Reproductive Toxicology 58 (2015) 213–221

Contents lists available at ScienceDirect

Reproductive Toxicology

journal homepage: www.elsevier.com/locate/reprotox

Review

Potential seminal transport of pharmaceuticals to the conceptus

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ARTICLE INFO

Article history:
Received 26 August 2015
Received in revised form
21 September 2015
Accepted 26 October 2015
Available online 3 November 2015

Keywords:
Semen
Male-mediated pregnancy effects
Monoclonal antibodies
Peptides
Pharmaceuticals

ABSTRACT

Small molecule pharmaceutical products are assumed to reach concentrations in semen similar to those in blood plasma. Exposure modeling for these small-molecule products in humans assumes a daily dose of 5 mL of semen and 100% absorption from the vagina with distribution to the conceptus through the maternal systemic circulation. Monoclonal antibody drugs are present in semen at concentrations about 2% or less of those in blood, and the modeling used for small molecules will over-estimate the possibility of conceptus exposure to immunoglobulins. It is not known whether peptide products reach semen, but in general peptide medications are destroyed by vaginal peptidases, and conceptus exposure is predicted to be minimal. Theoretical exposure routes to pharmaceuticals that might result in exposure of the conceptus greater than that of maternal systemic exposures include direct access through the cervical canal, adsorption to sperm for carriage into the oocyte, and direct delivery from the vaginal veins or lymphatics to the uterine artery. There is some evidence for direct access to the uterus for progesterone, terbutaline, and danazol, but the evidence does not involve exposures during pregnancy in most instances. Studies in mice, rats, rabbits, and monkeys do not suggest that exposure to small molecule pharmaceuticals in semen imposes risks to the conceptus beyond those that can be predicted using modeling of systemic maternal exposure. Monoclonal antibody and peptide exposure in semen does not pose a significant risk to the conceptus.

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http://dx.doi.org/10.1016/j.reprotox.2015.10.015

1. Introduction

Semen is a mixture of spermatozoa produced in the testicular seminiferous epithelium and seminal fluid originating from the epididymis, seminal vesicles, prostate, and to a lesser extent, other male accessory glands. Concern about the presence of pharmaceuticals (both small and large molecules) in semen and their transport to sexual partners has been reflected in recommendations or requirements that men receiving certain pharmaceutical products use condoms during sexual activity [1–3]. These recommendations have come from industry authors [1], the European Union Heads of Medicines Agency [2], and the U.S. Food and Drug Administration, which also provided guidance on quantitative assessment of risk [3]. Although there are concerns about potential drug toxicity in sexual partners of treated individuals, the possible transfer of pharmaceuticals to the developing conceptus is the predominant consideration when condom use is recommended, particularly during clinical trials with new pharmaceutical products when potential effects on gametes or the conceptus are not yet fully investigated.

Possible mechanisms of seminal transfer of pharmaceutical products and other chemicals have been reviewed, most recently in 2005 [4]. Since that publication, additional research has become available to inform risk assessment when considering possible conceptus exposure to pharmaceuticals or other chemicals in semen. Some of the additional research has been performed by a consortium of members of the Health and Environmental Sciences Institute (HESI) Developmental and Reproductive Toxicology Technical Committee [5]. The present review paper was prepared by an expert group coordinated by HESI and summarizes the current understanding of the potential for seminal transfer of pharmaceuticals to female gametes, the developing embryo, and fetus. The possible role of male exposures on transmissible genetic or epigenetic alterations of sperm chromatin and possible effects of pharmaceutical exposure on sperm function will not be considered here, although in the absence of specific transport mechanisms large peptides and proteins are not expected to enter the cell and interact with cellular DNA to pose a genotoxic risk [6,7].

2. Components of semen

The role of semen is to deliver spermatozoa to the female genital tract. Semen ejaculated into the vagina coagulates immediately and liquefies again after approximately 20 min, allowing spermatozoa to enter the cervix from which they are released to the uterine cavity and fallopian tubes [8]. By contrast, semen gains direct access to the uterine cavity in some other species including rat, pig, and horse [9,10]. Mammalian spermatozoa develop in the seminiferous tubules of the testis and undergo additional maturation during transit through the epididymis, which also stores spermatozoa. The epididymis gives rise to the vas deferens, which transmits spermatozoa. Behind the bladder, the vas deferens and seminal vesicles join to form the ejaculatory duct, which opens into the urethra at the base of the prostate gland the fluid of which is mixed with spermatozoa and seminal vesicle fluid to form semen.

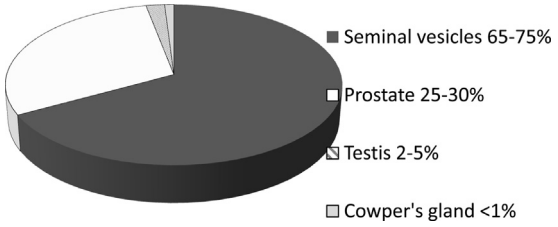

Fig. 1. Components of human semen.

The volume of human ejaculate ranges from 2.3 to 5.0 mL, with an average of 3.4 mL (review of 30 studies by Owen and Katz [11]). Spermatozoa make up only a small portion of whole human semen, *i.e.*, 1–5% of the total volume [12]. The testicular contribution to semen volume is minimal (Fig. 1). The so-called blood–testis barrier consists of tight junctions between Sertoli cells proximal to the spermatocytes, limiting access of blood-borne chemicals to postmitotic germ cells and to the lumen of the seminiferous tubules. Because most of the seminal volume originates from the seminal vesicles and prostate, partition of pharmaceuticals to these glands is more important than is testicular access in influencing semen concentration.

Seminal plasma components have nutritive, buffering, and protective functions for the spermatozoa. The contributions from the different accessory glands and the composition of the seminal plasma differ to some degree between different species. In the human, 65–75% of semen originates from the seminal vesicles (Fig. 1), and constituents include acid phosphatase, citric acid, inositol, calcium, chloride, magnesium, zinc, potassium, sodium, fructose, glucose, ascorbic acid, and prostaglandins. As the semen passes through the prostate, alkaline prostatic fluid is added, comprising about 25–30% of semen. The buffering capacity of this fluid protects sperm in the acidic vaginal environment until the sperm gain access to the cervical mucus. Proteins and amino acids are also present in seminal plasma, and albumin constitutes approximately one-third of the total protein concentration in semen [11].

The pH of human semen is a matter of some debate, and there is considerable variation in the pH measurements reported by different researchers. Nevertheless, the pH of semen lies generally slightly above neutral with a reported range of 7.4–8.4 (reviewed by Owen and Katz [11]). Semen has buffering capacity much higher than that of most other body fluids and maintains its pH near neutral even in the acidic vaginal environment, providing the spermatozoa with the opportunity to enter the neutral pH environment of the cervical mucus.

3. Vaginal and cervical enzymes

Enzymes in the vagina and in cervical mucus have been described, some of which are involved in protein degradation, especially aminopeptidases (*i.e.*, exopeptidases). While no *in vivo* data