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CORTICOTROPHINS [SEDA-35, 719; SEDA-36, 603; SEDA-37, 491; SEDA-38, 425, SEDA 42, 402]

Adrenocorticotropic hormone (ACTH) is a 39 amino acid polypeptide tropic hormone which is produced and secreted by the anterior pituitary lobe under the influence of hypothalamus. It stimulates the synthesis of glucocorticoids, mineralocorticoids, and androgens from adrenal glands. ACTH is reserved for children with childhood epilepsy who do not respond to traditional seizure therapy. In fact, it is used as a first-line agent for the treatment infantile spasms, and also found to application in Lennox-Gastaut syndrome, Landau-Kleffner syndrome, and electrical status epilepticus in sleep. Apart from this they are also used for patients who are diagnosed with multiple sclerosis and nonsuppurative thyroiditis. Positive outcomes including child’s developmental status have been noted in patients after treatment with ACTH. The mechanism of action of ACTH seizures is still unclear but direct stimulation of ACTH receptors on the brain and adrenal glands are correlated with its action. The use of (ACTH) has been reported to have adverse effects on cardiac function, nervous system, and mild rash (Brophy & Ray, 2015 [R]; Watson et al., 2019 [R]). The meta-analysis of 19 studies reviewing the use of ACTH reported edema as one of the most commonly reported adverse event followed by insomnia, mood swings, and hyper-glycemia (Kittanamongkolchai et al., 2016) [M]. Similarly, a 4-month-old infant girl developed dyskinetic movements such as arm elevations and tongue protrusion after the administration of ACTH. The drug was immediately discontinued and symptoms abated over the next 2 months (Arita et al., 2016 [A]). In another randomized open-label crossover study of 18 healthy patients, two patients reported a mild rash and one patient reported nausea when treated with porcine ACTH vs methylprednisolone (Lal et al., 2016) [c].

SYSTEMIC GLUCOCORTICOID [SED-15, 906; SEDA-33, 841; SEDA-34, 653; SEDA-35, 719; SEDA-36, 604; SEDA-37, 492; SEDA-38, 425, SEDA-42]

Systemic corticosteroids are drugs meant to mimic natural steroids produced by the adrenal glands. Systemic corticosteroids work in the same way as natural cortisol; hence, like natural cortisol they also help in metabolic regulation of protein, carbohydrate, lipid, and nucleic acid, are potent anti-inflammatory agents, and also regulate water and secretion of adrenocorticotrophic hormone (ACTH) from the pituitary gland. Glucocorticoids are mainly used due to their potent anti-inflammatory effects for the treatment or alleviation of symptoms in arthritis, ulcerative colitis, Crohn’s disease, asthma, bronchitis, or inflammatory conditions involving the nose, eyes and skin. As they mimic the end-product, they tend to affect the body as a whole body rather than a targeted area. This can be attributed to the fact that corticosteroids receptors are expressed throughout body. This is useful...
for conditions in which the whole body is in need of corticosteroids, however, is associated with significant systemic toxicities in many isolated conditions that are treated with corticosteroid. Many of these toxicities are well known hyperglycemia, hormonal axis depression, and immunosuppression whereas some long-term effects such as hypertension, and behavioral/cognitive changes has also been reported (Brophy & Ray, 2015 [R]; Kaplan & Brophy, 2017 [R]). Some of these effects are dose dependent and most of them wear off once the patient is off medication.

Cardiovascular risk

The use of low to moderate glucocorticoid can increase the cardiovascular risk in patients with 6 immune-mediated inflammatory diseases. A population-based cohort analysis of 389 primary care practices from the United Kingdom Clinical Practice Research Datalink (CPRD), from 1998 to 2017 were evaluated (Pujades-Rodriguez et al., 2020) [M]. The cumulative glucocorticoid prednisolone-equivalent dose-related risks and hazard ratios (HRs) of first all-cause and type-specific cardiovascular diseases (CVDs) was retrospectively studied for 87794 patients. Patients who received glucocorticoid prednisolone with no prior diagnosis of CVD were further categorized in those with giant cell arteritis and/or polymyalgia rheumatica (29.13% n = 25 581), inflammatory bowel disease (31.59% n = 27 739), rheumatoid arthritis (28.84% n = 25 324), systemic lupus erythematosus (4.5% n = 3951), and/or vasculitis (5.9% n = 5199) with a mean age was 56 years 65.9% females. After the 5-year follow-up it was found that the CVD occurred in 13 426 (15.3%) patients which included atrial fibrillation, heart failure, and acute myocardial infarction. The risk of CVD increased from 1.4% in periods of non-use to 8.9% for a daily prednisolone-equivalent dose of C21 0 ≥25.0 mg, whereas the 5-year cumulative risks increased from 7.1% to 28.0%, respectively. These results highlight the importance of prompt and regular monitoring of cardiovascular risk and use of primary prevention treatment at all glucocorticoid doses.

Complications

A retrospective study to evaluate the effect of corticosteroids on asthmatic children and adolescents (Sullivan et al., 2020) [M]. The data of children and adolescents with persistent asthma retrieved from the MarketScan database, from 2000 to 2017 and propensity score was used to pair patients in the systemic corticosteroids and control cohorts. It was observed that among 67 081 patients who were reviewed the odds of having a complication were high in patients receiving systemic corticosteroids in the first year of follow-up, asthma-related hospitalizations, or for asthma related visits to emergency departments vs the control.

Corticophobia

A study to evaluate the negative perception of asthmatic patients using Inhaled corticosteroids (ICS) due to lack of knowledge also called as corticophobia was evaluated by Yakar et al. (Yakar & Kanbay, 2020) [M]. A total of 150 patients were included in study which was conducted from 2017 to 2018. Patients were asked to answer a 10 question (5—fear/worries and 5—belief) TOPICOP survey. The results indicated that patients believed weight gain (68%), infection (52%), damage lungs (67.3%), and ICS passing into blood stream (73%) were the most common phobias against the use of ICS. The authors concluded that patients need to be educated to increase treatment adherence.

Cushing syndrome

The use of inhaled corticosteroids along with CYP450 inhibitors such as ritonavir lead to systemic accumulation of corticosteroids (Figueiredo et al., 2020) [A]. In a case of inhaled corticosteroids iatrogenic Cushing syndrome was reported by the authors in a HIV positive patient who was being treated with a protease inhibitor boosted with ritonavir, after the association of inhaled fluticasone. This study highlights the interaction between corticosteroids and cytochrome P450 inhibitors which can lead to severe consequences.

Hyperglycemia

The use of systemic corticosteroid to prevent postextubation airway complications and reintubation is recommended in mechanically ventilated patients to prevent postextubation airway complications and reintubation (Kuriyama et al., 2020 [M]). In an effort to understand the complications in blood glucose levels (≥100 mg/dL) associated with the use of the systemic corticosteroid in mechanically ventilated 251 adult patients in four tertiary-care hospitals were studied. These patients received predose of 20 mg methylprednisolone at 12, 8, 4, and 0 h before extubation and were followed for 72 h after extubation. Twenty three percent of patient (57/247) showed significant increase in blood glucose levels with 24 h and 30.3% patients showed a showed an increase in blood glucose levels within 72 h after receiving prophylactic corticosteroids. Hence, the authors concluded that the prophylactic corticosteroid use before extubation was associated with increased blood glucose levels and lower doses of prophylactic corticosteroids may need to be considered in patients with diabetes mellitus or hyperglycemia.
Infection

**Cutaneous leishmaniasis (CL)**

In a recent case report, an unconventional clinical manifestation and reactivation of CL in a patient undergoing systemic steroid therapy was reported (Mahdavi et al., 2021) [A]. A 42-year-old man presented with fever, extensive widespread skin lesions, and painful oral ulcers to the emergency department of Imam Reza hospital of Mashhad city, Iran. The lesions were intermitted and which started 2 years ago with periods of remissions and recurrences. Polymerase chain reaction (PCR) test reported *Leishmania tropica* species. The patient has been using prednisolone 30 mg per day for over 10 years for the treatment of rheumatoid arthritis (RA). Patient received glucantime IM injections, 20 mg/kg/day for 10 days which resulted in remarkable improvement and his systemic corticosteroid was tapered.

**General infections**

Oral glucocorticoid therapy is one of the most common treatment of choice in patients with inflammatory bowel disease (IBD). To evaluate the risk of common infections in individuals with (IBD) 18829 people with IBD were matched to 73316 controls. Authors found that the treatment of rheumatoid arthritis (RA). Patient received glucocorticoid therapy especially among individuals with chronic pulmonary disease and in pulmonary nocardiosis.

**Pneumocystis pneumonia**

Infections is one of the most common complication in patients with severe alcoholic hepatitis (AH). Use of oral corticosteroids in these patients to reduce short-term mortality. However, the use of systemic corticosteroids can result in infection. A case of 43 YOM treated with corticosteroids for severe AH was reported. After 26 days of the initiation of glucocorticoid therapy, patient developed a productive cough (Chung et al., 2020) [A] that was positive for *Pneumocystis jirovecii*. Thus, pneumocystis pneumonia (PCP) is a life-threatening opportunistic infection that most frequently affects the lungs (Margalit et al., 2020) [M]. A retrospective study was conducted based on medical records of consecutive adult patients (N = 60) with nocardiosis hospitalized during 2007–2018 at a tertiary hospital in central Israel. A matched comparison group of 120 patients was randomly selected among hospitalized patients with community-acquired pneumonia. The immunosuppressive pharmacotherapy was positively associated with nocardiosis (matched odds ratio [OR] 4.40, 95% confidence interval [CI] 2.25–8.62, *P* < 0.001), and corticosteroid therapy (matched OR 4.69, 95% CI 2.45–8.99, *P* < 0.001). Systemic corticosteroid therapy was strongly associated with pulmonary nocardiosis (matched OR 5.90, 95% CI 2.75–12.66, *P* < 0.001). The association between corticosteroid therapy and nocardiosis appeared stronger in patients with chronic pulmonary disease (OR 5.74, 95% CI 2.75–12.66, *P* < 0.001) than in the pooled analysis of all nocardiosis cases. In conclusion, the authors saw a strong correlation between nocardiosis and corticosteroid therapy especially among individuals with chronic pulmonary disease and in pulmonary nocardiosis.

**Pulmonary aspergillosis**

Similarly, in retrospective analysis of patients with Severe coronavirus disease 2019, pulmonary aspergillosis in identified 6 patients (6/46, 13.04%) (Chauvet et al., 2020) [M]. Chronic obstructive pulmonary disease, malnutrition, and systemic corticosteroid were attributed to the cause of pulmonary aspergillosis.

**Pulmonary nocardiosis**

Similarly, the use of corticosteroids is associated with pulmonary nocardiosis. Nocardia is an opportunistic pathogen that most frequently affects the lungs (Margalit et al., 2020) [M]. A retrospective study was conducted based on medical records of consecutive adult patients (N = 60) with nocardiosis hospitalized during 2007–2018 at a tertiary hospital in central Israel. A matched comparison group of 120 patients was randomly selected among hospitalized patients with community-acquired pneumonia. The immunosuppressive pharmacotherapy was positively associated with nocardiosis (matched odds ratio [OR] 4.40, 95% confidence interval [CI] 2.25–8.62, *P* < 0.001), and corticosteroid therapy (matched OR 4.69, 95% CI 2.45–8.99, *P* < 0.001). Systemic corticosteroid therapy was strongly associated with pulmonary nocardiosis (matched OR 5.90, 95% CI 2.75–12.66, *P* < 0.001). The association between corticosteroid therapy and nocardiosis appeared stronger in patients with chronic pulmonary disease (OR 5.74, 95% CI 2.75–12.66, *P* < 0.001) than in the pooled analysis of all nocardiosis cases. In conclusion, the authors saw a strong correlation between nocardiosis and corticosteroid therapy especially among individuals with chronic pulmonary disease and in pulmonary nocardiosis.

A narrative review aimed to sum up the studies on the side effects of corticosteroids used for joint pain and osteoarthitis condition (Stone et al., 2021) [R]. Although the use of corticosteroids has limited and short-term properties in reducing the pain and there is little proof that they can improve functioning, there has been a growing use of these medications since 1950. Numbers of databases including PubMed and Google Scholar were reviewed for this purpose. Some of the minor side effects discussed in this review are increased serum glucose particular in diabetic patients, skin rash (erythema of the face/torso, post-injection flare), reduced immunity, elevated pain. Nerve damage, charcot arthropathy, osteonecrosis, steroid arthropathy, tendon rupture, tissue arthropathy, fat necrosis, calcification, joint instability and hypothalamic-pituitary-adrenal axis suppression are among the moderate to severe adverse effects of corticosteroids. Moreover, toxic effects to articular cartilage, increased risk infection including viral infections has been observed which is of great concern given to COVID-19 pandemic.

**Severity of COVID-19**

This study evaluated the impact of having an autoimmune and chronic inflammatory disease (AICID) and class of immunosuppressive medications (biologics, nonbiologic immunosuppressives, or systemic corticosteroids) used to treat patients with AICID on developing...
adverse outcomes due to COVID-19. In a multicenter retrospective cohort study, 6792 patients who had tested positive for COVID-19 with PCR were evaluated (Ungaro et al., 2021) [M]. It was observed that patients with AICID who were on systemic corticosteroids had an eight-fold elevated risk of severe COVID-19. However, the use of biologics or non-biologics immunosuppressives was not associated with severe COVID-19 outcomes.

**Strongyloidiasis**

Strongyloidiasis is an infection caused by Strongyloides stercoralis a parasitic nematodes which is most prevalent in South America, Southeast Asia, and sub-Saharan Africa, but its incidence has increased in non-endemic areas of the United States due to immigration. Vast majority of the patients who are infected with Strongyloides stercoralis remain asymptomatic or present only mild GI respiratory or dermatological symptoms. A case of strongyloidiasis infection was reported by Ashida et al. The patient was treated for lupus erythematosus (SLE) (Ashida et al., 2020) [A]. Patient developed cytomegalovirus (CMV) enteritis, and her respiratory status rapidly deteriorated immediately after the withdrawal of Tac and MMF. Bronchoscopy revealed viable Strongyloides, leading to a diagnosis of strongyloidiasis infection syndrome, leading to patients’ death. Authors concluded that both corticosteroid therapy and HTLV-1 infection can be associated with a decrease of eosinophils, hence the risk of parasitic infection should be assessed in patients receiving immunosuppressants and steroids even in non-endemic areas.

In another case study, patient with acute exacerbation of asthma showed a worsening response on systemic corticosteroids (Salam et al., 2020) [A]. Lab results showed an increased eosinophilia, and the chest radiography showed blunting of the left costophrenic angle. The parasite larve was detected in his bronchoalveolar lavage sample and immediately ivermectin was initiated following which his symptoms subsided. This study shows that the patients on corticosteroid therapy can exacerbate the symptoms in individuals with undiagnosed Strongyloides infection and clinicians should vigilant when treating patients from tropical area where *S. stercoralis* is prevalent.

**Ocular issues**

**Acute retinal necrosis**

In a similar study, authors have reported the case of Toxoplasmosis chorioretinitis mimicking acute retinal necrosis associated with local corticosteroid (Crosson et al., 2020) [A]. All three patients were exposed to local corticosteroids and diffused retinal whitening and severe loss of vision was reported by all patients during initial presentation. Retinitis resolved with anti-parasitic medication; however, visual acuity failed to improve in all patients due to disease severity and presentation. Hence the Toxoplasma chorioretinitis should be considered in the differential diagnosis of patients presenting with clinical features of acute retinal necrosis, particularly following local corticosteroid injection regardless of their baseline systemic immune status.

**Avascular necrosis (AVN)**

The prolong use of corticosteroids in patients with childhood systemic lupus erythematosus (SLE) was shown to increase morbidity and including avascular necrosis (AVN) which is defined as the death of bone due to compromised blood flow. In a retrospective study of 1472 children (mean age 15.5 ± 3.3 years) with newly-diagnosed SLE, 39 patients (2.6%) developed symptomatic AVN during a mean follow-up of 4.6 ± 2.5 years (Tsai et al., 2020) [M]. The multivariate analysis showed that the risk of AVN was higher taking higher dose prednisolone (7.5–30mg) (HR 7.435, 95% CI 2.882–19.178, \(P < 0.001\)) and greater than 30mg/day (HR 9.366, 95% CI 2.225–39.418, \(P = 0.002\)) than in those with a dose ≤ 7.5mg/day. In conclusion, high daily doses of prednisolone were associated with a significant risk of AVN, suggesting that the corticosteroids should be used in combination of other drugs such as hydroxychloroquine as a preventive strategy for AVN. In another study, 127 patients with SLE using steroid were evaluated for AVN (Doğan et al., 2020) [M]. Results indicated that 8.7% (11/127) SLE patients had AVN with osteoporosis. Thus, the daily usage of steroid was attributed to the development of AVN.

**Intraocular pressure (IOP)**

Association between the use of corticosteroids and open angle glaucoma is well known. Recently, Joshua D. Stein and coworkers reviewed medications which can cause open angle glaucoma (Wu et al., 2020) [R]. Authors indicated that there is a strong association between the use of corticosteroids and increase in Intraocular Pressure (IOP). In fact, they found that approximately 5% of the patients receiving corticosteroids showed an IOP increase >15mmHg. The use of corticosteroids can lead to elevation of both acute and chronic IOP which can vary with the dosage and the potency of various corticosteroids. The mechanism of this increase in IOP, however, is not well understood.

**Optic neuritis**

A retrospective study to evaluate the effect of systemic high-dose corticosteroid on the choroid in patients with unilateral optic neuritis was conducted. Thirty-eight patients with unilateral optic neuritis that received...
systemic high-dose corticosteroid treatment were enrolled (Lee, Lee, Ra, et al., 2020) [M]. Both the Choroidal thickness (CT) and choroidal vascularity index (CVI) showed a significant decrease in affected eyes after 3 months ($P = 0.017$ and $P < 0.001$). The authors concluded that patients treated with high-dose systemic corticosteroid for optic neuritis show a significant decrement in CT and CVI after 3 months.

Osteoporosis

Osteoporosis a systemic skeletal disease is one of the significant comorbidities in chronic obstructive pulmonary disease (COPD). With an aim to aim to investigate the presence of osteoporosis and the factors that influence the prevalence of osteoporosis authors conducted study at the outpatient clinics at the Departments of Physical Medicine and Rehabilitation and Pulmonary Diseases in Bursa Uludag University Hospital, a tertiary reference center, in the northwest region of Turkey in 63 COPD patients (Ozakir et al., 2020) [M]. Thirty COPD patients were on inhaled corticosteroid (ICS) and the control group had 33 patients. For both groups, osteoporosis risk questioning, body mass index (BMI), bone mineral density (BMD), biochemical blood tests, vertebral fractures on lumbar and thoracic X-rays were recorded. COPD patients were also evaluated for lung functions via spirometry. The BMD was found to be significantly lower in Group 1 (patients on corticosteroids) as compared to the control controls. These findings suggest that corticosteroids can lead to osteoporosis in COPD patients.

Similarly, in another study by Matsunaga et al., the authors reviewed the benefit-risk balance of systemic corticosteroids (SCS) in asthma treatment (Matsunaga et al., 2020) [M]. Of the 10579 patients reviewed by the authors, 3103 (29.3%) patients were receiving SCS for asthma cohort. Mean SCS dosages at baseline were 0.08, 0.29, 0.79, and 4.58 mg/day in Q1, Q2, Q3, and Q4, respectively. Similar SCS dosages were used within each quartile throughout the study period. Authors did not observe any remarkable changes in asthma severity, however, in all SCS cohorts the use of corticosteroids was associated with osteoporosis, diabetes, anxiety/neurosis, and depression. Hence, the authors concluded that the use of SCS may negatively impact systemic health even at mean dosages $< 5$ mg/day. This effect of the glucocorticoid therapy can explain the fracture risk in patients treated with glucocorticoids, including patients with kidney disease as was seen in a population-based retrospective cohort study in South Korean. The authors observed fractures of any site in 16.30% (1406/8624) patients during the study period. In addition, the glucocorticoid-exposed group had more fractures than the unexposed (14.4% vs 8.8%, $P < 0.0001$). Authors also noted that the vertebral fractures were the most common, followed by upper limb, and lower limb fractures. The systemic glucocorticoid therapy group showed a remarkably higher ratio of fracture risk (HR 6.0, 95% CI 5.01–7.23) than the unexposed group, indicating was highly associated with fracture risk. Thus, similar to previous studies the authors concluded that the glucocorticoids were associated with higher risk of fracture even at a low daily dose and short term exposure (Lee, Lee, Park et al., 2020) [M].

Pancreatitis

A report of a 22-year-old woman with newly diagnosed case of systemic lupus erythematosus was admitted to our hospital. IV methylprednisolone was initiated for 3 days, followed by oral prednisolone at 40 mg/day thereafter (Atci et al., 2020) [A]. The patient experienced abdominal pain, back pain, distention, nausea, and vomiting during the first 3 days. The physical examination was compatible with acute abdomen and peritonitis and the explorative laparotomy revealed the presence of diffuse free fluid in the abdomen and edematous changes around the pancreas. The symptoms cleared once the postoperative prednol dose was reduced and on the sixth postoperative day, the drain was removed, and the patient was discharged without any problem. The authors concluded that acute pancreatitis should be taken into consideration in patients receiving pulse steroid therapy for systemic vascular diseases, such as systemic lupus erythematosus.

Reduce cognitive function

Impact of corticosteroids on the executive cognitive functioning, mood and anxiety disorders was studied in a retrospective study which involved 83592 adults (mean age 44 years, 59% women) (Savas et al., 2020) [M]. The Ruff Figural Fluency Test was used to measure executive cognitive functioning, whereas, and Mini-International Neuropsychiatric Interview survey was used to study mood and anxiety disorders. Authors also studied additional parameters such as effect of corticosteroids on the quality of life (QoL; RAND-36), and inflammation (high-sensitive C-reactive protein [CRP]). The results indicated that the use of corticosteroids was associated with lower cognitive scores especially for those receiving systemic and inhaled corticosteroids. The use of inhaled corticosteroids was also associated with higher incidence of mood and anxiety disorders (Mood: OR 1.40 [95% CI 1.19–1.65], $P < 0.001$), (Anxiety: OR 1.19 [95% CI 1.06–1.33], $P = 0.002$), respectively. These findings were independent of physical QoL. An interesting fact was noted by the authors that the systemic users of corticosteroids are more likely to show mood disorders in contrast to nasal and dermal corticosteroid users who were more likely to have anxiety.
Alprostadil

Alprostadil is a synthetic prostaglandin, that works by vasodilating the muscles and blood vessels. It activates prostaglandin and can increase (cAMP) levels. Alprostadil can be administered via topical, intravenous, or intracavernous routes. Indicated use for alprostadil is erectile dysfunction, and common side effects that patients experience are light headedness, redness of the penis, or mild pain.

Erectile dysfunction

Erectile dysfunction (ED) is defined as the inability to maintain an erection. Phosphodiesterase type 5 inhibitors (PDE5Is) are first line therapy when treating ED while alprostadil is used as a second line therapy. Because alprostadil is a vasodilator, it helps treat erectile dysfunction by increasing blood flow to the penis. A literature review was done to study the effects of intracavernosal, (injection into the base of the penis), and intraurethral, (administered through the urethra) to evaluate the efficacy and safety of the medication. It was shown that intracavernosal injections of alprostadil can cause priapism, prolonged erection of the penis, and penile fibrosis. Intraurethral injections can show more systemic side effects of testicular pain, hypotension, and scrotal edema (Gul & Serefoglu, 2019) [R].

When alprostadil is combined with a PDE5 inhibitor a synergistic action takes place. A prospective, non-randomized study was done on 170 males over the age of 18 years old, and in a stable sexual relationship. Patients were either assigned to a group that was treated with a single therapy (alprostadil) or with combination of agents (alprostadil and PDE5 inhibitor). The monotherapy was topical alprostadil 300 μg, and the combination therapy was a PDE5 inhibitor and topical alprostadil 300 μg/100 mg (Garrido-Abad et al., 2021) [C]. The creams were applied 20 min before sexual intercourse. Both groups experienced adverse effects due to alprostadil such as penile pain or burning (20%), urethral discomfort (5.3%), facial flushing (4.1%), dizziness (3.5%), headache (1.2%), and back pain (0.6%).

Renal injury

Contrast induced nephropathy (CIN) is a form of kidney damage where the kidneys have had a recent exposure to medical imaging. CIN is the third leading cause of AKI. Research has showed that alprostadil is beneficial for treating CIN by regulating the vasoactive substance in the kidneys and improving hemodynamics. A research study was done to look at the efficacy of alprostadil for the treatment of renal injury. The adverse effects that were recorded were hypotension, dizziness, and headache (Xie et al., 2019) [M].

Another retrospective study was done on 100 patients with AKI to test the efficacy and safety of alprostadil. Fifty patients were given continuous venous–venous filtration, and the other 50 patients received alprostadil. Each group received the medication once every 12h for 1 week. Minor side effects of headache and dizziness were present in the group that took alprostadil (Jia et al., 2021) [R].

Epoprostenol

Eproprostenol is a prostaglandin that is indicated for pulmonary hypertension. It works by relaxing blood vessels and increasing blood supply to the lungs. Epoprostenol is administered intravenously and contains a short half-life. Common side effects of epoprostenol are nausea, vomiting, diarrhea, and headache.

Prostanoid-related symptoms

Sarcoidosis is an inflammatory disease that can affect the lungs and lymph glands. Pulmonary hypertension has common complication of sarcoidosis. This is normally caused by interactions between the sarcoid effects on the lung parenchyma and the pulmonary vasculature. A retrospective study was conducted to review patients who were treated with epoprostenol over an 18-year time period. Patients were excluded if they had any history of HIV, cardiac disease, illicit drug use, and portal hypertension. Patients were treated with intravenous epoprostenol via a tunneled catheter (Abston et al., 2020) [M]. With the initiation of epoprostenol some patients developed prostanoid related symptoms including nausea and vomiting, hypotension, diarrhea, and flushing.

Hyperthyroidism

Pulmonary arterial hypertension (PAH) can be defined as having a mean pulmonary arterial pressure ≥25 mmHg. Prostacyclin analogues have been known to be a major treatment option for PAH. Epoprostenol has shown to improve symptoms, increase exercise tolerance, and improve pulmonary hemodynamics. A recent study showed that a more severe side effect of epoprostenol can be hyperthyroidism. PAH patients that were admitted to the hospital were treated with epoprostenol, and their thyroid function was monitored. Each patient that developed thyroid dysfunction had normal thyroid
Idiopathic pulmonary arterial hypertension

Idiopathic pulmonary arterial hypertension (PAH) is caused by vascular proliferation and endothelial remodeling that can lead to pulmonary vascular resistance. Inhaled iloprost is used in combination therapy when a patient has failed to reach therapeutic goals. Eight patients diagnosed with PAH were given inhaled iloprost 45μg daily for 12 weeks using an OMRON nebulizer, which administered 0.25mL/min for each inhalation. Side effects were classified as an upper airway side effect, such as, cough, chest pain or discomfort, and pharyngolaryngeal pain were reported in this study (Fernandes et al., 2021) [A].

Aerosolized Iloprost

A systematic review/meta-analysis study was done to analyze the efficacy and safety of aerosolized iloprost in patients with PAH. The data criteria included dosage of inhaled iloprost, duration of therapy, and quality assessment of each study. Of the 10 studies that met the inclusion criteria, 370 patients were treated with inhaled iloprost at a dose of 2.5–5μg per inhalation. The most common side effects were headache (31.4%), cough (36.5%), chest pain/discomfort (23.4%), jaw pain (7.4%), and flushing (23.5%). More severe side effects included peripheral edema (10.8%), gastrointestinal symptoms (20.4%), and vertigo (21.8%). Approximately 4.5% of patients had to discontinue treatment due to adverse effects (Khan et al., 2019) [M].

Misoprostol

Misoprostol, a prostaglandin analogue, works by mimicking prostaglandins and stimulating prostaglandin receptors. Misoprostol has been shown to help reduce the effects of stomach ulcers that were caused by NSAIDs (non-steroidal anti-inflammatory drugs). It works by aiding the stomach lining to prevent damage. Misoprostol comes in many routes of administration sublingual, oral, vaginal, and vaginal with addition of water. Common side effects are nausea and vomiting, diarrhea, and shivering. Severe side effects include gastrointestinal bleeding, myocardial infarction, and hysterorrhexis.

Obstetrics and gynecology

In recent years, researchers have studied the use of misoprostol on treating various condition such as post-partum hemorrhage including medical abortion, medical management of miscarriage, induction of labor, and cervical ripening before surgical procedures. Compared to other medications used for post-partum hemorrhage misoprostol has shown to be more cost effective, has a
longer stability at room temperature, and is easier to administer.

A randomized double blind control study was conducted on 211 women who presented in active stage of labor. Women with amenorrhea were considered for this study. Women who were at high risk of hemorrhaging or had coagulation disorders were excluded from the study. The groups were similar in terms of age, socioeconomic group, and education level. Each patient was either given a placebo or 400 μg misoprostol orally. The study showed that the post-partum hemorrhage rate was lower in those who took misoprostol compared to the placebo. Major side effects that were recorded were headaches, dizziness, vomiting, diarrhea, and metallic taste (Zgaya et al., 2020) [C]. It was recorded that incidents of shivering were seen twice as much in patients who received misoprostol than those who received the placebo. In addition, women who received misoprostol had a higher temperature after delivery compared to women who received the placebo. Major side effects that were recorded include abdominal pelvic pain (13%) and changes in heart rate.

A study was done to monitor pyrexia or increase in temperature in 635 women who took misoprostol. This study compared misoprostol to oxytocin. Oxytocin is the first line treatment when treating post-partum hemorrhage. When oxytocin is not available or cannot be used, sublingual misoprostol 800 μg is used as an alternative. Women who were in active labor and did not have an allergy to a prostaglandin or had a planned cesarean section were able to participate in the study. Four 200 μg of misoprostol were placed under the tongue if their hemorrhage bleeding reached 500 mL (Durocher et al., 2020) [A]. Participants’ temperature was checked in 30-min intervals. The temperature was taken for a total of 2 h post administration. The results showed majority of the women had an increase in temperature (above 40°C) with misoprostol. Delivery time and blood levels prior to delivery influenced body temperature. Women who had a rapid delivery had a higher risk of developing a higher temperature. In addition, if the patient was anemic before delivery, their risk for developing a higher temperature was increased. Besides an increase in fever, other side effects like chill, shivering, nausea and vomiting, and itchy palms were also recorded.

Treprostinil

A prostacyclin analogue, treprostinil, is commonly used for the treatment of PAH to improve hemodynamic function. Treprostinil can be administered via intravenous (IV), subcutaneous (SQ), inhalation and oral routes. Oral treprostinil (Orenitram®) was introduced in 2013 for use for treatment of PAH. A cohort analysis was performed for 16 all patients that were hospitalized with PAH and receiving oral treprostinil. Oral treprostinil was administered at 2mg/day and was compared against IV epoprostenol and IV and SQ treprostinil. The patients were initially started on IV or SQ doses and transitioned to oral treprostinil. Overall, oral treprostinil was well tolerated with common adverse effects of gastrointestinal side effects (44%) and headaches (25%) observed among these patients (Hohlfelder et al., 2020) [C].

Inhaled treprostinil

Treprostinil promotes vasodilation of pulmonary and systemic arterial vascular beds. When formulated as an inhalation, treprostinil was revealed to improve exercise capacity after 12 weeks of initiation. Inhaled treprostinil was tested on a group of patients that were over the age of 18 who were diagnosed with pulmonary hypertension due to interstitial lung disease. The patients were randomly assigned with inhaled treprostinil or a placebo. The inhaled treprostinil was dispensed in an ultrasonic, pulsed delivery nebulizer at 6 μg per breath (Waxman et al., 2021) [C]. To study a patient’s exercise capacity, patients were required to walk 6 min a day every 4 weeks. The inhaler was used throughout the patient’s walk. Common adverse effects were cough, headache, dyspnea, dizziness, nausea, fatigue, and diarrhea. Severe adverse reactions such as throat irritation, oropharyngeal pain, and an increase in brain natriuretic peptides (BNP) were also documented.

Intravenous treprostinil

A retrospective study was conducted on 61 patients with left heart valvular disease and moderate to severe PAH. The patients were divided into two groups where one group received intravenous treprostinil 1.25ng/ (kg/min), and the other group received vasodilators, cardiac drugs, and diuretics. The length of treatment was 1 year, and patients were brought in every 3 months during the time of treatment. The most common side effects associated with treprostinil were pain at the injection site, diarrhea, and jaw pain (Xu et al., 2020) [A].

CONCLUSION

Prostaglandin analogues bind to the prostaglandin receptors and help with pulmonary hypertension and other various ailments. Given the severity of certain side effects with prostaglandin analogues, it is pertinent that monitoring parameters and careful considerations are taken.
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