Available online at www.sciencedirect.com
SCIENCE DIRECT
Steroids 70 (2005) 563–572
Steroids
www.elsevier.com/locate/steroids

Metabolism of osaterone acetate in dogs and humans

Kouichi Minato [a,*], Seijirou Honma [a], Yoshihiko Shinohara [b], Takao Hashimoto [b]

[a] *Safety & Pharmacokinetics Research Department, Teikoku Hormone Mfg. Co. Ltd., 1604 Shimosakunobe, Takatsu-ku, Kawasaki-shi, Kanagawa 213-8522, Japan*
[b] *Department of Pathophysiology, School of Pharmacy, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji-shi, Tokyo 192-0392, Japan*

Received 18 November 2004; received in revised form 15 February 2005; accepted 7 March 2005
Available online 31 May 2005

Abstract

Osaterone acetate (17α-acetoxy-6-chloro-2-oxa-4,6-pregnadiene-3,20-dione; OA) is a steroidal antiandrogen. In order to clarify the species differences, metabolites of OA were examined in plasma, urine, and feces of dogs and humans after oral administration of OA. Eleven metabolites in plasma, urine, and feces were identified by their spectral properties and comparison to appropriate standards. The primary routes of OA metabolism involve 11β-, 15β- and 21-hydroxylation, 17α-deacetylation, and dechlorination. Other metabolites arise from combinations of these pathways to form multiple oxidized metabolites. All metabolites observed in humans occurred in dogs. 11β-Hydroxylated metabolites (11β-OH OA and 11-oxo OA) were found in the plasma and urine of dogs, but there was no evidence of their presence in humans. 11β-Hydroxylation of exogenous steroids represents a distinctive biotransformation pathway.

Keywords: Drug metabolism; Species differences; Osaterone acetate; 11β-Hydroxylation; 11β-HSD; Cytochrome P450

1. Introduction

Osaterone acetate (17α-acetoxy-6-chloro-2-oxa-4,6-pregnadiene-3,20-dione; OA) is a steroidal antiandrogen (Fig. 1). This compound has been shown to reduce the weight of the prostate [1–4]. OA is five times more potent than chlormadinone acetate [1], which has been used in the clinical treatment of prostatic hypertrophy and prostate cancer [5]. Chlormadinone acetate has been reported to be metabolized to 2-hydroxylated and 3-hydroxylated compounds in laboratory animals and humans [6]. OA is an analog of chlormadinone acetate, 2-oxa chlormadinone acetate. Incorporation of an oxygen atom into the steroid nucleus at 2 might affect the metabolism.

The metabolic pattern of OA has been reported in rats and mice [7]. The main metabolites were 17α-acetoxy-6-chloro-15β-hydroxy-2-oxa-4,6-pregnadiene-3,20- dione (15β-OH OA) and 17α-acetoxy-6-chloro-11β-hydroxy-2-oxa-4,6-pregnadiene-3,20-dione (11β-OH OA) in rats and mice, respectively. An initial study with ^{14}C-labeled OA in dogs demonstrated that OA was absorbed following oral administration, and radioactivity was excreted primarily into feces via bile [8]. However, characterization of the metabolism of OA in dogs could not be done. The metabolic fate in humans also remained unclear. In the present study, the metabolism of OA was investigated in dogs and humans, and the species difference was clarified.

2. Materials and methods

2.1. Chemicals

Osaterone acetate (17α-acetoxy-6-chloro-2-oxa-4,6-pregnadiene-3,20-dione) was synthesized by the organic chemistry department in Teikoku Hormone Manufacturing Co. as previously described [9]. 6-Chloro-17α-hydroxy-2-oxa-4,6-pregnadiene-3,20-dione (M1), 17α-acetoxy-6-chloro-15β-

* Corresponding author. Tel.: +81 44 812 8656; fax: +81 44 822 1265.
E-mail address: minato-k@teikoku-hormone.co.jp (K. Minato).

0039-128X/$ – see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.steroids.2005.03.012

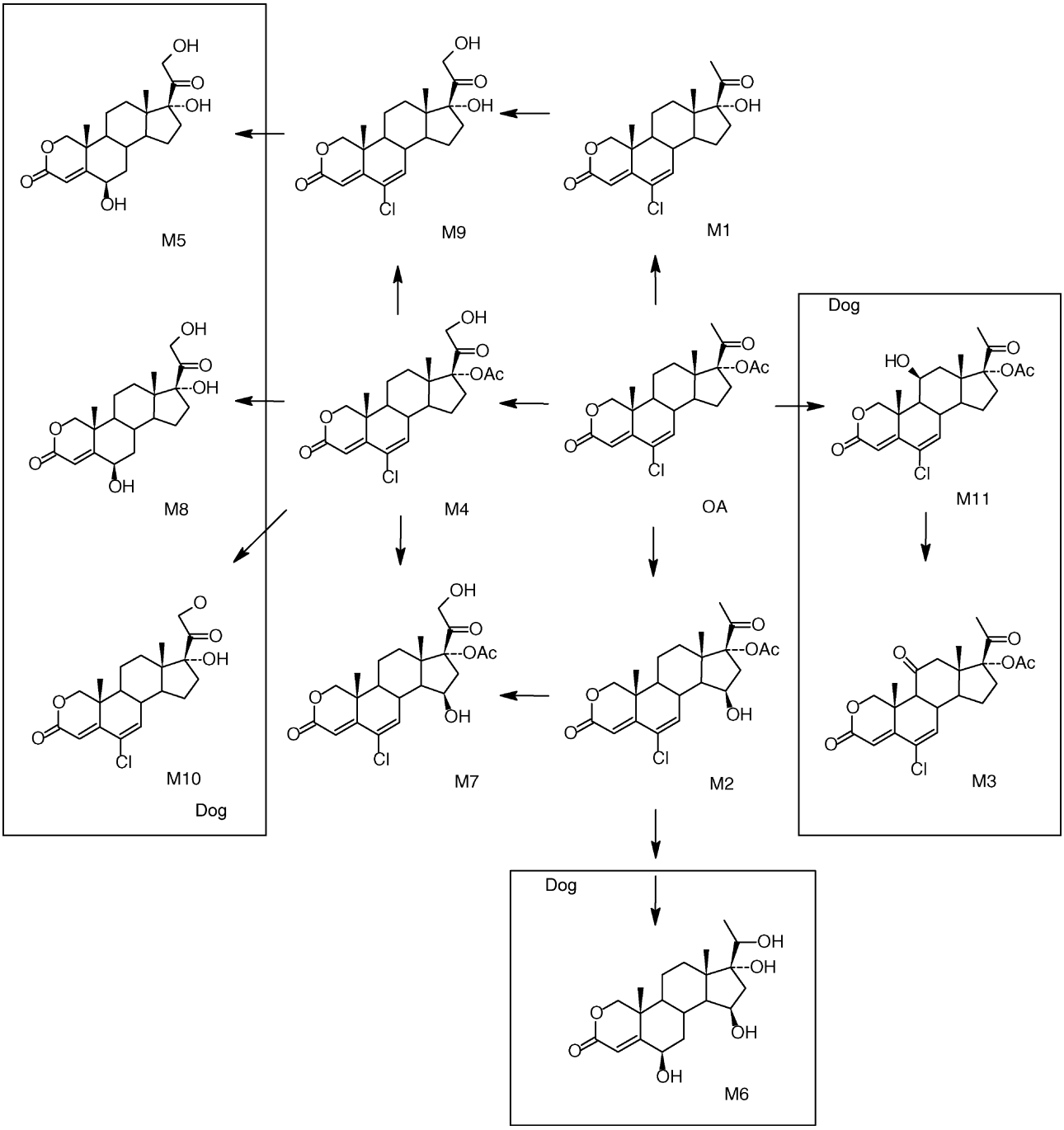

Fig. 1. Proposed biotransformation pathway for human and dog metabolites of OA in plasma, urine, and feces.

hydroxy-2-oxa-4,6-pregnadiene-3,20-dione (M2), 17α-acetoxy-6-chloro-2-oxa-4,6-pregnadiene-3,11,20-trione (M3), and 17α-acetoxy-6-chloro-11β-hydroxy-2-oxa-4,6-pregnadiene-3,20-dione (M11) were synthesized by the organic chemistry department in Teikoku Hormone Manufacturing Co. as previously described [10]. 17α-Acetoxy-6-chloro-21-hydroxy-2-oxa-4,6-pregnadiene-3,20-dione (M4), 6β, 17α,21-trihydroxy-2-oxa-4-pregnene-3,20-dione (M5), 17α-acetoxy-6-chloro-15β,21-dihydroxy-2-oxa-4,6-pregnadiene-3,20-dione (M7), 17α-acetoxy-6β,21-dihydroxy-2-oxa-4-pregnene-3,20-dione (M8), 6-chloro-17α,21-dihydroxy-2-oxa-4,6-pregnadiene-3,20-dione (M9), and 21-acetoxy-6-chloro-17α-hydroxy-2-oxa-4,6-pregnadiene-3,20-dione (M10) were supplied by the organic chemistry department in Teikoku Hormone Manufacturing Co.

[17α-Acetoxy-^{14}C]OA ([^{14}C]OA) and [1α-^{3}H]OA ([^{3}H]OA) were synthesized in Daiichi Pure Chemicals Co. (Tokyo, Japan). The specific radioactivities were 20 mCi/mmol and 16 Ci/mmol, respectively, and the radiochemical purity of these materials determined by thin