Preliminary results of propranolol treatment for patients with infantile hemangioma

Funda Çorapcıoğlu[1], Sema Büyükkapu-Bay[1], Köksal Binnetoğlu[1], Abdulkadir Babaoğlu[1], Yonca Anık[2], Melih Tugay[3]

Departments of [1]Pediatrics, [2]Radiology, and [3]Pediatric Surgery, Kocaeli University Faculty of Medicine, Kocaeli, Turkey

SUMMARY: Çorapcıoğlu F, Büyükkapu-Bay S, Binnetoğlu K, Babaoğlu A, Anık Y, Tugay M. Preliminary results of propranolol treatment for patients with infantile hemangioma. Turk J Pediatr 2011; 53: 137-141.

Propranolol, a non-selective β-blocker, has recently been introduced as a treatment for infantile hemangiomas. In this study, we evaluated the effect of propranolol in 12 infants with hemangioma.

Twelve infants (9 girls) with a median age of 4.5 months were included in the study. All of the patients in the study group received short-term (1-9 weeks, median: 4 weeks) systemic corticosteroids as a first-line therapy. All patients received propranolol 2 mg/kg/day, divided into three doses. They were treated in an inpatient setting for the first 72 hours of the treatment. Vital signs, blood pressure and blood glucose were monitored. Propranolol treatment was given for 4-9 months (median: 5 months). In the study group, regression rate of the mean dimension of the lesion was 38%±15 (range 15%-50, median 45%) at the 2nd month of therapy. Over 9 months, which was the maximum follow-up period, the regression rate of the mean dimension of the lesion was 55%±31 (range 20%-80, median 50%). One patient had transient bradycardia, which improved spontaneously. No other side effect was observed in the study population.

Propranolol appears to be an effective drug for infantile hemangiomas with good clinical tolerance. We suggest that propranolol is the preferable drug as the first-line therapy for infantile hemangiomas.

Key words: infant, hemangioma, propranolol.

Infantile hemangiomas (IH) are the most common vascular tumors of childhood. They are often absent or small at birth and generally grow rapidly in the first months of life followed by a variable period of involution spanning months to years. Most of these lesions are self- limited. Nevertheless, some hemangiomas can impair vital functions or cause morbidity and mortality. Infections and bleeding are the more common complications of those involving the skin folds and perianal region[1,2].

Systemic corticosteroids (usually prednisone or prednisolone) are the mainstay of therapy for life-threatening or function-threatening hemangioma, as well as for selected hemangiomas with a probability of leaving permanent disfigurements. While systemic corticosteroids can be effective in IH, response is variable, and side effects are insidious, difficult to monitor and potentially serious. Other medications such as interferon-α, vincristine and cyclophosphamide that have been used to treat corticosteroid-resistant cases have higher risks for adverse effects[3-7].

Propranolol, a non-selective β-blocker, has recently been introduced as a treatment for IH[8-12]. Propranolol causes vasoconstriction and reduces expression of angiogenic factors during the growth phase of hemangiomas. It is also thought to cause direct induction of apoptosis in capillary endothelial cells. Preliminary reports about the treatment of IH with propranolol suggest that propranolol proved itself effective in inducing regression of growing hemangiomas[13-16].

In this study, we evaluated the effect of propranolol in 12 infants with IH who were treated with oral prednisolone but did

not response completely to corticosteroid treatment.

Material and Methods

Twelve infants (9 girls) with a median age of 4.5 months were included in the study. All of the patients in the study group received systemic corticosteroids as a first-line therapy. The patient's characteristics are given in Table I. Three patients (No. 1, 2, 4) were diagnosed histopathologically, while in the other patients, diagnosis was confirmed with clinical features and radiologic findings (magnetic resonance [MR] and ultrasonography [USG]). The mean dimension of IH was 36.5±19.2 mm (15-89 mm). Oral prednisolone 2 mg/kg/day for 1-9 weeks (median: 4 weeks) was used in the study group. Steroid therapy indications were functional impairment in 6 patients, hemorrhagia and ulceration in 5 patients, and intratumoral massive hemorrhagia in 1 patient (patient with infantile hepatic hemangioma). It is well known that the duration of a maximum 9 weeks of steroid therapy is not sufficient to evaluate response to the treatment. Although the duration was short, 11 patients did not have objective measurable response to prednisolone and treatment was discontinued in 1 patient because of remarkable Cushingoid appearance at the 4th week of the steroid therapy. All the patients were switched to propranolol therapy with cessation of steroid. Steroid was tapered slowly in the patients who received the drug for longer than 4 weeks. Informed consent was obtained from the parents of all patients for treatment and research. All patients received propranolol (Dideral®, 40 mg oral tablets, Sanofi-Aventis) 2 mg/kg/day, divided into three doses. The oral 40 mg formulation was diluted with 10 ml water into an injector and the dosage was calculated by 4 mg/ml. They were treated in an inpatient setting for the first 72 hours of the treatment. Vital signs and blood pressure were monitored, blood glucose was measured at 8-hour intervals (1 hour after each propranolol dose), and electrocardiography was performed daily. After inpatient follow-up, electrocardiography, blood pressure and blood glucose were monitored at 2-4-week intervals. To evaluate cardiac functions, patients were examined with echocardiography at baseline and at 1-month intervals by an experienced pediatric cardiologist (A.B.). For the clinical treatment response, the patients were followed weekly with the measurement of the dimensions of the lesions. The response evaluation was made radiologically in patients with hepatic and parotid IH. Preliminary treatment response was defined as early response because of the short follow-up period in all patients.

Results

Propranolol treatment was given for 4-9 months (median: 5 months). The objective response to the treatment was observed at a median of 2 weeks (range: 3-30 days). Significant reduction was seen in 9 patients in the first 2 weeks of the treatment. In the study group, the regression rate of the mean dimension of the lesion was 38%±15 (range 15%-50, median 45%) at the 2nd month of therapy. Treatment of the study group is ongoing. During 9 months, which is the maximum follow-up period, the regression rate of the mean dimension of the lesion was 55%±31 (range 20%-80, median 50%). During the follow-up period, only 1 patient's heart rate was determined as 80/min after the second and third hours of the propranolol therapy. No other cardiac side effects were observed in the study population, and hypoglycemia was not determined in any patient.

Discussion

Propranolol is the prototypical non-selective β-blocker, and antagonizes both β1 and β2 receptors. It is mainly used in the treatment of hypertension. Propranolol has also been used in pediatric cardiology to treat congenital cardiac anomalies, supraventricular tachycardia, long Q-T syndrome, congestive heart failure, and arrhythmias[17,18].

Vasoconstriction is proposed as a basic effect on IH, but decreased expression of vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF)-beta genes and triggering of apoptosis of capillary endothelial cells are other possible explanations[4,11,12,14].

The use of propranolol in the treatment of IH was first reported by Léauté-Labréze et al.[12]. This observed response was discovered with an attempt to treat the adverse cardiac effects that developed as a result of high-dose systemic corticosteroids (index case).

An ideal dosage has not been established in the treatment of IH; most patients in the

Table I. Patients Characteristics and Response to Propranolol

#	Age (months)/ gender	Tumor type, max. diameters, localization	Treatment indication	Duration of prednisolone therapy (weeks)	Objective response time (days)	Treatment duration (months)	Response*** (%)
1	2/F	IH, 41x22 mm, parotid region	functional impairment	3	4	5	60
2	3/F	IH*, 89x65 mm, hepatic	intratumoral massive hemorrhagia	1	7	4	80
3	1/M	IH, 52x40 mm, parotid region	hemorrhagia and ulceration	2	3	9	80
4	23/M	IH, 44x35 mm, preauricular	functional impairment	4	7	5	50
5	6/F	IH, 30x30 mm, perianal	hemorrhagia and ulceration	4	5	5	70
6	3/M	IH, 23x20 mm, postauricular	functional impairment	4	15	6	50
7	9/F	IH, 28x25 mm, forearm	hemorrhagia and ulceration	6	30	5	20
8	3/F	IH, 30x27 mm, lumbar	hemorrhagia and ulceration	9	15	5	75
9	14/F	IH, 25x23 mm, scalp	hemorrhagia and ulceration	8	21	6	40
10	2/F	Hemangiomatosis**, 32x28x12 mm, multiple cutaneous (scalp, arm, foot)	functional impairment	4	7	5	40
11	10/F	Hemangiomatosis**, 29x29x10 mm, multiple cutaneous (scalp, trunk, nasal)	functional impairment	4	15	4	50
12	24/F	Hemangiomatosis**, 15x12x9 mm, multiple cutaneous (limb, trunk, axilla)	functional impairment	4	30	8	50

IH: Infantile hemangioma.

*Infantile hepatic hemangioma, localized type

**No other internal organ involvement determined radiologically

***Clinic/radiological reduction rate of the max. diameter (for all lesions in patients with hemangiomatosis)

initial reports received 2-3 mg/kg/day[9,11-16]. Recommendations for instituting treatment with propranolol in infants are a starting dose of 0.17 mg/kg given at 8-hour intervals, monitoring of vital signs and blood glucose 1 hour after each dose, and follow-up with slower dose escalation[9]. In our series, all patients received propranolol at a dose of 2 mg/kg/day without escalation.

Initial case reports have demonstrated that the efficacy of propranolol began in the first few days and by 7-60 days of therapy, dramatic clinical responses were observed[11,14-16]. In our study, although there were patients with very early clinical response, it will be disappointing for the pediatricians who are accustomed to the quick dramatic response to prednisolone. In this regard, we consider it proper to wait 2 weeks for the satisfactory response. The optimal duration of treatment, although not clear, varies between 4-7 months[8,9,14-16]. Standard recommendations have not been established as to whether rebound growth will occur upon cessation of treatment, but it is reported that re-introduction of the treatment is successful in children[15]. In our series, treatment was not completed yet, so we cannot comment about rebound growth or re-introduction therapy.

When β-adrenergic receptors are blocked, predictable events that include bradycardia, hypotension and hypoglycemia can occur[8]. Lawley et al.[9] reported two infants, 8 weeks old and 36 days old, treated with propranolol who suffered complications as bradycardia and occult hypoglycemia. Side effects are relatively easy to monitor and treat in an inpatient setting[9]. Infants with large hemangiomas, who have cardiac comorbidities and are younger than 3 months of age, should be treated in an inpatient setting, monitored closely and consulted with pediatric cardiologists[14]. In our series, three infants were younger than 3 months of age. We did not observe significant side effects that may require discontinuation of the treatment (except for temporary bradycardia in 1 infant). However, in our study group, all patients were treated in an inpatient setting for the first 72 hours of the treatment and were consulted with a pediatric cardiologist. We should emphasize that the study was performed in a small group and no predictable events were observed in this study related to patient number.

In conclusion, we suggest that propranolol is the preferable drug as the first-line therapy for IH. No predictable events were observed in this study. However, we should emphasize that the study was performed in a small group of patients, and we do not want to excessively encourage other authors, because many questions remain about the safety of propranolol in infancy.

REFERENCES

1. Garzon MC, Frieden IJ. Heamangiomas: when to worry. Pediatr Ann 2000; 29: 58-67.
2. Kilcline C, Frieden IJ. Infantile hemangiomas: how common are they? A systematic review of the medical literature. Pediatr Dermatol 2008; 25: 168-173.
3. Pandey A, Gangopadhyay AN, Gopal SC, et al. Twenty years' experience of steroids in infantile hemangioma- a developing country's perspective. J Pediatr Surg 2009; 44: 688-694.
4. Nguyen J, Fay A. Pharmacologic therapy for periocular infantile hemangiomas: a review of the literature. Semin Ophthalmol 2009; 24: 178-184.
5. Ezekowitz RA, Mulliken JB, Folkman J. Interferon alfa-2a therapy for life-threatening hemangiomas of infancy. N Engl J Med 1992; 326: 1456-1463.
6. Hasan Q, Tan ST, Gush J, Peters SG, Davis PF. Steroid therapy of a proliferating hemangioma: histochemical and molecular changes. Pediatrics 2000; 105: 117-121.
7. Boye E, Jinnin M, Olsen BR. Infantile hemangioma: challenges, new insights, and therapeutic promise. J Craniofac Surg 2009; 20: 678-684.
8. Frieden IJ, Drolet BA. Propranolol for infantile hemangiomas: promise, peril, pathogenesis. Pediatr Dermatol 2009; 26: 642-644.
9. Lawley LP, Siegfried E, Todd JL. Propranolol treatment of infancy: risk and recommendations. Pediatr Dermatol 2009; 26: 610-614.
10. van der Meijs BB, Merks JH, de Haan TR, Tabbers MM, van Rijn RR. Neonatal hepatic haemangioendothelioma: treatment options and dilemmas. Pediatr Radiol 2009; 39: 277-281.
11. Theletsane T, Redfern A, Raynham O, et al. Life-threatening infantile haemangioma: a dramatic response to propranolol. J Eur Acad Dermatol Venereol 2009; 23: 1465-1466.
12. Léauté-Labréze C, Dumas de la Roque E, Hubiche F, Boralevi F. Propranolol for severe hemangiomas of infancy. N Engl J Med 2008; 358: 2649-2651.
13. Bonifazi E, Colonna V, Mazotta F, et al. Propranolol in rapidly growing hemangiomas. Eur J Pediatr Dermatol 2008; 18: 185-192.
14. Marsciani A, Alaggio R, Brisigotti M, Vergine G. Massive response of severe infantile hepatic hemangioma to propranolol. Pediatr Blood Cancer 2010; 54: 176.

15. Sans V, de la Roque ED, Berge J, et al. Propranolol for severe infantile hemangiomas: follow-up report. Pediatrics 2009; 124: e423-431.

16. Mousa W, Kues K, Haas E, et al. Successful treatment of large hemangioma with propranolol. J Dtsch Dermatol Ges 2010; 8: 184-186.

17. Robinson RF, Nahata MC, Batisky DL, Mahan JD. Pharmacologic treatment of chronic pediatric hypertension. Paediatr Drugs 2005; 7: 27-40.

18. Yadav S, Khalil A. Propranolol. Indian Pediatr 1989; 26: 811-814.