Leading Article

Secretion of drugs into the human female genital tract

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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.

Propranolol has been successfully administered by the vaginal route in a patient unable to take it orally, 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. 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. Secondly, a drug may exert unwanted effects by reducing sperm motility and fertility. Orally administered propranolol has been shown to be highly concentrated in cervical mucus and other experiments have shown it to reduce sperm motility in vitro, 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.

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. 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. 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. However, the weakly basic drugs, metronidazole and antipyrine, reached concentrations in cervical mucus which were much lower than those reached in serum. These results are consistent with those of other investigators with co-trimoxazole, ofloxacin, and erythromycin 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.
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, 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 (pKa).

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.

Acknowledgements

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References


Table 1

<table>
<thead>
<tr>
<th>Drug</th>
<th>Nature</th>
<th>Molecular weight (g)</th>
<th>pK_a</th>
<th>Partition* coefficient</th>
<th>P-B%</th>
<th>Ratio CM/S</th>
<th>Dose</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-propranolol</td>
<td>Strong base</td>
<td>295.8</td>
<td>9.5</td>
<td>20.20</td>
<td>95.0</td>
<td>35.0</td>
<td>160 mg twice daily</td>
<td>13</td>
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<tr>
<td>Atenolol</td>
<td>Strong base</td>
<td>266.3</td>
<td>9.6</td>
<td>0.01</td>
<td>3.0</td>
<td>16.0</td>
<td>100 mg once</td>
<td>14</td>
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<tr>
<td>Antipyrine1</td>
<td>Weak base</td>
<td>188.2</td>
<td>1.4</td>
<td>28.00</td>
<td>10.0</td>
<td>0.9</td>
<td>1 gram once</td>
<td>12</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Weak base</td>
<td>171.2</td>
<td>2.5</td>
<td>1.18</td>
<td>15.0</td>
<td>0.8</td>
<td>400 mg twice daily</td>
<td>15</td>
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<tr>
<td>Ibuprofen</td>
<td>Strong acid</td>
<td>206.2</td>
<td>4.4</td>
<td>9.85</td>
<td>99.0</td>
<td>0.04</td>
<td>800 mg once</td>
<td>18</td>
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<tr>
<td>Lithium carbonate</td>
<td>Neutral</td>
<td>73.9</td>
<td>6.8</td>
<td>0.0</td>
<td>0.0</td>
<td>0.64</td>
<td>300 mg twice daily</td>
<td>19</td>
</tr>
</tbody>
</table>

*Octanol/water (aqueous phase at 7.4); 1Related to saliva parameters; 1Chloroform/water (aqueous phase at 7.4); 1Inorganic ions are insoluble in lipids, CM/S = cervical mucus concentration/serum concentration.