



# Bleomycin plasma spill-over levels in paediatric patients undergoing intralesional injection for the treatment of haemangiomas

G Ionescu, P Mabeta, N Dippenaar, T Muir, P Fourie, G Shelver

**To the Editor:** Haemangiomas are the most common tumours of infancy.<sup>1</sup> Although most are symptomless, some cause serious complications related to their anatomical location or biological behaviour and therefore require treatment.<sup>2</sup> The beneficial effect of intralesional bleomycin infiltration (IBI) in the treatment of haemangiomas has been reported.<sup>3,4</sup>

The Pretoria Vascular Malformation Study Group evaluated the effectiveness of IBI treatment in 37 patients with haemangiomas. Complete resolution or significant improvement occurred in 87% of patients with an extremely low side-effect profile, reported complications mainly including local pain and transient flu-like symptoms.<sup>4</sup> Ulceration and

flagellate pigmentation were observed in a small percentage of patients (unpublished data).

The major complication seen in cancer patients treated with systemic bleomycin is the development of pulmonary fibrosis, which is considered to be dose-dependent.<sup>5</sup> It is not known whether IBI treatment for haemangiomas carries the same degree of risk to the pulmonary vasculature as intravenous administration for cancer chemotherapy.

## Materials and methods

IBI was used for the treatment of 4 paediatric patients with haemangiomas at dosages of 0.2 - 0.9 mg/kg/treatment (Table I). The bleomycin sulphate formulation used was Blenoxane (Bristol-Myers Squibb, Bedfordview, South Africa), which is a mixture of glycopeptides containing approximately 69% bleomycin A<sub>2</sub> and 29% bleomycin B<sub>2</sub>.<sup>6</sup> The diagnosis of haemangioma was based on medical history and physical examination. Magnetic resonance imaging provided further useful information on the location and extent of the haemangioma, and involvement of deeper structures in the more complex lesions. Intralesional injections were followed by local application of pressure for 10 minutes after which, where possible, a pressure dressing was applied. Baseline blood samples were obtained from each patient before treatment and at 10 minutes, 30 minutes, 1 hour, 6 hours and 24 hours after IBI. As controls, blood samples were taken at the same time intervals as for the haemangioma patients from 4 paediatric cancer patients who received bleomycin intravenously. A Waters LC Module 1 HPLC fitted with a model 486 UV

*Department of Paediatric Surgery, University of Pretoria, and Department of Pediatric Surgery, Tawam Hospital, Al Ain, UAE*

**G Ionescu**, MD, PhD

*Department of Physiology, University of Pretoria*

**P Mabeta**, MSc

**N Dippenaar**, PhD

*Department of Plastic Surgery, University of Pretoria, and James Cook University Hospital, North Yorkshire, Middlesbrough, UK*

**T Muir**, MB ChB, MMed

*Unitas Interventional Unit, Unitas Hospital, Pretoria*

**P Fourie**, MB ChB, MMed

*Varian Inc., Walnut Creek, California, USA*

**G Shelver**, PhD

*Corresponding author: P Mabeta (peace.mabeta@up.ac.za)*

539

**Table I. Mean levels of bleomycin fractions bleomycin A<sub>2</sub> and B<sub>2</sub> (±SE) in plasma samples obtained over a 24-hour period from haemangioma and cancer patients\***

Patient No.	Age	Diagnosis	Dose (mg/kg)	Bleomycin A <sub>2</sub> (µg/ml)	Bleomycin B <sub>2</sub> (µg/ml)
1	10 mo.	Haemangioma	0.94 IBI	0.00	0.00
2	6 mo.	Haemangioma	0.60 IBI	0.00	0.00
3	13 mo.	Haemangioma	0.60 IBI	0.00	0.00
4	10 mo.	Haemangioma	0.20 IBI	0.00	0.00
5	10 yrs	Hodgkin's lymphoma	0.40 IV	273.16±121.26	164.44±63.86
6	12 yrs	Hodgkin's lymphoma	0.50 IV	678.44±164.7	237.48±83.92
7	14 yrs	Hodgkin's lymphoma	0.20 IV	211.95±106.56	99.98±51.24
8	15 mo.	Kaposi's sarcoma	0.50 IV	279.60±37.63	129.53±22.02

\*2 patient samples were analysed per treatment time.  
IBI = intralesional bleomycin infiltration; IV = intravenous.

detector (294 nm) (Waters Corp., Milford, MA, USA) and a C-18 Luna column (150×4.6 mm) (Phenomenex Corp., Sunnyvale, CA, USA) were used to separate and quantitate the Bleomycin fractions (bleomycin A<sub>2</sub> and B<sub>2</sub>) in plasma samples according to a method developed in our laboratory (unpublished data). Instrument control, data acquisition and quantitation were done using the (Galaxie CDS) data system (Varian Inc., Palo Alto, CA, USA). All samples were prepared and assayed in duplicate.

## Results

Following intralesional bleomycin treatment, peak levels of bleomycin fractions were detected in all 4 haemangioma patients after 1 hour. Table I shows the bleomycin plasma levels measured in haemangioma and cancer patients. Bleomycin was not detected in the plasma of haemangioma patients at 10 minutes, 30 minutes, 1 hour, 6 hours and 24 hours following IBI. At these time points, the mean levels of the two bleomycin fractions ranged from 211.95 to 678.44 µg/ml for bleomycin A<sub>2</sub> and 99.90 to 340.32 µg/ml for bleomycin B<sub>2</sub>.

## Discussion

Little is known about the mode of action of bleomycin or its systemic absorption after intralesional injection in the treatment of paediatric haemangiomas or low-flow vascular malformations. Systemic toxicity after intralesional bleomycin therapy has not been reported in haemangioma patients. Nevertheless, the potential for bleomycin-induced pulmonary toxicity when used in the treatment of non-malignant diseases remains a major concern. To study these potential side-effects, the determination of circulatory spill-over after intralesional bleomycin injection of vascular lesions was considered imperative.

The average doses of bleomycin injected into the haemangioma patients were between 0.2 and 0.9 mg/kg, which did not differ significantly from the average doses injected in the cancer therapy patients (0.2 - 0.5 mg/kg). However, injection was intralesional for haemangiomas, whereas it was systemic (intravenous) in the cancer patients. The mean levels of bleomycin A<sub>2</sub> and B<sub>2</sub> measured in samples of IBI-treated patients over the full 24-hour period were 0 µg/ml for both fractions and 360.79 and 183.57 µg/ml in samples of cancer patients treated with intravenous bleomycin (Table I). From these results it is apparent that the plasma bleomycin concentrations of haemangioma patients receiving bleomycin *intralesionally* were in the order of 100 times lower than plasma bleomycin concentrations obtained from samples of the cancer patients receiving bleomycin *intravenously*. These findings indicate that the low levels detected may translate to a significantly lesser risk of pulmonary fibrosis following IBI.

This study was funded by Bristol Myers Squibb. We thank Dr Ian Duncan for his expert guidance in the preparation of this manuscript.

## References

1. Mulliken JB, Young AE. *Haemangiomas and Malformations*. Philadelphia: WB Saunders, 1988: 39-65.
2. Tan ST, Velickovic M, Ruger BM, Davis PF. Cellular and extracellular markers of hemangioma. *Plast Reconstr Surg* 2000; 106: 529-537.
3. Kullendorf CM. Efficacy of bleomycin treatment for symptomatic hemangiomas in children. *Pediatr Surg Int* 1997; 12: 526-528.
4. Muir T, Kirsten M, Fourie P, Dippenaar N, Ionescu GO. Intralesional bleomycin injection (IBI) treatment for hemangiomas and congenital vascular malformations. *Int J Pediatr Surg* 2004; 19: 766-773.
5. James MP, Collier PM, Aherne W, Hardcastle A, Lovegrove S. Histologic, pharmacologic, and immunocytochemical effects of injection of bleomycin into viral warts. *J Am Acad Dermatol* 1993; 28: 933-937.
6. Dorr RT, Meyers R, Snead K, Liddil JD. Analytical and biological inequivalence of two commercial formulations of the antitumour agent bleomycin. *Cancer Chemother Pharmacol* 1998; 42: 149-154.

Accepted 18 February 2008.