Materials and Methods: Status of third molars was evaluated radio graphically for 150 subjects (75 males and 75 females) and the impaction status, eruption status and congenital absence of third molars were recorded.

Statistical Analysis Used: The results were analysed using chi-square test.

Results: Out of the expected number of molars in 150 patients i.e. 600, only 317 molars (52.8%) were completely erupted and 250(41.6%) failed to erupt completely and were impacted and 33(5.5%) molars were congenitally absent.

Conclusion: Third molar impactions have a mandibular predisposition. Third molar impaction showed a predilection towards females than males. Agenesis of third molars was more common in females than in males and was more common on the right side. The most common pattern of impaction was Mesioangular followed by vertical which is more common on the left side, horizontal which is common on the right side. The most commonly impacted teeth were 18 and 48.

Keywords: Bisoprolol; Amlodipine; Chronic obstructive pulmonary disease; Arterial hypertension

Abbreviations

COPD - Chronic Obstructive Pulmonary Disease; AH - Arterial Hypertension; ACE Inhibitor - Angiotensin-Converting-Enzyme Inhibitor; BP - Blood Pressure; SBP - Systolic Blood Pressure; DBP - Diastolic Blood Pressure; ABPM - Ambulatory 24-Hr Blood Pressure Monitoring; MSP - Mean Systolic Blood Pressure; MDP - Mean Diastolic Blood Pressure; PP - Pulse Pressure; MAP - Mean Arterial Pressure; TI - Time Index; BPV - Blood Pressure Variability; HRV - Heart Rate Variability; DNBPD - Degree Of Nocturnal Blood Pressure Drop

Introduction

Diseases affecting cardiovascular and respiratory systems are the most prevalent worldwide. Cardiovascular and respiratory pathological conditions also frequently coexist in modern clinical practice as they share the same risk factors and pathophysiological pathways which in turn influence treatment choices (Global Initiative for Chronic Obstructive Lung Disease, 2013) [1]. Data obtained by Caroli and Rebrov [2] demonstrated that 61.8% of COPD patients experienced concurrent cardiovascular problems. Arterial hypertension occurred among those patients at the frequency rate ranging from 6.8 to 76.3% with the mean value 34.3%. COPD was a comitant comorbidity in 28% of patients with AH [3]. According to the most researchers, low oxygen partial pressure stimulates vascular chemoreceptors thus potentiating peripheral sympathetic vasoconstriction. As AH progresses and bronchial obstruction worsens there is an increase in central alpha adrenergic activity. The COPD-induced chronic hypoxia potentiates increase in the blood pressure by inhibiting endothelial vasodilation [4,5]. Changes in the intrathoracic pressure occurring during exacerbations of bronchial obstruction are known to cause an activation of the sympathetic nervous system and subsequent vasoconstriction ultimately leading to the systemic hypertension.

Treatment of such patients remains a difficult task as coexistence of these morbidities results in a poorer overall prognosis due to a bidirectional negative impact on outcomes [6-9].

Fixed dose combination drugs are currently considered the most advanced in the correction of the hypoxia-induced endothelial damage and chronic inflammation thus preventing hemodynamic instability with subsequent target organ damage [8,9]. Beta-blockers are known to be of limited use in patients with the bronchial airway obstruction due to their negative impact on the pulmonary function tests. In patients with comorbidities (AH and chronic obstructive bronchitis) beta-blocker may worsen airway obstruction by blocking the bronchial beta-2 adrenergic receptors. Cardioselective beta-blockers were found not to cause an increased frequency of exacerbations, reduced airway function, or worsening of quality of life in COPD patients; pulmonary function tests were not altered with the use of cardioselective beta-blockers [10,11]. Cardioselective beta-blockers act precisely on beta-1 adrenergic receptors thus exhibiting the low rate of bronchial complications.

Bisoprolol is a modern highly selective beta-1 adrenoreceptor blocker which effectively controls the blood pressure during 24-hour period, reduces blood pressure variability, improves endothelial

*Corresponding author: Yuliya Vladimirovna Mishina, M.D., Ph.D., Voronezh State Medical University, Department of Propaedeutics of Internal Medicine, 394088, 31 Boulevard Pobedi 135, Voronezh, Russia, Tel: +79092138794; E-mail: jvmishina@yahoo.com

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function, does not affect carbohydrate and lipid metabolism, and does not have a negative impact on bronchial obstruction [7,12].

Calcium channel blockers are considered the drugs of choice in the treatment of AH in patients with COPD [13] as these pharmaceutical agents cause not only systemic vasodilatation but also pulmonary, as well as act as bronchodilators [7,13]. As a result of vasodilatation, these medications improve pulmonary hemodynamics and therefore the right heart function [1,14]. Calcium channel blockers preserve the target organs by preventing or delaying vascular remodelling thus reducing arterial stiffness and ultimately improving endothelial vasodilatation [2,7]. Amlodipine is the most clinically tested calcium channel blocker.

Concor AM is a new fixed dose combination drug for the treatment of AH. This agent combines cardioselective beta-blocker bisoprolol and long-acting dihydropyridine calcium channel blocker amlodipine, and is recommended for the treatment of AH by Russian Medical Organization for Arterial Hypertension [14]. Concor AM is also available in Latvia, Lithuania, Bulgaria, Germany, India, and some other countries.

The aim of the study was to evaluate the efficacy of Concor AM in COPD patients with arterial hypertension.

Materials and Methods

38 patients (26 males and 12 females) diagnosed with COPD stage II in clinical remission accompanied by concurrent AH I-II degree with the risk of cardiovascular complications 2-3 were involved in this study. The mean patient age was 57.6 ± 6.5 years. On initial evaluation all patients exhibited elevated blood pressure and symptoms of COPD in remission. The duration of COPD and AH was from 6 to 17 years, 8.5 ± 1.4 years on average. Exclusion criteria: COPD exacerbations, III degree respiratory failure, severe COPD, similar diseases - bronchial asthma, bronchiectasis, malignant tumors; chronic congestive heart failure Class III - IV (based on the New York Heart Association Functional Classification), presence of poorly controlled comorbidities with complications.

COPD was diagnosed based on clinical signs and symptoms (cough, dyspnea, sputum production), history, clinical and laboratory examination (FEV1/FVC < 70%, FEV1 on post bronchodilator test less than 80% of predicted) according to the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) by the World Health Organization, and following the guidelines of “Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease” [15]. Arterial hypertension was diagnosed based on “Recommendations for the diagnosis and management of arterial hypertension” by Russian Cardiology Organization, [16].

Before the study, hypertension in patients with AH and COPD was corrected with monotherapy by calcium antagonists (9 patients), ACE inhibitors (14 patients), diuretics (4 patients), and combination therapy with two antihypertensive medications but without beta-blockers (6 patients). The target blood pressure was not achieved in any of these patients.

The clinical blood pressure was calculated as a mean value of three measurements on each arm with the patient seated and after 5-10 min of rest. Ambulatory 24-hr blood pressure monitoring was conducted using automated portable monitor BP Lab (Russia). Regular intervals for the blood pressure measurements were set at 15 min during the daytime and at 30 min at night. Blood pressure levels < 135/85 mm Hg while the patient was awake and < 120/70 mm Hg during sleep were considered normal [16]. Parameters evaluated by ABPM included mean systolic blood pressure (MSP), mean diastolic blood pressure (MDP), pulse pressure (PP), mean arterial pressure (MAP), and heart rate at the different time points. Blood pressure load was estimated based on Time Index (TI) calculated as the percentage of systolic/diastolic blood pressures exceeding 140/90 mmHg while awake and 120/80 mmHg during sleep. BP variability (BPV) was calculated as a standard deviation from the mean values (over daytime and night-time periods), 15 mmHg for systolic BP during the day and at night, and for diastolic BP - 14 mm Hg during the day and 12 mm Hg at night [17].

Biphasic rhythm was estimated based on the degree of nocturnal BP drop (DNBPBD) or 24-hour index. 24-hour index was calculated as a subtraction of mean daytime and mean night-time BP levels expressed as a percentage of mean daytime BP (Mean Daytime BP - Mean Night-time BP/Mean Daytime BP × 100%). Based on DNBPBD and 24-hr BP curves all patients were distributed into four groups: dippers, non-dippers, over-dippers, and night-peakers [17]. Morning BP surge was calculated as a difference between the highest and the lowest BP from 4 am to 10 am. Velocity of morning BP surge was calculated as a ratio of morning BP surge to the time needed for BP elevation. Pulse pressure above 60 mm Hg was considered elevated [18].

Criteria for assessing drug efficacy were clinical BP levels (achieved target SBP < 140 and DBP < 90 mm Hg) and ABPM readings (daytime SBP 135 and DBP 85 mm Hg, and night-time SBP 120 and DBP 70 mm Hg) [16].

Quality of life was evaluated by a self-administered questionnaire based on a scale assessing frequency and severity of clinical signs and symptoms, from 0 to 4 points, 2 was reported as the highest number. 24-hr Holter monitoring was conducted according to “Cardiotechnique 4-08” standard protocol (“Inkart”, Saint Petersburg, Russia). Examined Heart Rate Variability (HRV) values included Mean NN, SDNN, SDNNi, SDANN, RMSSD, pNN50.

Echocardiography test was performed using Vivid-3 (GE) ultrasound scanner. Systolic and diastolic heart function was evaluated [18]. The velocity and direction of blood flow were studied by Doppler echocardiography and calculated as required. Left ventricular dysfunction was estimated according to [18].

Aer flow limitation was measured by spirometry - PC-based spirometer ATRDS-Pneumo ver. 4.3-9406-No-Arc56-In3 displaying the graphs “a flow-volume loop”. The following parameters were measured: Vital capacity (VC), Forced vital capacity (FVC), Forced expiratory volume in 1 second (FEV1), Tiffeneau-Pinelli index - FEV1/FVC ratio (FEV1%), Peak expiratory flow (PEF), Forced expiratory flow 25%, 50% and 75% (FEF25, FEF50 and FEF75). The test results were calculated as percent of the “predicted values” for the patients of similar characteristics (age, sex, height, and weight). The following values were considered normal: VC > 79.8% predicted, FVC > 77.9% predicted, FEV1 > 78.7% predicted, FEF25 > 85.0% predicted, PEF > 73.0% predicted, FEF25 > 68.5% predicted, FEF50 > 61.7% predicted, FEE75 > 55.0% of the predicted values.

Statistical analyses were performed using Microsoft Excell 2010 and STATISTICA version 8.0. For all tests, a two sided p value of < 0.05 was considered significant.

Results and Discussion

Concor AM (Takeda, Japan) was administered at the dose range

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from the initial 5/5 mg daily up to the highest 10/10 mg daily with 2.5/2.5 mg daily dose increments. The dose was titrated at the 2nd, 4th and 8th weeks until the target clinical BP was achieved. The duration of the study was 12 weeks. Perindopril at the dose 5 - 10 mg daily was added in case of insufficient antihypertensive effect. 34 (89.5%) patients continued treatment with Concor AM 8 weeks later. 32 (84.2%) patients treated with the drug at the average dose 7.5/10 mg daily reached goal BP. 4 individuals dropped out of study during first 8 weeks due to poor compliance with the treatment or adverse drug reactions.

The desired clinical effect was achieved after dosage was adjusted to 7.5/10 mg daily: SBP decreased in 89.3% of study subjects, DBP - in 85.8%, and hearts rate - in 98.1% of patients. Quality of life was also improved after the treatment with Concor AM as demonstrated by decreased frequency and severity of clinical manifestations reported by the study patients (Figure 1).

Statistical analysis demonstrated correlation between daily BP levels and certain clinical COPD manifestations. There was a statistically significant inverse correlation between the degree of SBP and DBP nocturnal decrease and frequency of COPD exacerbations (r = -0.36), and a direct correlation between SBP variability (r = 0.31), DBP variability (r = 0.34) and frequency of COPD exacerbations. Daily BP levels were estimated by ABPM (Table 1).

At 12th week, the mean SBP decreased by 14.4 mm Hg (p < 0.05), daytime and night-time SBP - by 14.5 mm Hg (p < 0.05) and 8.9 mm Hg, respectively. There was also a statistically significant decrease in DBP: 24-hr - by 9.3 mm Hg (p < 0.05), mean daytime - by 9.5 (p < 0.05), mean night-time - by 4.4 mm Hg (p < 0.05). Heart rate slowed significantly from 77.9 ± 4.2 to 66.8 ± 8.5 beats per min, 16.8% of the base-line.

Blood pressure load exhibited significant change after 12-week treatment with Concor AM as there was statistically significant (p < 0.05) reduction in mean 24-hr TI SBP and TI DBP (24.6% and 17.3%, respectively), as well as in mean daytime (24.5% and 18.6%) and mean night-time (24.8% and 10.1%) TI SBP and TI DBP, respectively.

Study also showed a statistically significant improvement in blood pressure variability over 12-week trial period, SBP and DBP variability measurements were restored to the normal values.

Base-line PP (85.6 ± 6.7) in the experimental cohort was moderately elevated which is associated with an unfavorable cardiovascular prognosis. Statistically significant decrease in PP (13.2 mm Hg which corresponded to 15.5% of base-line) appeared to be a positive outcome in the treatment of AH in COPD patients.

Studied patients demonstrated a moderate increase in the morning SBP and DBP surge and also in the velocity of morning DBP surge. Over 12-week treatment period with Concor AM, there was a reduction in the highest SBP and DBP values early in the morning. A significant decrease in velocity of morning SBP and DBP surge (21.7% and 31.8%, respectively) and in morning SBP and DBP surge (37%) was documented. It was also found that therapy helps restore biphasic BP rhythm raising number of patients with "a dipper" 24-hr BP profile (from 31% to 58%) and lowering the number of patients with an abnormal circadian BP variability.

These findings most likely resulted from a drug mechanism of action that affected the BP predominantly at night, especially in those patients whose nocturnal BP stayed elevated (non-dippers). As demonstrated, SBP decreased from 132.1 ± 17.3 to 125.2 ± 12.8 mm Hg at the 4th week of treatment and to 123.2 ± 14.8 mm Hg at the 12th week; and DBP - from 73.9 ± 8.9 to 70.2 ± 5.1 mm Hg at the 4th week and to 69.5 ± 1.8 mm Hg at the 12th week of therapy.

The study showed an improvement in 24-hr BP profile over course of treatment (Figure 2). Number of "dippers" increased from 31% to 58%, number of "non-dippers" decreased from 62% to 40%, and number of "night-peakers" decreased from 7% to 2%.

In order to achieve an antihypertensive effect that is evenly distributed over 24 hr the individual dose selection is required. ABPM is a valuable tool for the evaluation of patient's condition initially before the treatment and also in the treatment process to control the effectiveness of therapy. Analysis of ABPM measurements demonstrated stable long-term antihypertensive effect and significant improvement of the values with the Concor AM therapy. Study demonstrated

<table>
<thead>
<tr>
<th>Value</th>
<th>Before treatment</th>
<th>After 12-week treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 24-hr SBP, mm Hg</td>
<td>145.2 ± 16.5</td>
<td>130.8 ± 13.1*</td>
</tr>
<tr>
<td>Mean 24-hr DBP, mm Hg</td>
<td>85.7 ± 6.9</td>
<td>76.4 ± 5.8*</td>
</tr>
<tr>
<td>24-hr SBP variability, mm Hg</td>
<td>18.7 ± 4.5</td>
<td>15.8 ± 2.3*</td>
</tr>
<tr>
<td>24-hr DBP variability, mm Hg</td>
<td>15.8 ± 3.4</td>
<td>12.6 ± 2.1*</td>
</tr>
<tr>
<td>24-hr TI SBP, %</td>
<td>57.6 ± 9.5</td>
<td>33.0 ± 7.1*</td>
</tr>
<tr>
<td>24-hr TI DBP, %</td>
<td>37.1 ± 5.2</td>
<td>19.6 ± 3.8</td>
</tr>
<tr>
<td>Mean daytime SBP, mm Hg</td>
<td>149.6 ± 15.9</td>
<td>135.1 ± 12.6*</td>
</tr>
<tr>
<td>Mean daytime DBP, mm Hg</td>
<td>90.4 ± 6.2</td>
<td>80.9 ± 6.0*</td>
</tr>
<tr>
<td>Daytime SBP variability, mm Hg</td>
<td>18.0 ± 3.3</td>
<td>14.6 ± 2.3*</td>
</tr>
<tr>
<td>Daytime DBP variability, mm Hg</td>
<td>15.2 ± 3.3</td>
<td>11.3 ± 2.5</td>
</tr>
<tr>
<td>Daytime TI SBP, %</td>
<td>53.9 ± 4.5</td>
<td>29.4 ± 3.1*</td>
</tr>
<tr>
<td>Daytime TI DBP, %</td>
<td>39.4 ± 3.5</td>
<td>20.8 ± 4.2*</td>
</tr>
<tr>
<td>Mean night-time SBP, mm Hg</td>
<td>132.1 ± 17.3</td>
<td>123.2 ± 14.8</td>
</tr>
<tr>
<td>Mean night-time DBP, mm Hg</td>
<td>73.9 ± 8.9</td>
<td>69.5 ± 1.8</td>
</tr>
<tr>
<td>Night-time SBP variability, mm Hg</td>
<td>13.8 ± 6.5</td>
<td>13.1 ± 3.4</td>
</tr>
<tr>
<td>Night-time DBP variability, mm Hg</td>
<td>10.1 ± 4.8</td>
<td>9.3 ± 3.6</td>
</tr>
<tr>
<td>Night-time TI SBP, %</td>
<td>60.2 ± 8.8</td>
<td>35.4 ± 9.1*</td>
</tr>
<tr>
<td>Night-time TI DBP, %</td>
<td>25.7 ± 3.2</td>
<td>15.6 ± 3.3*</td>
</tr>
<tr>
<td>Heart Rate, bpm</td>
<td>77.9 ± 4.2</td>
<td>66.8 ± 8.5*</td>
</tr>
<tr>
<td>24-hr PP, mm Hg</td>
<td>85.6 ± 6.7</td>
<td>72.4 ± 5.7*</td>
</tr>
</tbody>
</table>

Table 1: Changes in ABPM measurements with Concor AM treatment (mean ± SD). Statistical significance - *p < 0.05. SD - standard deviation.
progressive lowering of the nocturnal BP resulted in restored circadian BP rhythm and therefore increased number of ‘dippers’. Increased risk of cardiovascular complications in patients with AH is associated with the early morning BP surge, and positive changes in the morning SBP and DBP values illustrated by the study reflect a favorable treatment outcome. Currently special attention is given to the restoration and preservation of the normal BP variability. As shown by the study, Concor AM administered to the patients with COPD decreased their SBP and DBP variability.

HRV values measured by 24-hr Holter monitoring also demonstrated a positive impact of treatment with Concor AM: Mean NN increased by 15% (p < 0.001) reflecting negative chronotropic effect of bisoprolol; SDNN increased by 10% (p < 0.05), RMSSD - by 38% (p < 0.05), pNN50 - by 118% (p < 0.05). Overall, there was a significant improvement in HRV with the administration of Concor AM. HRV values were greater improved in patients with the normal base-line HRV measurements, and those patients required the lowest daily drug dose after titration.

Echocardiography performed before the treatment detected abnormal early diastolic filling, increased blood flow velocity in atrial contraction, high E/A ratio, and prolonged isovolumic relaxation time (IVRT) in 27 (71%) patients. All patients who had diastolic dysfunction exhibited also elevated clinical SBP (150.1 ± 2.9 mm Hg) tand DBP (92.7 ± 1.8 mm Hg), and their COPD duration was longer when compared to the average group value. Positive changes were observed with Concor AM treatment as illustrated by a rising peak velocity of early diastolic filling E by 13.6% and a shortening of IVRT by 14%; there was also a falling peak velocity of late diastolic filling A by 6.6%, resulting in an increase in the early to late filling ratio E/A by 18.7% (Figure 3).

Diastolic dysfunction may precede the development of left ventricular hypertrophy, thus precipitating heart failure even if systolic heart function remains normal [12,14]. Therefore, choosing antihypertensive pharmaceutical agent that improves left ventricular diastolic function is an important factor in prevention of the congestive heart failure. As shown by the study, treatment with Concor AM improved diastolic performance of the heart with even greater long-term effect.

All patients completed pulmonary function testing (spirometry) before and after the therapy with Concor AM. No statistically significant changes were detected after 12-week treatment course (Table 2).

Post bronchiodilator test after administration of 400 mcg of salbutamol demonstrated an increase in FEV1 from 9.34% maximum to 7.68% minimum.

Overall, treatment with Concor AM was not associated with any worsening of the bronchial airflow in patients with COPD and concurrent AH, as shown by spirometry parameters that did not change significantly from the baseline.

In conclusion, the obtained data suggests that fixed dose combination agent Concor AM may be recommended for the treatment of patients with COPD and concomitant AH.

### Funding

This study was funded by the Voronezh State Medical University. The university had no influence over the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

### Competing Interests

All authors declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; any other relationships or activities that could appear to have influenced the submitted work.

### Ethical Approval

The study was conducted according to the Good Clinical Practice (GCP) guidelines and approved by the VSMA Medical Research Ethics Committee.

### References


### Table 2: Spirometry values in patients with COPD and arterial hypertension before and after treatment (mean value and 25th and 75th percentile in parenthesis).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before treatment</th>
<th>After 12 weeks of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC</td>
<td>72.74 (72.46; 77.24)</td>
<td>74.60 (69.84; 78.23)</td>
</tr>
<tr>
<td>FVC</td>
<td>66.14 (63.45; 68.65)</td>
<td>67.14 (64.32; 68.70)</td>
</tr>
<tr>
<td>FEV1</td>
<td>62.60 (58.13; 71.44)</td>
<td>64.33 (60.28; 79.44)</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>64.28 (62.26; 68.65)</td>
<td>66.28 (59.04; 6838)</td>
</tr>
<tr>
<td>PEF</td>
<td>60.46 (57.48; 62.16)</td>
<td>62.18 (59.54; 73.48)</td>
</tr>
<tr>
<td>FEF25</td>
<td>58.64 (51.38; 62.54)</td>
<td>61.91 (58.35; 65.16)</td>
</tr>
<tr>
<td>FEF50</td>
<td>44.88 (41.33; 48.26)</td>
<td>45.99 (40.24; 51.16)</td>
</tr>
<tr>
<td>FEF75</td>
<td>46.59 (42.84; 52.48)</td>
<td>48.15 (41.35; 53.84)</td>
</tr>
</tbody>
</table>

## Figure 3: Changes in Doppler indexes of diastolic function before and after Concor AM therapy.
hypertens 15: 71-77.


