Leading Article

Secretion of drugs into the human female genital tract

I.G. Salas-Herrera, Paul Turner and R.M. Pearson

Department of Clinical Pharmacology, St Bartholomew's Hospital, London EC1A 7BE, UK

Drug disposition out of and into the female genital tract has received relatively little attention from clinical pharmacologists. This is surprising, for, at least in about 50% of the population, the vaginal route is available for parenteral drug administration. The systemic bioavailability of drugs after vaginal administration is much greater than after oral administration, not unexpectedly because the venous drainage of the vascular vaginal wall is directly into the inferior vena cava, so by-passing the hepatic circulation.¹

Propranolol has been successfully administered by the vaginal route in a patient unable to take it orally,² and, recently, vaginal bromocriptine has been used successfully to treat a prolactin-producing pituitary tumour in a patient in whom side effects precluded oral administration of the drug.³ Subsequent studies in volunteers by the authors of this latter report showed that circulating levels of bromocriptine were significantly higher following vaginal than oral administration.

The extent of secretion of drugs into the female genital tract after oral administration is important for several reasons. Firstly, a drug may exert its therapeutic action through its concentration in cervical mucus. For example metronidazole given orally can be used to treat vaginal trichomonas infections.⁴ Secondly, a drug may exert unwanted effects by reducing sperm motility and fertility.⁵ Orally administered propranolol has been shown to be highly concentrated in cervical mucus⁶ and other experiments have shown it to reduce sperm motility *in vitro*,⁷ although only at concentrations much higher than those achieved in cervical mucus after therapeutic oral doses. A preliminary study involving insertion of 80 mg propranolol tablets in the vaginas of 198 female volunteers has shown that propranolol is an effective vaginal contraceptive.⁸

The extent to which a drug and its metabolites appear in human body fluids depends on their physicochemical properties, including lipid

solubility, protein binding and dissociation constant. Some local factors may also influence their concentration in cervical mucus, including environmental pH and the concentrations of various proteins in the mucus. Albumin and alpha-1-acid glycoprotein (AGP) in serum play an important role in the binding of drugs, but their role in cervical mucus is obscure. The albumin concentration in cervical mucus is merely 1% of that in serum, and AGP is present only in traces during the mid-cycle period when it has been measured.^{9,10} The protein-binding of propranolol and ibuprofen in cervical mucus has been found to be 26% and 66% respectively, and this has not correlated with the concentrations of either albumin or AGP.^{11,12} It is unlikely, therefore, that cervical mucus protein concentration is an important determinant of drug disposition into cervical mucus.

In order to determine the influence of the physicochemical properties of a drug, namely its lipid solubility, serum protein binding, and dissociation constant (pKa) on its cervical mucus concentration, we have studied serum and cervical mucus concentrations of seven drugs with different properties given by mouth at midcycle to healthy female volunteers. Midcycle was chosen because mucus production is greatest at this time. Each study was approved by the local ethics committee, all subjects gave informed consent to participate, and at least 6 subjects took part in each study. Table I summarizes the results of these studies. Strongly basic drugs such as D-propranolol, which is lipid-soluble, and atenolol, which is water soluble, reached markedly higher concentrations in cervical mucus when compared with serum.^{13,14} However, the weakly basic drugs, metronidazole and antipyrine, reached concentrations in cervical mucus which were much lower than those reached in serum.^{12,15} These results are consistent with those of other investigators with co-trimoxazole, ofloxacin,¹⁶ and erythromycin¹⁷ which have indicated that strongly basic compounds are concentrated in acidic fluids, such as vaginal secretions, at levels greater than in blood.

Conversely, the acidic, lipid-soluble drug ibuprofen reached concentrations in cervical mucus which were less than 5% of those in serum.¹⁸

Table I The penetration of some drugs into the female lower genital tract

Drug	Nature	Molecular weight (g)	pK _a	Partition* coefficient	P-B%	Ratio CM/S	Dose	References
D-propranolol	Strong base	295.8	9.5	20.20	95.0	35.0	160 mg twice daily × 5 days	13
Atenolol	Strong base	266.3	9.6	0.01	3.0	16.0	100 mg once	14
Antipyrine†	Weak base	188.2	1.4	28.00‡	10.0	0.9	1 gram once	12
Metronidazole	Weak base	171.2	2.5	1.18	15.0	0.8	400 mg twice daily × 5 days	15
Ibuprofen	Strong acid	206.2	4.4	9.85	99.0	0.04	800 mg once	18
Lithium carbonate	Neutral	73.9	6.8	0.0‡	0.0	0.64	300 mg twice daily × 5 days	19

*Octanol/water (aqueous phase at 7.4); †Related to saliva parameters; ‡Chloroform/water (aqueous phase at 7.4); §Inorganic ions are insoluble in lipids, CM/S = cervical mucus concentration/serum concentration.

This is probably due to the absence of ‘ion-trapping’ in the acidic environment of cervical mucus. Lithium carbonate, a neutral drug, reached lower levels in cervical mucus than in serum,¹⁹ which is, again, consistent with simple diffusion rather than ion trapping.

It appears, therefore, that strongly basic drugs are concentrated in the acidic environment of cervical mucus to a much greater extent than acidic and neutral drugs. Lipid solubility and protein binding appear to be of relatively little importance compared with dissociation constant (pK_a).

These findings may have important consequences in terms of disposition of drugs and other chemicals into the female genital tract, both for their therapeutic effects, and for potential adverse effects on sperm motility, fertility, and other toxicological actions.

For example, it is probable that weakly basic and acidic drugs with potential therapeutic use within the vagina will require local rather than oral administration in order to achieve predictable effective therapeutic concentrations. On the other hand, strongly basic drugs would be expected to be concentrated in cervical mucus, such as some narcotic opiate analgesics which have been shown to possess inhibitory actions on human sperm motility.²⁰

Acknowledgements

We thank the Humane Research Trust and Family Health International, together with the British Council and the University of Costa Rica for their financial support.

References

- Patel, L.G., Warrington, S.J. & Pearson, R.M. Propranolol concentrations in plasma after insertion into the vagina. *Br Med J* 1983, **287**: 1247–1248.
- Smith, R.C. & Berg, M. Systemic absorption after intra-vaginal propranolol. *Lancet* 1985, **i**: 112.
- Katz, E., Weiss, B.E., Schran, H.F. & Adaski, E.Y. Increased circulating levels of bromocriptine following vaginal as compared to oral administration. *Fertil Steril* 1990 (Prog. Suppl) S4.
- Fleury, F.J., Van Berger, W.S. & Prentice, R.L. Single-dose of two grams of metronidazole for trichomonas vaginal infection. *Am J Obstet Gynecol* 1977, **128**: 320.
- Turner, P. Recent observations on drugs and human fertility. *Postgrad Med J* 1988, **64**: 578–580.
- Pearson, R.M., Ridgway, E.J., Johnston, A. & Vadukul, J. Concentration of D-propranolol in cervicovaginal mucus. *Lancet* 1984, **ii**: 1480.
- Hong, C.Y., Chaput-de Saintonge, M. & Turner, P. Inhibitory action of procaine, DL-propranolol and D-propranolol on human sperm motility: antagonism by caffeine. *Br J Clin Pharmacol* 1981, **12**: 751–753.
- Zipper, J., Wheeler, R.G., Potts, D.M. & Rivera, M. Propranolol as a novel, effective spermicide: preliminary findings. *Br Med J* 1983, **287**: 1245–1246.
- Schumacher, G.F.B. Soluble proteins of human cervical mucus. In: Blandau, R.J., Moghissi, K. (eds) *Biology of the Cervix*. University of Chicago Press, Chicago, 1973, pp. 201–233.
- Salas, I.G., Pearson, R.M. & Turner, P. Quantitation of albumin and alpha-1-acid glycoprotein in human cervical mucus. *Hum Exp Toxicol* 1991, **10**: 137–139.
- Salas, I.G., Pearson, R.M. & Turner, P. The binding of propranolol to cervical mucus proteins. *Eur J Clin Pharmacol* 1989, **36** (Suppl): A218.
- Salas, I.G. *Secretion of drugs into human cervical mucus*. Ph.D. Thesis. 1990. University of London, p. 192.
- Salas, I.G., Pearson, R.M. & Lawson, M. Concentration of (+) propranolol in cervico-vaginal mucus and serum after repeated oral dose administration. *Br J Clin Pharmacol* 1989, **28**: 243p–244p.
- Salas, I.G., Pearson, R.M. & Turner, P. Atenolol concentrations in cervical mucus. *Eur J Pharmacol* 1990, **183**: 293–294.

15. Salas, I.G., Pearson, R.M., Lawson, M., Turner, P. Metronidazole concentrations in cervical mucus and serum after repeated oral doses. *J Antimicrob Chemother* 1991, in press.
16. Tartaglione, T.A., Johnson, C.R. & Brust, P. Pharmacodynamic evaluation of ofloxacin and trimethoprim-sulphamethoxazole in vaginal fluid in women treated for acute cystitis. *Antimicrob Agents Chemother* 1988, **32**: 1640–1643.
17. Iliopoulou, A., Thin, R.N. & Turner, P. Fluorimetric and microbiological assays of erythromycin concentrations in plasma and vaginal washings. *Br J Venereal Dis* 1981, **57**: 263–267.
18. Salas-Herrera, I.G., Pearson, R.M. & Turner, P. Concentration of ibuprofen in cervical mucus. *J Pharm Pharmacol* 1991, **43**: 142–144.
19. Salas, I.G., Pearson, R.M. & Lawson, M. Lithium carbonate concentrations in cervico-vaginal mucus and serum after repeated oral administration. *Br J Clin Pharmacol* 1989, **28**: 751P.
20. Hong, C.Y. Drugs and male reproductive function. In: Turner, P., Volans, G.N. (eds) *Recent Advances in Clinical Pharmacology and Toxicology*, Vol. 4. Churchill Livingstone, Edinburgh, 1989, pp. 105–120.