ARCHIVES OF ORAL BIOLOGY 54 (2009) 6–11

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Permanent reduction of mandibular size and bone stiffness induced in post-weaning rats by cyclophosphamide

*María I. Olivera, María P. Martínez, María I. Conti, Clarisa Bozzini, Carlos Eduardo Bozzini *, Rosa M. Alippi*

Department of Physiology, Faculty of Odontology, University of Buenos Aires, Buenos Aires, Argentina

ARTICLE INFO

Article history:
Accepted 12 August 2008

Keywords:
Mandible
Mandibular growth
Bone biomechanics
Cyclophosphamide

ABSTRACT

It has been previously reported that several doses of cyclophosphamide (CPA) reduce body weight gain, diaphyseal torsional strength and longitudinal femoral growth in the growing rat. The present study was thus designed to estimate both the initial and the possible long-term effects of CPA treatment, by analyzing mandibular dimensions and biomechanical performance of the bone in adulthood in rats treated with the drug around weaning. Female Sprague–Dawley rats ($N = 20$), 26 d of age, received 100 mg/kg of CPA by the intraperitoneal route during days 0, 7 and 21 of the experimental period. Controls (C) received saline. Groups of rats were sacrificed at day 28 to estimate initial changes induced by the drug and on day 126 in order to determine long-term effects. The dimensions of the excised mandibles were measured directly between anatomical points; the geometry and material biomechanical quality of mandibular bone were assessed using a three-point bending mechanical test in an Instron Universal Testing Machine model 4442. CPA reduced body weight, body length and mandibular size (posterior part of the bone) significantly, when the parameters were measured at day 28. They did not recover with time, which means that catch-up growth did not occur and that the overall growth of the body was permanently affected by the drug. CPA treatment was also associated with a marked depression of the natural increase in the mandibular bone mass (cross-sectional area). The bending cross-sectional moment of inertia of the fracture sections (xCSMI) was also negatively affected by treatment. Significant decreases of both ultimate load and stiffness were also observed. The above structural parameters did not recover enough with time to attain control values at the end of the study. The intrinsic stiffness (E) of the mandibular bone was not affected by treatment. These findings suggest that CPA treatment during early postnatal life causes permanent changes in mandibular morphology and affects the adaptation of mandibular bone architecture to body growth, thus not allowing complete compensation at the end of the study because of an inadequate distribution of the resistive material through its cross-section rather than a qualitative impairment of cortical bone.

1. Introduction

A significant increase in both acute and chronic toxicity associated with the more successful chemotherapy regimens used to treat childhood cancers has been reported.[1] The incidence of childhood cancers coincides with periods of accelerated skeletal development and, consequently, children do not grow normally. Therefore, short stature and osteoporosis

* *Corresponding author at:* Cátedra de Fisiología, Facultad de Odontología, Universidad de Buenos Aires, Marcelo T. de Alvear 2142, Buenos Aires 1122, Argentina. Tel.: +54 11 4964 1275; fax: +54 11 4508 3995.
E-mail address: cebozi@fisio.odon.uba.ar (C.E. Bozzini).

0003-9969/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.archoralbio.2008.08.004