EXPLORATORY EVALUATION OF NOVEL, NON-HORMONAL MALE CONTRACEPTIVE DRUG PROTOTYPES ACTING IN VAS DEFERENS

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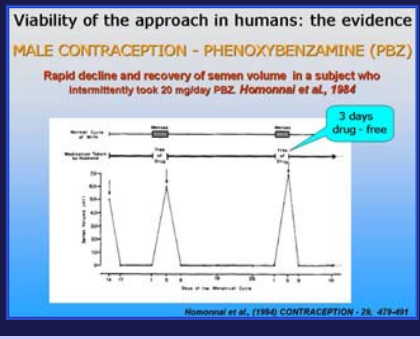
1 BACKGROUND

The development is based on our discovery of the mode of drug action for a side-effect shared by two therapeutic drugs, thioridazine and phenoxybenzamine (PBZ)

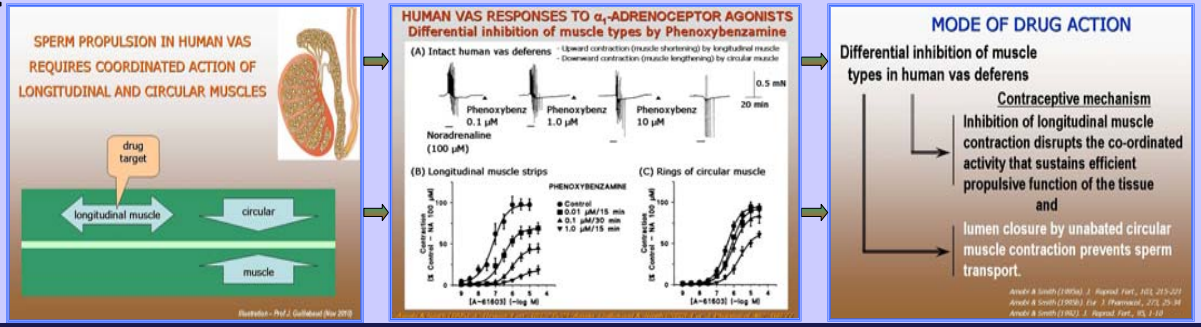
INHIBITION OF SEMEN EMISSION, WHICH OCCURS WITHOUT AFFECTING PENILE ERECTION, ORGASM OR LIBIDO

1. Greenberg H R & Carrillo C (1968). Thioridazine-induced inhibition of masturbatory ejaculation in an adolescent. The American journal of psychiatry, 124(7), 991-3.
2. Singh H (1963). Therapeutic use of thioridazine in premature ejaculation. The American journal of psychiatry, 119, 891.
3. Kedia K R & Persky L (1981). Effect of phenoxybenzamine (dibenzyline) on sexual function in man. Urology, 18(6), 620-1.
4. Homonnai Z T, Shilon M & Paz G F (1984). Phenoxybenzamine--an effective male contraceptive pill. Contraception, 29(5), 479-91.

- **The potential of PBZ as a male contraceptive was tested** by Homonnai et al.(1984) – Reported **total inhibition of semen emission** within 3-4 days with little probability of female impregnation thereafter. Ejaculate recovery occurred within 5 days after cessation of dosing. **However, for medical reasons PBZ and thioridazine are unsuitable for routine male contraceptive purposes.**



2 PROPULSIVE MECHANISM AND MODE OF DRUG ACTION UNDERLYING THE SIDE EFFECT

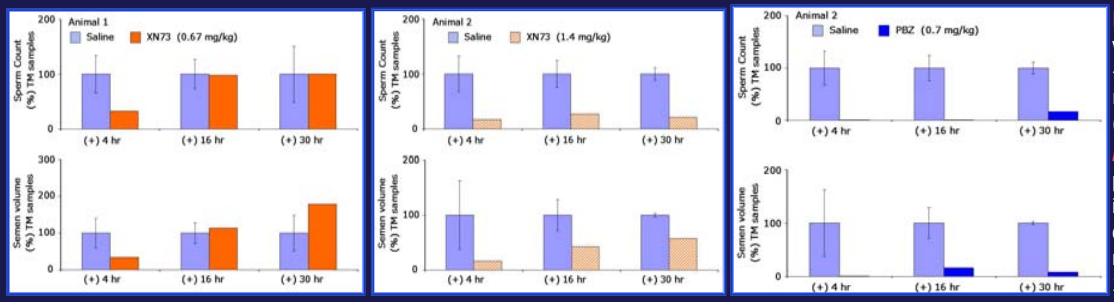


Dual effect of longitudinal muscle inactivation (persistent tissue slack) and unabated circular muscle contractility (lumen closure) disrupts the coordinated activity that sustains efficient propulsive function in semen emission.

CURRENT STUDY - NOVEL PROTOTYPES [diphenyl- aryloxy- alkylamine derivatives] replicating this action in human and ram vasa were evaluated *in vivo* in order to identify prototypes producing ≥ 50% reduction in ram ejaculate within 4-16 hr.

3 RESULTS

PROTOTYPE XN73 – DIFFERENT DOSES REDUCED *IN VIVO* EJACULATE SPERM CONTENT & VOLUME IN TWO RAMS BY 67- 83%

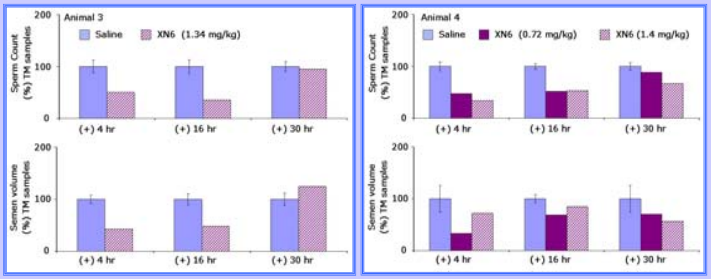


[TM; time-matched controls (saline), Interval between tests with saline (controls) and drug prototypes – 12 days]

BLOOD SAMPLE ANALYSIS - XN73 plasma levels were 16.7 ng/ml (IV - 0.67 mg/kg) and 66.2 ng/ml (IV - 1.4 mg/kg) after 4 hr of administration but declined rapidly to undetectable levels (animal 1) & 10 ng/ml (animal 2) within 16 hr.

IN SILICO ANALYSIS of microspecies revealed a predominance of ionized microspecies with zero un-ionized microspecies at pH 1.5, 5.0, 6.5 & 7.4. The decline in plasma drug levels and inadequate microspecies distribution underlie the less than 100% efficacy in the ram experiments and corrected for in the latest chemically modified prototypes.

4 PROTOTYPE XN6 – REDUCED *IN VIVO* SPERM CONTENT & VOLUME BY 64 – 66%



BLOOD SAMPLE ANALYSIS XN6 plasma levels were 94 ng/ml (IV-0.7 mg/kg) and 44-138 ng/ml (1.4 mg/kg IV) after 4 hr and within 16 hr were 94 ng/ml (animal 3; IV 1.34 mg/kg) and 0-0.6 ng/ml (animal 4; IV 0.7 & 1.4 mg/kg) .

We gratefully acknowledge the support of CONRAD (USA) for this pivotal *in-vivo* prototype study.

5 CONCLUSION

The prototypes, though unoptimized, have demonstrable potential in terms of

- **Short-term inhibition of semen emission for male contraception &**
- **Drug-like properties**

Collaborative milestone-based funding is required to start work on evaluating the modified prototypes and select drugs with the best contraceptive efficacy profile, oral bioavailability, metabolic stability and safety attributes.