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Mini-Review

Usefulness of bosentan in the treatment of pulmonary arterial hypertension in children

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ABSTRACT

Pulmonary arterial hypertension (PAH) is a disease characterized by increased pulmonary vascular resistance and severe hypoxemia. The cause of PAH in children is very different compared to the etiology in adults; in children PAH can be idiopathic in a vast majority of cases or associated with congenital heart disease (CHD). PAH is a disease that demands early diagnosis and this is crucial for a better prognosis of the patient. Bosentan (BST) is the first and the only oral drug approved by the health authorities for the treatment of the disease. In addition, it is a drug with the highest level of evidence "A", defined by the World Health Organization (WHO), for the treatment of PAH. Recent experience with BST in pediatric patients with PAH has shown that the drug offers a safe, effective and easy-to-administrate therapy. It is a specific and competitive antagonist of endothelin A (ETA) and endothelin B (ETB) receptors with high affinity for ETA. BST decreases the pulmonary and systemic vascular resistance, resulting in increased cardiac output without increasing heart rate. Furthermore, it has been observed that it is well tolerated and does not negatively affect systemic blood pressure or the liver transaminase levels. For the proper management of BST pharmacokinetics it is necessary to know the pharmacokinetic profile specifically in children, where dosage is a variable that determines pharmacological parameters and to consider the aspects that guarantee its efficacy and safety, which are the main points reviewed in this paper.

KEYWORDS: bosentan, children, increased vascular resistance, pulmonary arterial hypertension.

1. Introduction

Pulmonary arterial hypertension (PAH) is a disease marked by an uncontrolled increase in pulmonary vascular resistance and severe hypoxemia. PAH is frequently associated with pulmonary parenchymal abnormalities, pneumonia or sepsis. In newborns, it can occur when there is pulmonary hyperplasia, poor postnatal adaptation of the pulmonary vascular net due to perinatal stress, or poor intrauterine pulmonary vascular adaptation from unknown causes [1]. PAH in children is diagnosed with a mean pulmonary arterial pressure of ≥25 mmHg at rest or ≥30 mmHg during exercise, with the normal interlocking pressure being ≥15 mmHg [2]. Children with PAH often have an exaggerated pulmonary vascular bed response to exercise as well as in response to hypoventilation.

PAH is a condition with poor prognosis characterized by a progressive increase in

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pulmonary vascular resistance that ultimately leads to right ventricular heart failure [3].

Agents such as nitric oxide (NO) and prostacyclin (PG) favor arterial dilatation. On the contrary, endothelin (ET) and thromboxane A2 (TxA2) promotes vasoconstriction. Excessive vasoconstriction has been associated with abnormal function or expression of the potassium channels in the vascular smooth muscle, as well as with endothelial dysfunction. Endothelial dysfunction is involved in the decreased production of vasodilator agents such as NO and PG, along with increased expression of vasoconstrictor and proliferative substances such as ET and TxA2. In PAH, there is an imbalance in the production of these mediators towards those that favor vasoconstriction, inflammation, cellular proliferation and vascular thrombosis compared to those that exercise the opposite mechanism. Therefore, the knowledge of these mediators is not only crucial to understand the natural history of the disease, but also they are the targets to which different current treatments and new lines of research are directed. At present, three pathogenic pathways - NO, PG and ET - are recognized and are the subject of the therapeutic targets.

Majority of the children with elevated mean pulmonary arterial pressure (mPAP) have congenital heart disease (CHD), particularly a prominent chronic left-to-right shunt [4]. If the diagnosis is delayed, prognosis may worsen and sometimes limit treatment options [5, 6].

PAH is a consequence of an acute and chronic alteration of pulmonary vasculature. It is characterized by an increase in pulmonary arterial pressure. In both lungs, this pressure is greater than 25 mmHg in resting state, measured by right cardiac catheterization, with an interlocking pulmonary arterial pressure of less than 15 mmHG. The prognosis for children with PAH has improved due to new therapies and aggressive treatment strategies; nonetheless, the use of these therapies is based primarily on studies in adults rather than in children [7].

1.1. Pathophysiology of PAH

PAH is a progressive disease with relatively poor prognosis if not identified and treated early in children. In this group, especially in pediatric age, the transition of pulmonary circulation from fetal life to the neonatal period plays a key role in keeping pulmonary vascular resistance low. PAH is due to increased blood pressure and pulmonary vascular resistance of the right ventricle (RV). It can be caused by an array of disorders that give rise to remodeling of pulmonary vascular endothelium. The long-term consequences of these changes may lead to RV failure and finally to death [8].

PAH is a relatively rare disease. According to French registry, it has a prevalence of 15 cases per million inhabitants [9]. Women appear to be more likely diagnosed with PAH than men [10]. The pathology of PAH is not fully understood; however, it is characterized by pulmonary vascular and smooth muscle vasoconstriction [7].

The treatment of PAH has witnessed significant progress in the last 20 years. There are currently three groups of drugs: endothelin receptor blockers, phosphodiesterase inhibitors and the inhibitors of prostacyclin and their analogues, that have demonstrated their usefulness in the treatment of the disease.

It is well established that endothelin, nitric oxide and prostacyclin pathways play a crucial role in the development of PAH. In fact, the therapeutic options currently available for the treatment of the disease act in one of these mechanistic pathways. Nevertheless, this is an exciting time for the clinicians and scientists, as the greater understanding of the mechanisms involved in the pathogenesis and progression of PAH has given rise to the development of a number of new therapeutic options. New compounds such as macitentan, riociguat and selexipag act on endothelin, nitric oxide and prostacyclin pathways respectively, and have the potential to further improve the prognosis for patients with PAH [11].

2. Diagnosis

Clinical suspicion of PAH is based on both the symptoms and results of specific clinical tests and investigations that confirm PAH diagnosis. The symptoms of PAH are nonspecific and include breathing difficulties, fatigue, weakness, angina, dry cough and syncope. Symptoms at rest are

typical in more advanced cases. Idiopathic pulmonary arterial hypertension (IPAH) and PAH associated with congenital heart defects represent the highest modalities seen in pediatric population. The management mainly consists of the so-called support therapy coupled with specific medications. It is crucial to identify the cause of PAH and evaluate if specific therapies are of benefit for its management. The treatment and follow-up in children, unlike that of adults, is not preferentially guided by functional class, but based on risk determinants [1].

3. Pharmacological treatment

Over the past few decades, various pharmacological approaches including calcium channel blockers (CCB), prostacyclin analogues, ETA/ETB endothelin receptor antagonists and more recently, phosphodiesterase inhibitors have been introduced.

Bosentan (BST) has demonstrated improvement in cardiopulmonary hemodynamics, the ability and endurance to exercise, the quality of life and survival in adult patients with PAH. ETA-specific antagonists have also been demonstrated to have the same beneficial profile. BST is the first and the only oral drug approved by the health authorities for the treatment of the disease. In addition, it is a drug with the highest level of evidence "A", defined by the World Health Organization (WHO), for the treatment of PAH [12].

Recent experience with BST in pediatric patients with PAH indicated that the results obtained in adult patients can be extrapolated to children, which offers a safe, effective and easy-to-administrate therapy [13].

BST is a dual endothelin receptor agonist (ERA) with affinity for ETA and ETB receptors. It decreases both vascular and systemic vascular resistance, thus, giving rise to increased cardiac output without increasing the heart rate.

The predominant actions of the endothelin-1 (ET-1)/ETA binding are vasoconstriction and vascular remodeling, while the ET-1/ETB binding produces vasodilation and anti-proliferative effects [14].

ET-1 is a neurohormone and one of the most potent vasoconstrictors ever known. It also induces fibrosis, cellular proliferation, cardiac hypertrophy and remodelation as well as neuroinflammation. These effects are mediated by ET binding to ETA and ETB receptors in the vascular smooth muscle cells and in the endothelium cells. ET-1 concentrations in tissues and plasma increase in different cardiovascular disorders and in connective tissue diseases including in PAH, scleroderma, acute and chronic heart failure, myocardial ischemia, hypertension and atherosclerosis thus, suggesting ET-1 pathogenic role in these diseases. In PAH and heart failure, elevated ET-1 levels are closely correlated with severity and prognosis of the disease. Bosentan competes with ET-1 for binding to ETA/ETB receptors. BST is a specific antagonist of ET receptors and does not bind with other receptors [15]. ET-1 seems to be a key mediator in the pathogenesis of PAH where it has been demonstrated to have elevated plasma concentration. BST, an ET receptor antagonist, has been approved by the Food and Drug Administration (FDA) as an effective treatment for PAH in recent studies testing its efficacy [16].

3.1. Therapeutic effect of BST

As we have mentioned earlier ETA is found predominantly in vascular muscle cells; it is a powerful neurohormone and vasoconstrictor with the ability to promote fibrosis, while ETB, in addition to inducing constriction at the vascular level it also stimulates smooth muscle hyperplasia. The action of bosentan is to antagonize these receptors in the lung tissue, causing the smooth muscle along the pulmonary vasculature to relax, lowering pulmonary pressure and resistance; it inhibits fibrosis process and cell proliferation as well as prevents tissue remodeling. Plasma and pulmonary tissue ET-1 concentrations are elevated in patients with PAH, which suggests the pathogenic role of ET-1 in this disease. BST is a specific and competitive antagonist of ETA and ETB receptors with a slightly higher affinity for ETA than for ETB receptors. BST decreases pulmonary and systemic vascular resistance, which leads to an increase in cardiac output without increasing heart rate [17].

4. Pharmacokinetics of BST

Pediatric pharmacokinetic data have shown that the plasma BST concentrations were lower than

those in adults, and did not increase on raising BST doses to above 2 mg/Kg of body weight twice daily.

Based on the result of pharmacokinetic (PK) studies, high doses are unlikely to be more efficacious, but it is certain that such an increase in doses would increase the rate of adverse effects in young children. Therefore, the initial and maintenance doses is 2 mg/Kg of body weight in the morning and at night. No clinical studies have been performed to compare this relation.

When using any therapeutic scheme to treat PAH in children, the detection of long term adverse effects should be considered while planning the clinical trials for new PAH therapies due to the physiological changes that occur as children grow and develop [18]. In adults, BST reaches maximum plasma concentration (C_{max}) in 3 to 5 hours with C_{max} of 1000 ng/ml. In pediatric patients, C_{max} is reached in 1 to 4 hours. Its bioavailability is 50%. With regard to food, BST does not have any adverse effect with food consumption [19].

BST has a percentage of binding to plasma proteins of 98%, mainly albumin, and the volume of distribution (VD) is 18 L. It presents extensive hepatic distribution through CYP3A4 and CYP2C9 with metabolite active Ro 48-5033 and has self-induction metabolism by CYP3A. The activity of CYP3A4 and CYP2C9 increases after birth and reaches adult level after 1 year of age [19]. It is mainly excreted *via* the bile. Its renal excretion is less than 3% and its clearance is 4 L/hr, while the half-life elimination is 5 hours. The steady-state concentrations are reached within 3 to 5 days after multiple-dose administrations [19].

Furthermore, Steinhorn *et al*. [20] showed that BST doses of 2 to 4 mg/Kg did not alter the plasma concentrations in children, as well as the concentration time of overlapping doses of 2 and 4 mg/Kg, thus, suggesting that a plateau of exposure to a dose of 2 mg, twice a day was reached, probably due to the small size of their intestinal surface area and the different absorption characteristics.

5. Safety and efficacy

The common adverse reactions are airway infections, pyrexia, elevation of liver aminotransferase and liver failure [21]. BST was found to be well tolerated in one study and did not adversely affect systemic blood pressure or liver transaminase levels. The blood concentrations of BST were low and variable on day 1 and reached steady state on day 5 [20].

The FDA has approved the use of bosentan in adults and children above 3 years. Regarding its efficacy, it is truly effective in adults and in pediatrics, the evidence is in favor of its effectiveness. Its strength of recommendation for adults is class IIa, and in pediatrics, it is class IIb (Table 1). In terms of its strength of evidence in adults, it is Category A, and in pediatrics, it is Category B (Table 2) [22].

The cause of discontinuation of BST therapy for pediatric IPAH includes worsening of cardiac insufficiency and progressive pulmonary hypertension. Adverse effects (AEs) that BST may present are headache, nausea, facial flush and hypotension. According to the studies of Berger *et al.* for detecting BST's long-term AEs in children, it was deemed that the physiological changes that occur as children grow and develop should be taken into consideration [18].

Future study-1 was an open-labeled study of the effectiveness of BST tablets which in adults with PAH was 62.5 mg/40 Kg, taken twice daily, and in children with IPAH or hereditary PAH it was 32 mg, with an initial dose of 2 mg/Kg, administered for 4 weeks plus a maintenance dose of 8 weeks [15]. The conclusion of the study was that BST can be effective in pediatric treatment. Future study-2 was aimed to provide data on tolerability, safety and efficacy of BST therapy in children >2 and <12 years of age with IPAH and hereditary PAH who completed the treatment of Future study-1 and were considered to have obtained good benefits. These patients were given a dose of 4 mg/Kg of weight and emerging AEs were determined. It was found that these emerging AEs occurred in 32 (88.9%) of the patients. Of these 32 patients, AEs related to the treatment were produced in 15 (41.7%) of the patients. Of 51 severe adverse effects three were considered to be related to the treatment, 2 to incidents related to the worsening of PAH and 1 to hepatitis. There were 6 deaths that were not related to the treatment. In general, the pediatric formulation

Table 1. Recommendations based on bosentan clinical trials.

Class	Type of recommendation	Significance
I	Recommended	It has been demonstrated that the trial or the given treatments are useful and should be performed or administered.
IIa	Recommended in majority of the cases	The trial and given treatment are generally considered useful and this is indicated in majority of the cases.
IIb	Recommended in some cases	The trial and treatment may be useful and this is indicated in some cases but not in the majority.
III	Not recommended	The trial and treatment are not useful and should be avoided.
Undetermined	Undetermined evidence	

Table 2. Level of recommendation for preventive intervention.

Level of recommendation	Interpretation
A	There is good evidence to recommend preventive clinical intervention.
B	There is moderate evidence to recommend preventive clinical intervention.
C	The available evidence is conflictive and does not allow to make recommendation in favor or against preventive clinical intervention; nevertheless, other factors could influence the decision.
D	There is moderate evidence to recommend against preventive clinical intervention.
E	There is good evidence to recommend against preventive clinical intervention.
I	There is sufficient evidence (in quality and amount) to make a recommendation; nevertheless, other factors could influence the decision.

was well tolerated. When administered in children, its safety profile was comparable to that of the adult population [15].

Ivy *et al*. [23] performed a retrospective observational study in the United States of America with the objective of evaluating the age-related survival rate of children with PAH subjected to BST therapy along with other specific or independent PAH therapies. They found this at 1, 2, 3 and 4 years to be 98, 88, 82 and 82%, respectively. Despite the differences in pharmacological response of the children, BST therapy significantly prolonged the survival time.

A similar conclusion was reached in studies carried out by Barst *et al*. [24], Hislop *et al.* [25] and Berger *et al.* [26]. Each study showed a significant survival benefit with BST in pediatric patients with IPAH. The survival after a 3-year BST treatment was around 90%. In preliminary studies of patients with PAH, BST therapy improved exercise capacity and cardiopulmonary hemodynamics [27].

In a clinical trial done by Dhillon *et al.* [28], BST therapy also significantly improved several other hemodynamic variables and delayed the clinical worsening of the disease. Furthermore, in a small

open-labelled uncontrolled trial conducted in pediatric patients, the majority with mild symptoms, there was a significant improvement, right from the initial time, in several hemodynamic variables with bosentan administered at 31.25-125 mg, twice a day for three months. The dose of 125 mg, twice a day, was not associated with significant increase in adverse events. Nonetheless, the increase of the dose to 250 mg, twice a day, led to a higher frequency in the increase in transaminase levels [29, 30].

Hence, based on this, the therapeutic dose that would be administered in pediatric patients is confirmed. Long-term evaluation of BST benefits brought into limelight that it guarantees significant improvement in the symptoms as well as prolongs the life of the patients who used it [31].

6. Conclusion

Analysis of the information obtained leads to an overwhelming conclusion that BST is the drug of first choice in the treatment of PAH. This conclusion is heavily buttressed by the analyzed BST action mechanism, effectiveness and safety, as well as by the fact that adverse effects were not observed to elevate in patients in whom the drug was tried. Hence, we conclude that BST therapy in PAH children older than 2 years is reliable, prolongs the life of the patients, guarantees well-being and ensures long-term improvement. To obtain safe and tolerable therapeutic effects, we recommend the use of a dose less than 250 mg/Kg.

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CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Authors give their consent for publication.

AVAILABILITY OF DATA AND MATERIAL

The data used to support the findings of this study are available from the corresponding author upon request.

CODE AVAILABILITY

Not applicable.

AUTHORS' CONTRIBUTIONS

HJO[a,b,c,d,e], LSR[b,c,d,e], QVC[b,c,d,e], DCG[b,c,d,e], FTJ[b,c,d,e]

(a) Contributed to the conception and design of the work. (b) Contributed to the collection, analysis, or interpretation of data. (c) Critically revised the manuscript for important intellectual content. (d) Drafted manuscript. (e) Gave final approval.

CONFLICT OF INTEREST STATEMENT

All authors report that there are no conflicts of interest for this article.

REFERENCES

1. Caicedo-Cuenca, L. M. 2017, Revista Colombiana de Cardiología, 24, 89-97.
2. Montani, D., Günther, S., Dorfmüller, P., Perros, F., Girerd, B., Garcia, G., Jaïs, X., Savale, L., Artaud-Macari, E., Price, L. C., Humbert, M., Simonneau, G. and Sitbon, O. 2013, Orphanet J. Rare Dis., 8, 97.
3. Humbert, M., Sitbon, O., Yaïci, A., Montani, D., O'Callaghan, D. S., Jaïs, X., Parent, F., Savale, L., Natali, D., Günther, S., Chaouat, A., Chabot, F., Cordier, J. F., Habib, G., Gressin, V., Jing, Z. C., Souza, R. and Simonneau, G. 2010, Eur. Respir. J., 36, 549-555.

4. Gupta, S. K., Saxena, A. and Gulati, G. S. 2011, Indian J. Pediatr., 78(11), 1417-1419.
5. Subramanyam, N., Bobby, D. and Philip, J. 2010, Cardiol. Rev., 18(2), 76-84.
6. Chen, S. J., Huang, J. H., Lee, W. J., Lin, M. T., Chen, Y. S. and Wang, J. K. 2019, Korean J. Radiol., 20(6), 976-984.
7. Bevacqua, J. R., Bortman, G. and Perrone, V. S. 2018, Insuf. Card., 8(2), 77-94.
8. Tsutomu, S., Tomotaka, N. and Hiroyuki, M. 2008, Nihon Rinsho, 66(11), 2193-2199.
9. Sanges, S., Yelnik, C. M., Sitbon, O., Benveniste, O., Mariampillai, K., Phillips-Houlbracq, M., Pison, C., Deligny, C., Inamo, J., Cottin, V., Mouthon, L., Launay, D., Lambert, M., Hatron, P. Y., Rottat, L., Humbert, M. and Hachulla, E. 2016, Medicine (Baltimore), 95(39), e4911.
10. Memon, H. A. and Park, M. H. 2017, Cardiovasc. J., 3(4), 224-237. doi:10.14797/mdcj-13-4-224.
11. Sitbon, O. and Morreli, W. N. 2012, Eur. Respir. Rev., 21, 321-327.
12. Zamanian, R. T., Kudelko, K. T., Sung, Y. K., Perez, V. J., Liu, J. and Spiekerkoetter, E. 2015, Circ. Res., 115(1), 131-147. doi:10.1161/CIRCRESAHA.115.303827.
13. Maneenil, G., Thatrimontrichai, A., Janjindamai, W. and Dissaneevate, S. 2017, Pediatr. Neonatol., p58-64.
14. Calderón, A. C. 2009, Bosentan, Medication Report. Salud Madrid.
15. Berger, R. M. F., Haworth, S. G., Bonnet, D., Dulac, Y., Fraisse, A., Galiè, N., Ivy, D. D., Jaïs, X., Miera, O., Rosenzweig, E. B., Efficace, M., Kusic-Pajic, A. and Beghetti, M. 2016, Int. J. Cardiol., 202, 52-58.
16. Wang, Y., Chen, S. and Du, J. 2019, Front. Pediatr., 7, 302.
17. Product Information: Tracleer™, Bosentan. Actelion Pharmaceuticals Canada Inc., Laval, Quebec, 2001.
18. Berger, M. F. R., Gehin, M., Beghetti, M., Ivy, D., Kusic-Pajic, A., Cornelisse, P., Grill, S., Bonnet, D. and FUTURE-3 Investigators. 2017, Br. J. Clin. Pharm., 83, 1734-1744.
19. Product Information. Actelion Pharmaceuticals US, Inc (per FDA), South San Francisco, CA, 2017.
20. Steinhorn, R. H., Fineman, J., Kusic-Pajic, A., Cornelisse, P., Gehin, M., Nowbakht, P., Pierce, C. M., Beghetti, M. and FUTURE-4 Study Investigators. 2016, J. Pediatr., 177, 90-96.
21. Food and Drug Administration Center for Drug Evaluation Research. 2019, Approval date(s) and history, letters, labels, comments for bosentan. Washington, DC.
22. Product Information: Actelion Pharmaceuticals Canada Inc., Laval, Quebec, 2001.
23. Ivy, D. D., Rosenzweig, E. B., Lemarié, J. C., Brand, M., Rosenberg, D. and Barst, R. J. 2010, J. Cardiol., 106(9), 1332-1338.
24. Barst, R. J., McGoon, M. D., Elliott, C. G., Foreman, A. J., Miller, D. P. and Ivy, D. D. 2012, Circulation, 125(1), 113-122.
25. Hislop, A. A., Moledina, S., Foster, H., Schulze-Neick, I. and Haworth, S. G. 2011, Eur. Respir. J., 38(1), 70-77.
26. Berger, R. M., Beghetti, M., Humpl, T., Raskob, G. E., Ivy, D. D., Jing, Z. C., Bonnet, D., Schulze-Neick, I. and Barst, R. J. 2012, Lancet, 379(9815), 537-546.
27. Channick, R. N., Simonneau, G. and Sitbon, O. 2001, Lancet, 358, 1119-1123.
28. Dhillon, S. and Keating, G. M. 2009, Am. J. Cardiovasc. Drugs, 9(5), 331-350.
29. Mylona, P. and Cleland, J. G. 1999, Eur. J. Heart Fail, 1, 197-200.
30. Krum, H., Charlon, V., Widmann, T. and Packer, M. 1999, Circulation, 100(Suppl. I), 646-646.
31. Denton, C. P., Humbert, M., Rubin, L. and Black, C. M. 2006, Ann. Rheum. Dis., 65(10), 1336-1340.