Pathophysiology

of

Mifepristone-Induced Septic Shock

Due to

Clostridium sordellii

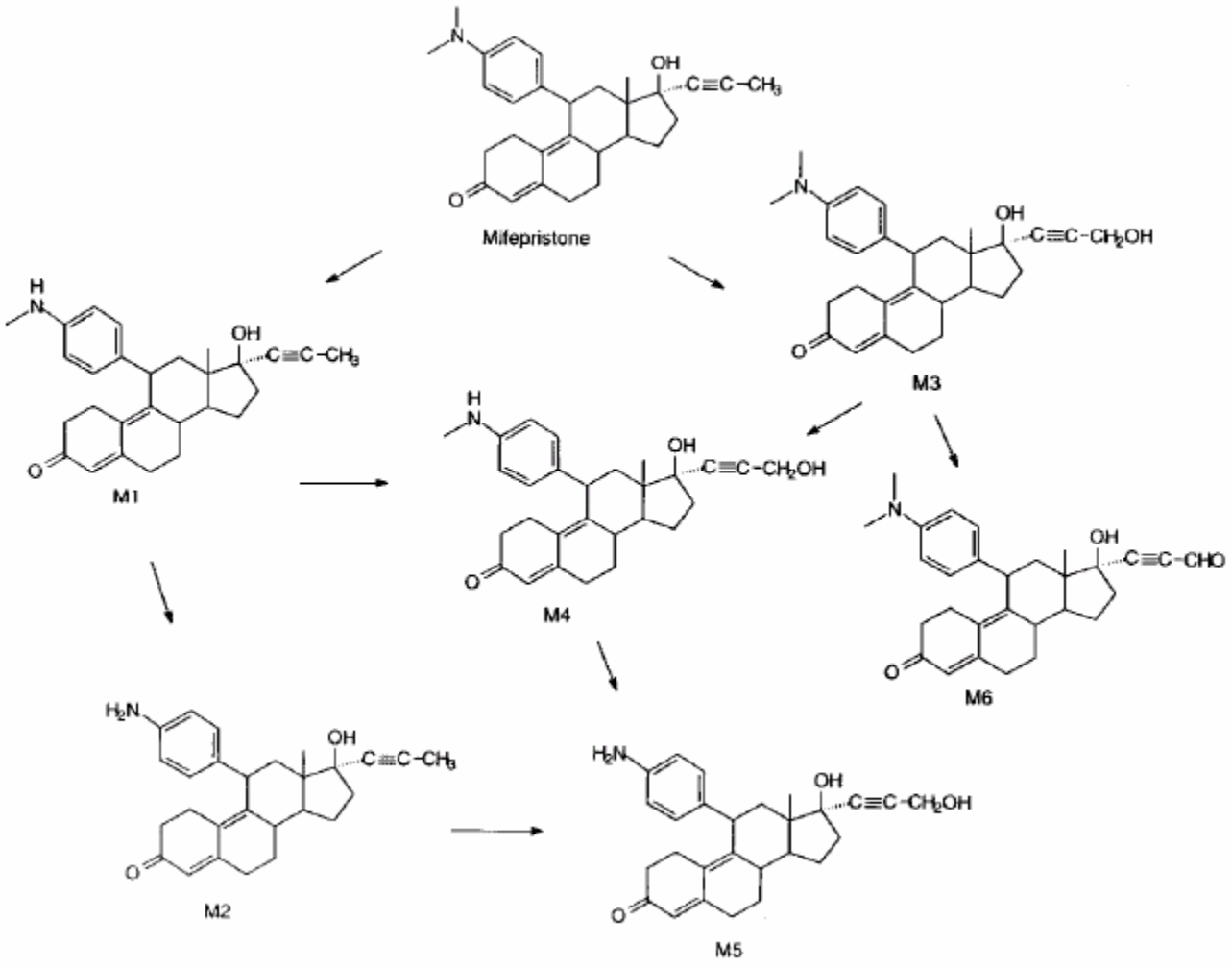
Biological Half-Life of Mifepristone

Usual half-life = 20 to 30 hours

Half-life in some individuals = 90 hours.

2. Europ. J. Obstet. Gynec. & Reprod. Biol. 2002, 101:113-120

Metabolism of Mifepristone



3. Xenobiotica: 1999, 29(11): 1089-1100

CYP450-3A4

The Main Liver Microsomal Enzyme

Responsible for

the Metabolism of Mifepristone

4. J. Pharmacol. Exp. Ther. 1999, 288(2):791-7

Mifepristone binds with high affinity

to both

progesterone receptors

&

glucocorticoid receptors

$K_d = < 10^{-9} M)$

5. Annu. Rev. Med. 1997, 48:129–56

RU38486 = Mifepristone = RU486

Anti-glucocorticoid Actions

(1) causes an increase release of ACTH and cortisol

(2) causes disordered release of cytokines

Anti-progesterone Actions

(1) cervical ripening,

(2) ischemia of the decidua,

(3) necrosis of the products of conception and

(4) sensitization of the myometrium to contraction by prostaglandins.

6. Annu. Rev. Med. 1997, 48:129–56

Pathogen Associated Molecular Pattern molecules

bind to Toll Receptors

on uterine macrophages

to activate the Innate Immune System

to synthesize and secrete

Pro-Inflammatory Cytokines

TNF-alpha, IL-1 & IL-6

7. NEJM: 2003, 348(2):138-150.

7a. Nature Reviews (Immunology): 2004, (4):512-520

Streptococcal Cell Wall Mortality in F344/N Rats

	Moratility Rate
Control……	13%
Mifepristone Treated……	100%

8. Proc. Natl. Acad. Sci. 1989, 86: 2374-8

Animal Model of Poly-microbial Induced Septic Shock

[Ligated Cecum with Needle Puncture]

	Mortality Rate
Control……	29%
Singe Dose of Mifepristone…….	85%

8a. Circulatory Shock: 1992, 36(3): 180-4

Lethal Toxin secreted by *Clostridium sordellii*

inactivates Rho & Ras GTPases,

the molecular switches

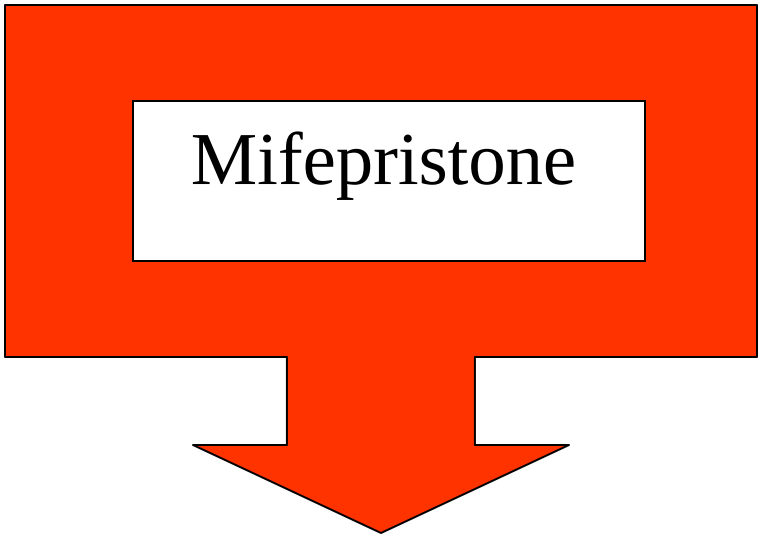
that activate or inhibit vital

cellular biochemical cascades

&

genetic transcription functions

9. Biochimica et Biophysica Acta: 2004, 1673:66-74, (Review)



Blockade of progesterone receptors causes

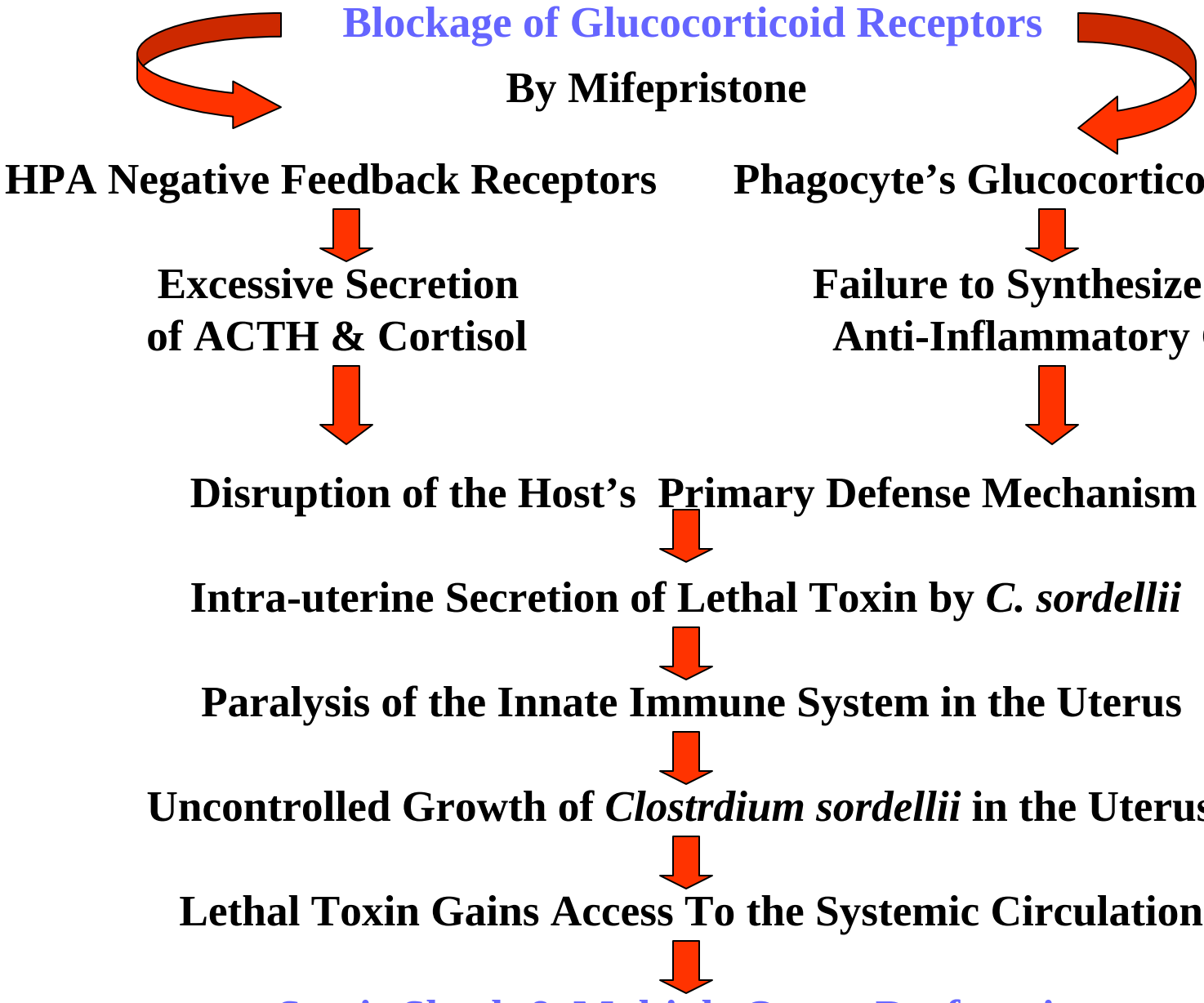
(1) Ischemic decidua

(2) Necrotic products of conception

(3) Opening of the Cervical Os

(4) Intra-uterine nidus of C. sordellii from vaginal flora

10. Annals of Pharmacotherapy: 2005, 39(9):1483-1488.



11. Annals of Pharmacotherapy: 39(9):1483-1488.