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Ergot Alkaloids

Current Status and Review of Clinical Pharmacology and Therapeutic Use Compared with Other Oxytocics in Obstetrics and Gynaecology

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Contents

Abstract

Ergot alkaloids are well known preparations. Ergot alkaloids used in obstetrics and gynaecology are ergometrine (ergonovine; EM), methylergometrine (mether-

gine; ME) and bromocriptine. The pharmaceutical properties of ME EM) are critical. To guarantee stability, ME and EM ampoules should be stored in a cool, dark place. ME and EM tablets are unstable in all conditions and they show an unpredictable bioavailability, which prevents oral use of the drugs for any purpose.

ME and EM are known for their strong uterotonic effect and, compared with other ergot alkaloids, for their relatively slight vasoconstrictive abilities. ME and EM do have a place in the management of the third stage of labour as they are strong uterotonics. They act differently from oxytocin and prostaglandins, and have different adverse effects. Oxytocin should be used as prophylaxis or a the drug of first choice; next, ME or EM should be used, and if none of these drugs produce the desired effects, prostaglandins should be used to control bleeding.

Ergot alkaloid use in gynaecology has been limited and today is discouraged even in essential menorrhagia. It is suggested that EM and ME be used (parenterally) only in first trimester abortion curettage, to reduce blood loss. Bromocriptine has been used for lactation suppression. However, alternatives such as cabergoline, which possess fewer adverse effects, are now available and therefore preferred for this indication.

In sum, there is no place for the prophylactic use of ME and EM in obstetrics or gynaecology. They can be used for therapeutic purposes in the third stage of labour. During use, the practitioner must be alert for adverse effects.

1. Historical Background

1.1 Introduction and Toxic Effect

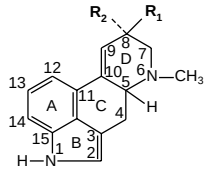
Ergot alkaloids are well known and were first mentioned around 600 BC on an Assyrian cuneiform tablet as a 'noxious pustule in the ear of grain'. The Roman historian Lucretius (98-55 BC) called erysipelas *ignis sacer*, i.e. holy fire, the name which was given in the Middle Ages to ergotism because of burning sensations in the limbs. Supposed bones of the Egyptian hermit St. Anthony (251-356 AD) were sprinkled with holy water and wine and given to the sufferers of ergotism. In 1095, the order of St. Anthony was founded in Vienne, France. Toxic effects due to ergot derivatives have been described since the twelfth century. At that time, epidemics of ergotism occurred frequently.[1] Ergotism resulted in gangrene of the limbs and CNS disturbances, and ultimately in death. People flocked to the hospitals of the Antonines during epidemics of ergotism. Soon the hospitals were called 'hôpitaux des démembrés', because at their entrance the spontaneously amputated and lost limbs (due to ergotism) were exhibited as a kind of *ex voto*. Victims of ergotism could identify themselves easily with the lifelong suffering of St Anthony. Epidemics of ergotism were a source of inspiration for artists and were popularly known as 'St Anthony's Fire', holy fire or *ignis sacer*.[2,3]

A distinction was made between gangrenous and convulsive ergotism.[4] Symptoms of the gangrenous form include abortion, amenorrhoea, failure to lactate, lassitude, vascular changes of the feet and hands, jaundice and severe diarrhoea. The symptoms of convulsive ergotism are fatigue, giddiness, paraesthesia, formication, nausea and vomiting, burning sensation, clonic/tonic spasms, flexion of arms or hands, paralysis, hemi(para)-plegia, maniacal excitement, hallucinations, visual disturbances, delusional insanity, psychosis, convulsions, dullness and cataract.[2]

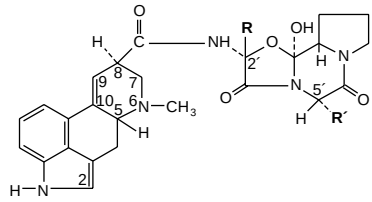
1.2 Use in Obstetrics

Ergot alkaloids were used in obstetrics for the first time in 1582. Adam Louicer mentioned then that delivery could be speeded up by administering 3 sclerotia (= ergot 0.5mg).[2,3] However, their use for labour induction ended in 1822. Too often uterine ruptures occurred, resulting in stillbirth and

Amine alkaloids and congeners



Amino acid alkaloids



Alkaloid	R_1	R_2
d-Lysergic acid	—COOH	—H
d-Isolysergic acid	—H	—COOH
d-Lysergic acid diethylamide (LSD)	—C(=O)—N(CH_2CH_3)$_2$	—H
Ergometrine	—C(=O)—NH—CH(CH_2OH)—CH_3	—H
Methylergometrine	—C(=O)—NH—CH(CH_2OH)—CH_2CH_3	—H
Methysergide[a]	—C(=O)—NH—CH(CH_2OH)—CH_2CH_3	—H
Lisuride	—H	—NH—C(=O)—N(CH_2CH_3)$_2$
Lysergol	—CH_2OH	—H
Lergotrile[b,c]	—CH_2CN	—H
Metergoline[a,b]	—CH_2—NH—C(=O)—O—CH_2—phenyl	—H

Alkaloid[d]	R(2′)	R′(5′)
Ergotamine	—CH_3	—CH_2—phenyl
Ergosine	—CH_3	—$CH_2CH(CH_3)_2$
Ergostine	—CH_2CH_3	—CH_2—phenyl
Ergotoxine group		
ergocornine	—$CH(CH_3)_2$	—$CH(CH_3)_2$
ergocristine	—$CH(CH_3)_2$	—CH_2—phenyl
α-ergocryptine	—$CH(CH_3)_2$	—$CH_2CH(CH_3)_2$
β-ergocryptine	—$CH(CH_3)_2$	—$CHCH_2CH_3$ (CH_3)
Bromocriptine[e]	—$CH(CH_3)_2$	—$CH_2CH(CH_3)_2$

a Contains methyl substitution at N1
b Contains hydrogen atoms at C9 and C10
c Contains chlorine atom at C2
d Dihydro derivatives contain hydrogen atoms at C9 and C10
e Contains bromine atom at C2

Fig. 1. Natural and semisynthetic ergot alkaloids (from Rall,[12] with permission).

maternal death, because of inaccurate dosage. The *pulvis ad partum* was renamed *pulvis ad mortem*.[5] By the end of the nineteenth century, ergot alkaloids were no longer used during parturition.

The first pure ergot alkaloid was described in 1875 by Tanret in France.[6] Many more derivatives of ergot alkaloids followed. In 1932, Dudley and Moir isolated ergometrine (ergonovine; EM). This compound had a very specific uterotonic action with little vasoconstrictive ability, and prevented excessive bleeding after childbirth.[7] It is still used for this purpose today, though for preventive measures oxytocin (a different oxytocic) is preferred because it has fewer adverse effects.[2,8]

Since the end of the 1970s, another semisynthetic ergot alkaloid – bromocriptine, an amino acid alkaloid – has also frequently been used in obstetrics to inhibit puerperal lactation.[9] It is a partial dopamine agonist and antagonist in various CNS areas and inhibits prolactin secretion induced by α-ergocryptines. Today, alternatives such as cabergoline are available that produce fewer adverse effects.

1.3 Use in Gynaecology

Ergot alkaloids such as EM have been and probably still are widely used to treat essential menorrhagia. However, these uterotonics do not diminish the amount of menstrual blood loss and therefore should not be used for this purpose.[10,11]

2. Chemical Background

2.1 Naturally Existing Ergot Alkaloids

Ergot alkaloids can all be considered as derivatives of the tetracyclic compound 6-methylergoline (fig. 1).[12] The naturally existing alkaloids

of therapeutic interest are amide derivatives of *d*-lysergic acid. They contain a substituent at position 8 and a double bond in ring D between C9 and C10 and are called 9-ergolenes. The substituent at position 8 can be either in the α-configuration or in the β-configuration. Optical isomerism is due to the presence of 2 asymmetrical carbon atoms (positions 5 and 8) in the lysergic acid moiety of the molecule. The 8H atom is called 8α when it is *trans* and 8β when it is *cis* to the 5-H. Traditionally, the α-isomer is distinguished from the β-form by the prefix *iso-* or by the ending *-inine*. Thus, the 8α-configuration is called *d*-isolysergic acid, the 8β-configuration is called *d*-lysergic acid. The substituent at position 8 forming *d*-lysergic acid is the working compound.

When combined with water and exposed to light, specifically at UV frequencies, H_2O can be added to the double bond between C9 and C10, leading to the formation of 6-hydroxy derivatives (lumi-derivatives). An acid environment facilitates this reaction.[12,13] Furthermore, the ergot alkaloids are very easily oxidised, resulting in oxidation products that are coloured.[11]

2.2 Semi-Synthetic Ergot Alkaloids

2.2.1 Amine Alkaloids

EM (fig. 1) is an amide derivative of *d*-lysergic acid; it contains a double bond between C9 and C10 (ring D). Upon hydrolysis, EM yields lysergic acid and an amine; consequently, it is named an amine alkaloid. Methylergometrine (methergine; ME) is a semi-synthetic amide derivative of *d*-lysergic acid. It contains an extra methyl group in the substituent in the β-configuration at position 8.[12,14] The enantiomers (optical isomers) are called ergometrinine and methylergometrinine. The naturally existing enantiomers are always present due to spontaneous epimerisation in the asymmetric centre C8. However, the 8α-configuration (-inine) forms a very small part.[12] ME and EM have greater uterotonic than vasoconstrictive properties.

2.2.2 Amino Acid Alkaloids

The amino acid alkaloids comprise the naturally occurring ergotamine and ergotoxine and the semi-synthetic bromocriptine. Prolactin secretion inhibition is caused by α-ergocryptine. The synthesis of bromocriptine (2-bromo-α-ergocryptine) in 1965 heralded the new era of dopamine receptor stimulation. Interestingly, it was known for some time that during epidemics of ergotism the milk production of nursing mothers and cows stopped.

3. Uterotonic Effect

3.1 Mechanism of Action of Ergot Alkaloids

In general, ergot alkaloids act as partial antagonists at α-receptors and have a direct vasoconstrictive action. They mainly affect the dilated arterioles, induce contractions of uterine musculature and stimulate central dopamine receptors.[15] Activity profiles of the vasoconstrictive and uterotonic properties of peptide alkaloids, dihydropeptide alkaloids, lysergic acid amides and lysergic acid alkaloids are given in table I.[16,17] In obstetrics, ergot alkaloid derivatives with very specific uterotonic actions and without vasoconstrictive properties are used in the management of the third stage of labour to reduce postpartum blood loss. The vasoconstrictive action of both ME and EM is less than that of other ergot alkaloids (table I). EM and ME are pharmacologically similar,[12,13] as both decrease postpartum blood loss by enhancing the muscle tone of the uterus, superposed by fast

Table I. Activity profile of structural groups of ergot alkaloids

Activity profile	Vasoconstriction (systemic)	Uterotonic contraction	Ergotism
Peptide alkaloids (ergotamine)	+++	++	+++
Dihydropeptide alkaloids (dihydroergotamine)	++	±	±
Lysergic acid amides [ME and EM]	±	+++	±
Lysergic acid alkaloids [lysergic acid diethylamide (LSD)]	±	++	++

EM = ergometrine (ergonovine); **ME** = methylergometrine (methergine); ± = moderate effect; ++ = strong effect; +++ = very strong effect.

rhythmic contractions of the myometrium, the so-called tetany. The myometrial blood vessels are compressed as a corollary, resulting in restricting the loss of blood.[18]

3.2 Pharmacological Action of Methylergometrine (ME) and Ergometrine (EM)

Little is known about how ME and EM achieve their oxytocic effect. Interaction with nifedipine suggests that the Ca^{++} channel of smooth muscle cells is of importance for this mechanism.[19] For oxytocin, a receptor mechanism has been described. In contrast to oxytocin, which has its own receptors on the uterus which increase during pregnancy, a specific ME and EM receptor has never been described. Cibils and Hendricks[20] studied the interaction between oxytocin and ME and EM by the effect on pressure in postpartum uteri. They could not detect any major interference between these 2 drugs. They observed no response to oxytocin when patients were premedicated with ME and EM. Intra-amniotic infusion of ME did not induce any uterine response.[20]

Daels[21] described the existence of 2 different zones in the myometrium related to the embryological origin of the uterus: the inner zone [the archemyometrium (rudimentary corpus uteri: oldest muscle layers)] and the outer zone (para- or neomyometrium). Daels showed that in myometrium strips of nonpregnant, pregnant and postpartum women, the different layers had different contractile characteristics and different reactions to epinephrine (adrenaline) and oxytocin. Tonic contraction in the inner layer occurred in postpartum myometrial strips after administration of epinephrine, whereas oxytocin affected the spontaneous motility of the inner layer only marginally *post partum*. Oxytocin strongly affected the amplitude and frequency of contractions in the outer layer of postpartum myometrial strips. From these observations, de Koning Gans et al.[22] suggested that ME affects the inner layer (archemyometrium) of the uterus in contrast to oxytocin and prostaglandins, which are said to affect the outer muscle layer (neomyometrium).[22,23]

Saameli[23] supported the concept that the oxytocic effect of ergot alkaloids and of both norepinephrine (noradrenaline) and adrenaline is due to stimulation of the same α-adrenoreceptors in the inner myometrial layer. This was shown in experimental studies in rabbits in which dihydroergotoxine, piperoxane and phenoxybenzamine, but not hexamethonium or atropine, showed antagonist effects when concomitantly administered with ME, adrenaline or noradrenaline.[23]

ME and EM are said to enhance the muscle tone of the uterus.[18] De Koning Gans et al.[22] suggested that the amplitude and frequency of contractions occur in the outer layer, the new uterus, while ME and EM affect the basal tone of the inner layer (old uterus). This might explain a certain constancy in the relationship between amplitude and frequency; a decrease of amplitude causes an increase of frequency. Intensity seems to have a maximum level. This physical maximum level can be described by maximum relaxation and maximum contraction of the uterine muscle. If the maximum level is changed by alterations in basal tone, adaptations in frequency seem a logical consequence. ME and EM increase the basal tone. If an intensity maximum exists, the amplitude of contraction must decrease when basal tone increases. In other words, an increase in basal tone, caused by ME and EM, implies that the maximum contraction will be reached earlier than without the drug, which will lead to an increase in frequency of the contractions. This is exactly the pharmacological action ascribed (formerly) to ME and EM.

3.3 Mechanism of Action of the Other Oxytocics: Oxytocin and Prostaglandins

The ergot alkaloids were the first oxytocic drugs, followed by oxytocin and prostaglandins, each belonging to a different pharmacological group (table II). As described above in section 3.2, the mechanisms of action of ME and EM are still not fully understood. For oxytocin, a receptor mechanism is described which depends on gesta-

Table II. Oxytocics used as prophylaxis for postpartum haemorrhage after vaginal delivery

Drug	Route of administration	Remarks
Ergot alkaloids		Serious adverse effects
ergometrine (ergonovine)	PO, IM, IV	
methylergometrine (methergine)	PO, IM, IV	
'Syntometrine'[a]	IM	
Oxytocin	Buccal	No accurate dosing
	IM	Drug of choice; very accurate dosing
	IV	Very accurate dosing
Prostaglandins		
misoprostol	PO	Experimental stage
sulprostone	IV	Not as prophylaxis; no bolus injection

a Ergometrine 0.5mg + oxytocin 5IU.

IM = intramuscular; **IV** = intravenous; **PO** = oral.

tional age. The effect of oxytocin is an increase in the frequency of the contractions. Due to its short half-life, the effect of a single dose of oxytocin diminishes quickly after administration.[18,24] The uterotonic effect of prostaglandins is independent of gestational age. After both local and systemic administration prostaglandins give a strong myometrial contraction of the neomyometrium, resulting in an increased uterine tone.[18]

4. Stability of ME and EM

The stability of ergot alkaloids was not discussed until recently. In 1988 Walker et al.[25] showed alarming results concerning the potency of EM. Therefore, further investigations were made to assess the problem of the instability of this vital drug. From longitudinal studies, the conclusion was drawn that the problem of activity was based on instability and not caused by low initial quality; considerable differences in stability existed between different brand-name formulations of the drug.[26]

4.1 Ampoules

Like the field studies, simulated stability studies showed alarming results.[27] Injectable EM proved to be very unstable when stored unrefrigerated. The deterioration is more pronounced with higher storage temperatures and with exposure to light.[26,27] No difference in stability was found between EM and ME; the differences observed were between the various brands of the same drug.[27]

4.2 Tablets

Simulated stability studies on oral ME and EM showed deterioration within weeks, immediately after the tablets were taken from their sealed package or container. Again, the effect increased with temperature and in particular with higher relative humidity.[27,28]

4.3 Comparison with Other Oxytocics

Comparative studies of parenteral oxytocics have shown that oxytocin is more stable than either ME or EM (table III).[27,29,30]) However, the buccal form of oxytocin was not stable after it had been removed from its package or container (table III).

Misoprostol, an oral prostaglandin E_1 (PGE_1) analogue proposed for use in the third stage of labour, is said to be thermostable with no special storage conditions needed to guarantee its shelf life. However, this agent has only been used for active management of the third stage of labour in the research setting.[31] Its clinical usefulness as an oxytocic in the third stage of labour awaits further study.

In conclusion, ME and EM have stability problems. In their injectable formulation, they should be protected from light. The loss of active ingredient can easily be detected by regular visual check of the colour of the solution.[32] In the case of tablet formulations, humidity is the main adverse factor. The simulation study showed ME and EM tablets to be unstable in all conditions. This instability raises doubt about their use, particularly if storage conditions cannot be guaranteed. For prophylactic use in the prevention of postpartum haemorrhage, none of the oral preparations of either ergot alkaloids or oxytocin are suitable because of these instability concerns.[30]

Table III. Results of simulation studies on the stability of oxytocics under tropical conditions (from Hogerzeil and Walker,[27] with permission)

Storage	No. of brands	No. of batches	Mean remnant of active ingredient[a] after 12mo storage (%)		
			dark 4-8°C	dark 30°C	light 21-25°C
Injectable oxytocics[30]					
Ergometrine (ergonovine)	4	8	95 (80-100)	69 (56-83)	9 (2-15)
Methylergometrine (methergine)	4	8	96 (92-100)	82 (69-94)	9 (0-22)
Oxytocin	3	6	101 (99-102)	86 (83-90)	93 (91-95)
Oral oxytocics[b][31]					
Ergometrine	1	1	54	9	44
Methylergometrine	1	1	59	50	57
Oxytocin	1	1	83	33	85
Desamino-oxytocin	1	1	51	36	56

a Percentage of initial amount (95% confidence limits).

b Tablets removed from their container, kept at approximately 75% (4-8 and 30°C) or 30% (21-25°C) relative humidity.

5. Pharmacokinetics and Pharmacodynamics of ME and EM

5.1 Pharmacokinetics

After oral administration, both EM and ME are rapidly absorbed;[8,33] however, extreme interindividual variation in bioavailability in men (table IV) and nonpregnant women[34] for ME, and men for EM,[35] was shown. The oral route thus does not appear to be the most reliable route of administration for accurate dosing. After intravenous administration, the problem of unpredictable bioavailability does not exist and a mean terminal half-life of 120 minutes has been reported.[8,36]

5.2 Pharmacodynamics

5.2.1 Postpartum Uterus

The uterotonic effect of ergot alkaloids on a postpartum uterus was first described by Moir and Dale[37] using an intrauterine bag method. Dudley and Moir[38] isolated EM and described its action as: '. . . the onset is sudden, and accompanied by uterine spasm, which appears to be caused by a succession of contractions so rapid that the organ as a whole has no time to relax'. Later the effects of ME and EM were studied by Hendricks et al.,[39] who described the postpartum contractions as being complicated, uncoordinated contraction complexes at a diminishing frequency compared with

Table IV. Mean pharmacokinetic parameters of methylergometrine after intravenous and oral doses in 6 male volunteers (after de Groot,[8] with permission)

Parameter	Dose (μg)		% of co-variance	p-Value
	IV 152 (SD)	PO 95 (SD)		
$t_{½}$ (h)	1.85 (0.28)	2.08 (0.43)		0.31*
CL (L/h)	32.2 (11.8)	31.1 (10.3)		0.50*
V_{ss} (L)	71.5 (25.9)	94.4 (38.9		0.11*
F (%)		84.9 (37.2)	44	
$t_{½abs}$ (h)		0.08 (0.08)	100	
MAT		0.87 (0.72)	83	

CL = total body clearance (dose divided by the area under the concentration-time for time zero to infinity); **F** = bioavailability (AUC_{oral} • $Dose_{iv}$/AUC • $Dose_{oral}$, where AUC = area under the concentration-time curve); **MAT** = mean absorption time (MRT_{po}-t_{lag}, where MRT_{po} = the mean residence time; **SD** = standard deviation; $\mathbf{t_{lag}}$ = lag-time; $\mathbf{t_{½abs}}$ = absorption half-life, calculated by least-square linear regression analysis; $\mathbf{t_{½}}$ = elimination half-life, calculated by least-square linear regression analysis; $\mathbf{V_{ss}}$ = volume of distribution at steady-state; ***** not statistically significant. The p-values measured the statistically significant differences in intrinsic pharmacokinetic paramaeters such as $t_{½}$, CL and V_{ss}. No statistically significant differences were found. After oral administration the absorption is subject-dependent.

the contractions during labour. They measured intrauterine pressure (IUP) transabdominally.[39] The effect of ME *post partum* was an enhancement of the pre-existing type of contraction, meaning well coordinated contractions in the first hours *post partum*.[24]

5.2.2 Nonpregnant Uterus

In contrast to oxytocin, ME and EM do have an effect on the nonpregnant uterus.[40] After intravenous administration of ME, a rapid increase of the frequency of uterine contractions and basal tone occurs with a decrease of amplitude, lasting at least 30 minutes. Oral administration has a longer latency time and an unpredictable and less marked effect on uterine motility in the menstruating uterus.[41] This might be due to the unpredictable bioavailability in contrast with the fast and predictable effect after intravenous administration (fig. 2).

Remarkably different effects on IUP were noted from an intravenous dose of ME, depending whether it was preceded with oral ME 0.5mg 24 hours beforehand or not (fig. 3). A clearly reduced effect of intravenously administered ME maleate 24 hours after oral administration suggests long-lasting receptor blockade, as if the uterus were insensitive to the intravenous dose. ME maleate probably blocks α-receptors in the inner layer, specifically affecting the basal tone of this layer.[8,21,22]

5.2.3 Comparison with Other Oxytocics

Oxytocin

The human myometrium contains oxytocin receptors. During labour there is an increase in the number of these receptors in both the myometrium and decidua.[42] The pattern of uterine contractions after postpartum administration of intravenous oxytocin is described as a short period of hypercontractability, followed by an increased frequency in contractions. Due to its short half-life, the response to a single dose diminishes within as little as 10 minutes.[24]

Prostaglandins

Prostaglandins are not widely used as prophylaxis in the third stage of labour.[31,42-45] Prostanoids give strong contractions[40] in a nonpregnant uterus, although the exact mechanism by which they influence uterine contractility is not fully understood. Recently, Izumi et al.[46] suggested that prostaglandins induce contractile responses due to Ca^{++} release from storage sites in the cell, while oxytocin can release Ca^{++} only indirectly. Besides the direct action on the myometrium, prostaglandins also increase oxytocin levels.[47] IUP after either oral or intramyometrial administration of prostaglandins has not yet been investigated.

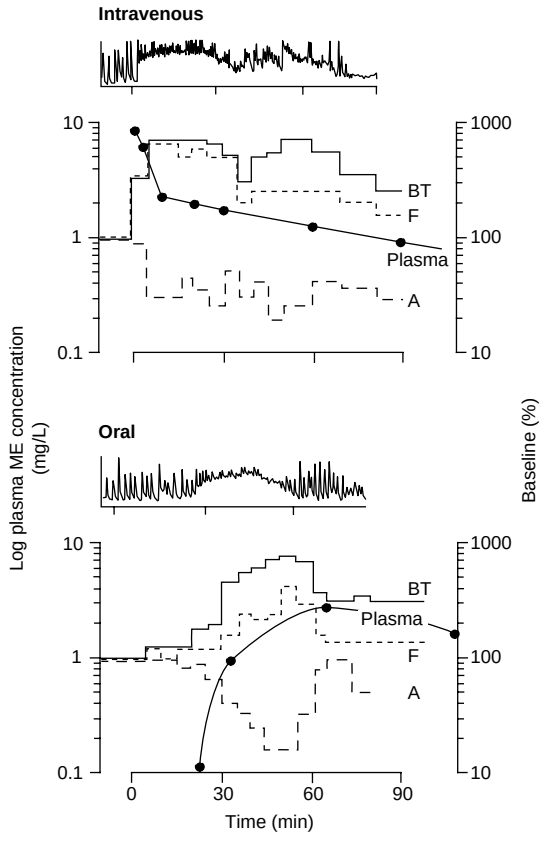


Fig. 2. Effect of methylergometrine maleate (ME; methergine) after intravenous (0.2mg) and oral (0.5mg) administration in one volunteer. ME was administered at t = 0. The top trace records the effect on intrauterine pressure; the bottom trace shows the effect on frequency (F), basal tone (BT) and amplitude (A). The mean values of F, B and A during the 30 minutes before drug administration were regarded as baseline values and set at 100%, the increase in a 5-minute period was expressed as a percentage of baseline value and plotted versus time after administration of intravenous ME 0.2mg and oral ME 0.5mg.

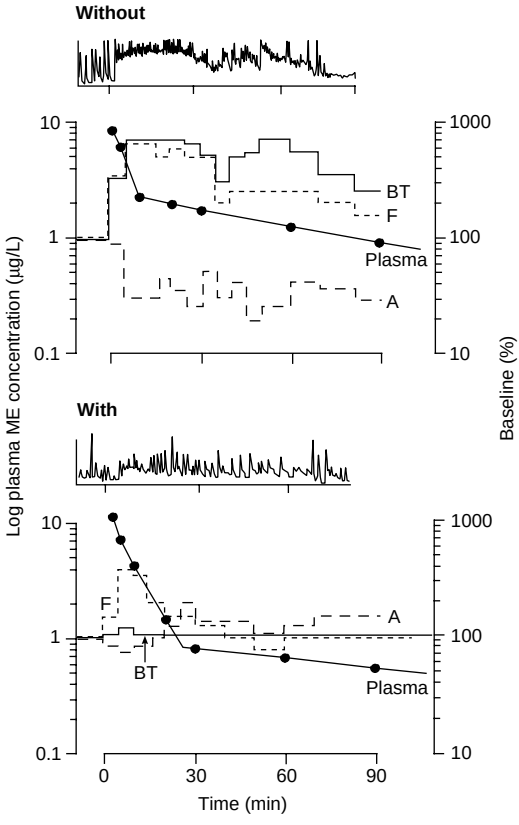


Fig. 3. Effect of methylergometrine maleate (ME; methergine) after intravenous administration of 0.2mg with and without preceding oral ME in one volunteer. ME was administered at t = 0. For explanation of tracings, see figure 2.

6. Therapeutic Potential of Ergot Alkaloids

6.1 Ergot Alkaloids as Uterotonic Agents in Obstetrics

6.1.1 Prophylactic Use

During pregnancy the use of ergot alkaloids is contraindicated. Their direct vasoconstrictive action may cause fetal distress or even fetal death.[12,48] In obstetrics, ergot alkaloid derivatives with very specific uterotonic action and with small vasoconstrictive properties are used in the third stage of labour to reduce blood loss after childbirth. The ergot alkaloids were the first oxytocic drugs; oxytocin and prostaglandins followed (table II). Any oxytocic drug reduces the incidence of postpartum haemorrhage (PPH) by about 40%.[49,50] The choice of which oxytocic to use depends on factors such as the effectiveness of the drug, its route of administration, its pharmacokinetic properties, its adverse effects and its stability.

6.1.2 Effectiveness

McDonald et al.[51] showed that intramuscular oxytocin 10IU was as effective as the combination of EM 0.5mg and oxytocin 5IU ('Syntometrine') in preventing PPH. In addition, 'Syntometrine' caused more nausea and vomiting and had a greater hypertensive effect than oxytocin.[51] Therefore, oxytocin is the oxytocic of choice when used as intramuscular or intravenous preventive treatment for PPH.[49,50,52]

The optimal dose of oxytocin is still unclear. The WHO advocates 10IU,[50] but 5IU may be as effective. A randomised trial of oxytocin 5 and 10IU is needed to give the answer. At the time of writing, a randomised trial of oxytocin 5IU and spontaneous placental expulsion in low risk women is being performed by midwives attending home births in The Netherlands. Home births in The Netherlands form a unique situation, in which active management of the third stage of labour is still not routine [Leiding Nageboorte Tijdperk Eerste lijn (Management of Third Stae of Labour Amongst Midwives; LENTE study), Technisch Natuurwetenschappelijk Onderzoek (Technical Scientific Institute; TNO)-Preventive Gezondheidszorg (Preventive Health; PG), Leiden].

6.1.3 Route of Administration

Drugs used for the prophylaxis of PPH in obstetric care should be easy to administer. Oxytocin, the drug of choice, can only be administered by (intramuscular) injection. Oral ME and EM, however, are not a satisfactory alternative in the prevention of PPH, because the tablets for the oral route are less effective, unstable and pharmacokinetically unreliable.[8] The role of misoprostol as a third-stage prophylactic oxytocic still requires study.[31]

Currently, the route of administration for oxytocin, ME and EM is by intramuscular injection, while prostaglandins can only be administered in-

travenously. As all preparations are administered by injection, route is not the deciding factor in the choice of oxytocics.

6.1.4 Adverse Effects

ME and EM

Adverse effects of ergot alkaloids used in obstetrics and gynaecology have been reviewed[53] are shown in table V. The prophylactic use of EM in the management of third-stage labour was criticised in 1962 by Ringrose.[54] In 1993, we also reported numerous adverse effects associated with ME and EM.[48] Due to their serious and unpredictable adverse effects, their place among oxytocic drugs is controversial in the prevention of PPH. Recently, vasospastic events were described after oral ME and EM;[55,56] in addition, mention has been made more recently about their toxic and teratogenic effects during use in pregnancy.[57]

Oxytocin

Oxytocin has fewer and less severe adverse effects than EM and ME, though severe hypotension may occur after intravenous administration of oxytocin 10 or even 2IU (table IV).[58-60]

Prostaglandins

Different prostaglandins have been used therapeutically in the third stage of labour. These include the natural substances $PGF_{2\alpha}$ and PGE_2 and the synthetic 15-methyl$PGF_{2\alpha}$, sulprostone. PGE_2 causes vasodilation and may result in life-threatening hypotension, whereas $PGF_{2\alpha}$ increases heart rate, systemic arterial blood pressure and cardiac output.[61]

Gastrointestinal adverse effects have been reported after local intracervical or intramuscular administration of sulprostone.[62] Fatigue, dizziness and headache have been observed in some patients treated with this drug. Acute myocardial infarction is associated with the spasmogenic properties of sulprostone after intramuscular administration.[63-65] Its propensity to induce severe cardiac effects has not been fully determined. Until more data are available, sulprostone is relatively contraindicated in women who are heavy smokers and over 35 years of age. If used it should be with caution, as an infusion. The oral administration of misoprostol is not yet widely used in obstetric practice. Its indication until now has been the treatment of peptic ulcer disease and termination of pregnancy.[66] For these indications no serious complications have been described for dosages varying from 200 to 800µg daily. Misoprostol is undergoing trial for use in the prevention of PPH; a single dose of 600µg is being used for this indication.[31]

6.1.5 Stability

As described above, ME and EM are less stable than oxytocin. From a pharmaceutical point of

Table V. Adverse drug reactions to methylergometrine (methergine), ergometrine (ergonovine), oxytocin and prostaglandins (after De Groot 1995[53])

Drug	Route	Adverse reaction
Ergometrine	Oral	Ergotism, nausea, vomiting, puerperal psychosis, asthmatic attack, fetal death
	Intravenous/intramuscular	Ergotism, bradycardia, tachycardia, hypertension, coronary artery spasm, postpartum myocardial infarction, renal artery spasm, myocardial infarction, puerperal psychosis; in the neonate, hypertonia, convulsion, hyperthermia, respiratory failure
Methylergometrine	Oral	Ergotism
		Ergotism
	Intravenous/intramuscular	With simultaneous administration of oxytocin, severe hypertension *post partum*, cerebral oedema, convulsion, reversible cerebral arteriopathy
Oxytocin	Buccal	None
	Intramuscular	None
	Intravenous	Feeling of warmth, hypotension
Prostaglandins (misoprostol; sulprostone)	Oral	Nausea, vomiting
	Intravenous/intramuscular	Nausea, vomiting, diarrhoea (maternal death)
	Intramyometrial	Coronary artery spasm, myocardial ischaemia

view, oxytocin is the drug of choice when used as a prophylactic measure.

In conclusion, the best choice of oxytocic for prophylactic use in the third stage of labour at this time is oxytocin given intramuscularly; the optimal dose is still unknown.

6.2 Therapeutic Use of ME and EM

Oxytocics are not only used for the prevention of PPH. They also play an important role in the management of PPH if bleeding is severe and due to a disturbance in uterine contraction or retraction (uterine hypotonia or inertia). PPH is an acute obstetric problem.[18,53,67] The bladder should be empty and haemodynamic stability must be guaranteed by well functioning (double) intravenous access for proper fluid replacements (crystalloid fluids and blood components). The attendant practitioner should rule out retained placental fragments or trauma of the birth canal as a cause of severe bleeding. If these factors are not the cause, the bleeding should be ascribed to a disturbance in uterine contraction or retraction. Pharmacological intervention with intramuscular oxytocin either 5 or 10IU, followed by a drip infusion of 10IU in 500ml of 0.9% normal saline NaCl is needed, or alternatively ME and EM 0.2mg intramuscularly or intravenously, when there is no history of hypertension and the stability of the product has been guaranteed by proper storage.[51-53,67-69]

If the bleeding is not controlled by therapeutic use of either oxytocin or ME and EM, sulprostone 100 μg/hour may be given intravenously.[43,53,67] The dosage should not exceed a maximum of 500 μg/hour or 1500 μg/24 hours. Because of possible severe cardiogenic adverse effects, sulprostone is only registered for gradual intravenous infusion in The Netherlands.[70] Before administering prostaglandins, the practitioner must be certain that the patient has no cardiac problems and that she is not a heavy smoker, and bolus injection should be avoided.[71]

If pharmacological intervention does not succeed in controlling the bleeding, assessment of the genital tract under general anaesthesia is indicated. This may reveal a different aetiology. At that stage, embolisation of the pelvic vessels or hysterectomy may be the only way to stop the bleeding.[72]

Recently, B-Lynch et al.[73] described a technique in which the uterus remains *in situ* and a 'brace suture' (B-Lynch suture) is made around the uterus, which may lead to satisfactory haemostasis. This method might be an attractive alternative to hysterectomy; however, the number of patients described was limited to 5.[73] Further experience needs to be gained with the B-Lynch technique before it can be made widely available.

6.3 Lactation Suppression

Bromocriptine has been used to inhibit prolactin secretion (sections 1.2 and 2.2.2). Because of the risk of hypertensive crises and vasospasm, the US Food and Drug Administration advocates stopping or at least limiting its use for suppression of lactation. The use of cold packs, compression bandages and pain medication appears to be equally effective. However, if necessary, bromocriptine should be administered more than 4 hours after parturition and its use should be guided by the patient's blood pressure.[74,75]

6.4 Use in Gynaecology

6.4.1 Menorrhagia

As discussed in section 1.3, ergot alkaloids are of no practical use in the treatment of essential menorrhagia.[10]

6.4.2 Abortion

The effect on blood loss of the routine use of oxytocic drugs during first trimester (suction) curettage is under discussion. The amount of the blood loss depends primarily on gestational age, and during early gestational age contraction of the uterus seems to be less influenced by administration of oxytocics.[76] However, a significant reduction in blood loss has been described after administration of oxytocin 10IU intravenously.[77] There do not appear to have been any recent studies on the effect of ME and EM in this therapeutic indication.

7. Conclusions

Ergot alkaloids are well known preparations used in obstetrics. EM and ME are of therapeutic use in the third stage of labour; however, for preventive purposes oxytocin is the drug of choice due to a more favourable adverse effect profile.

The pharmacological properties of EM and ME are of great importance; ampoules should be stored in a cool, dark place, and tablets are unstable under any conditions. Thus, the instability of EM and ME tablets and their unpredictable bioavailability prevents their oral use for any purpose. Finally, there is no place for the use of ergot alkaloids for gynaecological purposes.

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