**Misoprostol**

**Different Routes of Administration**

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**Chemical structure of misoprostol**

- 15-deoxy-16-hydroxy-16-methyl PGE$_1$
- synthetic prostaglandin E$_1$ analogue
- methyl ester at C-1 (increases the antisecretory potency and duration of action of misoprostol), a methyl group at C-16 and a hydroxyl group at C-16 rather than at C-15 (improve oral activity, increase the duration of action, and improve the safety profile).

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**Routes of administration**

- Oral
- Vaginal
- Sublingual
- Buccal
- Rectal

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**Pharmacokinetic parameters**

- Peak concentration (C$_{max}$)
- Time to peak concentration (T$_{max}$)
- Area under the curve (AUC)
- Half-life
Pharmacokinetics studies on various routes of administration

<table>
<thead>
<tr>
<th>Route</th>
<th>C&lt;sub&gt;max&lt;/sub&gt;/pg/mL</th>
<th>T&lt;sub&gt;max&lt;/sub&gt;/min</th>
<th>AUC&lt;sub&gt;240&lt;/sub&gt;/pg.hr/mL</th>
<th>AUC&lt;sub&gt;360&lt;/sub&gt;/pg.hr/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zieman</td>
<td>277±124</td>
<td>34±17</td>
<td>273±110</td>
<td>300±103</td>
</tr>
<tr>
<td>Tang</td>
<td>287±144</td>
<td>28±15</td>
<td>369±155</td>
<td>402±152</td>
</tr>
<tr>
<td>Khan</td>
<td>259±84</td>
<td>14±7</td>
<td>152±61</td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zieman</td>
<td>165±86</td>
<td>80±27</td>
<td>503±270</td>
<td>956±542</td>
</tr>
<tr>
<td>Tang</td>
<td>125±54</td>
<td>72±35</td>
<td>330±140</td>
<td>434±183</td>
</tr>
<tr>
<td>Meckstroth</td>
<td>445±428</td>
<td>92±82</td>
<td>925±568</td>
<td>1025±572*</td>
</tr>
<tr>
<td>Khan</td>
<td>210±63</td>
<td>65±21</td>
<td>446±172</td>
<td>--</td>
</tr>
<tr>
<td>Sublingual</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tang</td>
<td>575±250</td>
<td>26±12</td>
<td>702±275</td>
<td>744±291</td>
</tr>
<tr>
<td>Buccal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meckstroth</td>
<td>265±171</td>
<td>84±82</td>
<td>475±312</td>
<td>520±339*</td>
</tr>
<tr>
<td>Rectal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meckstroth</td>
<td>202±196</td>
<td>20±14</td>
<td>281±276</td>
<td>312±281*</td>
</tr>
<tr>
<td>Khan</td>
<td>87±45</td>
<td>72±24</td>
<td>189±126</td>
<td>--</td>
</tr>
</tbody>
</table>

Choice of routes of administration

- Efficacy of the regimens
- Clinical indications
- Side effects
- Practicability
- Convenience
- Acceptability

1 Zieman et al, 1997; 2 Tang et al, 2002; 3 Meckstroth et al 2006; 4 Khan et al, 2004
5 *AUC<sub>300</sub>
Misoprostol: clinical manifestation of action

- Serum drug level
- Sensitivity of end organ: uterus and cervix
- Gestation
- Clinical indication
- Use of mifepristone
- Local effect on the cervix with vaginal application
- Effect of local pH, secretion and bleeding on absorption


Mean uterine tone in millimeters of mercury

Uterine activity was measured in Montevideo Units

Mean uterine activity in Alexandria Units

Mean uterine activity in Alexandria Units

Effect on the cervix

• The biochemical events that have been implicated in cervical ripening are
  (1) a decrease in total collagen content,
  (2) an increase in collagen solubility,
  (3) an increase in collagenolytic activity.

• The mean proline incorporation per µg protein and collagen density, estimated by light intensity was significantly less than the control. The diameter of the collagen fibres was smaller in the misoprostol group although the difference was not statistically significant (El-Refaey et al., 1994).

Clinical applications of misoprostol in O&G

• Medical abortion in first and second trimester
• Cervical priming before surgical evacuation
• Management of miscarriages
• Induction of labour
• Management of postpartum haemorrhage

First trimester medical abortion
Medical abortion: first trimester
Vaginal vs Oral
(<9wks, mifepristone 600mg)

<table>
<thead>
<tr>
<th></th>
<th>Oral misoprostol (800μg) N=130</th>
<th>Vaginal misoprostol (800μg) N=130</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete abortion</td>
<td>87%</td>
<td>N=130</td>
</tr>
<tr>
<td>Vomiting</td>
<td>44%</td>
<td>31%*</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>36%</td>
<td>18%*</td>
</tr>
</tbody>
</table>

* p<0.05
(El-Refaey et al, 1995)

Medical abortion: first trimester
Vaginal vs Sublingual
(<9wks, mifepristone 200 mg)

<table>
<thead>
<tr>
<th></th>
<th>Sublingual misoprostol (800μg) N=112</th>
<th>Vaginal misoprostol (800μg) N=112</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete abortion</td>
<td>98.2%</td>
<td>93.8 %^</td>
</tr>
<tr>
<td>Vomiting</td>
<td>37 %</td>
<td>13%*</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>40 %</td>
<td>16%*</td>
</tr>
<tr>
<td>Chills</td>
<td>30%</td>
<td>9%*</td>
</tr>
<tr>
<td>Fever</td>
<td>39%</td>
<td>3%*</td>
</tr>
</tbody>
</table>

* p<0.05
• ^ 3 on-going pregnancies
(Tang et al, 2003)

Medical abortion: first trimester
Buccal vs Vaginal
(<8wks, mifepristone 200 mg)

<table>
<thead>
<tr>
<th></th>
<th>buccal misoprostol (800μg) N=216</th>
<th>vaginal misoprostol (800μg) N=213</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete abortion</td>
<td>95 %</td>
<td>93 %</td>
</tr>
<tr>
<td>Vomiting</td>
<td>37 %</td>
<td>32%</td>
</tr>
<tr>
<td>Nausea</td>
<td>70%</td>
<td>62%</td>
</tr>
<tr>
<td>Fever</td>
<td>42%</td>
<td>51%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>36%</td>
<td>18%</td>
</tr>
</tbody>
</table>

* p<0.05
(Middleton et al, 2005)

Second trimester medical abortion
## Medical abortion: second trimester
### Oral vs Vaginal
(pretreatment 200 mg mifepristone)

<table>
<thead>
<tr>
<th></th>
<th>Oral misoprostol (200µg x5)</th>
<th>Vaginal misoprostol (200µg x5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>49</td>
<td>49</td>
</tr>
<tr>
<td>Success rate in 24h</td>
<td>69 %</td>
<td>90 %*</td>
</tr>
<tr>
<td>Induction-abortion-interval</td>
<td>27.8 h</td>
<td>14.8 h*</td>
</tr>
<tr>
<td>Nausea</td>
<td>30 %</td>
<td>40 %</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20 %</td>
<td>28 %</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>32 %</td>
<td>18 %</td>
</tr>
</tbody>
</table>

P<0.05 (Ho et al, 1997)

## Medical abortion: second trimester
### Oral vs Sublingual
(pretreatment 200mg mifepristone)

<table>
<thead>
<tr>
<th></th>
<th>Oral misoprostol (400µg x5)</th>
<th>Sublingual misoprostol (400µg x5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Success rate in 24h</td>
<td>85 %</td>
<td>91 %</td>
</tr>
<tr>
<td>Induction-abortion-interval</td>
<td>7.5h</td>
<td>5.5h*</td>
</tr>
<tr>
<td>Nausea</td>
<td>43 %</td>
<td>37 %</td>
</tr>
<tr>
<td>Fever</td>
<td>0%</td>
<td>12%*</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>21%</td>
<td>13%</td>
</tr>
</tbody>
</table>

P<0.05 (Tang et al, 2005)

## Medical abortion: second trimester
### Vaginal vs Sublingual

<table>
<thead>
<tr>
<th></th>
<th>Vaginal misoprostol (400µg x5)</th>
<th>Sublingual misoprostol (400µg x5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>112</td>
<td>108</td>
</tr>
<tr>
<td>Success rate in 24h</td>
<td>86 %</td>
<td>72 %</td>
</tr>
<tr>
<td>Induction-abortion-interval</td>
<td>10 h</td>
<td>12 h*</td>
</tr>
<tr>
<td>Nausea</td>
<td>47%</td>
<td>42%</td>
</tr>
<tr>
<td>Fever</td>
<td>59%</td>
<td>44%*</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>26%</td>
<td>32%</td>
</tr>
</tbody>
</table>

P<0.05 (Tang et al, 2005)

## Cervical priming before surgical evacuation
Cervical priming before surgical evacuation
Oral vs Vaginal
(Misoprostol given 3 h before)

<table>
<thead>
<tr>
<th></th>
<th>oral misoprostol (400µg) N=40</th>
<th>vaginal misoprostol (400µg) N=40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline cervical</td>
<td>7.5 (5-8)</td>
<td>7.0 (3-8)</td>
</tr>
<tr>
<td>dilalation/ mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative force/ N</td>
<td>19 (1-101)</td>
<td>22 (5-71)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td>12.5%</td>
<td>13.5%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>20%</td>
<td>21.6%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0 %</td>
<td>0 %</td>
</tr>
</tbody>
</table>

(Ngai et al, 1999)

Cervical priming before surgical evacuation
Vaginal vs Sublingual
(Misoprostol given 3 h before)

<table>
<thead>
<tr>
<th></th>
<th>sublingual misoprostol (400µg) N=40</th>
<th>vaginal misoprostol (400µg) N=40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline cervical</td>
<td>8.0 (4.5-10)</td>
<td>8.0 (6.0-9.5)</td>
</tr>
<tr>
<td>dilalation/ mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative force/ N</td>
<td>5.5 (0-38)</td>
<td>5.0 (1-21)</td>
</tr>
<tr>
<td>Nausea</td>
<td>20%</td>
<td>35%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.5%</td>
<td>7.5%</td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td>37.5%</td>
<td>22.5%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>85%</td>
<td>77.5%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>2.5 %</td>
<td>2.5 %</td>
</tr>
</tbody>
</table>

(Tang et al, 2004)

Conclusion

• Different routes of administration give different pharmacokinetic profile.
• Choice of the route of administration depends on the clinical indication, efficacy, practicability and acceptability.