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BRIEF REPORT / KISA RAPOR

Subcutaneous use of treprostinil in pediatric pulmonary hypertension patients: A report of three cases

Pediatrik pulmoner hipertansiyon hastalarında subkutan treprostinil kullanımı: Üç olgu sunumu

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ABSTRACT

Treprostinil was approved by the United States Food and Drug Administration for use in the treatment of pulmonary arterial hypertension in 2002. Intravenous or subcutaneous treprostinil is used in pulmonary arterial hypertension patients in the functional classes of II-IV to alleviate exercise-related symptoms, or in cases where epoprostenol treatment should be reduced due to side effects. In this article, we describe three pediatric cases of pulmonary arterial hypertension in whom subcutaneous treprostinil was used.

Keywords: Pulmonary arterial hypertension, subcutaneous, treprostinil.

ÖZ

Treprostinil 2002 yılında Amerika Birleşik Devletleri Gıda ve İlaç Dairesi tarafından pulmoner arteriyel hipertansiyon tedavisinde kullanım için onaylanmıştır. İntravenöz veya subkutan treprostinil fonksiyonel sınıflaması II-IV arasında olan pulmoner arteriyel hipertansiyon hastalarında, egzersiz ilişkili semptomları azaltmak amacıyla veya yan etkiler nedeniyle epoprostenol tedavisinin azaltılması gerektiği durumlarda kullanılmaktadır. Bu yazıda, subkutan treprostinil kullanılan pulmoner arteriyel hipertansiyonlu üç pediatrik hasta sunuldu.

Anahtar sözcükler: Pulmoner arteriyel hipertansiyon, subkutan, treprostinil.

Add-on treatment with prostacyclin analogues is occasionally necessary in severe refractory pediatric pulmonary arterial hypertension (PAH). The main therapy utilized in this circumstance is intravenous (IV) epoprostenol; however, the central venous line exposes the patient to infectious, mechanical, and thromboembolic problems.[1] Treprostinil is a chemically stable prostacyclin analogue with some similarities to epoprostenol in terms of pharmacological activities, since both activate the prostacyclin receptor, but treprostinil has certain unique qualities, such as staying stable at room temperature and having a longer half-life.[1]

In this report, we describe three pediatric cases of PAH in whom subcutaneous treprostinil was used and discuss the effects of treprostinil. This report is important, as it is the first pediatric experience in Türkiye.

BRIEF REPORT

Case 1- A five-year-old female patient referred to our clinic due to increased complaints of getting fatigued easily and bluish tint on her skin. Her laboratory findings revealed a pro-brain natriuretic peptide (pro-BNP) level of 6,314 pg/mL and troponin I of 44 ng/L. Her oxygen saturation level was 74%. The tricuspid annular plane systolic excursion (TAPSE) value was 1.8 cm on echocardiography. The 6-Min Walk Test (6MWT) could not be performed due to her age. Also, the New York Heart Association (NYHA) functional class (FC) IV was assigned to the patient. She was taking iloprost, bosentan, and sildenafil. Due to the patient's clinical condition, the iloprost was ceased and subcutaneous treprostinil (2.7 ng/kg/min) was started. The dose was progressively increased to 26 ng/kg/min at the end of three months.

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At 13 months of the treatment, the general condition of the patient improved, her FC was I-II and, for the first time, she could walk 229.6 m in 5 min at 6MWT. The TAPSE value of the patient was 2.06 cm at her final follow-up at 27 months, and she was able to walk 280 m in the 6MWT and her oxygen saturation was 84%. Also, a pro-BNP levels of 1,385 pg/mL and troponin T of 10 ng/L were found in her laboratory tests. The evolution of pro-BNP measurements over the course during follow-up is depicted in Figure 1. The patient is still taking bosentan, sildenafil, and treprostinil (27 ng/kg/min) and is clinically stable on this regimen.

Case 2- A 17-year-old male patient was referred to our clinic with the diagnosis of idiopathic PAH (IPAH). At the time of admission, he was using bosentan, iloprost, and sildenafil. At 52 months of follow-up, we decided to replace the bosentan treatment with macitentan, as the pro-BNP value increased significantly (4,473 pg/mL), her 6MWT decreased from 456 m to 285 m, and the TAPSE was 1.6 cm with an oxygen saturation of 95%. His tests at the initial follow-up after starting macitentan revealed a pro-BNP level of 3,372 pg/mL, which increased to 4,062 pg/mL throughout monitoring and his exercise capacity deteriorated. An echocardiographic examination indicated that the right ventricle (RV) was significantly dilated and the left ventricle (LV) seemed to be squashed. As a result, the iloprost treatment was discontinued and subcutaneous treprostinil (1 ng/kg/min) was initiated. Treprostinil dose was steadily increased, until it reached 10 ng/kg/min after one month and 23 ng/kg/min after three months. At 13 months of the treprostinil treatment, the 6MWT score was 523.8 m, oxygen saturation was 97%, and pro-BNP level was 537.5 pg/mL. Echocardiographic examination revealed that the TAPSE value was 2.2 cm. Figure 2 depicts the patient's pro-BNP levels, as the levels changed during the course of the follow-up. Sildenafil, macitentan, and treprostinil (23 ng/kg/min) are currently used to treat the clinically stable patient.

Case 3- A 12-year-old female patient was referred to our clinic with the diagnosis of IPAH. At the time of admission, the patient was receiving bosentan, sildenafil, iloprost, digoxin, enalapril, and spironolactone. Her initial blood tests indicated that a pro-BNP level of 3,735 pg/mL and troponin T of 13 ng/L. Her oxygen saturation level was found to be 72%. In the 6MWT, the patient was able to walk 60 m and was classified as NYHA FC IV. The RV was significantly dilated with a TAPSE value of 1.7 cm on echocardiography. The iloprost treatment was discontinued, subcutaneous treprostinil (1 ng/kg/min) was initiated, and the treprostinil dose was gradually increased to 20 ng/kg/min at the end of three months. The physical condition of the patient improved significantly and reached FC II. At the final follow-up, the patient was able to walk 120 m at 6MWT and oxygen saturation was 79%. Her laboratory tests revealed a pro-BNP level of

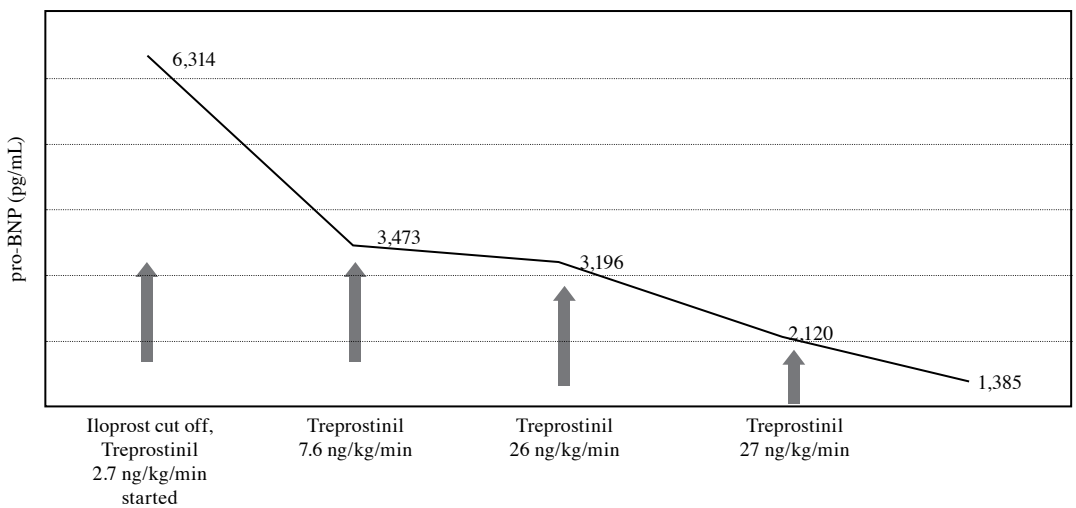

Figure 1. Changes in pro-BNP values throughout the follow-up of Case 1.
pro-BNP: Pro-brain natriuretic peptide.

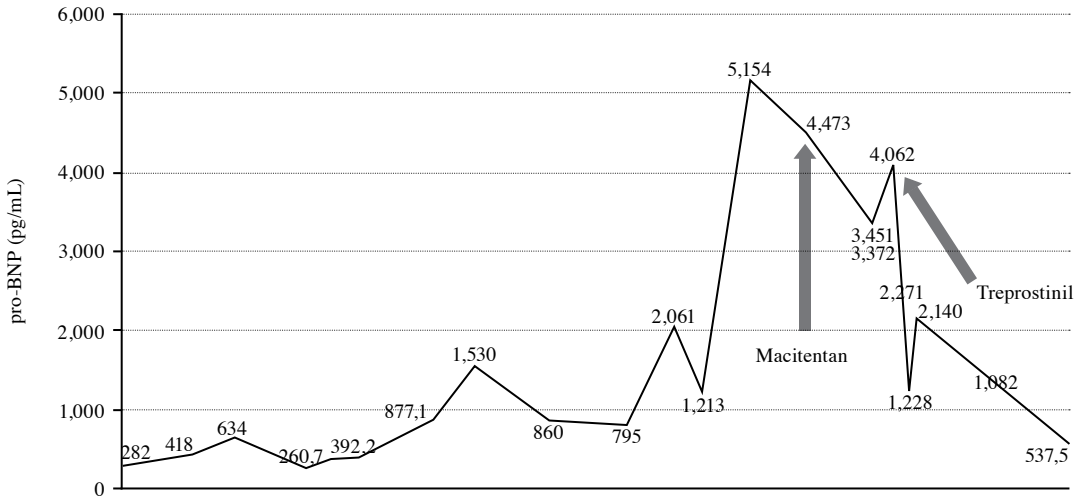

Figure 2. Changes in pro-BNP values throughout the follow-up of Case 2.
pro-BNP: Pro-brain natriuretic peptide.

2,002 pg/mL and troponin T of 11 ng/L. The patient is currently clinically stable on bosentan, sildenafil, and treprostinil (24 ng/kg/min) treatment.

DISCUSSION

Current pediatric guidelines recommend that children with severe and/or rapidly progressing PAH receive continuous IV/subcutaneous prostacyclin analogue treatment (epoprostenol or treprostinil).[2,3] However, there are several serious risks for IV treatment.

For this purpose, treprostinil is an effective therapeutic option that may be given as a continuous subcutaneous infusion before IV prostacyclin treatments. Prior to IV prostacyclin therapy, subcutaneous treprostinil seems to be a useful treatment choice instead of inhaled prostacyclin.

Despite the fact that there is no single, approved dose of treprostinil for children with PAH, we start treatment with a subcutaneous dose of 1-2 ng/kg/min based on the examination results of each patient, consistent with the most recent literature.[4,5] We steadily increase the dose until our patients benefit and tolerate it. We determine the level at which our patients' symptoms stabilize and continue their treatment by increasing the dose by a particular amount (2 ng/kg/min) every four days, until we reach our goal dose of 20 to 25 ng/kg/min. In any of the three cases presented in this report, there was no need to terminate or postpone treatment due to systemic or local adverse effects of treprostinil.

In conclusion, although treprostinil may cause nausea, vomiting, diarrhea, headache, dizziness, jaw pain, flushing, weakness, abdominal pain, redness, swelling and pain at the injection site, these side effects can be managed much more easily in children than in adults.[6] Regarding the safety of using treprostinil in children, randomized trials with extensive case series are required; nonetheless, the few results from experienced facilities, such as those in this report, are quite informative. Taken together, treprostinil should be considered as a back-up plan in experienced centers before administering parenteral prostacyclin treatment.

Patient Consent for Publication: A written informed consent was obtained from the parents and/or legal guardians of the patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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