Rebound of Involuted Infantile Hemangioma After Administration of Salbutamol

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Since the discovery of propranolol in the treatment of infantile hemangioma (IH), there has been emergent investigation of β-adrenergic receptor (β-AR) signaling in IH and the mechanisms of action for which β-AR blockers regulate hemangioma cell proliferation. However, β-AR agonists and antagonists are known to act antithetically via the same intracellular β-AR–driven proangiogenic pathways. We present the case of a patient with involuted IH treated with propranolol that showed a full and rapid regrowth during the intravenous administration of salbutamol, a selective β2-adrenergic agonist, for an episode of severe obstructive bronchitis. This observation brings forward the clinical implication of β-signaling effects in IH and raises awareness of the potential proliferative response of IH to β-AR agonists such as salbutamol.

Infantile hemangiomas (IHs) are the most frequent soft-tissue tumors of infancy, with an incidence between 3% and 10%. They are benign in nature and regress spontaneously; however, it is estimated that ~15% result in high-risk IH and therefore need prompt treatment. For decades, systemic corticosteroids were the mainstay therapy for IH. However, because of the poor risk/benefit ratio, most IHs were left untreated. After the serendipitous discovery of propranolol, their treatment has undergone a revolutionary shift worldwide, and there has since been an emergence of β-blockers for treating IHs, including the use of topical β-blocker timolol for noncomplicated IH.1,2 Herein, we report the case of a 26-month-old girl with an involuted IH after propranolol therapy who exhibited a full and rapid rebound during the intravenous (IV) administration of salbutamol, a selective β2-adrenergic agonist, for an episode of severe obstructive bronchitis.

CASE REPORT

A 9-week-old girl was referred for the evaluation of a rapidly growing IH on her left shoulder. She was a preterm twin infant born at 26 weeks’ gestation with a birth weight of 860 g. Physical examination revealed a focal hemangioma measuring 2.0 × 2.0 × 0.8 cm on her left shoulder (Fig 1A). The patient remained hospitalized for prematurity, and at the age of 35 weeks’ gestation, treatment with propranolol was initiated at a dose of 2 mg/kg per day in 3 daily doses under monitoring of her heart rate and blood pressure. Fading of color and decrease in size of the IH were noted rapidly during the first 3 months of treatment, and there was a continued effect for up to 10 months of treatment with the same weight-adapted dose of 2 mg/kg per day. When no further change was noted, propranolol was stopped (without tapering) after a total of 14 months of treatment (Fig 1B). The IH remained flat and pale during the
additional follow-up. At the age of 26 months, she was admitted to our ICU for an acute episode of severe obstructive bronchitis with respiratory failure despite salbutamol and ipratropium bromide inhalation therapy. She required rescue treatment with continuous IV salbutamol (2 μg/kg per min), IV methylprednisolone (2 mg/kg per day), and ipratropium bromide inhalation (125 μg 3 times daily) and was mechanically ventilated for 5 days. Within 24 hours of IV salbutamol administration, a significant increase in redness and remarkable swelling of the IH were observed (Fig 1C). These changes persisted during the 4 days of IV salbutamol and methylprednisolone treatment and reduced somewhat during the following days after switching to salbutamol inhalation therapy. Reevaluation of the IH 2 months later again revealed a flat lesion with residual redness (Fig 1D).

**DISCUSSION**

Here, we document the impressive reaction of an IH under initial treatment with a β-adrenergic receptor (β-AR) antagonist and later with a β-AR agonist. Propranolol therapy induced the expected characteristic involution of this proliferating IH. However, we were intrigued to see a rapid and marked swelling of the IH with the initiation of systemic β-AR agonistic treatment with salbutamol at the age of 26 months despite concurrent systemic corticosteroid therapy. The occurrence of rebound growth of IH after propranolol withdrawal is well documented in up to 25.3%. In our patient, propranolol treatment had been stopped 10 months earlier, and the presence of a rapid and impressive rebound within 24 hours immediately after the administration of salbutamol led us to firmly believe a cause-and-effect relationship between both events.

In 2008, Léauté-Labrèze et al described the rapid effect of propranolol treatment in IH with fading of color within 24 hours but also early softening of the tumor. Advances have since been made in the understanding of β-adrenergic signaling involved in IH. Emerging evidence reveals that catecholamines can promote angiogenesis and tumor progression by stimulating β1-adrenergic receptor and β2-adrenergic receptor (β2-AR) expressed in hemangioma-derived endothelial cells and pericytes. First, β-AR agonists lead to vasodilatation via release of nitric oxide, which would explain the rapid increase in color and volume seen in this case. Second, they might stimulate the synthesis of proangiogenic factors such as vascular endothelial growth factor, basic fibroblast growth factor, and matrix metalloproteinase 9, and thus upregulate vasculogenesis signaling cascades.

According to the results obtained by Phillips et al, messenger RNA expression levels of β2-AR were detected with no significant differences in proliferative, involuted, and propranolol-responsive hemangioma tissue, which might explain salbutamol’s action during all stages of IH. Our observation supports its effect in an involuted IH that resulted in rapid regrowth. What is more, according to the data shown on β2-AR expression in IH, such response would be analogous in proliferating IH, and physicians treating IH should be aware of this potential event. To the best of our knowledge, this is the first demonstration of IH regrowth triggered by a β2-AR agonist. Yet salbutamol is widely prescribed in young children for the treatment of acute bronchospasms. Although not shown here, we believe to have observed mild rebound growth in a few patients with IH during episodes of salbutamol inhalation therapy. Apart from demonstrating the clinical relevance of β-signaling effects in IH, this case raises awareness of the potential proliferative response of IH to β2-AR agonist treatment such as salbutamol.

**ABBREVIATIONS**

IH: infantile hemangioma
IV: intravenous
β-AR: β-adrenergic receptor
β2-AR: β2-adrenergic receptor

**REFERENCES**


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