International Research Journal of Pharmacy and Medical Sciences
ISSN (Online): 2581-3277

Medroxyprogesterone Acetate as a Respiratory Stimulant in Hypercapnic COPD, Postmenopausal COPD, Obesity Induced Hypoventilation, Obstructive Sleep Apnea, and Polycythemia

Nagarathna Poojary[1], Ishan Ashok Capoor[2], Manish Kundar[3]
[1]Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, PES University (formerly PES College of Pharmacy), Bangalore, Karnataka, India-560050
[2]Department of Medicine and Pulmonology, Narayana Health City, Bangalore, Karnataka, India-560099
[3]Department of Pharmacy Practice, Shree Devi College of Pharmacy, Mangalore, Karnataka, India-574142
Email address: [1]nagipoojarypgs@gmail.com, [2]drishancapoor@gmail.com, [3]manishkundar6@gmail.com

Abstract*—Respiratory failure occurs in many conditions like chronic obstructive pulmonary disease, post-menopause, obesity-induced hypoventilation, polycythemia, etc. Maintaining adequate ventilation and rescuing vital organs from oxygen deprivation are crucial. Though long-term oxygen therapy is beneficial in alleviating hypoventilation, it prolongs hospitalization, acknowledges opportunistic infections, and affects patients' mobility. Invasive and non-invasive ventilation is limited to tertiary healthcare setup. Many hormones are proposed to have a physiological role in breathing via peripheral and central pathways. Progesterone, leptin, thyroxin, and corticotropin-releasing hormones are known to have a stimulant effect on respiration. There are several respiratory stimulants currently in use but welcoming new respiratory stimulants with sufficient clinical evidence is beneficial. As to existing clinical evidence, Medroxyprogesterone acetate (MPA) not only illustrates a contraceptive role but is also involved in regulating respiratory mechanisms through central stimulation. Genomic and non-genomic mechanisms of action of MPA are widely considered. However, mechanisms affecting genioglossal muscle activity have been attributed to reducing upper airway collapsibility. Hyperventilation increased mouth occlusion pressure and increased peak inspiratory flow rate was discovered in response to medroxyprogesterone treatment. Long-term MPA therapy showed enough respiratory stimulation in various conditions like post-menopausal sleep apnea, obstructive sleep apnea, and chronic type II respiratory failure with excessive carbon dioxide retention. There is also clinical evidence of combination therapies of MPA with Acetazolamide/Chlormadinone/Estrogen/Domperidone up-righting the advantages of MPA therapy. Hence MPA can play a vital role in revamping failed respiratory mechanisms, preventing long-term oxygen therapy, and also putting a stop to extensive hospitalization.*

***Keywords*—** *Medroxyprogesterone acetate; respiratory stimulant; apnea; hypoventilation; post-menopause.*

I. INTRODUCTION

Respiratory failure is a primary care situation where the respiratory system becomes unable to perform its principal responsibility of delivering oxygen to various organs in the body. The respiratory system is comprised of two wedges: a gas exchanging organ and the pump that ventilates the lungs. Failure of these wedges by various pathological conditions leads to two types of respiratory failure based on blood gas peculiarity. They include Hypoxaemia with normocapnia or hypocapnia (Type I) and/or alveolar hypoventilation with hypercapnia (Type II).[1] In type I (Hypoxemic) respiratory failure, PaO_2<60mmHg with normal or subnormal $PaCO_2$. In this type, gas exchange is compromised at the alveolar-capillary membrane level. In type II (Hypercapnic) respiratory failure, $PaCO_2$ > 50mmHg and is because of respiratory pump failure.[2] Hypoxia and hypercapnia are contemplated to be the self-standing prognostic markers for the progression of COPD. Current treatment for respiratory failure involves long-term oxygen therapy, antibiotics, bronchodilators, corticosteroids, and supporting therapies like fluids, nutrition, physical therapy, positioning the body, and pulmonary rehabilitation.[3] History reveals the use of respiratory stimulants like direct receptor activators (ephedrine), competitive antagonism of inhibitory receptors (atropine), promotion of neurotransmitter release from presynaptic nerve terminals (ephedrine, amphetamines), inhibition of neuronal neurotransmitter reuptake (cocaine, methylphenidate), and inhibition of second messenger degradation (methylxanthines).[4] Though long-term oxygen therapy improves tissue oxygen saturation, prolonged hospitalization affects patients' quality of life. Hence more scientific works related to respiratory stimulant drugs with a long duration of action are of concern. Medroxyprogesterone Acetate (MPA) is known to have a respiratory stimulant property which is our focused area in this review. Contents are gathered by using Boolean operators (AND, OR, NOT), MeSH terms, and random search with Medroxyprogesterone, respiratory stimulant, respiratory failure, COPD, post-menopause, and apnea in online databases like PubMed, Google Scholar, guidelines, sciencedirect.com, and Cochrane websites.

II. PROGESTERONE AND ITS FUNCTIONS

Progesterone is a steroid biosynthesized from cholesterol in the corpus luteum of the ovaries in later stages of the

Nagarathna Poojary, Ishan Ashok Capoor, and Manish Kundar, "Medroxyprogesterone Acetate as a Respiratory Stimulant in Hypercapnic COPD, Postmenopausal COPD, Obesity Induced Hypoventilation, Obstructive Sleep Apnea, and Polycythemia," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 5, Issue 5, pp. 1-8, 2022.

menstrual cycle under the influence of Luteinising hormone (LH) and by the placenta during the second trimester of pregnancy. It binds to progesterone receptors which are in limited distribution in the body and found mainly in the female genitals, breast, pituitary, and central nervous system. Upon binding, progesterone receptors undergo dimerization and get attached to the progesterone receptor element (PRE) on the target gene and regulate the transcription through coactivators.[5] Progesterone circulates in the bloodstream by binding to albumin and globulin proteins. It is having a very short half-life of 5 minutes. Metabolized in the liver into sulfates and glucuronides and get excreted through urine.[6] It performs several functions in the body. Maintains pregnancy by nurturing uterine endometrial layer, acts on the secretory phase of the menstrual cycle by maturing and proliferating endometrial glands, and decreases fallopian tube motility and uterine contraction. It is hostile to sperm penetration by converting watery cervical secretions to thick, viscous, and acidic. It prepares the breast for lactation and is responsible for the release of prolactin after the delivery. Increases LDL and lowers HDL. Also, favours fat deposition by increasing lipoprotein lipase activity. Causes sodium-water retention due to mineralocorticoid action.[7] Progesterone controls the estrogenic-primed endometrial glands by decreasing the number of estrogen receptors, thus preventing endometrial cancer[8], and regulates mitosis in fully differentiated endometrial cells.[9]

III. Progestational Agents

Natural and synthetic analogues (progestins) are available in injectable, intravaginal, and oral formulations.[10] There are several classes of pregestational agents (Figure 1) that perform innumerable functions such as regulation of the menstrual cycle, treatment of dysfunctional uterine bleeding, prevention of endometrial cancer, and hyperplastic precursor lesions, and contraception.[11] Apart from its methodical tasks, progestational agents play an important role in several tissues not belonging to the reproductive system, such as breastfeeding, the cardiovascular system, central nervous system, and bones.[12]

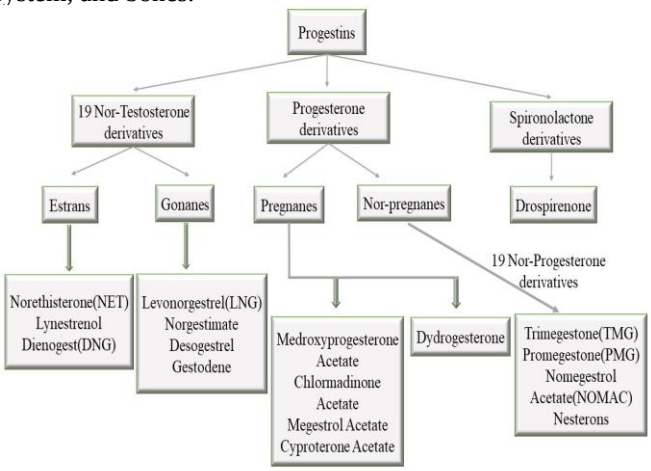

Fig. 1. Classification of synthetic progesterone (Progestins).

Progesterone has been recognized as a respiratory stimulant as well. It is known to exhibit an effective controller of arterial blood gases in respiratory failure conditions. Enlargement of the uterus during pregnancy increases intra-abdominal pressure which increases diaphragmatic breathing resulting in hyperventilation and increased tidal volume.[13] Many studies established a connection between central stimulation of Medroxyprogesterone and hyperventilation. However, the appropriate mechanism of action of medroxyprogesterone as a respiratory stimulant is still unclear.

IV. Hypercapnic COPD

Daily administration of intramuscular progesterone in oil resulted in an increase in both the total ventilation and alveolar ventilation in seven patients with severe pulmonary emphysema and two normal subjects. James H et al demonstrated that the alveolar ventilation in three out of 7 emphysematous patients was empowered by the hyper ventilatory effect of progesterone which significantly reduced carbon dioxide tension. However, this study was inconclusive as to whether progesterone has stimulated the respiratory centre.[14] J B Skatrud et al conducted a clinical study on seven healthy male adults with the administration of oral medroxyprogesterone acetate. They were able to identify the decrease in arterial $PaCO_2$ at rest and exercise within 48 hours of administration of MPA. They found that the MPA-related materials were found in lumbar cerebrospinal fluid as well as in plasma which showed hyperventilation as acclimatization to MPA. These MPA-related materials could efficiently cross Blood-Brain-Barrier (BBB) and could potentially exert their ventilatory stimulant effect by some central mechanism.[15] The author again conducted a randomized placebo-controlled study in 17 patients with chronic ventilatory failure and carbon dioxide retention in 1980 to establish the effects of MPA on the ventilatory drive and acid-base status. 4 weeks of treatment with MPA significantly reduced $PaCO_2$ with a 14% increase in mouth occlusion pressure, 11% increase in tidal volume and 15% increase in alveolar ventilation. Nevertheless, hyperventilation and an improvement in tidal volume were observed rather than breathing frequency.[16]

In 1981, J B Skatrud et al conducted a randomized placebo-controlled study in 3 normal patients and 5 patients with COPD and chronic CO_2 retention to evaluate the consequences of MPA on ventilatory control and pulmonary gas exchange during sleep. Chronic increase in inspiratory effort, tidal volume, and alveolar ventilation was established in awake and during all stages of sleep, in patients with chronic CO_2 retention despite severe mechanical impairment and maldistribution of ventilation: perfusion. MPA drives ventilation by a mechanism of action that is independent of many other peripheral and central ventilatory stimuli and/or inhibitors including higher central nervous system influences on ventilatory control that are dependent on the state of wakefulness.[17] J B Skatrud et al in 1983 supervised the effectiveness of MPA and acetazolamide in a comparative, randomized, placebo-controlled study in correcting chronic CO_2 retention during waking and sleeping states in patients with chronic obstructive airway disease resulting in significant correction of carbon dioxide retention. But the increased

Nagarathna Poojary, Ishan Ashok Capoor, and Manish Kundar, "Medroxyprogesterone Acetate as a Respiratory Stimulant in Hypercapnic COPD, Postmenopausal COPD, Obesity Induced Hypoventilation, Obstructive Sleep Apnea, and Polycythemia," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 5, Issue 5, pp. 1-8, 2022.

hydrogen ion concentration in plasma and cerebrospinal fluid by acetazolamide was not associated with ventilatory stimulation.[18]

20mg of MPA for one month in 19 COPD patients increased mean PaO_2 levels, decreased $PaCO_2$ and increased pH in a randomized, placebo-controlled study conducted by F R Dolly et al MPA also decreased the number of minutes of total sleep time when SaO_2 was less than 90% (p=0.06). Although, MPA showed marginal improvement in saturation during sleep.[19] L Delaunois et al concluded that 75 mg of medroxyprogesterone once daily for one week in 15 chronic obstructive hypercapnic patients showed a reduction in $PaCO_2$ and increased tidal volume. An increase in tidal volume is a result of greater mechanical performance due to central nervous system stimulation.[20] Randomized, double-blind, cross-over study by K Tatsumi et al in 20 COPD patients with once-daily treatment of chlormadinone acetate (CMA), potent synthetic progesterone reduced $PaCO_2$, increased minute ventilation, tidal volume, and mean inspiratory flow. Normocapnic ventilatory and occlusion pressure responses to hypoxia were increased ($p<0.01$). CMP not only augments respiratory neuromuscular response to hypercapnia but also flow resistance load compensation in patients with COPD.[21]

S Al-Damluji et al. in seven male patients with hypercapnic chronic bronchitis manifested improved arterial blood gases without changes in the degrees of airway obstruction with 20 mg of MPA three times daily for 4 weeks. There was an increase in PaO_2 and a decrease in $PaCO_2$, but these effects were achieved without changes in Peak Expiratory Flow Rate (PEFR), and Forced Expiratory Volume in one second (FEV1), or Forced Vital Capacity (FVC). However, oxygen therapy for hypercapnic patients interferes with the patient's mobility but this can be eradicated with oral administration of MPA.[22] When T. Morikawa et al. administered chlormadinone acetate (CMA), medroxyprogesterone acetate (MPA), and placebo to 16 normal male subjects using a randomized double-blind crossover study, there was an increase in alveolar ventilation and a decrease in $PaCO_2$ upon CMA and MPA administration. The author concluded that the effect of CMA on ventilation was similar to that of MPA in normal males.[23] A double-blind, placebo-controlled, cross-over trial by S Javaheri et al compared MPA 20 mg three times daily (TID) and DP (20 mg TID) alone and together in 8 healthy male human subjects for one month h showed increased alveolar ventilation (VA), and slopes of hypercapnic and hypoxic ventilatory responses with MPA and increased the slope of the hypoxic response with domperidone. The combination of MPA and DP resulted in ventilatory changes like MPA alone.[24] 20mg of Oral medroxyprogesterone three times daily for 9 weeks administered in patients with hypoventilation secondary to brainstem stroke resulting in chronic type II respiratory failure with acute onset of nausea, unsteady gait and dysphagia showed fall in $PaCO_2$ to <7 kilopascals. There was also an improvement in higher mental function, speech, and swallowing.[25]

A double-blind randomized study conducted by Michiel Wagenaar et al. in 2002 with 30mg Medroxyprogesterone three times daily and 250mg Acetazolamide twice daily for 2 weeks decreased mean daytime CO2 tension in arterial blood and improved minute ventilation. Hypercapnic and hypoxic ventilatory responses significantly increased. There was also a decrease in nocturnal end-tidal CO_2 tension with Medroxyprogesterone and Acetazolamide combination.[26] A double-blind, randomized, cross-over study conducted by Michiel Wagenaar et al. in 2003 compared 30mg of Medroxyprogesterone Acetate (MPA) twice daily with acetazolamide 250mg twice daily in stable hypercapnic COPD patients. Resting minute ventilation increased significantly only with MPA. An increase in PaO_2 and a decrease in $PaCO_2$ were observed with Acetazolamide. Mean nocturnal end-tidal carbon dioxide tension decreased with both treatments.[27] Long-term therapy with 60mg daily MPA on a cyclical basis markedly improved blood gases, morning headaches, and quality of life in a post-menopausal woman with respiratory failure due to end-stage COPD.[28]

V. Postmenopause

In the normally menstruating woman, the concentration of carbon dioxide in the alveoli is depressed during the postovulatory phase of the menstrual cycle.[29] The alveolar concentration of CO_2 will be lower in pregnant women than it was in non-pregnant women. Alveolar CO_2 tension was depressed in the luteal phase of the cycle and if pregnancy occurred this depression continued throughout gestation, rising shortly after delivery. Hyperventilation can be seen in the luteal phase of the menstrual cycle as well. This suggests that progesterone might play a role in the genesis of the decrease in alveolar CO_2 tension. Human pregnancy is characterized by significant increases in ventilatory drive both at rest and during exercise. The increased ventilation and attendant hypocapnia of pregnancy have been attributed primarily to the stimulatory effects of female sex hormones (progesterone and estrogen) on central and peripheral chemoreflex drive to breathe.[30] Men are more prone to disturbances during sleep than women, but this changes with menopause in a reverse manner, suggesting the hormone plays a protective role in women against sleep disorder breathing. Instances of snoring, sleep apnea, and dysrhythmic breathing are less in premenopausal women when compared to men and after menopause. Since progesterone is high in pre-menopausal women, it has been always thought it might have a ventilatory stimulant kind of response. In some studies, it has been also seen that progesterone has limited effect in men in terms of response to progesterone. And in some studies, it has been seen that it reduced the duration of hypopneas but not the episodes. (Oestrogen increases the progesterone receptors). In premenopausal females, endogenous progesterone stimulates leptin hormone release which is known to increase ventilation.[31] But after menopause females normally gain weight and will have a higher prevalence of sleep-disordered breathing which causes a decline in endogenous progesterone levels in the body.[32]

In post-menopausal females with respiratory impairment, MPA effectively reduced PaCO2 levels and short therapy with progestins ameliorated ventilation and improved carbon dioxide tension in arterial blood gases.[33] A placebo versus

Nagarathna Poojary, Ishan Ashok Capoor, and Manish Kundar, "Medroxyprogesterone Acetate as a Respiratory Stimulant in Hypercapnic COPD, Postmenopausal COPD, Obesity Induced Hypoventilation, Obstructive Sleep Apnea, and Polycythemia," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 5, Issue 5, pp. 1-8, 2022.

estrogen and progestin in 9 study participants were given MPA-20mg, conjugated equine estrogen1.25mg with MPA three times daily, and estrogen twice daily. The study was done for 2 weeks,7 days for placebo, and 7 days for MPA and estrogen combination. The result of the study showed estrogen + progestin showed a decrease in sleep disorder episodes from 137 to 28/night in healthy, non-obese postmenopausal women. Therefore, it concluded that a decrease in the number of apnea and hypopneas, indicating that even modest amounts of sleep-disordered breathing were improved with combined hormone treatment.[34] A Placebo-controlled single-blind trial with 14 post-menopausal women with a permanent or previous episode of hypercapnic or hypoxic respiratory failure was on 14 days of placebo and MPA 60mg/day and a 6-week follow-up. The study was conducted for 12 weeks. The study results suggest that postmenopausal women with chronic respiratory insufficiency consistently improve on MPA at a dose of 60mg daily for 14 days. Lower $PaCO_2$ is sustained for at least 3 weeks after cessation of MPA. The sustained effects in gas exchange were also noticed. Some women had withdrawal bleeding after cessation of therapy, some had a benign endometrial polyp. The initial effect of 60 mg MPA per day appears at 48 hours and maximal stimulation is achieved in 7 days. After MPA therapy for 2 weeks, the ventilatory effects subside within 14 days.[35] A pilot study on 5 women who has sleep apnea syndrome after menopause underwent 2 nights of polysomnography for baseline and returned after 3-4 weeks after taking micronized 17 beta oestradiol 2mg and 10-12 days after taking Estrogen(E2) (2mg) +MPA10 mg at bedtime. The result was that both groups showed a reduction in SAS within 1-month respiratory distress index, decreased by 25%in former and a 50% dip in the latter. They were seen to reduce SAS and increase REM sleep; this is significant because SAS tends to increase in deeper stages of sleep. Progesterone stimulates respiratory drive in the awake as shown in the luteal phase of the menstrual cycle and pregnancy.

Like progesterone, synthetic progestin like MPA also has the same effect. But this effect is minimal in post-menopausal suggesting the introduction of estrogen may help in the hypoestrogenic case. Oestrogen can increase the progesterone receptors, or it plays role in a respiratory drive by part taking insensitive structures involved in the regulation of respiration during sleep. SAS makes menopausal women at risk of sudden death and /or myocardial infarction. Sex steroids can reduce this risk.[36] Decrease in lung volumes or lean body mass, weakening of respiratory muscle capacity probably due to decreased IGF-I induced anabolic effects, and the alterations in various other hormones are also likely to compromise breathing in the elderly. MPA may increase Insulin-like growth factor-I (IGF-I) directly or indirectly through several possible mediator hormones. The IGF-I increase may also be secondary to an altered environment including improved ventilation, improved nutritional status, or improved sleep quality. Fourteen postmenopausal women with permanent or episodic hypercapnic or hypoxemic respiratory failure in a single-blinded placebo-controlled trial showed increased serum levels of IGF-I on treatment with 60 mg once daily dose of MPA for 2 weeks resulted in a decrease in PaCO2 and the increasing trend in PaO_2.[37]

Tarja Saaresranta et al conducted a placebo-controlled single-blind trial in postmenopausal females with predominantly partial upper airway obstruction during sleep with an MPA daily dose of 60mg for 14 days. The author compared the effect of MPA to that of nasal continuous positive airway pressure (nCPAP) in sleep-disordered breathing and found that there was an improvement in ventilation in post-menopausal females with partial upper airway obstruction during sleep without compromising sleep. Medroxyprogesterone acetate was more efficient in decreasing the partial pressure of carbon dioxide, but continuous positive airway pressure was superior in decreasing respiratory efforts. The ventilatory improvement was sustained for at least 3 weeks post improvement.[38] Women suffering from sleep and nocturnal breathing after menopause showed improvement in saturated levels of oxygen with MPA therapy. MPA effectively improved oxygenation and tissue carbon dioxide during REM sleep in women with moderate to severe COPD. A study conducted by Tarja Saaresranta et al demonstrated that the SaO_2 increased in 11 out of 13 patients during sleep. However, progestin therapy is gender-specific. Duration of treatment with MPA may differ between healthy individuals and those with COPD or sleep-disordered breathing. Normally, homeostatic regulatory mechanisms maintain all the functions in the body. But the respiratory centre is maintained longer in patients with respiratory impairment than in healthy individuals. The elimination rate of MPA is slow in diseased patients compared to healthy individuals. 60mg per day is divided into 3 doses daily. There is also a finding that metabolites of MPA show respiratory stimulant effects rather than MPA itself.[39]

VI. Obesity-Induceduced Hypoventilation Syndrome/Pickwick's Syndrome

Pickwickian syndrome clinically called obesity-induced hypoventilation characterized by elevated levels of carbon dioxide in the blood resulting in long-term changes in the body's health manifested as fatigue, sleepy, morning headaches, swelling, or a bluish colour in fingers, toes, or legs caused due to obesity, impaired functioning of the respiratory system, brain's inability to properly control breathing and inadequate oxygen supply to the brain, heart, and other essential organs.[40] Individuals with a body mass index (BMI) of 35 or higher are at risk for obesity hypoventilation syndrome designated as daytime hypercapnia (arterial PCO_2 greater than 45 mm Hg [5.9 kilopascals]) with the consequence of diminished ventilatory drive and capacity related to obesity (BMI over 30) in the absence of an alternate neuromuscular, mechanical or metabolic explanation for hypoventilation. The load on respiratory mechanics reflects in daytime hypercapnia in obese patients. Combination of the mechanical load on the respiratory pump leads to low tidal volumes and blunting of the chemoreflex to carbon dioxide leading to inappropriate central respiratory effort in those with marked obesity manifest with complex conditions like Sleep-disordered breathing, Impaired pulmonary mechanics, Blunted respiratory drive, Leptin resistance.[41] Continuous positive

Nagarathna Poojary, Ishan Ashok Capoor, and Manish Kundar, "Medroxyprogesterone Acetate as a Respiratory Stimulant in Hypercapnic COPD, Postmenopausal COPD, Obesity Induced Hypoventilation, Obstructive Sleep Apnea, and Polycythemia," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 5, Issue 5, pp. 1-8, 2022.

airway pressure (CPAP) or bi-level positive airway pressure (BiPAP) is considered to be the first-line treatment along with weight loss, lifestyle modifications, surgical interventions, and other pharmacological therapies.[42]

100 mg of progesterone daily by intramuscular injection increased alveolar ventilation by an additional 29.3 per cent and total minute ventilation by 20.6 per cent in a study conducted by Harold A. Lyons et al in 8 very obese patients of body weight 325 pounds. Arterial blood gas tensions and pH were returned toward normal and respiratory acidosis was abolished. Abnormal ventilatory-carbon dioxide response curves were restored to normal by progesterone therapy. It was observed that the abnormal state recurred after the withdrawal of progesterone.[43] 10 patients suffering from Pickwickian syndrome with clinical manifestations of obesity, hypoxemia, hypercapnia, polycythemia, and cor pulmonale were administered a long-term treatment of sublingual medroxyprogesterone acetate. Though there was no significant change in the weight of patients, F D Sutton Jr et al. could see a significant fall in PaCO2 and an increase in PaO2. There was no recurrence of cor pulmonale. Arterial blood gases and the clinical state of patients were found to be improved with MPA therapy. Withdrawal of MPA showed deterioration of arterial oxygen and carbon dioxide tensions to pre-treatment values. But reconstitution of MPA showed improvement.[44]

VII. OBSTRUCTIVE SLEEP APNEA

Sleep apnea is uncommon in premenopausal women but increases in prevalence after menopause. Normal hormonal function in premenopausal women is associated with a lower prevalence of sleep-disordered breathing.[45] The use of hormonal replacement therapy (HRT) has been reported to be effective in the treatment of sleep. A randomized study to contrast the prevalence of sleep-disordered breathing in a large sample of women compared with men from the general population across a wide age range (20 to 100 years) while controlling for age, obesity, and, in women, menopause, and HRT. The results of this study indicate that women have a prevalence of sleep apnea that is less than the prevalence in men. In women, it is thought that progesterone levels may play a role in protecting them from sleep apnea before menopause. Women experience an increase in the ventilatory drive during the luteal phase of the menstrual cycle when progesterone levels are the highest. Oral progesterone has been associated with a slight but definite improvement in ventilatory indices during sleep in both male and female sleep apnea patients.[46]

Obstructive Sleep Apnea (OSA) is a disorder characterized by the repetitive sleep-induced collapse of the pharyngeal airway. So pharyngeal muscle (genioglossal muscle) activity is important during wakefulness and sleep. OSA is a male predominant condition but in females, it increases after menopause. The gender difference can be because of anatomy or chemo responsiveness but it lacks evidence to demonstrate. Physiological changes in hormonal status during pregnancy and the luteal phase of the menstrual cycle cause an increase in alveolar ventilation. Hence in both cases, serum progesterone levels are elevated. So, the increase in alveolar ventilation has been attributed to this hormone. There is a significant impact of progesterone on pharyngeal muscle as opposed by some other studies. Even though there is conflicting evidence more study is required to document the exact mechanism and influence of MPA on genioglossal muscle activity. Some data show MPA affects the upper airway dilator muscle activity like estrogen and progesterone which were noted to reduce upper airway collapsibility in men. MPA is known to increase its ventilatory mechanism in hypercapnic and hypoxia in men (chemosensitivity of men citation) but the exact mechanism is unknown. Some evidence suggests a central mechanism.[47] A study on 21 individuals for one month where 11 subjects were given 30mg medroxyprogesterone and 10 received a placebo. The respiration, saturation, and electroencephalogram were taken a night before treatment and one night after treatment. In the placebo group, there were no changes in symptoms during the interval of the study that is there is no difference in baseline saturation, duration of saturation, and duration of apnea. But, in some subjects, there was an improvement in saturation and duration and the incidence of apnea decreased markedly. Since MPA has shown its respiratory stimulant effect in 7 days and initial effects at 48 hours.[48]

Hormonal change during pregnancy, postpartum period, and menstrual phase is known to alter sleep. In menopause, it causes nocturnal awakening followed by difficulty to get back to sleep is the common complaint. Some studies by sleep laboratory showed changes in sleep pre-and post-menopausal women and also those who are not taking hormone replacement therapy after menopause. The metabolite of micronized progesterone, alloprogesterone and pregnanolone which are absent in medroxyprogesterone acetate had anxiolytic and hypnotic effects. The study had two treatment groups. Group 1 received estrogen + MPA, group 2 received estrogen $_+$ oral micronized progesterone. They were studied for two nights before and after 6 months of treatment. The study showed improvement in sleep efficiency (which is defined as the time spent asleep over the recording time after sleep onset) in estrogen + micronized progesterone but not in estrogen + MPA. This result cannot be said as an effect of estrogen because a similar effect was not noted in another group even though the estrogen was present in the study. This study suggests that estrogen and micronized progesterone can ameliorate sleep disturbances in menopausal women.[49] A randomized, double-blind crossover study conducted on men with OSA showed no changes in severity or parameter during the study with MPA,150 mg/day, and placebo. Each patient took tablets for one week and then had a second polysomnogram. After a three-week washout, the patient again took tablets for a week before the third and final sleep study. There was no significant difference between drug and placebo for DBE (disordered breathing time) time and saturation etc. Hence conclude that treatment with MPA does not alter indices of severity of the OSA syndrome.[50] Medroxyprogesterone acetate administration (10 mg/day for four days) was followed by partial suppression of the sleep-induced peak of Human Growth Hormone (HGH) secretion in 5 normal subjects.[51]

Nagarathna Poojary, Ishan Ashok Capoor, and Manish Kundar, "Medroxyprogesterone Acetate as a Respiratory Stimulant in Hypercapnic COPD, Postmenopausal COPD, Obesity Induced Hypoventilation, Obstructive Sleep Apnea, and Polycythemia," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 5, Issue 5, pp. 1-8, 2022.

A randomized cross-over study to compare the two respiratory stimulants that act by different mechanisms was done with 1.5 mg/kg almitrine and 100 mg of medroxyprogesterone or matched placebo daily for 15 days. It was found that both active drugs improved blood gases during wakefulness, but that 1.5 mg/kg of almitrine is superior to 100 mg of medroxyprogesterone in improving SaO_2 during sleep. Medroxyprogesterone is a central respiratory stimulant. It increases respiratory drive, the ventilatory and neuromuscular response to hypercapnia, and the ventilatory response to hypoxia and it restores the impaired load compensation. When the MPA showed a favourable positive result there was an increase in tidal volume and mean inspiratory flow. On the other hand, almitrine is a peripheral chemoreceptor stimulant. It stimulates peripheral chemoreceptors therefore it increases the ventilatory response to hypoxemia and alveolar ventilation. Almitrine is also noted to have a significant beneficial effect on the ventilation-perfusion relationship.[52] Adverse reactions that may be associated with this MPA include impotence, breast discomfort, alopecia, hirsutism, cutaneous reactions, and thromboembolic phenomena. It has been reasoned that a ventilatory stimulant might increase the output of the respiratory centre to the muscles of the upper airway during sleep since MPA metabolites cross BBB. Such increased stimulation could improve muscle tone and prevent the collapse of the upper airway during sleep.[53]

VIII. Polycythemia of High Altitude

Hypoxia serves as an additional complication to blood clot formation in polycythemia patients. 10 weeks of therapy with 20 mg of medroxyprogesterone acetate three times per day in 17 patients with excessive polycythemia condition increased Mean resting ventilation due to increased tidal volume and also there was an elevation in arterial PaO_2 levels. Medroxyprogesterone acetate is a productive therapy in excessive polycythemia at high altitudes because of its effects on ventilation and tidal volume, and the resultant increase in arterial O_2 saturation.[54] 5 normal subjects and 5 patients with excessive polycythemia when participated in a double-blind, placebo-controlled, crossover trial conducted by M Kryger et al. significant improvement in nocturnal SaO_2 occurred when the polycythemia patients with MPA.[55]

IX. Conclusion

Medroxyprogesterone acetate increased alveolar ventilation, partial pressure of oxygen and decreased partial pressure of carbon dioxide in conditions of chronic obstructive pulmonary disease, respiratory failure, sleep apnea, and obesity-induced hypoventilation. Dose, frequency, and route of administration of MPA revolve around 10mg,20mg,30mg,60mg,75mg, and 100mg once daily/twice daily/three times daily in the oral/intramuscular/sublingual route. MPA was also shown to improve mouth occlusion pressure, tidal volume, and inspiratory effect when administered along with Chlormadinone, Domperidone, Acetazolamide, and estrogen as a combination. It is observed that the metabolites of MPA are having ventilatory effects than MPA itself. Many studies suggested that long-term treatment with MPA is required to have prolonged effects of respiratory stimulation. Because an increase in minute ventilation and decrease in carbon dioxide tension was terminated on cessation of MPA. Though more studies are supporting the role of MPA as a respiratory stimulant in various respiratory failure conditions, the exact mechanism in which MPA stimulates the central nervous system for the respiratory effects is still unclear. As per our literature search, there are studies from 1959 to 2005. Furthermore, clinical studies are needed to evaluate MPA for respiratory stimulation and to effectively treat post-menopausal apnea conditions. The cons of medroxyprogesterone acetate are of paramount importance together with all the mentioned pros. Hormone therapy increases the risk of venous thromboembolism, possibly through a negative effect on coagulation inhibitors.[56] Venous thromboembolism is a major adverse drug reaction associated with progestin-only contraceptives (POCs).[57] Nevertheless, this adverse drug reaction is dose-dependent, and the risk is increased for injectable depot-medroxyprogesterone acetate in contraceptive users.[58] No study highlighted venous thromboembolism when MPA was given for respiratory stimulation. However further studies should be encouraged to give complete data on MPA including its dose, mechanism of action and adverse drug interactions in respiratory stimulation.

APPENDIX

ABBREVIATION

COPD-Chronic Obstructive Pulmonary Disease
MPA-Medroxyprogesterone Acetate
PaO2-Partial pressure of oxygen
PaCO2- Partial pressure of Carbon Dioxide
LH-Luteinizing Hormone
PRE-Progesterone Receptor Element
BBB-Blood Brain Barrier
CMA-Chlormadinone Acetate
PEFR-Peak Expiratory Flow Rate
FEV1-Forced Expiratory Volume in one second
FEV-Forced Vital Capacity
TID-Three Times Daily
VA-Alveolar Ventilation
E2-Estrogen
SAS-Sleep Apnea Syndrome
REM-Rapid Eye Movement
IGF 1-Insulin-like Growth Factor one
nCPAP - nasal Continuous Positive Airway Pressure
BiPAP- Bi-level Positive Airway Pressure
HRT- Hormone Replacement Therapy
OSA- Obstructive Sleep Apnea
DBE- Disordered Breathing Time
HGH-Human Growth Hormone
POCs- Progestin Only Contraceptives

Conflict of interest: No conflict of interest
Acknowledgment: Nil

REFERENCES

[1] C. Roussos and A. Koutsoukou, "Respiratory failure," European Respiratory Journal, vol. 22, issue 47, pp. 3s-14s, 2003.

[2] E. Shebl, V. Mirabile and B. Burns, "Respiratory Failure," StatPearls Publishing. Treasure Island (FL), 2022.

[3] "Respiratory Failure - What Is Respiratory Failure? | NHLBI, NIH", Nhlbi.nih.gov, 2022. [Online].

[4] J. Peppin, J. Pergolizzi, J. Fudin, T. Meyer and R. Raffa, "History of Respiratory Stimulants," Journal of Pain Research, vol. 14, pp. 1043-1049, 2021.

[5] A. Edelman, G. Cherala and F. Stanczyk, "Metabolism and pharmacokinetics of contraceptive steroids in obese women: a review," Contraception, vol. 82, issue 4, pp. 314-323, 2010.

[6] J. Cable and M. Grider, Physiology, Progesterone. StatPearls Publishing, Treasure Island (FL), 2022.

[7] F. Demayo, B. Zhao, N. Takamoto and S. Tsai, "Mechanisms of Action of Estrogen and Progesterone," Annals of the New York Academy of Sciences, vol. 955, issue 1, pp. 48-59, 2002.

[8] H. Jabbour, R. Kelly, H. Fraser and H. Critchley, "Endocrine Regulation of Menstruation," Endocrine Reviews, vol. 27, issue 1, pp. 17-46, 2005.

[9] A. Ferenczy and M. Gelfand, "The biologic significance of cytologic atypia in progestogen-treated endometrial hyperplasia," American Journal of Obstetrics and Gynecology, vol. 160, issue 1, pp. 126-131, 1989.

[10] N. Zachariah and Z. Chakmakjian, "Estrogen and progesterone receptors in human breast cancer," Journal of Steroid Biochemistry, vol. 9, issue 9, pp. 893, 1978.

[11] M. Edwards and A. Can, Progestin. StatPearls Publishing, Treasure Island (FL), 2021.

[12] A. Schindler, "Classification and pharmacology of progestins," Maturitas, vol. 46, pp. 7-16, 2003.

[13] P. Soma-Pillay, C. Nelson-Piercy, H. Tolppanen and A. Mebazaa, "Physiological changes in pregnancy," Cardiovascular Journal of Africa, vol. 27, issue 2, pp. 89-94, 2016.

[14] J. Cullen, V. Brum and W. Reidt, "The respiratory effects of progesterone in severe pulmonary emphysema," The American Journal of Medicine, vol. 27, issue 4, pp. 551-557, 1959.

[15] J. Skatrud, J. Dempsey and D. Kaiser, "Ventilatory response to medroxyprogesterone acetate in normal subjects: time course and mechanism," Journal of Applied Physiology, vol. 44, issue 6, pp. 939-944, 1978.

[16] J. Skatrud, J. Dempsey, P. Bhansali and C. Irvin, "Determinants of Chronic Carbon Dioxide Retention and Its Correction in Humans," Journal of Clinical Investigation, vol. 65, issue 4, pp. 813-821, 1980.

[17] J. Skatrud, J. Dempsey, C. Iber and A. Berssenbrugge, "Correction of CO2 retention during sleep in patients with chronic obstructive pulmonary diseases," American Review of Respiratory Disease, vol. 124, issue 3, pp. 260-268, 1981

[18] J. Skatrud and J. Dempsey, "Relative Effectiveness of Acetazolamide versus Medroxyprogesterone Acetate in Correction of Chronic Carbon Dioxide Retention," American Review of Respiratory Disease, vol. 127, issue 4, pp. 405-412, 1983.

[19] F. Dolly and A. Jay Block, "Medroxyprogesterone Acetate And Copd," Chest, vol. 84, issue 4, pp. 394-398, 1983.

[20] L. Delaunois, J. Delwiche and J. Lulling, "Effect of Medroxyprogesterone on Ventilatory Control and Pulmonary Gas Exchange in Chronic Obstructive Patients," Respiration, vol. 47, issue 2, pp. 107-113, 1985.

[21] K. Tatsumi, "Effect of chlormadinone acetate on ventilatory control in patients with chronic obstructive pulmonary disease," American Journal of Respiratory and Critical Care Medicine, vol. 133, issue 4, pp.552-557, 1986.

[22] S. Al-Damluji, "The effect of ventilatory stimulation with medroxyprogesterone on exercise performance and the sensation of dyspnoea in hypercapnic chronic bronchitis," British Journal of Diseases of the Chest, vol. 80, pp. 273-279, 1986.

[23] T. Morikawa, Y. Tanaka, R. Maruyama, Y. Nishibayashi and Y. Honda, "Comparison of two synthetic progesterones on ventilation in normal males: CMA vs. MPA," Journal of Applied Physiology, vol. 63, no. 4, pp. 1610-1615, 1987.

[24] S. Javaheri and L. Guerra, "Effects of domperidone and medroxyprogesterone acetate on ventilation in man," Respiration Physiology, vol. 81, issue 3, pp. 359-370, 1990.

[25] A. Smyth, "Chronic respiratory failure: an unusual cause and treatment," Thorax, vol. 57, issue 9, pp. 835-836, 2002.

[26] M. Wagenaar, P. Je Vos, Y. Heijdra, L. Teppema and H. Folgering, "Combined treatment with acetazolamide and medroxyprogesterone in chronic obstructive pulmonary disease patients," European Respiratory Journal, vol. 20, issue 5, pp. 1130-1137, 2002.

[27] M. Wagenaar, P. Vos, Y. Heijdra, L. Teppema and H. Folgering, "Comparison of Acetazolamide and Medroxyprogesterone as Respiratory Stimulants in Hypercapnic Patients With COPD," Chest, vol. 123, issue 5, pp. 1450-1459, 2003.

[28] T. Saaresranta and O. Polo, "Long-term progestin therapy for female chronic respiratory insufficiency?," Respiratory Medicine, vol. 98, issue 2, pp. 194-195, 2004

[29] R. Goodland, J. Reynolds and W. Pommerenke, "alveolar carbon dioxide tension levels during pregnancy and early puerperium," The Journal of Clinical Endocrinology & Metabolism, vol. 14, issue 5, pp. 522-530, 1954.

[30] D. Bayliss, D. Millhorn, E. Gallman and J. Cidlowski, "Progesterone stimulates respiration through a central nervous system steroid receptor-mediated mechanism in cat," Proceedings of the National Academy of Sciences, vol. 84, issue 21, pp. 7788-7792, 1987.

[31] C. O'DONNELL, "Leptin Prevents Respiratory Depression in Obesity," American Journal of Respiratory and Critical Care Medicine, vol. 159, issue 5, pp. 1477-1484, 1999.

[32] E. Mannucci, "Relationship between leptin and oestrogens in healthy women," European Journal of Endocrinology, vol. 139, issue 2, pp. 198-201, 1998.

[33] T. Saaresranta, K. Irjala and O. Polo, "Effect of medroxyprogesterone on arterial blood gases, leptin and neuropeptide Y in postmenopausal females," European Respiratory Journal, vol. 20, issue 6, pp. 1413-1418, 2002.

[34] C. Pickett, J. Regensteiner, W. Woodard, D. Hagerman, J. Weil and L. Moore, "Progestin and estrogen reduce sleep-disordered breathing in postmenopausal women," Journal of Applied Physiology, vol. 66, issue 4, pp. 1656-1661, 1989.

[35] T. Saaresranta, P. Polo-Kantola, K. Irjala, H. Helenius and O. Polo, "Respiratory Insufficiency in Postmenopausal Women," Chest, vol. 115, issue 6, pp. 1581-1587, 1999.

[36] D. Keefe, R. Watson and F. Naftolin, "Hormone Replacement Therapy May Alleviate Sleep Apnea in Menopausal Women: A Pilot Study," Menopause, vol. 6, issue 3, pp. 196-200, 1999.

[37] T. Saaresranta, K. Irjala, P. Polo–Kantola, H. Helenius and O. Polo, "IGF-I and ventilation after short-term progestin in postmenopausal women with chronic respiratory insufficiency," Respiratory Medicine, vol. 94, issue 9, pp. 909-916, 2000.

[38] Saaresranta, T. Aittokallio, K. Utriainen and O. Polo, "Medroxyprogesterone improves nocturnal breathing in postmenopausal women with chronic obstructive pulmonary disease," Respiratory Research, vol. 6, issue 1, 2005.

[39] T. Saaresranta, P. Polo-Kantola, E. Rauhala and O. Polo, "Medroxyprogesterone in postmenopausal females with partial upper airway obstruction during sleep," European Respiratory Journal, vol. 18, issue 6, pp. 989-995, 2001

[40] J. Masa, J. Pépin, J. Borel, B. Mokhlesi, P. Murphy and M. Sánchez-Quiroga, "Obesity hypoventilation syndrome," European Respiratory Review, vol. 28, issue 151, p. 180097, 2019.

[41] P. Ghimire, A. Sankari and P. Kaul, Pickwickian Syndrome. StatPearls Publishing, Treasure Island (FL), 2022.

[42] A. Piper, D. Wang, B. Yee, D. Barnes and R. Grunstein, "Randomised trial of CPAP vs bilevel support in the treatment of obesity hypoventilation syndrome without severe nocturnal desaturation," Thorax, vol. 63, issue 5, pp. 395-401, 2008

[43] H. Lyons and C. Huang, "Therapeutic use of progesterone in alveolar hypoventilation associated with obesity," The American Journal of Medicine, vol. 44, issue 6, pp. 881-888, 1968.

[44] F. SUTTON, "Progesterone for Outpatient Treatment of Pickwickian Syndrome," Annals of Internal Medicine, vol. 83, issue 4, p. 476, 1975.

[45] E. BIXLER, "Prevalence of Sleep-disordered Breathing in Women," American Journal of Respiratory and Critical Care Medicine, vol. 163, issue 3, pp. 608-613, 2001.

[46] R. Popovic and D. White, "Upper airway muscle activity in normal women: influence of hormonal status," Journal of Applied Physiology, vol. 84, issue 3, pp. 1055-1062, 1998.
[47] R. Millman, "Medroxyprogesterone and Obstructive Sleep Apnea," Chest, vol. 96, issue 2, pp. 225-226, 1989.
[48] C. Pickett, J. Regensteiner, W. Woodard, D. Hagerman, J. Weil and L. Moore, "Progestin and estrogen reduce sleep-disordered breathing in postmenopausal women," Journal of Applied Physiology, vol. 66, issue 4, pp. 1656-1661, 1989.
[49] Montplaisir, Jacques, "Sleep In Menopause: Differential Effects Of Two Forms Of Hormone Replacement Therapy," Menopause, vol. 8, issue 1, pp. 10-16, 2001.
[50] W. Cook, J. Benich and S. Wooten, "Indices of Severity of Obstructive Sleep Apnea Syndrome Do Not Change During Medroxyprogesterone Acetate Therapy," Chest, vol. 96, issue 2, pp. 262-266, 1989.
[51] C. LUCKE and S. GLICK, "Effect of Medroxyprogesterone Acetate on the Sleep Induced Peak of Growth Hormone Secretion, " The Journal of Clinical Endocrinology, vol. 33, issue 5, pp.851-853, 1971.
[52] E. Daskalopoulou, D. Patakas, V. Tsara, F. Zoglopitis and E. Maniki, "Comparison of almitrine bismesylate and medroxyprogesterone acetate on oxygenation during wakefulness and sleep in patients with chronic obstructive lung disease," Thorax, vol. 45, issue 9, pp. 666-669, 1999.
[53] Rajagopal, K., Abbrecht, P. and Jabbari, B, " Effects of Medroxyprogesterone Acetate in Obstructive Sleep Apnea," Chest, vol. 90, issue 6, pp.815-821,1986.
[54] M. Kryger, RE. McCullough, D. Collins, CH. Scoggin, JV. Weil and RF. Grover, "Treatment of excessive polycythemia of high altitude with respiratory stimulant drugs," American Review of Respiratory Disease , vol. 117, issue. 3, pp. 455-464, 1978.
[55] M. Kryger, "Impaired Oxygenation During Sleep in Excessive Polycythemia of High Altitude: Improvement with Respiratory Stimulation," Sleep, vol. 1, issue 1, pp. 3-17, 1978.
[56] N. Keramaris, "The differential effect of estrogen, estrogen-progestin and tibolone on coagulation inhibitors in postmenopausal women," Climacteric, vol. 10, issue 5, pp. 400-407, 2007.
[57] N. Tepper, M. Whiteman, P. Marchbanks, A. James and K. Curtis, "Progestin-only contraception and thromboembolism: A systematic review," Contraception, vol. 94, issue 6, pp. 678-700, 2016.
[58] A. van Hylckama Vlieg, F. Helmerhorst and F. Rosendaal, "The Risk of Deep Venous Thrombosis Associated With Injectable Depot–Medroxyprogesterone Acetate Contraceptives or a Levonorgestrel Intrauterine Device," Arteriosclerosis, Thrombosis, and Vascular Biology, vol. 30, issue 11, pp. 2297-2300, 2010.