

NEW SUSTAINED RELEASE FORMULATION OF TRIPTORELIN ACETATE IN DOGS.

D. Martínez, F. Navarro, D. Basart, J. A. Cordero, C. Peraire, R. Cherif-Cheikh

Formulation and Innovation Unit, Metabolism and Pharmacokinetics Service, Research and Development Department, Ipsen Pharma S.A. Laboratories, Sant Feliu de Llobregat, Barcelona, Spain.

Abstract

In this study we would like to evaluate in vivo a new sustained release formulation (SRF) of triptorelin acetate (microimplant) as a potential improvement of the commercial microspheres (Decapeptyl®).

Introduction

Triptorelin is an agonist analogue of natural gonadotrophin releasing hormone (GnRH) (1, 2). By continuous exposure the agonist causes, after a transitory phase of hyperstimulation (flare-up) corresponding to series of intracellular responses, a down-regulation of GnRH receptor and a post-receptor desensitisation of the gonadotrophic cell. The result is a reversible biochemical castration. The reduction of testosterone levels in males is used as an indicator of the pharmacodynamic response. Therefore, triptorelin is involved in the therapeutic arsenal for diseases which are dependent on sex hormones: hormone-dependent cancers, precocious puberty, endometriosis, uterine fibromyomas, etc.

Material and Methods

Formulation

The microimplant is a solid rod of cylindrical shape with triptorelin acetate (35-45%) and biodegradable polymer (65-55%).

6 mg of triptorelin free base at 0.309 mg/mg.

Formulation length: 27 mm

Formulation diameter: 0.84 mm

Microimplant is a solid pharmaceutical form obtained by melt extrusion of the product and

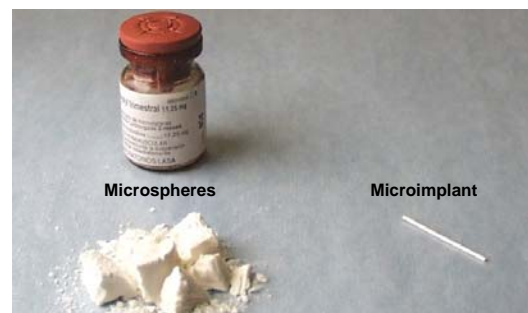
PLGA polymer in order to achieve a controlled release of triptorelin.

In order to understand the galenic and pharmacokinetic improvements, the already commercialized Microspheres (Decapeptyl®) were used as a reference:

- *Lyophilised microspheres:* Triptorelin acetate, biodegradable polymer, mannitol, polysorbate 80 and sodium carboxymethylcellulose.
- *Solvent:* Mannitol and water for injection.

Microspheres containing the active ingredient incorporated in the polymer are freeze-dried in order to allow storage of the finished product at room temperature.

Figure 1. Picture showing physical characteristics of the two SRF's assayed.



In vivo study design

In vivo studies were carried out following a parallel design using 12 male Beagle dogs (6 dogs per formulation) administered by subcutaneous (microimplant) and intramuscular (microspheres) routes at doses of 6 and 11.25 mg, respectively.

Analytical methodologies

Triptorelin and testosterone plasma levels were analysed by previously validated radioimmunoassays methods. The limits of quantification were 0.020 ng/ml for triptorelin and 0.11 ng/ml for testosterone.

Results and Discussion

The mean±SD triptorelin plasma levels after the parenteral administration of both formulations to dogs are depicted in the following figure:

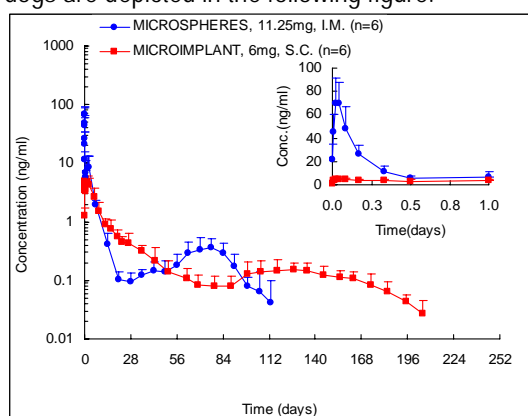


Figure 2. Comparative plot of triptorelin plasma concentrations (ng/ml) between the two SRF's assayed. One day profile (burst) in the small graph.

The key pharmacokinetic-pharmacodynamic (PK-PD) parameters of both SRF's are compared in the following tables:

Table 1. Triptorelin pharmacokinetic parameters

Parameter	Units	Microspheres		Microimplant	
		MEAN	SD	MEAN	SD
Dose	mg	11.25	-	6	-
t _{max} *	h	1	0.5-2	2	0.5-72
C _{max}	ng·ml ⁻¹	75.0	20.4	5.5	0.7
t _{1/2 app}	d	9.0	2.2	27.7	6.7
AUC	ng·ml ⁻¹ ·d	76.1	16.6	65.0	10.3
MRT	d	18.2	7.0	43.2	7.5
F	%	42.0	5.9	65.8	11.8

*: The median and range of values were reported

Table 2. Testosterone pharmacodynamic parameters

Parameter	Units	Microspheres		Microimplant	
		MEAN	SD	MEAN	SD
t _{lag <0.5}	d	10.6	3.3	14.9	3.7
t _{castr <0.5}	d	123.4	17.5	204.8	9.8

Castration in dogs is achieved when testosterone plasma levels are below 0.5 ng/ml (3)

As a summary, the potential improvements of this new microimplant formulation are not only based on the more prolonged duration of drug release but also on the optimized use of peptide through reduced burst, reduced amount of injected polymer and the absence of extemporaneous reconstitution need.

Bibliography

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Autor de contacto:

Nombre y Apellidos: Concepción Peraire

e-mail: concepcion.peraire@ipsen.com

Institución: Ipsen Pharma, S.A.

Dirección: Ctra. Laureà Miró, 395

Ciudad: St. Feliu de Llobregat (Barcelona)

Telf.: 93 685 81 00

Fax: 93 685 10 53