Misoprostol

Pharmacokinetics and Pharmacodynamics

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Overview

• Pharmacokinetics
  – what the body does to the drug
• Clinical Implications
• Pharmacodynamics
  – what a drug does to the body
• Available products
Pharmacokinetics

- study of the time course of drug and metabolite concentrations in different fluids, tissues, and excreta of the body, and of the mathematical relationships required to develop models to interpret such data
Chemistry

- discovered in 1973
- prostaglandin E1 analogue
- slight structural modifications to:
  - increase anti-secretory potency
  - increase duration of action (half life of naturally occurring prostaglandins seconds)
  - improve oral bioavailability
  - improve safety profile
Absorption

- rapidly absorbed after oral doses
- peak plasma concentrations occur after about 15 to 30 minutes
- food reduces the rate but not the extent of absorption
- concomitant antacid use reduces total availability
Distribution

- high variability of plasma levels between and within studies
- mean plasma levels after single oral doses show a linear relationship with dose over the range of 200-400 mcg
- no accumulation of misoprostol noted in multiple dose studies
- serum protein binding less than 90%, concentration-independent in the therapeutic range
Metabolism

- undergoes rapid de-esterification to its free acid which is clinically active (misoprostol acid)
- misoprostol acid further metabolised by oxidation, primarily in the liver
Excretion

- mainly urinary excretion - oral administration of radiolabeled misoprostol ~ 80% of detected radioactivity appears in urine
- plasma elimination half-life reported to be between 20 and 40 minutes
- misoprostol acid is distributed into breast milk
- PK studies in patients with varying degrees of renal impairment have shown:
  - approximate doubling of T1/2, Cmax, and AUC compared to normal controls
  - no clear correlation between the degree of impairment and AUC.
- no routine dosage adjustment recommended in patients with renal impairment, but dosage may need to be reduced if the usual dose is not tolerated
- does not affect the hepatic mixed function oxidase (cytochrome P-450) enzyme systems in animals - no known drug interactions
Vaginal Administration

- longer time to peak plasma conc. (70-80 min.)
- longer duration of action
- greater overall bioavailability (AUC)
- large degree of variation in bioavailability between women
- mechanism for direct vagina → uterus transport of progesterone exists
Sublingual Administration

- tablet dissolves in approx. 20 mins.
- shorter time to peak conc. than oral and vaginal
- highest peak concentration
- greatest bioavailability
- no first pass metabolism in the liver
Pharmacokinetics in Pregnancy

![Graph showing plasma misoprostol concentration over time for sublingual, oral, vaginal, and vaginal + water routes.](image)
Buccal Route

- similar concentration profile to vaginal administration
- lower bioavailability (~50%)
Rectal Route

- similar concentration profile to vaginal administration
- lower bioavailability (~33%)
- onset of action significantly slower than other routes
Pharmacokinetics in Pregnancy

![Graph showing serum level over time for different administration methods: Vaginal Dry, Vaginal Moist, Buccal, Rectal.](image)
Clinical Implications
## Recommended Dosages

<table>
<thead>
<tr>
<th>Dosage</th>
<th>1st Trimester</th>
<th>2nd Trimester</th>
<th>3rd Trimester</th>
<th>Postpartum</th>
</tr>
</thead>
</table>
| 800µg  | Induced abortion<sup>1</sup>  
800µg vaginal  
12 hrly (max x3) | Missed abortion  
800µg vaginal  
3 hrly (max x2)  
OR  
600µg sublingual  
3 hrly (max x2) | Incomplete abortion<sup>2,3</sup>  
600µg oral  
Single dose | PPH treatment & prophylaxis<sup>6</sup>  
600µg oral or sublingual single dose |
| 600µg | Cervical ripening pre-instrumentation  
400µg vaginal  
3 hrs before procedure | Induced abortion<sup>1,4</sup>  
interruption of pregnancy  
400µg vaginal  
3 hrly (max x5) | | |
| 400µg | Intraterine fetal death<sup>4</sup>  
(12-17 wks)  
200µg vaginal  
6 hrly (max x4) | | | |
| 200µg | Intraterine fetal death<sup>4</sup>  
(18-26 wks)  
100µg vaginal  
6 hrly (max x2) | | | |
| 100µg | Intraterine fetal death<sup>4</sup>  
(27-43 wks)  
25µg vaginal  
4 hrly (max x6)  
OR  
20µg oral solution  
2 hrly (max x12) | Induction of labour<sup>2,5</sup>  
25µg vaginal  
4 hrly (max x6)  
OR  
20µg oral solution  
2 hrly (max x12) | | |
| 50µg | | | | |
| 25µg | | | | |

Care with previous uterine scar and caesarean section
Pharmacodynamics

• study of the physiological effects of drugs on the body and the mechanisms of drug action and the relationship between drug concentration and effect
Pharmacodynamics

• prostaglandins (PGs) induce myometrial contraction in the pregnant and non-pregnant uterus ‘triggers of labour’
• sensitivity of uterine muscle to PGs increases with gestation
• PGs lead to cervical ripening and relaxation
• naturally occurring PGs rapidly broken down
• PGs produced as needed in tissues- not stored
• endometrium and myometrium have substantial PG synthesising capacity
Pharmacodynamics

- role in parturition not fully understood
- NSAIDs interfere with cyclo-oxegenase (involved in PG production) and hence prolong labour
- $EP_1$ & $EP_2$ receptors contraction promoting, abundant in the fundus
- $EP_3$ & $EP_4$ receptors relaxation promoting, found in lower uterine segment
- varying expression of receptors may be responsible for differing sensitivity of myometrium throughout gestation and at delivery
Pharmacodynamics

- regulation of PG receptor expression not extensively studied
- progesterone and oestrogen thought to play a role in PG receptor expression
- progesterone antagonist mifepristone increases myometrial response to exogenous prostaglandins
- thought to up-regulate expression of contraction-promoting PG receptors
Physiological Effects

Uterotonic

- single oral dose $\uparrow$ tonus (for 1-2h)
- repeated oral doses $\rightarrow$ regular contractions
- single vaginal dose will produce regular contractions (sustained plasma conc.)
- increased tonus more rapid and more pronounced with oral/sublingual (8/11 min.) compared with vaginal (20 min.)
- differing durations of action
Physiological Effects

Cervical softening

• misoprostol reduces the force required for cervical dilatation
• appears to have an action on collagen, encouraging disintegration and dissolution
Adverse Effects

- diarrhoea & abdominal pain
- headache
- nausea
- flatulence
- chills/shivering/fever
  - Hyperpyrexia (>40°) - doses >600 micrograms
  - Delerium - doses >800 micrograms
- uterine rupture
- uterine hyperstimulation
- amniotic fluid embolism

{ case reports }
Formulations

• Cytotec® 200 microgram (oral) tab
• Isprelor® 25 microgram vaginal tab
• Gymiso® 200 microgram (oral) tab
• Prostokos® 25 microgram vaginal tab
• Vagiprost® 25 microgram vaginal tab
• Extemp. 1 microgram/ml oral sol.
• Misopess® Controlled-Release Hydrogel Polymer Vaginal Insert
• Licensing issues!!
References

Thank You!