

Review Article

Recent observations on drugs and human fertility

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Summary: The transmembrane migration method has permitted quantification of the effect of drugs on human sperm motility. Calcium ionophores and calcium antagonists have paradoxical effects on motility depending on the stage of sperm maturity. Drugs with membrane stabilizing properties inhibit sperm motility. Propranolol, for example, has been shown to have contraceptive activity when administered intra-vaginally. Pharmacokinetic studies have shown that the systemic availability of vaginally administered propranolol is markedly greater than after oral administration. Seminal fluid concentrations of propranolol after oral administration are similar to those in plasma, but cervicovaginal mucus concentrations are much higher, and residence times much longer. The clinical consequences of these observations await elucidation.

There is increasing interest in the clinical pharmacology of human sperm motility, for several reasons. Firstly, the development of *in vitro* fertilization has necessitated research into factors influencing the motility and ovum-penetrating properties of sperms. Secondly, the demonstration that drugs taken by male patients may influence their fertility by interfering with spermatogenesis or sperm function has increased the awareness of the importance of this subject. Thirdly, and related to this, there is the possibility that drugs taken orally or otherwise by a woman, or inserted intravaginally, might influence the motility of sperms deposited into her vagina during intercourse. Finally, there is widespread interest in finding alternatives to animal models to study the pharmacological properties of drugs, among which are *in vitro* systems using isolated human cells and tissues. It may be that human sperms could provide such a model.

Sperm motility has been observed since the earliest use of the microscope by Leeuwenhoek. Several techniques are now available to quantify sperm motility, including multiple exposure photography, laser Doppler spectroscopy and turbidometry,¹ but they are complicated and time-consuming, and do not lend themselves to pharma-

cological studies involving dose-response relationships on single ejaculates of seminal fluid.

The transmembrane migration method for measuring drug effects on sperm motility

The transmembrane migration method (TMM) was specifically designed to permit the determination of inhibitory or facilitatory concentrations of drugs on human sperm motility, from dose response curves in duplicate or single ejaculates of seminal fluid.² In principle it involves measurement of the proportion of sperms moving across the 5 micron pores of a Nucleopore membrane from an aliquot of semen into a buffer solution. In the original method, different drug concentrations were added only to the chamber containing the seminal fluid, but recently a modified version has been introduced³ which involves adding drug, in addition, to the buffer solution into which the sperms penetrate, and which produces EC50 concentrations which are more similar to those obtained by other methods.

Using the TMM, sperm immobilizing potencies of several groups of drugs have been determined, including antidepressants, antiarrhythmics, antihistamines, cannabis, local anaesthetics, neuroleptics, opiates, vaginal contraceptives, calcium antagonists and beta-adrenoceptor blocking agents.¹ These studies have demonstrated that drugs immobilize human sperms by acting on the cell membrane. Lipid solubility, which determines the absorption of drugs into the cell membrane, correlates with the sperm immobilizing potency.⁴ Drugs that inhibit

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mitochondrial activity, such as cyanide, and microtubular function, such as colchicine, do not inhibit sperm motility.^{5,6} For these reasons, human sperm motility has been suggested as a potential model for the study of membrane stabilizing drugs.^{7,8} It may be that other ciliated or flagellated organisms could be used, for it has been shown that propranolol inhibits the motility of the flagellate protozoa *Giardia lamblia* and *Trichomonas vaginalis*.⁹

Calcium ions and sperm motility

The effects of calcium ions on sperm motility are paradoxical, depending upon the state of maturity of the sperms¹⁰ (Table I). Although evidence in human epididymal sperms is lacking, studies on several other mammalian species, including bull, mouse and hamster, have shown that calcium ions increase the motility of immotile sperms collected from the epididymis. Furthermore, there is evidence for a motility-promoting calcium-binding calmodulin-like protein in the sperm membrane at this stage of development.

Paradoxically, however, there is now substantial evidence that calcium ions inhibit the motility of ejaculated human sperms. Calcium chelators such as EGTA and EDTA as well as calcium antagonists such as diltiazem, flunarizine and verapamil stimulate sperm motility in ejaculated human semen. On the other hand, the calcium ionophore A23187, which increases intracellular calcium concentrations, inhibits human, dog and sea-urchin sperm motility. A protein that inhibits calcium uptake by ejaculated sperm has been purified from bovine seminal plasma, probably produced by the seminal vesicle.

Finally during their passage through the female genital tract, sperms are separated from seminal plasma and undergo capacitation. Calcium ions trigger the acrosome reaction, a calcium ionophore

inducing a premature acrosome reaction in uncapacitated sperms.¹⁰

It is evident that calcium ion concentration has a profound influence on motility of sperms according to their stage of maturity. Its relevance in procedures such as *in vitro* fertilization requires careful

Caffeine and other xanthines

Caffeine increases the motility of human sperms and also antagonizes the inhibitory effect of other drugs such as propranolol and procaine.¹¹ The motility-enhancing activity of other xanthines such as isobutyl methylxanthine (IBMX) appears to correlate with their phosphodiesterase-inhibiting activity.¹² Their safety in respect of teratogenic or sperm-injuring potential has not been established, however, and it would be premature to recommend their use to enhance sperm fertilizing ability at the present time.

Propranolol, contraception and genital fluid concentration

The TMM demonstrated that propranolol was a potent inhibitor of sperm motility *in vitro*, and that this activity appeared to reside in its membrane-stabilizing dextro-isomer.¹¹

Zipper, noting an earlier report that propranolol, chlorpromazine and phenoxybenzamine inhibited sperm motility *in vitro*,¹³ carried out a study to evaluate the efficacy and tolerability of propranolol as a vaginal contraceptive. He found¹⁴ that an 80 mg tablet of propranolol inserted into the vagina nightly from the last day of menstruation until the first day of the next menstrual period, without any other method of contraception, was associated with a one year life table pregnancy rate of 3.4/100 women, and a Pearl index of 3.9/100 women years. No major adverse effects were encountered. A subgroup of these women were asked to insert the propranolol tablet intravaginally at 2100 h and have intercourse at about 0700 h the following morning. A post-coital test carried out 3 hours after intercourse did not show any motile sperms in the endocervical samples.

While it is probable that the direct sperm immobilizing action of propranolol demonstrated in the TMM studies accounts for its contraceptive action, the possibility of systemic action cannot be excluded. The systemic bioavailability of propranolol after vaginal administration is much greater than oral administration,¹⁵ not unexpectedly because the venous drainage of the vascular vaginal wall is directly into the inferior vena cava, so bypassing the hepatic circulation and avoiding the

Table I The paradoxical relationship between calcium and sperm motility

| Stage of maturation | Influence of calcium | Transport factors |
|-----------------------|----------------------------|--|
| Storage in epididymis | Promotes motility | Calmodulin-like protein in sperm tail |
| Ejaculation | Inhibits motility | Calcium-transport inhibitory protein bound to sperm membrane |
| Capacitation | Promotes acrosome reaction | Removal of calcium-transport inhibitor |

Based on Hong *et al.*¹⁰

extensive first-pass metabolism which follows oral administration of propranolol. This must be remembered if the vaginal route is used as an alternative to oral in patients unable to swallow propranolol.¹⁶

The observation of a contraceptive action of propranolol administered by the vaginal route raises the question as to whether its oral use in a male could result in seminal fluid concentrations likely to inhibit his sperm motility, or whether oral ingestion by women could result in cervico-vaginal mucus concentrations which might inhibit the motility of their partners' sperms. Clinical pharmacological studies have shown that seminal fluid concentrations of propranolol after oral administration are similar to those in plasma, do not show any evidence of accumulation, and are unlikely to reach sperm-immobilizing levels after therapeutic doses.¹⁷ In females, however, cervico-vaginal mucus concentrations of propranolol after single oral doses show marked and extensive accumulation extending beyond 24 h after oral administration, when plasma levels are not measurable beyond 8–12 h.¹⁸ This is, perhaps, not surprising, because the basic drug propranolol would be expected to be trapped in the acidic medium of the vagina, and to

bind extensively to the glycoproteins of the vaginal mucus. Vaginal pH and mucus production vary, however, during the menstrual cycle and with age, and the clinical implications of these preliminary observations await further investigation and evaluation.

Conclusion

The pharmacokinetics of drugs into and out of genital compartments has been a neglected area of clinical pharmacology. It is evident, however, that drug penetration into, and residence within genital fluids may have important therapeutic and toxicological implications as well as an influence on fertility. Better understanding of the pharmacological basis of sperm motility should lead to a more rational approach to the design and performance of *in vitro* fertilization.

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