Misoprostol
Different Routes of Administration

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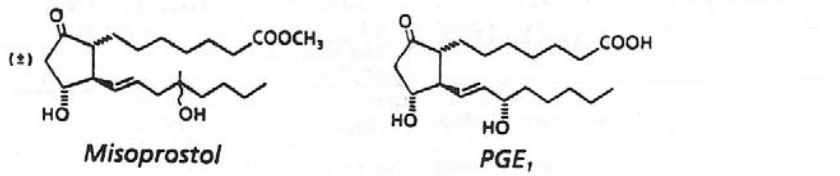
Chemical structure of misoprostol



- 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).

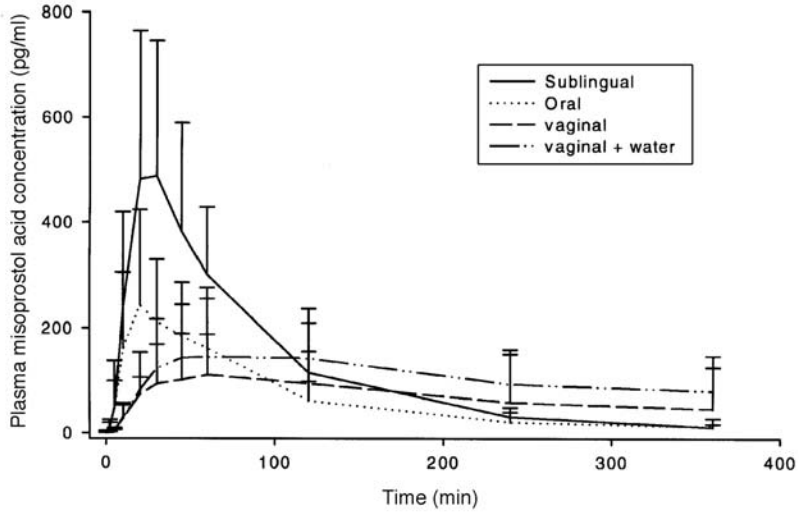
Routes of administration

- Oral
- Vaginal
- Sublingual
- Buccal
- Rectal

Pharmacokinetic parameters

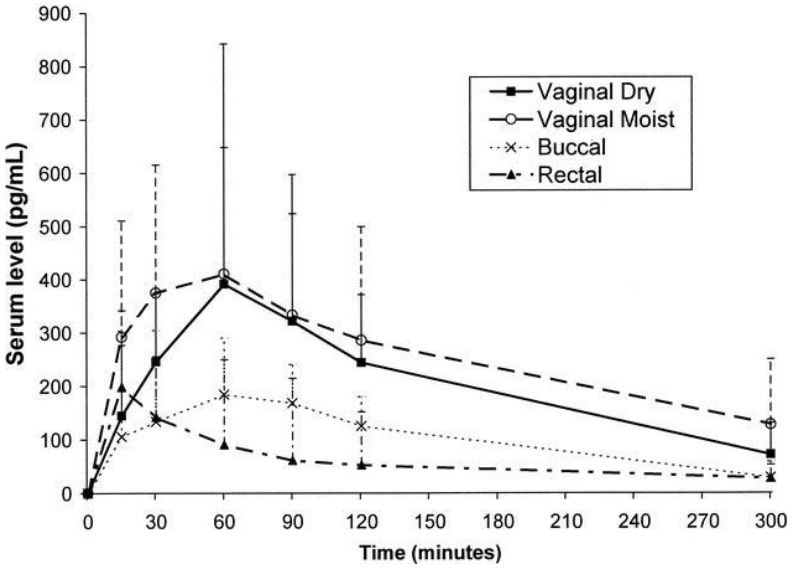
- Peak concentration (C_{max})
- Time to peak concentration (T_{max})
- Area under the curve (AUC)
- Half-life

Mean plasma concentrations of misoprostol acid over time



Tang, O. S. et al. Hum. Reprod. 2002

Mean plasma concentrations of misoprostol acid over time



Meckstroth et al. Obstet Gynecol 2006.

Pharmacokinetics studies on various routes of administration

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

[1] Zieman et al, 1997; [2] Tang et al, 2002 ; [3] Meckstroth et al 2006; [4] Khan et al, 2004

* AUC_{300}

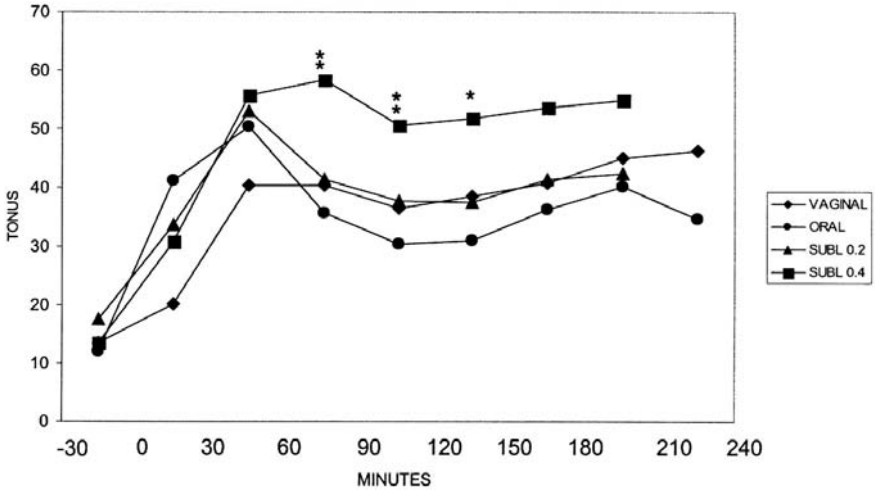
Choice of routes of administration

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

Misoprostol: clinical manifestation of action

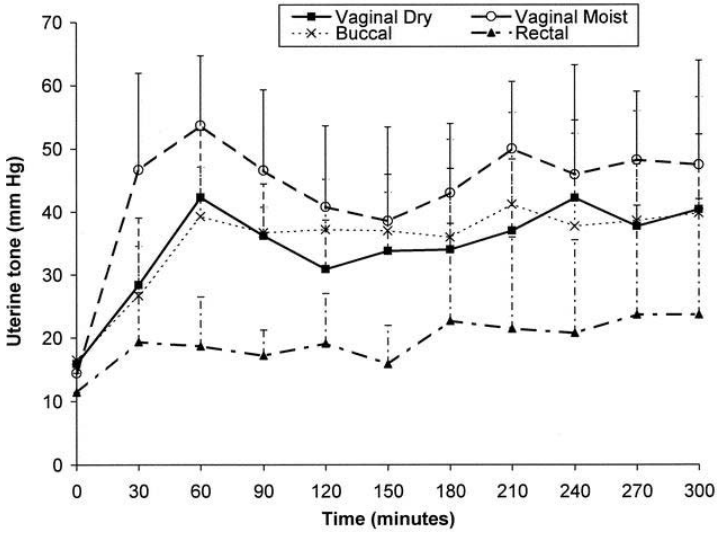
- Serum drug level
- Sensitivity of end organ: uterus and cervix
- Gestation
- Clinical indication
- Use of mifepristone
- Local effect on the cervix with vaginal application
- Effect of local pH, secretion and bleeding on absorption

Uterine tonus was measured in mmHg



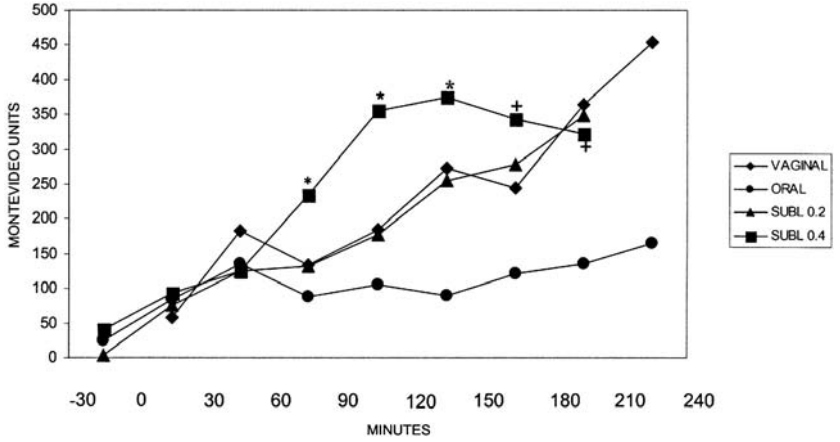
Aronsson, A. et al. Hum. Reprod. 2004

Mean uterine tone in millimeters of mercury



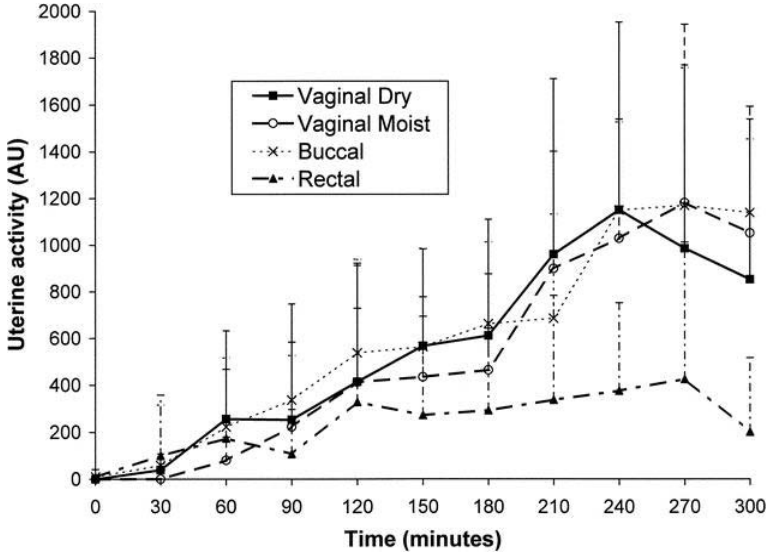
Meckstroth et al Obstet Gynecol 2006

Uterine activity was measured in Montevideo Units



Aronsson, A. et al. Hum. Reprod. 2004

Mean uterine activity in Alexandria Units



Meckstroth et al. Obstet Gynecol 2006

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)

	Oral misoprostol (800µg) N=130	Vaginal misoprostol (800µg) N=130
Complete abortion	87%	95%*
Vomiting	44%	31%*
Diarrhoea	36%	18%*

* p<0.05

(El-Refaey et al, 1995)

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

	Sublingual misoprostol (800µg) N=112	Vaginal misoprostol (800µg) N=112
Complete abortion	98.2%	93.8 %^
Vomiting	37 %	13%*
Diarrhoea	40 %	16%*
Chills	30%	9%*
Fever	39%	3%*

- p<0.05
- ^ 3 on-going pregnancies

(Tang et al, 2003)

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

	buccal misoprostol (800µg) N=216	vaginal misoprostol (800µg) N=213
Complete abortion	95 %	93 %
Vomiting	37%	32%
Nausea	70%	62%
Fever	42%	51%
Diarrhoea	36%	18%

* p<0.05

(Middleton et al, 2005)

Second trimester medical abortion

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

	oral misoprostol (200µg x5) N=49	Vaginal misoprostol (200µgx5) N= 49
Success rate in 24h	69 %	90 %*
Induction-abortion-interval	27.8 h	14.8 h*
Nausea	30 %	40 %
Vomiting	20 %	28%
Diarrhoea	32%	18%

P<0.05

(Ho et al, 1997)

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

	oral misoprostol (400µg x5) N=60	sublingual misoprostol (400µgx5) N= 60
Success rate in 24h	85 %	91 %
Induction-abortion-interval	7.5h	5.5h*
Nausea	43%	37%
Fever	0%	12%*
Diarrhoea	21%	13%

P<0.05

(Tang et al, 2005)

Medical abortion : second trimester
Vaginal vs Sublingual

	vaginal misoprostol (400µg x5) N=112	sublingual misoprostol (400µgx5) N= 108
Success rate in 24h	86 %	72 %
Induction-abortion-interval	10 h	12 h*
Nausea	47%	42%
Fever	59%	44%*
Diarrhoea	26%	32%

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)

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

(Ngai et al, 1999)

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

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

(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.