

## OTE-F

### Two well-known compounds to treat oligozoospermia

#### Background

Contrary to female reproduction, male reproductive problems have received remarkably little attention in the past. Only during recent years, hormonal male contraception and hormonal consequences of male aging are being discussed and investigated. For a long time, male factors are known to be important as cause of male infertility but this problem has suffered from lack of interest as well as lack of successful treatment modalities. It is estimated that 20-25% of the couples experience some kind of infertility. It is believed that half of the cases is due to the male part.

No medical pharmaceutical treatment for male infertility has been proven to be effective except for the rare cases of gonadotrophin treatment of serious male hypogonadism. The introduction of IVF by Intra Cytoplasmatic Sperm Injection (ICSI) as a mechanical solution of male infertility has been shown to be very effective and has discouraged further research into pharmaceutical approaches.

#### Concept

Pantarhei has designed and a new method to improve fertility in infertile males who ejaculate too low amounts of sperm (oligozoospermia). This is expected to be achieved by a combined treatment with oxytocin and an estrogen. Oxytocin (OT) will stimulate the effective emptying of sperm stores in the cauda epididymis and the ductus deferens and the estrogen will increase the amount of OT receptors in those tissues thereby increasing the potency of oxytocin.

The peptide hormone OT has a well-established function in many mammalian species, including humans. It is not only effective in the central nervous system in the induction of maternal behaviour, but also in the mediation of uterine contraction during partition and milk ejection during lactation.

In the male, OT is produced in concentrations similar to those found in the female, yet little is known about its function associated with reproductive physiology. Next to the reproductive system and the central nervous system, oxytocin receptors (OTR) are also found in: heart, kidneys, pancreas, adrenal gland, adipocytes, osteoblasts and the retina (1). OT is abundantly present in the male reproductive tract and has been shown to increase the propulsion of sperm by enhancement of epididymal contractions (2) and to modulate the spermatogenesis and testicular steroidogenesis (testicular up-regulation of 5 alpha-reductase). In Oxford Down cross rams, administration of 10 microgram OT (5 IU), significantly increased both the output of fluid and the number of spermatozoa (2;3). Similar results were also found among oligozoospermic men after receiving a bolus of 2.5 IU OT, intravenously. Intranasal administration of 16 IU OT did not lead to sperm changes, although increasing the strength of the ejaculation (4-7). This lack of effect might also be explained by insufficient uptake and bioavailability (8). Finally, intravenous administration of OT (4 IU/100ml/120min) did not effect serum testosterone levels (9). Because under natural circumstances OT is released in a pulsatile manner by the pituitary gland, the way of administration (continuously or as a bolus) can make a difference.

Meistrich et al. (10) suggested that, next to spermatogenesis, sperm transport within the epididymal tract may be controlled by estrogens. Kumari et al. (11) showed an increase in concentration of estradiol in the cauda epididymis and vas deferens, suggesting a possible role for estrogens in the storage and transport of spermatozoa. Estrogens are essential for the expression of the OTR and vice versa (12;13). In vivo there appears to be a marked association between estrogen levels (or cytochrome P450 aromatase expression (14)) and the expression of the OT gene in most tissues (15). E2 also plays a role in the re-initiating of spermatogenesis in bears after winter-sleep (16).

It is hypothesised that estrogens are necessary for OT to exert its biological effect, i.e. spermatogenesis, testicular steroidogenesis and sexual drive (6;17-19).

### Proof-of-principle

Pantarhei has designed a phase IIA proof-of-principle study. The aim of this study is to investigate whether OT alone has a beneficial effect on total sperm count, sperm volume and other sperm parameters in normogonadotropic, oligozoospermic males and whether OT and E2 have a synergistic effect on total sperm count, sperm volume and/or other sperm parameters as compared with OT alone.

As a follow-up step, a combined phase IIB/III should be conducted. Market entry is envisaged within 5-6 years.

### Patent application

A patent application has been filed on March 27, 2003. The European patent application has been published on October 20, 2004, under number EP 1 468 690.

### Partnering

Due to resource allocation, this concept did not get the attention it deserves. For that reason, Pantarhei is looking for partner that is willing to further develop the concept (eventually with the assistance of Pantarhei). Several deal structures are discussable.

### References

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