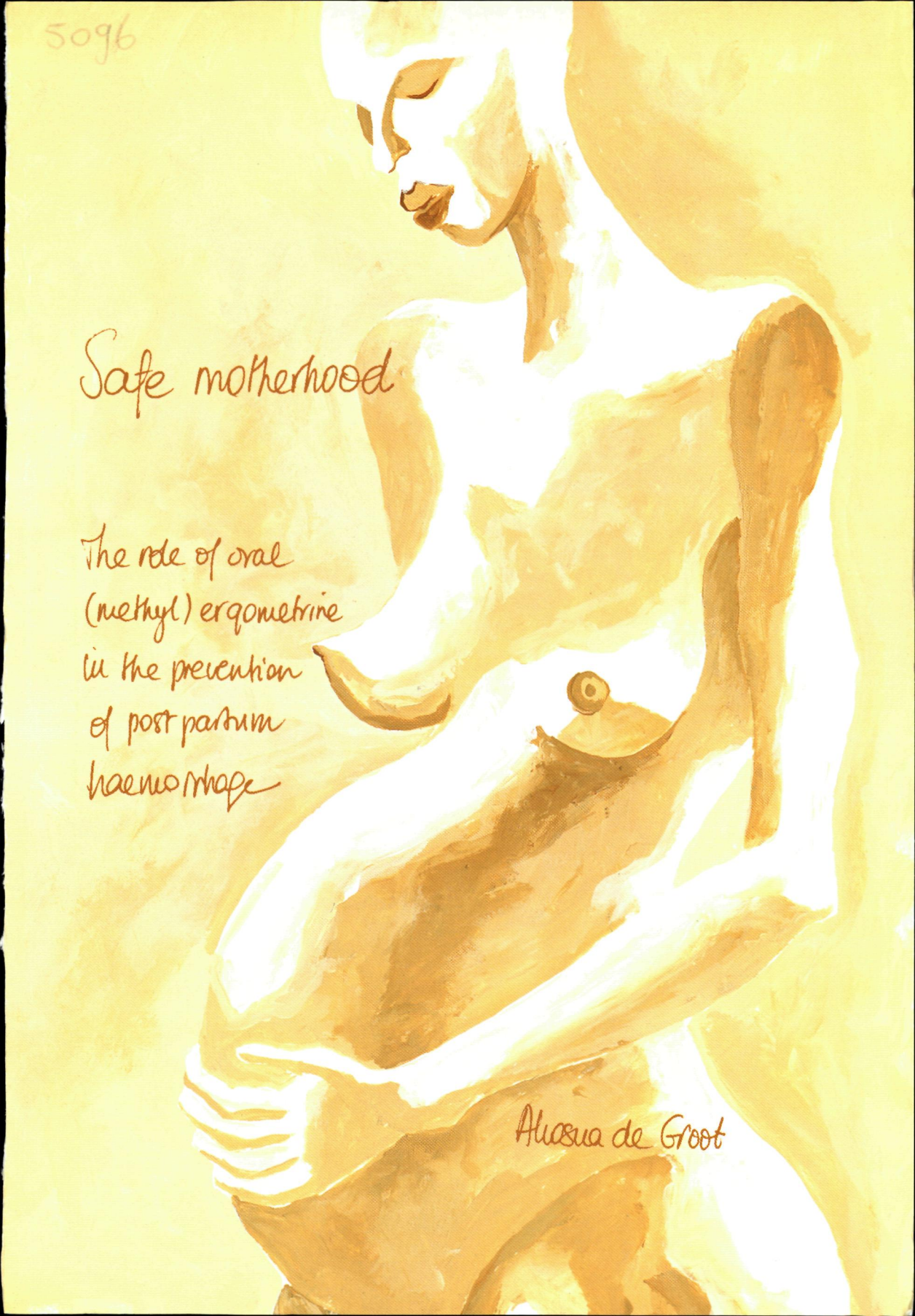

Safe motherhood

The role of oral (methyl) ergometrine in the prevention of post partum haemorrhage

Aluasia de Groot

Safe motherhood

The role of oral (methyl)ergometrine in the prevention of postpartum haemorrhage

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Safe motherhood

The role of oral (methyl)ergometrine in the prevention of postpartum haemorrhage

een wetenschappelijke proeve
op het gebied van de Medische Wetenschappen

Proefschrift ter verkrijging van de graad van doctor aan de
Katholieke Universiteit Nijmegen,
volgens besluit van het College van Decanen in het openbaar te verdedigen
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door
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geboren op 10 september 1964 te Nijmegen

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Aan mijn ouders,
Wim en Jeanny

Contents

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List of abbreviations

A	Amplitude
ADR	Adverse Drug Reactions
APH	Antepartum haemorrhage
AUC	Area Under the Curve
BP	British Pharmacopoeia
BT	Basal Tone
CD	Cyclus Day
CEOM	Committee Experimental Research Involving Human Subjects
CL	Total body clearance
C Purpurea	Claviceps Purpurea
CRF	Corticotrophine Releasing Factor
CV	Coefficient of variation
D	Dark
E	Ergometrine
F (IUP n/5min)	Frequency
F (%)	Bioavailability
HPLC	High Pressure Liquid Chromotography
I	Intensity
ID	Inner Diameter
IUP	Intra Uterine Pressure
IVS	Intravillous Space
i v	Intravenous
L	Liter
$L\ h^{-1}$	Liter per hour
LSD	Lysergic acid diethylamine
MAT	Mean Absorption Time
MRT	Mean Residence Time
ME	Methylergometrine
MMR	Maternal Mortality Rate
OT	Oxytocin
OD	Outer Diameter
PAI-1	Plasminogen Activator Inhibitor-1
PAI-2	Plasminogen Activator Inhibitor-2
PG	Prostaglandins
PPH	Postpartum Haemorrhage
p o	per os
RH	Relative Humidity
RIA	Radio Immuno Assay
RR	Recurrence Risk
SD	Standard Deviation
sE	Syntometrine
TBA	Traditional Birth Attendant
t-PA	tissue-type Plasminogen Activator
V_{ss}	Volume of distribution in steady state
WHO	World Health Organization
WHO/DAP	World Health Organization/Drug Action Programme

1 Introduction

1.1 Motive and aim of the study

"Every four hours, day in, day out, a jumbo jet crashes and all on board are killed. The 250 passengers are all women... They are all either pregnant or have recently given birth to a child".

This shocking statement was given by Malcolm Potts at the World Health Organization's (WHO) interregional Meeting on the prevention of maternal mortality, November 1985 (Anonymous 1986). This statement is the more intolerable because most of these deaths are theoretically preventable with present knowledge and equipment. The majority of maternal deaths occurs in developing countries (Royston & Armstrong 1989). It shows the poignant inequality in maternal health between the rich and the poor. Postpartum haemorrhage is one of the most important causes of maternal mortality in developing countries (Kwast, 1991b).

A Technical Working Group on the prevention and management of postpartum haemorrhage was convened by WHO in Geneva, 3-6 July 1989. A consensus was reached on the active management of the third stage of labour for all parturients, in particular for those for whom the access to hospital services is difficult or time-consuming. The major drawback was to find a drug to be used as prophylactic oxytocic that was easy to administer and stable (WHO 1990). During the working group, one of the midwives, Barbara Kwast, suggested giving oral ergometrine. From that day on the project on oral ergometrine began. The core of the ergot-taskgroup was formed by Pieter van Dongen (PhD, obstetrician, University Hospital Nijmegen, The Netherlands), Jos van Roosmalen, a member of the Technical Working Group in Geneva (PhD, obstetrician University Hospital Leiden, The Netherlands), Yechiel Hekster (PhD, clinical pharmacist), and Tom Vree (PhD, chemist), both from the department of clinical pharmacy, University Hospital Nijmegen, The Netherlands.

The research project consisted of 3 studies, oriented toward the following questions:

- Pharmaceutical study: Is oral (methyl)ergometrine in contrast to intravenous (methyl)ergometrine stable under tropical conditions?
- Pharmacological study: Are the pharmacokinetic and pharmacodynamic properties of (methyl)ergometrine tablets favourable enough to use them as prophylactic drugs in the third stage of labour?
- Clinical study: Do ergometrine tablets have effect on blood loss after childbirth, in spite of the answers on the questions mentioned above?

The three questions are related, but were answered independently. Assuming that the pharmacological and clinical study would lead to possitive results, the pharmaceutical study was started first as there was doubt about the stability of the tablets under tropical conditions. While this stability study was being set up and started, the pharmacological and clinical parts of the project were started simultaneously. This set up of the research project had been chosen to underline the three-fold question, each related to the completely different grounds for which an answer had to be given before an answer could be given to the principle question: "Is oral (methyl)ergometrine a suitable alternative prophylactic drug to prevent postpartum haemorrhage?". Such an approach to the question would also detect which aspect (pharmaceutical, pharmacological or clinical) might need to be ameliorated.

This thesis starts with an introduction on prevention of postpartum haemorrhage (Chapter 1). It then compares the process of menstruation and placental separation, as in the pharmacodynamic study menstruating non-pregnant women were examined to simulate the process of placental separation. Chapter 2 describes the history of ergot alkaloids and summarizes their chemical background, pharmacological properties and adverse drug reactions. Chapters 3, 4, 5 and 6 describe the studies performed with oral and intravenous (methyl)ergometrine. Chapter 7 summarizes the results of the separate studies and presents the overall conclusions of the complete research project.

The research project was supported by WHO (Technical Services Agreement MHR-0145) and the Dutch "Praeventiefonds" grant no. 28.2196.

1.2 Prevention of postpartum haemorrhage*

Each year at least half a million women die world wide from causes related to pregnancy and childbirth. All but about 6000 occur in developing countries, which account for 86% of the world's birth. In the USA and Europe the maternal mortality rate is very low in contrast to that in developing countries: less than 10 deaths per 100,000 live births versus 600-1500 per 100,000 live births (Royston & Armstrong 1989).

Obstetric haemorrhage claims the lives of 150,000 women annually (Kwast 1991a). It is the most important cause of maternal mortality in the developing world (Royston & Armstrong 1989; Kwast 1991b). Obstetric haemorrhage can be divided into antepartum (APH) and postpartum haemorrhage (PPH): the latter causes most maternal deaths.

Death from PPH invariably occurs within a few hours after birth. In hospitals, where facilities for the prevention and management of PPH are often available, the consequences of PPH are possibly less dramatic than elsewhere in the health-care system. However, even in developed countries, e.g., the Netherlands, PPH causes 13% of all recorded maternal deaths (Schuitemaker et al. 1991). Proper management and better prevention are necessary at all levels of obstetric care because emergency referral is often difficult to arrange, especially in many third world countries.

This Chapter deals with the prevention of PPH. It elucidates the internationally accepted WHO definition (Royston & Armstrong 1989), assesses risk factors for PPH and discusses recent trials on management of the third stage of labour. All these aspects help to set priorities and delineate strategies to prevent PPH and reduce its incidence and the subsequent morbidity and mortality. Guidelines for clinical practice of primary prevention are given in the conclusion.

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*Based upon: **Prevention of postpartum haemorrhage. In: Baillière's Clinical Obstetrics and Gynaecology, international practice and research. Preventive care in obstetrics. Steegers EAP, Eskes TKAB, Symonds EM, editors. London: Baillière Tindall, 1995a; 9: 619-631.**

1.2.1 Definition of PPH

PPH, defined by the WHO (Royston & Armstrong 1989) as postpartum blood loss ≥ 500 ml, is a clinical diagnosis that encompasses excessive blood loss after delivery and, if untreated, may result in shock and death of the mother. The choice of 500 ml is arbitrary but is a loss that most mothers can tolerate without risk. Women who are at risk are those with severe anaemia, eclampsia, antepartum haemorrhage, intrapartum blood loss or those who have had a difficult instrumental delivery. In countries where many women have severe anaemia, maternal blood loss of even 250 ml may be fatal (Lawson 1967). Another reason for the 500 ml criterion is that blood loss is often underestimated: accurately measured loss is usually about twice the estimated loss. This is particularly so when an estimation of "moderate" blood loss is made; estimation of very small or large amounts of blood are more accurate (Brant 1967; Duthie et al. 1990). The clinical consequences of postpartum blood loss depend on both the amount and rate of blood loss and whether the mother's health is good, a factor included in part in the definition of PPH.

Gilbert et al. (1987) reported an incidence of about 10% for PPH in all vaginal births in Britain. It is, however, difficult to compare figures on PPH, because of large variations in management protocols, different populations studied -for instance home deliveries or high risk deliveries in hospital- and because blood loss is often estimated rather than measured. These factors are important when using the incidence of PPH as a measurement and evaluation for care in the third stage of labour.

1.2.2 Physiology of postpartum bleeding

The mechanism by which the uterine bleeding stops after placental separation is not clearly understood. In fact, concepts of the physiology of the postpartum uterus are scarce.

At least three processes can be discriminated: placental separation, uterine activity before and after placental separation and coagulation cascade, fibrinolysis after placental separation. Chapter 1.3.3 describes these processes extensively. Uterine activity after placental separation can be described by retraction and contractions. Retraction is the start of the involution of the uterus,

characterized by shortening of the uterine musculature, despite relaxation of individual muscle fibres and increasing intra-uterine tone (Knaus 1948). Contractions are characterized by the short period in which the muscle fibres contract and which are followed by relaxation of the muscle fibres.

Disturbances in postpartum bleeding (PPH) may be explained by interference with retraction, a retained placenta or a full bladder (to be diagnosed by a high positioned or flaccid uterus), disturbances of uterine contractility or intra-uterine coagulation, as will be explained in Chapter 1.3.

Prevention of PPH includes facilitating retraction, which means preventing a full bladder and reassurance of the absence of retained placental fragments. When the bladder is empty and the placenta is completely born, oxytocic drugs enhancing uterine contractility lower further blood loss.

1.2.3 Primary prevention of PPH

"Risk factors" for PPH and the use of the risk approach in primary prevention of PPH

Primary prevention includes the prophylactic treatment of those women at risk for PPH. The main causes of PPH are (Kapernick 1991):

1. Disturbance of uterine retraction (often called uterine atony) (frequency $\geq$ 50%);
2. Vaginal/ cervical lacerations (frequency $\pm$ 20%);
3. Retained placenta (or placenta fragments) (frequency $\pm$ 5-10%);
4. Coagulation defects (low frequency).

Risk factors for PPH, are given in Table 1.2.3.1. There are two categories of risk factors: those predisposing a woman to be at "moderately" or "very high" risk for developing PPH. All the risk factors in Table 1.2.3.1 predispose mainly to disturbance of uterine contraction, the prime cause of PPH. Vaginal or cervical lacerations may occur after any delivery, although they usually result from precipitate, uncontrolled or instrumental deliveries. In case of PPH, the doctor or midwife should always check that excessive bleeding is not also

caused by lacerations since PPH may result from a combination of causes. Retention of placental fragments may be due to placental abnormalities or mismanagement of the third stage and this often leads to disturbance of uterine contraction. The recurrence risk (RR) of retained placenta is 2.4 and of PPH 3.3 (Hall et al. 1985).

There is no uniform definition of risk factors for PPH. Management differs according to the factor. Data on their relative importance or frequency are rare (Combs et al. 1991; Stones et al. 1993). If a woman has a risk factor, this does not immediately imply that she should not have her baby at home or that intravenous treatment facilities have to be available during labour. For instance, nulliparity is a risk factor, but, in the Netherlands, nulliparity is no contra-indication for a home delivery. When the nulliparous woman has her baby at home, she will not get routine active management of the third stage, as this is (still) not the standard management protocol. Factors given in Table 1.2.3.1 are generally accepted as risk factors for PPH, but their relative risk on PPH varies. This may explain why the third stage is managed in different ways.

Women with one of the factors in Table 1.2.3.1 are judged to be at "high" risk for PPH. The group at "very high" risk should deliver in a hospital with proper facilities for managing PPH. Appropriate referral only occurs if risk factors are easily identified an almost unrealistic goal.

Table 1 2.3.1 Risk factors for PPH stratified in "moderately" and "very" high risk

Moderately high risk for PPH	**Very high risk for PPH**
- nulliparity, grand multiparity > 5 [2,5]	- history of PPH (RR=3.3)[4,5]
- priming; induction or augmentation of labour[1,5]	- history of retained placenta (RR=2.4)[4,5]
- long 1st and/or 2nd stage[1,5]	- anticoagulant therapy [5]
- instrumental deliveries[1,5]	- uterine fibroids [2]
- tocolysis prior to delivery[1]	- antepartum haemorrhage[1,5]
	- polyhydramnios[6]
	- multiple pregnancies[1,5]

1 = Stones et al 1993 3 = Gilbert et al 1987 5 = van Dongen et al 1991
2 = Kwast, 1991b 4 = Hall et al 1985 6 = Begley, 1990
RR = recurrence risk

Moreover, women at low risk for PPH are not excluded from excessive loss of blood after delivery. Therefore, implementation of the risk approach in preventing PPH will not be suitable in circumstances where a woman's immediate referral to a hospital is logistically impracticable, as is the case in many third world countries. In these circumstances preventive measures against PPH are required for all women, not only for those at "high" risk for PPH. This has also been recommended by a WHO Technical Working group on prevention and management of PPH (1990). It has been suggested that PPH should be prevented by active management of the third stage. Identification of women who are at "low" or "high" risk for PPH is only of use in those countries where pregnant women in the low risk group have immediate access to a hospital with facilities to manage PPH.

Active management

Active management of the third stage of labour includes prophylactic administration of any parenteral oxytocic drug, early clamping of the umbilical cord and controlled cord traction. It implies a "cascade of interventions" in managing the third stage of labour. Whether these interventions themselves cause complications in women at low risk for PPH has never been studied. Routine use of oxytocics and active management of the third stage still remains a controversial issue (Inch 1985; Thilaganathan et al. 1993).

When analyzing trials to compare active versus expectant management procedures, we met several problems:

- Management protocols for third stage of labour vary from hospital to hospital within a country; including:
  - active management only in cases in which there is an increased risk for third stage complications (e.g. a history of previous third stage complications; prolonged labour, instrumental delivery, use of oxytocic drugs in the first or second stage of labour, multiple pregnancy)
  - awaiting signs of placental separation, after which the placenta is delivered by the mother's own efforts or by fundal pressure or controlled cord traction by the birth attendant.

The term "expectant" management is confusing because it means different things to different people. For example, in the Netherlands, it means waiting for signs of placental separation, after which the placenta is delivered either by maternal effort alone, or maternal effort aided by fundal pressure. In some parts of Africa it means controlled cord traction without a prophylactic oxytocic. In the United Kingdom it usually means no intervention of any kind other than to stimulate the mother to deliver the placenta, as soon as signs of separation are present. Investigators are used to their own management protocols and thus are often unfamiliar with the "trial" policy, which influences the outcome of the trial.

- The behaviour of the person responsible for the delivery might be influenced by the knowledge that no oxytocic is given and therefore influences the results of the study, as was suggested in the Bristol trial (Prendiville et al. 1988b). At present, 98% of obstetric units in the United Kingdom routinely use active management and British obstetricians would now consider management without the use of oxytocic drugs "unethical".
- A proper double blind trial is not possible. The use of drugs (either medication or placebo) is always different from "expectant" management.
- Inclusion criteria for the different trials are not equal, because there is no uniform definition of "high" and "low" risk groups for PPH.

These practical difficulties give rise to different trial outcomes and to controversial opinions about management of the third stage. The evidence of the effectiveness of active management with an oxytocic was mainly based on a meta-analysis of controlled trials (Elbourne et al. 1988; Prendiville et al. 1988a) and on the outcome of the Bristol third stage trial, conducted by Prendiville, one of the WHO Working Group participants (Prendiville et al. 1988b). He advocates routine active management of the third stage of labour.

Thilaganathan et al. (1993) on the other hand expressed disagreement with the need for active management in the group of women at low risk for PPH.

Effectiveness of active management with oxytocic drugs

The effectiveness of active management with an oxytocic drug can be judged by examining the meta-analysis of controlled trials. After administration of any oxytocic drug an average decrease of 40% in the incidence of PPH was noted, from 10% to 6%. The incidence of PPH, defined as a postpartum blood loss ≥500 ml, was reduced to 5.9% as compared to 17.9% after expectant management. Moreover, there was less need for additional oxytocic drugs after prophylactic administration (Prendiville et al. 1988b).

Even women at low risk for PPH showed significant beneficial effects from active management: they had less blood loss and required less oxytocin (odds ratio 0.28 and 20 resp; 95% confidence interval: 0.20-0.39 and 0.15-0.26, resp. (Elbourne et al. 1991)). The study populations included women at both low and high risks for PPH. Centres participating in the studies were accustomed to the "active" management protocol when the trial was started. The results of the Bristol (Prendiville et al. 1988b) and Dublin (Begley 1990) trials accorded with those of the two trials mentioned above, reported in the meta-analysis. However, in the Dublin trial (Begley 1990), the low risk women faced an increased risk of manual removal of the placenta after active management with ergometrine 0.5 mg intravenously given. Recently it has been suggested that active management does not reduce blood loss in women at low risk for postpartum haemorrhage (Thilaganathan et al. 1993). Therefore, we question the need for active management in the group of low risk women as a routine in countries where acute management of PPH in hospital is readily available. A randomised trial, investigating whether or not expectant management is preferable in women at low risk for PPH, is best conducted by midwives because they are used to this management protocol.

However, in countries with difficult access to hospitals, the prophylactic use of an oxytocic drug is justifiable to reduce both the risk of PPH and the need for further oxytocic therapy. The main reason for this strategy is that the risk approach is not a practical tool for dividing women at the lowest level of obstetric care into a group for whom active management is mandatory and another group for whom "expectant" management can be allowed.

Table 1 2 3 2 Oxytocics used as prophylaxis for postpartum haemorrhage after vaginal delivery

Drug	Route of administration	Remarks
• **Ergot alkaloids**		
ergometrine (E)	oral· (M)E	
methylergometrine (ME)	intramuscular· (M)E,sE	→ serious side effects
syntometrine (sE)	intravenous. (M)E	
(0 5mg E+ 5IU OT)		
• **Oxytocin** (OT)	buccal	
	intramuscular	→ drug of choice 5 IU
	intravenous	
• **Prostaglandins**		
sulprostone	intramuscular	
	intramyometrial (250μg)	→ not as prophylaxis

modified from van Dongen et al, 1991

Choice of an oxytocic

Any oxytocic drug reduces the incidence of PPH by about 40%. The question is which one to choose. The decision depends on factors such as: effectiveness of the drug, its adverse side-effects, its route of administration and its stability under extreme (tropical) conditions. Oxytocic drugs can be divided in three pharmaceutically different groups (Table 1.2.3.2).

Mechanism of action

- **(Methyl)ergometrine**

Methylergometrine and ergometrine maleate decrease the blood loss postpartum by enhancing the muscle tone of the uterus, superposed by fast rhythmic contractions of the myometrium, the so-called tetany. As a corollary the myometrial blood vessels are compressed resulting in the restriction of the loss of blood. The tetany continues for several hours; the mean terminal half life elimination is about 120 minutes (Anonymous 1988a). Recently, interindividual variation in pharmacokinetics have been described (de Groot et al. 1994a; 1994b).

- **Oxytocin**

The human myometrium contains oxytocin receptors. During labour the amount of oxytocin receptors in both the myometrium and decidua increases (Fuchs & Fuchs 1984). Therefore, an injection with oxytocin will result in fast and long lasting contractions, upon the basal tone of the myometrium (Brindlye & Sokol 1988). The plasma half-life of oxytocin in vitro is 3 to 5 minutes. This short half life often necessitates an intravenous infusion to produce sustained activity. Syntometrine (5 IU oxytocin + 0.5 mg ergometrine) has been designed to take advantage of the rapid onset of action of oxytocin, with the longer action of ergometrine. Recently, a long-acting synthetic analogue of oxytocin (carbetocin) has been developed with a rapid onset of action and a prolonged duration of action relative to oxytocin. Its half life is about 40 minutes (Sweeny et al. 1990). The effectiveness of carbetocin compared with oxytocin awaits further studies.

- **Prostaglandins**

The uterotonic action of prostaglandins is independent of gestational age. After both local and systemic administration it gives a strong myometrial contraction resulting in an increased uterine tone. The use of prostaglandins as prophylaxis in third stage is not widely practised (Hayashi 1990; Poeschmann et al. 1991). Because of its fast and strong effect on the uterus its role in management of atonic uterine bleeding, however, is quite promising (Hayashi 1990, van Dongen et al. 1991). van Dongen et al. (1991) advocate intra-myometrial administration of 250 µg (Table 1.2.3.2). However 250 µg sulprostone costs 50 times as much as 0.2 mg methergin^{R}.

Effectiveness

A randomised controlled trial of oxytocin versus Syntometrine showed that intramuscular oxytocin 10 IU was as effective as Syntometrine in preventing PPH. The latter caused more nausea and vomiting and had a greater hypertensive effect than oxytocin (McDonald et al. 1993). Therefore, oxytocin is the oxytocic of choice when used as an intramuscular or intravenous preventive treatment for PPH (Prendiville et al. 1988b; Begley 1990; van Dongen et al. 1991; Hogerzeil et al. 1994). Whether the usual 5 IU oxytocin will also have similar effects remains to be settled.

Adverse side-effects

- **(Methyl)ergometrine**

The prophylactic use of ergometrine in the management of third stage was criticized in 1962 by Ringrose. In 1993 we also reported numerous side effects of intravenous (methyl)ergometrine (de Groot et al. 1993)(see Chapter 2.4). Due to its serious and unpredictable side-effects, its place among the oxytocics is controversial in prevention of PPH.

- **Oxytocin**

Oxytocin has less (severe) side-effects than ergometrine, though severe hypotension may occur after intravenous administration of 10 or even 2 IU oxytocin (Hendricks & Brenner 1970; Johnstone 1972; Anonymous 1988b).

- **Prostaglandins**

Gastrointestinal side effects after local intracervical/intramyometrial administration of sulprostone are reported (Fruzzetti et al. 1988). Fatigue, dizziness, and headache have been observed in some patients treated with sulprostone. Acute myocardial infarction is possibly associated with the spasmogenic properties of sulprostone after intramuscular administration (Ulmann et al. 1992).

Route of administration

Drugs used for the prophylaxis of PPH at the most peripheral level of obstetric care should be easy to administer. In most countries traditional birth attendants (TBA's), even after training, either do not have the skills to give injections or are not allowed to use oxytocic drugs. Therefore, different routes of administration are advisable, preferably one by mouth. (Methyl)ergometrine is the only oral oxytocic available. The feasibility of oral (methyl)ergometrine as prophylaxis for PPH has been tested in a trial in our department.

Stability

Instability of oxytocics during transport and storage in hot climates is a major problem (Walker et al. 1988; Hogerzeil et al. 1994). Oxytocin is the most stable injectable oxytocic.

► The best choice of oxytocics for prophylactic use in third stage is oxytocin 5 IU given intramuscularly.

1.2.4 Conclusion

Primary prevention of PPH is advocated at all levels of obstetric care. This implies active management of the third stage also at the first and most peripheral levels of obstetric care, where access to hospital services is difficult or time-consuming. Women at "very" high risk for PPH should deliver in hospital. In these women prevention and anticipatory management includes availability of intravenous treatment as well as active management with an oxytocic. This is summarized in the flowchart: "Guidelines for clinical practice" (Figure 1.2.4.1).

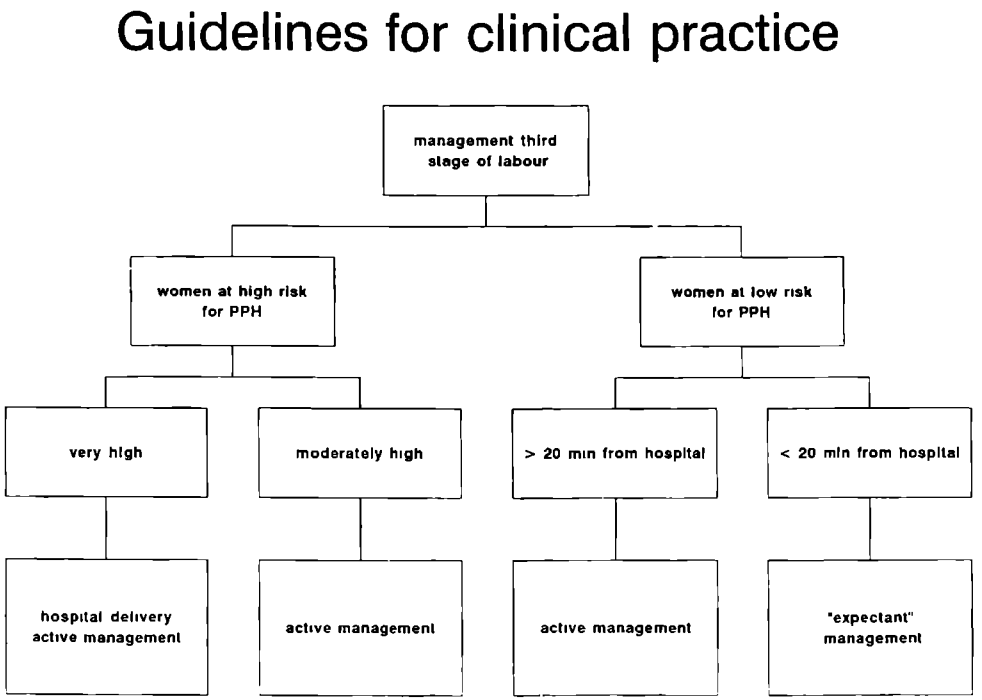

Figure 1.2.4 1 Flowchart illustrating guidelines for clinical practice

1.3 The process of menstruation and placental separation

A model has been constructed to assess the pharmacodynamic properties of methylergometrine on the uterus. A comparison between the menstruating uterus and the postpartum uterus is described. Because of the similarities between the non-pregnant and pregnant situation, it was thought that studies during menstruation would be also valid during the phases of placental separation.

1.3.1 Uterine structure, vascularisation, and contractions

The uterine wall consists of three parts, from outside to inside. There are the perimetrium, the myometrium and the endometrium. The perimetrium is a modification of the peritoneum. The myometrium is the contractile element which however is not a uniform muscle. It is composed of smooth muscle cells from mesodermal origin, consisting of two layers having different structure and function: the *archemyometrium* (old inner layer of the uterus) and the *para or neomyometrium* (younger outer layer of the uterus) (Daels 1974). The endometrium consists of a functional (lamina functionalis) and a basal (lamina basalis) layer. After conception the lamina functionalis is called decidua.

Uterine structure

The human uterus develops in the eighth week of embryonic life when the ends of the paramesonephric (Müllerian) ducts fuse. Between the fifth and the seventh month, the primordial musculature of the uterine body develops producing a modification of the circular musculature from the Müllerian ducts, which are connected by horizontal fibres at the midline. Even during pregnancy two sets of oblique spirals cross each other. This so-called circular layer is derived from primordial musculature forming the inner parts of the uterine body as well as most of the isthmic region. A longitudinal layer is formed between the circular layer and the peritoneum (Goerttler 1931; Fuchs & Fuchs 1991) (Figure 1.3.1.1). Renn (1970) described the structure of the myometrium differently. In his histologic studies he found that muscle bundles were arranged

in a three-dimensional network, running in all directions instead of having a strict structure. He emphasized the importance of the muscle sheaths around the arterial and venous vessels. However, whichever opinion is correct, the typical arrangement of the circular muscular layer provides a strong uterine wall, allows three-dimensional expansion without compromising wall strength during pregnancy, and causes a compression of arterial (and venous) blood vessels during contraction of muscle cells. This might explain the relative limited amount of blood loss during menstruation (Markee 1950) or at placental separation (Renn 1970).

The muscular tissue of the uterus is responsible for the myometrial contractile activity. The fundal uterine part contains 80% musculature, gradually decreasing towards the cervix with approximately 15% muscular tissue. The muscular proportion of the cervix is not uniform; it decreases gradually towards the distal

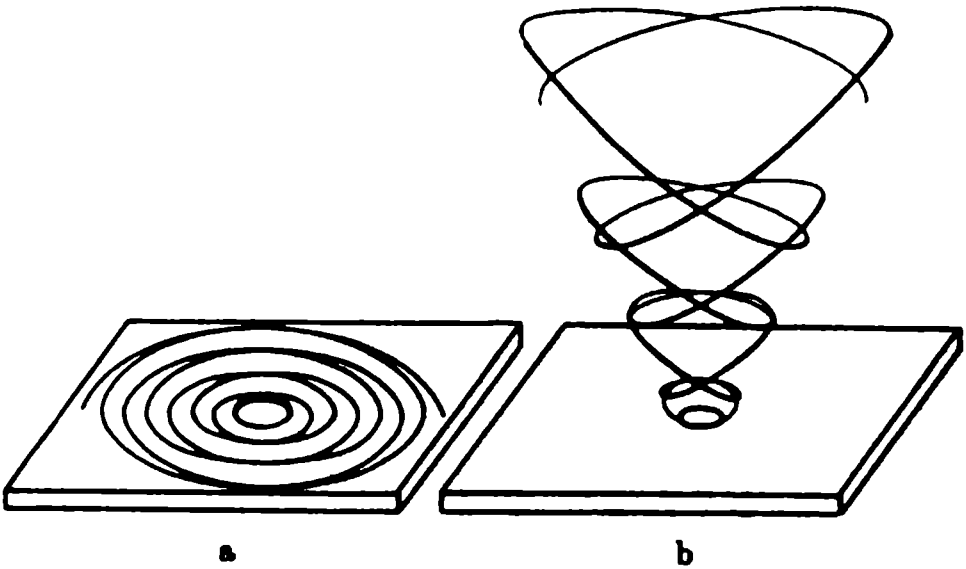

Figure 1.3.1 1 Typical arrangement of circular uterine muscle layer schematically showing its three-dimensional expansion.
a. at rest: two sets of crossing spirals
b. at term: stretching of two crossing spirals

(Reproduced with permission of Morphologischer Jahrbuch, Figure 21 from Goerttler 1931)

portion, from 30% in the isthmic region to 7% in the last third segment. In the third month of pregnancy, the isthmus lengthens and widens down to the level of the histologic internal os. This process is complete in the fifth month of pregnancy, and the isthmus is now part of the uterine wall. The anatomic ostium internum functions as a sphincter between the (thickening) upper uterine segment and the lower uterine segment. The cervical fibrous connective tissue is a determining factor in holding a pregnancy until term (Danforth 1974; van Dongen et al. 1991).

Uterine vascularisation

The uterus is supplied by two major vessels: the uterine and ovarian arteries. The most important blood supply is through the uterine arteries, both of which separate into ascending and descending (vaginal) branches. The ascending branch supplies the uterine body by the arcuate arteries, which course through the myometrium parallel to the lumen. Radial arteries split off and provide the myometrium with blood through *myometrial flow*. After passing the myoendometrial junctions, the radial arteries continue in the direction of the surface endothelium in a corkscrew appearance and are called spiral arteries. The vasculature of the endometrium is well summarized by Ramsey (1977).

In the *non-pregnant* uterus, the coiling of the spiral artery increases during proliferation and secretion phases. It forms an arcade by turning back towards its origin, forming a subepithelial plexus. From the plexus the blood drains to the myometrial arcuate veins into the uterine vein. The spiral arteries are end-arteries, and, therefore there are no arterio-venous shunts (Flowers & Wilborn 1978; Christiaens 1981). Studies in non-pregnant women using two thermistor probes showed a reduction of endometrial blood flow at the onset of menstruation (Hansson 1987).

During *pregnancy*, the composition of the spiral arteries changes by the altered endocrinologic conditions. The resulting "funnels" create a low resistance vascular bed in the intervillous space (IVS), which facilitates increased *utero-placental blood flow* during pregnancy (Fuchs & Fuchs 1991). Pijnenborg (1994) recently reviewed morphological studies on endovascular trophoblast invasion in humans. He describes a first wave of trophoblast invasion at 8 weeks and a second, at 14-15 weeks. During the second wave, the disruption of smooth muscle layers in the inner myometrium takes place. After this

process, the invasion normally stops, and as this is a strictly controlled process staying within physiological limits, it does not lead to haemorrhage or thrombosis in physiological circumstances (Kliman 1994). Although the mechanisms are still not fully understood, the role of the trophoblast is crucial in keeping this process within physiological barriers (Pijnenborg 1994).

The uterus has no auto-regulation which means that uterine vascular resistance is not adjusted to sustain a uniform blood flow when the flow changes (Moll 1974; Low 1977). Maternal blood enters the intervillous space from the endometrial spiral arterioles as systolic "spurts" (Ramsey 1977). The word "spurt" suggests a head of pressure, close to normal arterial pressure values. For obvious reasons these values are not known. It is noteworthy to know that the pressures measured in the placental spiral arteries of the rhesus monkey did not exceed 20 mmHg (Moll et al. 1974). If this is also the case in the human, one must conclude that the architecture of the spiral arteries with their wide nozzles at the end, invaded by trophoblast, markedly reduces the head of arterial pressure in blood flow to the placenta. This would favour a marsh-like intervillous blood flow, a low pressure medium at the placental bed, and a low-pressure arterial "flow" in the remaining uterine bed when the placenta is expelled. Blood pressure in utero-placental arteries drops from 70-80 mmHg to a mean value of 10 mmHg in the IVS in a relaxed uterus and to 30-50 mmHg during uterine contractions; the maternal blood then passes into the utero-venous plexus ($\leq$ 8 mmHg) (Hendricks 1959; Hamilton & Hamilton 1977). *Utero-placental flow* is affected by muscular activity. In studies using an electromagnetic flow probe in ewes, flow reduction is observed with each uterine contraction. During delivery uterine blood flow decreased minimally; a second diminution followed placental expulsion (Greiss 1965). Lees et al. (1971) demonstrated with radio-nuclide microspheres a diminution of blood flow to the maternal placenta during contractions. In pregnant women, a decreased utero-placental blood flow (with vast inter-individual differences) was observed by radio-angiographic methods after each uterine contraction independent of the level of intra-uterine pressure elevation (Borell et al. 1964). The passive constriction of spiral arteries by increasing intra-uterine pressure during contraction, the rise in IVS-resistance secondary to IVS-compression, and possible hormonal factors influencing vascular activity are said to decrease utero-placental flow during contraction (Low 1977). *Myometrial blood flow* is

essential in supplying the *uterine muscle* with its nutrients. Only a small part from the uterine blood flow is distributed to myometrium. Experiments in rhesus monkeys showed that the myometrial blood flow is hardly affected by uterine contractions. This was shown in both the non-pregnant uterus and the uterus at term (Lees et al. 1971). Rosenfeld (1980) performed studies immediately postpartum in chronically instrumented ewes with radio-nuclide microspheres and could not demonstrate significant changes in myometrial blood flow.

Uterine contraction

Excitation of myometrial smooth muscle cells

The myometrial smooth muscle cell consists of contractile proteins which are organized in a contraction-relaxation model, as are other smooth muscle cells. Their typical intracellular organization enables the smooth muscle to develop force over a broad range of operating length (Fuchs & Fuchs 1991). The smooth muscle cell can be activated by either electrical or hormonal stimulus. Hormone binding to a receptor at the cell surface, called pharmacomechanical coupling, can activate a chain of events which eventually leads to muscle contraction (Wray 1993). Unique for the myometrium is the hormonal influence on the biosynthesis of contractile proteins and other cellular constituents of importance for excitability of the cell and propagation of excitation from cell to cell (Fröhlich 1974). The presence of gapjunctions in the uterine smooth muscle cell leads to simultaneous and co-ordinated muscular contractions at time of parturition. The formation of gapjunctions, a steroid dependent phenomenon, plays an important role in the onset of co-ordinated uterine activity (Garfield 1977; Ramondt 1991). Experiments in rats show that the amount of gapjunctions depends on time of gestation. A maximum of gapjunctions was seen 3-6 hours after onset of delivery. During the postpartum period, a rapid, i.e. within 12 hours, resolution of gapjunctions was observed in Raymondt's study. The sudden decline in oestrogen-receptors, the rise in progesterone concentration and progesterone receptors, and the decline in mechanical uterine muscle tension have been proposed as a possible explanation (Saito et al. 1985).

The current opinion is that myosine light-chain kinase activated by the Ca^{2+} calmodulin complex, results in phosphorylation of the myosine light-chain

which leads to smooth muscle contraction (Fuchs & Fuchs 1991). Ca^{2+} enters the cell through either a voltage or hormone controlled Ca^{2+}-channel (Carsten & Miller 1987). Experiments with skinned muscle tissues of human myometrium suggest that in human myometrium both the amount of contractile proteins and the sensitivity to Ca^{2+} may increase at term as compared with the non-pregnant state (Izumi et al. 1990). They recently suggested that calmodulin (intracellular receptor for Ca^{2+}) increases the Ca^{2+} sensitivity for contractile elements (Izumi et al. 1994).

Cyclic activity

The contractile function of the myometrium seems to depend merely on intrinsic factors (Fuchs & Fuchs 1984). The myometrium is known to have a (cyclic) characteristic repetitive activity-pattern, independent of whether it is a non-pregnant, a pregnant, or a postpartum uterus (Eskes 1962; Hein 1972). The contractions noted in the puerperium show about the same pattern as those present early in the menstrual period (Eskes 1962; Hein 1972) (Figure 1.3.1.2).

There is no marked difference between the contractions of primiparous or multiparous women. The cyclic activity of the myometrium clearly shows interindividual differences. Patterns characteristic for the different phases of the menstrual cycle (menstrual, early pre-ovulatory, mid-pre-ovulatory, peri-ovulatory, and late postovulatory (the late luteal phase) remain present during registration (Hendricks 1966; Hein 1972). This cyclic pattern might be caused by the different levels of progesterone and oestrogens. Acute withdrawal of oestrogen is associated with marked increase in the generation of spontaneous myometrial activity; this is also observed during the early postpartum period in the rat (Fuchs & Fuchs 1984; Fuchs & Poblete 1970).

In addition to the cyclic changes of the myometrium, differences in innervation and concentration of oxytocin receptors exist between the non-pregnant, pregnant, and puerperal uterus. Maternal endogenous hormonal circadian rhythms exist and may play a role in the sensitivity of the oxytocin receptors, myometrial activity and timing of delivery (Honnebier 1993).

Comparison intra-uterine pressure (IUP)-recordings during menstruation and immediately postpartum.

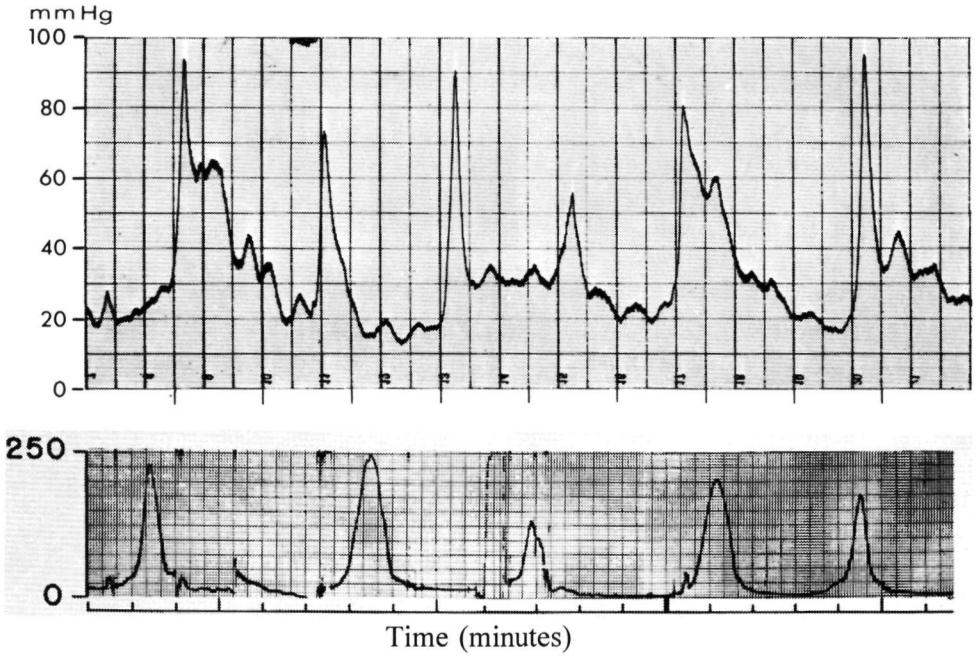

Figure 1.3.1.2
Top-trace: IUP-recording at 2nd day of menstruation; three little blocks represent one minute. (Reproduced with permission of Hein, figure 3 from Hein 1972)
Bottom-trace: IUP-recording 1 hour postpartum; three little blocks represent one minute. (Reproduced with permission of Eskes, figure 23 from Eskes 1962)

Factors influencing uterine contractility

The following factors possibly influence contractility of the non-pregnant, pregnant and puerperal uterus although their contribution differs during various hormonal conditions (Hein 1972, Wray 1993).

- **Intrinsic activity of the uterus and uterine distension**
- **Adrenergic autonomic nervous system**
- **Progesterone and oestrogens**
- **Prostaglandins and oxytocin**
- **Metabolic factors**

- **Intrinsic activity of the uterus**

Both the structure of the uterine musculature and the muscular content of uterine body and cervix are essential determinants for the process of contraction power of the (non)-pregnant and postpartum uterus. The increase of uterine volume during pregnancy is an important stimulus for myometrial growth. Stretch in general, or distension in case of the uterus, stimulates smooth muscle contraction. It is not clear whether stretch leads to contraction directly or indirectly by stimulating other e.g. hormonal factors (Wray 1993).

- **Adrenergic autonomic nervous system**

The uterus is innervated by autonomic nerves, forming a dense plexus: the uterovaginal plexus. It contains a mixture of sympathic, parasympathic and afferent nerves. Adrenergic innervation is under hormonal control; in fact the role of external innervation is not clearly understood as the nerve endings do not have a close apposition to the separate smooth muscle cells. This corresponds with the knowledge that all separate smooth muscle cells can function as a single tissue.

Adrenergic autonomic innervation diminishes during pregnancy (Sjöberg 1967). Experimental studies in chronically instrumented oophorectomized ewes show that the autonomic nervous system or its receptors do not play a role in maintenance of spontaneous myometrial activity as the uterus can contract without an external nerve supply (Verhoeff 1985). Myometrial strips removed from the body will continue contracting rhythmically, without neuronal or hormonal stimuli, as shown in many in vitro studies (Wray 1993).

- **Progesterone and oestrogens**

Administration of oestradiol induces the formation of gapjunctions, which is associated with an increase in co-ordination of myometrial activity; on the other hand, progesterone inhibits formation of gapjunctions (Garfield 1977). In oophorectomized ewes, the concentration of estradiol rose sharply 12 hours before delivery, while plasma progesterone levels fell four days before delivery (Verhoeff 1985). Saito et al. (1985) suggest that it is not the estradiol-concentration per se but its receptor-pharmacokinetics which determine the number of gapjunctions. Based on this study in rats, Saito et al. (1985) emphasize the importance of estradiol and progesterone nuclear receptors and their relation

with the number of gapjunctions. It is generally accepted that changes in hormone receptor-levels are related to an increase in gapjunction area. An increase in the gapjunction area improves the co-ordination of contractility of the uterus, and, thus the onset and process of labour (Fuchs & Fuchs 1991; Wray 1993).

- **Prostaglandins and oxytocin**

Prostaglandins give strong contractions (Frölich 1974) in a non-pregnant uterus and influence myometrial activity and contractions (Ramondt 1991). In oophorectomized ewes inhibition of prostaglandin synthesis interferes neither with an estradiol-induced increase in number of gapjunctions nor with the improvement in the co-ordination of myometrial activity (Verhoeff 1985; Ramondt 1991). Recently, Izumi et al. (1994) suggested that prostaglandines induce contractile responses due to Ca^{2+} release from store-sites while oxytocin can release Ca^{2+}, only indirectly.

Regulators for initiation of parturition are still not fully understood. An important role is attributed to oxytocin receptors, the concentrations of which increase 100 to 200 fold during pregnancy, similiar to concentration of oxytocin itself. Corticotrophin releasing factor (CRF) is produced in large quantities in the placenta and influences contractility by potentiating the effect of oxytocin as well as stimulating prostaglandin synthesis. Concentration of CRF strongly increases six weeks before labour, independent of gestational age, which suggests that it may play an important role in the onset of labour (Quartero 1991).

- **Metabolic factors**

Uterine activity might change oxygen-supply as well as pH in the uterus. Until now little attention has been paid to the possible influence of these metabolic changes on uterine function. The role of metabolic changes in uterine activity might be of importance. In vitro studies are needed to show whether they influence the spontaneous rhythmical contractions of a myometrial strip (Wray 1993).

1.3.2 (Patho)physiology of menstrual bleeding

Markee (1950) suggested that the rapid regression of endometrium (due to hormonal withdrawal) causes changes in the coiling of the spiral arteries which would lead to vascular stasis and result in tissue shedding and menstrual bleeding.

Christiaens (1981) critized this "vascular" menstruation theory by reviewing studies which showed that the location of vasoconstriction is unclear and that beside vasoconstriction, other mechanisms may explain vascular narrowing. However, she agreed that a partial vessel occlusion might occur during menstruation. She described the haemostatic plug formation during menstruation based on histologic studies and showed differences between haemostasis in the endometrium and in skin wounds. In contrast to plugs elsewhere in the human body, the hemostatic plugs in the menstrual endometrium have a complete intravascular location. She suggested that as long as tissue shedding continues, plug formation is important for bleeding arrest. According to her, tissue regeneration and re-epithelization are the *result* and not the cause of haemostasis.

Moreover, she demonstrated that menstrual blood contains fibrin and platelets. Christiaens (1981) demonstrated that during shedding of the endometrium (and despite loss of blood vessel continuity in the uterine cavity) the uterine bleeding stops due to haemostatic plug formation (platelet aggregation, fibrin formation), vasoconstriction and regeneration of the endometrium on one hand and vasodilatation, fibrinolysis and prostaglandins influenced platelet inhibition on the other hand. According to her, the high fibrinolytic capacity of the endometrium has a three-fold function. It promotes the emptying of the uterus by liquefaction of the shed tissue, it prevents implantation during menstruation and it improves the regeneration of the endometrium. She illustrated the importance of haemostatic plug formation for haemostasis in menstrual endometrium with the fact that in patients with platelet and coagulation disorders menorrhagia often occurs. The exact function of prostaglandins in menstrual haemostasis is not elucidated, but it is certain that they play a role in menstrual physiology (Christiaens 1981).

1.3.3 (Patho)physiology of postpartum bleeding

The mechanism by which uterine bleeding stops after placental separation is not clearly understood. In fact, concepts of the physiology of the postpartum uterus are scarce. At least three processes can be discriminated: placental separation, uterine activity before and after placental separation, and the coagulation cascade and fibrinolysis after placental separation.

Placental separation

In the third stage of labour, two processes take place in regard to the placenta:

- It separates from its insertion: the detachment takes place between the endometrium "functionalis" and the endometrium "basalis" (Friedländer 1876).
- It is expelled from the uterine body through the birth canal, passing the cervix and vagina.

A few weeks before parturition, several degenerative and necrobiotic processes take place to create the circumstances for easy expel of the placenta. After parturition the vessels in the placental site are characterized by thrombosis, hyalinization, and obliterative fibrinoid endarteritis in the arteries. Many of the thrombosed and hyalinized veins are extruded with the slough of the necrotic placental site. Restoration of the endometrium occurs within 16 days. (Williams 1931; Anderson & Davis 1968).

Uterine activity after placental separation

When the child is born, uterine activity can be described as follows:

- Retraction

Immediately after delivery, the position of the uterine fundus is lowered from the upper abdomen to the umbilicus, the so called "retraction" (Schwenzer 1977). Retraction is the start of the involution of the uterus. Whereas contractions are characterized by the short period in which muscle fibre contracts and which is followed by relaxation of the muscle fibre, retraction is characterized by shortening of the uterine musculature, in spite of relaxation of the individual muscle fibres and increasing intrauterine tone (Knaus 1948).

Uterine activity during and after (placental) delivery.

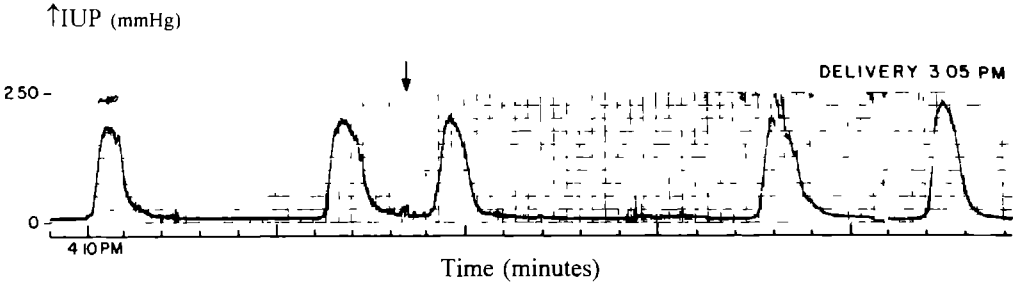

Figure 1.3.3.1 Placenta delivered at arrow. (Reproduced with permission of American Journal of Obstetrics and Gynecology, figure 4 from Hendricks et al 1962).

Retraction is probably facilitated by the typical arrangement of uterine muscular (circular) fibres (Goerttler 1931).

- Contraction

After approximately two to three minutes, the first postpartum contraction can be observed. The intensity or amplitude is two to three times higher than before delivery (Pascal's Law: pressure is force divided by area), and the uterine activity (product of frequency and intensity) decreases exponentially. This pattern is independent of the presence or absence of the placenta within the uterine cavity (Eskes 1962; Hendricks et al. 1968) (Figure 1.3.3.1).

Coagulation cascade and fibrinolysis after placental separation

Changes in coagulation factors during pregnancy, in particular at the time of delivery and in early puerperium, are summarized below.

Coagulation and Fibrinolysis

During an uncomplicated pregnancy, the concentration of most plasma procoagulants is increased, with the exception of factors XI and XIII. In the first days after delivery, the plasma concentration of factors V, VII, and X increases (Wallenburg 1987).

In the fibrinolytic system, the tissue-type plasminogen-activator inhibitors

type I (PAI-1) and type 2 (PAI-2) increase until the end of the thirty-eight gestational week, after which they all decrease except t-PA antigen (Lindoff et al. 1993). Fibrinolysis appears to be enhanced after placental separation (Shimada 1989; Gerbasi et al. 1990). Prostaglandins, involved in the initiation and maintenance of labour (Keirse et al. 1977) also have an effect on variables of fibrinolysis (Bertelé et al. 1989). Bremer et al. (1994) found a rise in t-PA antigen as well as a fall in PAI-1 antigen and PAI activity in venous blood of electively induced women. The rise in t-PA antigen can be explained by physical exercise known to release t-PA from vascular endothelium (Rijken et al. 1983; Kruithof et al. 1987) or vascular damage in the utero-placental bed (Yoshimura et al. 1992). After placental separation the fibrinolytic potential of the maternal blood appears to increase.

Platelets

During normal pregnancy, platelet reactivity increases due to an enhanced activity of the cyclo-oxygenase pathway and an elevated sensitivity of the platelet membrane (Louden et al. 1992).

Inflammation

In contrast to former (histological) observations by Williams (1931), biochemical studies show that a low-level inflammatory process may be a normal occurrence in the term placenta. A close interrelation was observed between the levels of the mediators released during inflammatory processes (Tumor Necrosis Factor, Interleukin 1,2, and 6). This process induces the production of cytokines playing a role in the regulation of parturition as well as local coagulation at the placental bed during expulsion (Halgunset et al. 1994).

Haemostasis in the utero-placental bed

In the uterine veins, morphologic changes are seen such as thrombosis, hyalinisation and endophlebitis. In the uterine arteries obliterative fibrinoid endarteritis has been observed (Anderson 1968). The infiltration of trophoblast cells in the arterial walls which occurs in early pregnancy could contribute towards the hyalin changes in these arteries (Pijnenborg 1994).

The precise mechanism of coagulation during and after placental separation is unknown; however, the following processes do play a part in local haemostasis.

- The contraction of muscle sheaths around the spiral arteries, which leads to platelet plug formation (also described for menstrual bleeding in 1.3.2) (Renn 1970).
- Retraction of the uterus (1.3.3) causing mechanical occlusion of the arteries facilitating plug formation (Schwenzer 1977).
- The activation of the coagulation cascade and fibrinolysis during and after placental separation as shown above.

1.3.4 Discussion

From a physiologic point of view, there are no big differences between the endometrium and the decidua. It is noteworthy that the differences in spiral arteries between the non-pregnant and pregnant state are mainly due to trophoblastic invasion into the vessels (1.3.1).
The similarities between menstrual and postpartum bleeding are shown in Table 1.3 4.1.

Christiaens (1981) suggested that myometrial contractions have no major role during menstruation haemostasis. During the placental separation, the process of retraction (volume reduction) influences in particular uterine activity.

Table 1 3 4 1 Comparison between menstrual bleeding and placental separation

	Menstrual bleeding	*Placental separation*
Endometrium	Detachment between endometrium "functionalis" and "basalis"	Detachment between decidua "functionalis" and "basalis"
Blood vessels	Spiral arteries	Spiral arteries
Myometrium	Contractility in the menstrual period	Contractility in the postpartum period
Coagulation factors	Coagulation cascade Fibrinolysis	Coagulation cascade Fibrinolysis

It is reasonable to suppose that the retraction of the uterus compresses uterine vessels (including spiral arteries) and, therefore, plays a role in haemostatic plug formation. The exact mechanism, however, is unknown (Schwenzer 1977). As for the fibrinolytic and coagulation process, no systemic change of coagulation factors (as shown in the peripheral blood of pregnant and postpartum women) takes place during menstruation. At local uterine level, however, the changes in coagulation factors, the increasing fibrinolytic activity and the function of the platelets in the haemostatic plug formation are comparable.

On the assumption that there are similarities between menstrual bleeding and postpartum bleeding, we have used the menstruating uterus as a model for the postpartum uterus in one of our studies (Chapter 5: Pharmacodynamics), while keeping in mind that by using this model we only partly simulated the process of placental separation.

2 Ergot alkaloids as uterotonics

2.1 History of ergot alkaloids From ergotism to ergometrine*

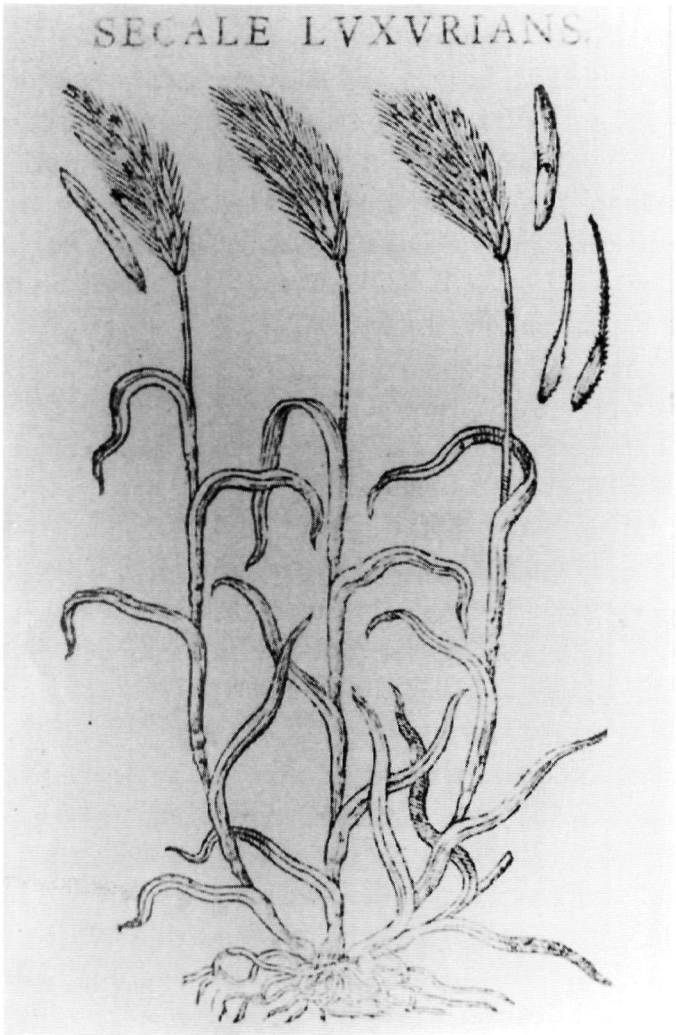

Figure 2.1.1 The first illustration of ergot. Woodcut in Caspar Bauhin's Theatrum Botanicum (1685)

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*van Dongen PWJ, de Groot ANJA. History of Ergot alkaloids; From ergotism to ergometrine. Eur J Obstet Gynec Reprod Biol 1995; 60: 109-116.

Primum non nocere

Early history

The very fertile crescent of Mesopotamia between the Euphrates and Tigris produced the first agricultural settlements around 9.000 BC. The wild grasses were cultivated and yielded good harvests of grain from wheat and rye. Assyria and Babylonia could develop because of the stable supply of this staple food. However, grasses and especially rye can be contaminated by the fungus Claviceps purpurea during wet seasons, producing the typical ergot, i.e. the sclerotium, in the ears of grain (Figure 2.1.1).

Ergot is probably 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, which name was given in the Middle Ages to ergotism. In one of the holy books of the Parsees in the 7th century ergotism was described as "..... noxious grasses that cause pregnant women to drop the womb and die in childbed" (Barger 1931; Clark 1984).

Ergotism

Epidemics of ergotism occurred frequently in the Middle Ages. It was caused by eating rye bread contaminated with C. purpurea, resulting in gangrene of limbs, disturbances in the function of the central nervous system and ultimately death.

Ergot is derived from the old French word argot, meaning the cock's spur. The violet or black sclerotia consist of hyphae and are at least three times longer than the grains. Before or at harvest time the sclerotia fall on the ground and remain inactive till they germinate in the next warm and moist spring by developing 15 till 60 white spherical heads on stalks (hence the name claviceps; Figure 2.1.2). Ascospores are set free by rupture of the head and propelled into the air by several centimetres. Within eight days the infection of the flowering rye causes a secretion, the so-called honey-dew, in which the conidia (asexual spores) develop. This secondary infection leads to the production of the mycelium and then to the solid sclerotium, closing the lifecycle of C. purpurea (Tulasne 1853; Bauer 1973; Luyendijk-Elshout 1983).

If bread was prepared without removing the black spurs, epidemics of ergotism sprang up. Rye was mainly eaten by the poor people, especially during famines. The suffering from ergotism was then doubled, because the spurs were also collected because of hunger. The Russians in the late Middle Ages considered the spurs as a necessity to produce good quality bread. The German mythology explained the "sudden" appearance of ergot by transgression of the "Kornmutter" (grain-mother) through fields during foggy weather (Barger 1931).

The first mentioning of *gangrenous ergotism* can be found in the "Annales Xantenses" (Germany) in 857 AD: "A great plague of swollen blisters consumed the people by a loathsome rot so that their limbs were loosened and fell off before death" (Fuchs 1834).

The first epidemic of *convulsive ergotism* is described in 945 in Paris, France (Barger 1931). It was accompanied by erythema, diarrhoea, vomiting, formication and agonizing burning sensations as if the limbs were burning, often

Figure 2.1.2 Fully developed heads of the Claviceps purpurea magnification 12 times

Table 2 1 1 Symptoms of ergotism

Gangrenous ergotism	Convulsive ergotism
• abortion	• fatigue
• amenorrhoea	• giddiness
• failure to lactate	• paraesthesia
• lassitude	• formications
• lumbar pain	• nausea/vomiting
• calf pain	• burning sensation
• feet/hands	• clonic/tonic spasms
- swollen	• flexion of arms/hands
- vesicles	• paralysis, hemi(para)plegia
- inflammation	• maniacal excitement
- alternating hot or cold	• hallucinations
- livid, black	• visual disturbances
- analgesia	• delusional insanity
- gangrene	• psychosis
- amputation	• convulsions
• jaundice	• dullness
• severe diarrhoea	• cataract

preceded by convulsions, catalepsy, dullness or maniacal excitement, hence the mentioning of "dancing epidemics". Most victims died, but some who fled to the church of St Mary or Martial survived, because most probably they got non-contaminated food as was seen in the epidemic of Aquitaine, France (994 AD) in which 40,000 people perished (Barger 1931).

The gangrenous type was mostly seen in France and the convulsive one in Germany The two distinct types of ergotism (gangrenous and convulsive) may be considered as acute and chronic varieties of ergotism. The different symptoms described are given in Table 2.1.1 As the formication is typical in the convulsive type, it was called "Kriebelkrankheit" in Germany. Mixed types were described as well, especially in other European countries. (Clark 1984).

Holy Fire

In 1095 the order of St. Anthony was founded in Vienne, France Especially in the twelfth and thirteenth centuries people flocked during epidemics to the hospitals of the Antonines. The bones of the Egyptian hermit St. Antony (251 - 356 AD) were sprinkled with holy water and wine and given to the sufferers of ergotism Soon the hospitals were called the "hôpitaux des démembrés" because at its entrance the spontaneously amputated limbs were exhibited as kinds of ex

Figure 2.1.3 Woodcut by Hans Wächtlin, Straßburg."Von der kalten Brandt" in: Feldtbuch der Wundartzney, Hanns von Gersdorff (1517)

votos. Due to the good treatment by providing non-contaminated bread, the popular hospitals spread all over Europe till a zenith of 390 settlements (Bauer 1973).

The frequent epidemics were called St. Anthony's Fire, "Holy Fire" or Ignis Sacer because of the burning sensations in the limbs as is depicted in the art of the time (Dixon 1984; Crijns 1992; Sello 1992; van Dongen 1995). Victims of

ergotism could identify themselves easily with the lifelong tortured St. Anthony. In the woodcut from 1517 (Figure 2.1.3) a farmer who lost his right foot, extends his left arm engulfed in symbolic flames towards St. Anthony for help and protection. Medieval medicines were thought to restore the balance between hot and cold, wet and dry ailments. The Holy Fire was of course considered as a very hot disease, treatable with cooling elixirs, holy vintage with rare and costly ingredients, fish and water, thistle and mandrake (mandragora)-apple and -root. The juice of the mandragora-apple was also used for analgesia but overdoses caused often untimely death, hence the nickname of "devil's apple". It contains the two belladonna-alkaloids hyoscyamine and hyoscine with parasympathicolytic properties of mydriasis, bradycardia, reduced glandular secretions but also visual hallucinations, especially sensations of flying. The famous St. Anthony Tryptich (Lisbon, Museu Nacional de Arte Antiga) shows not only the temptations of St. Anthony, all "cold" treatments for ergotism including the mandragora-apple and -roots, suffering ergotants but also strange flying aircrafts. Jeroen Bosch (1452-1516) painted all three interior panels with outrageously strange and diabolic scenes as if seen by a hallucinating brain. Ergot when baked with dough may be transformed into lysergic acid diethylamine (LSD), a reknown hallucinogen. Ergotants were therefore twice afflicted by hallucinations: first by the transformed ergot-alkaloids and then from the belladonna-alkaloids from the mandragora (Bauer 1973; Dixon 1984; Sello 1992; van Dongen 1995).

Use of ergot as an oxytocic drug

The Renaissance in Europe may be defined as the transition from the medieval, magical-religious society to the modern world. For ergotism, the Middle Ages ended in 1582 when Adam Lonicer in Germany mentioned for the first time the use of ergot to stimulate uterine contractions of labour ("pains of the womb") by administering three sclerotia (equals 0.5 mg ergot).

The first accurate description of the ergot is also from his Kreuterbuch: ".... long black hard narrow corn pegs, internally white, often protruding like long nails from between the grains in the ear" (Clark 1984).

The honour of the first description in a medical journal is given to Paulizky in 1787. Ergot as "pulvis ad partum" was prescribed by midwives and physicians alike. It showed an action which was "..... more rapid and powerful than any

other known drug" (Paulitzky 1787). John Stearns from New York (1807) wrote in a famous letter to Mr. S. Akerly about the properties, dosage and side effects of ergot (Stearns 1807). The crude ergot was given in a dosage of 5-10 grams to parturients resulting in a rapid and sudden termination of labour with an induction delivery time of not more than three hours. However, this "pulvis parturiens" was not suitable for accurate therapeutic administration because of the large variation of active ingredients and the severe adverse events like violent nausea and vomiting. The period of administering ergot as means of quickening birth ended in 1822 when Hosack from New York stated that many stillbirths were due to uterine rupture with resulting maternal death. The "pulvis ad partum" was renamed "pulvis ad mortem" (Hosack 1824). By the end of the 19th century its use as an oxytocic was virtually abandoned.

Cause and prophylaxis of ergotism

The first suggestion that ergotism was caused by blighted grains was already mentioned in 1125. Caspar Schwenkfeldt (Poland, 1600) thought that the honey-dew of the rye was the cause of the ergot epidemics (Bauer 1973).
During an epidemic of gangrenous ergotism in Sologne (France, 1630), Tullier Sr did animal research by giving "cornicula nigra" to chickens, geese and pigs: they all died. Unfortunately, he did not publish his results. Only in 1676, Dodart with help from the son of Tullier, solved the problems of the epidemiology and cause of the gangrenous ergotism. Likewise, Johann Brunner, described the cause of the convulsive type in 1695 in Leipzig, Germany (Bauer 1973).

Although the cause of ergotism was known, it took more than a century to specify the first prophylactic measures by L'Abbé Tessier in 1778. A vast epidemic of gangrenous ergotism with more than 8000 victims in Sologne, France, was caused because the grains were not cleansed from ergot. He proposed drainageways, cultivation of potatoes in stead of rye and the enforced cleaning of grains (Percebois 1977). A second description of preventing ergotism by controlling the quality of bread in hospitals was elucidated by Johann Taube in his magnificent book "Die Geschichte der Kriebelkrankheit" (Göttingen, Germany, 1782). Moreover, his clinical pictures of the neurologic and psychiatric disorders are still valuable today. His recommended treatments of ergotism were waterbaths of 20°C, electrotherapy and anthelmintic drugs (Bauer 1973).

The last epidemic of convulsive ergotism in Germany (Oberhessen) was eloquently depicted by Siemens in 1879 (Siemens 1881). He noted that neurological symptoms, like painful tonic contractions of the flexors, ataxy of the limbs, instability and epilepsy, preceded always psychiatric disturbances like decreased awareness, delirium and hallucinations. Moreover, the damage proved to be irreversible (Table 2.1.1).

Analysis and mode of action of ergot alkaloids

Although the word alkaloids is a misnomer, it is still used widely. Originally, alkaloids were described in 1913 as "..... basic substances occurring in plants" (Henry 1913). Nowadays, nitrogenic constituents are included as well. One may say that ergot is a "treasure chest of valuable pharmaceuticals" (Table 2.1.2, Clark 1984).

Table 2.1.2

A choice of pharmaceutical constituents found in ergot alkaloids*

acetylcholine	ergotinine
agmatine	ergotocin
amino-sulphonic acid	ergotoxine
betaine	guanosine
cadaverine	histamine
choline	histidine
ergobasine	iso-amylamine
ergochrysin	iso-leucine
ergoclavine	leucine
ergocornine	putrescine
ergocristine	sclerocrystallin (= secalonic acid)
ergokryptine	secale cornutum
ergoflavin	sensibamine
ergometrine (= ergonovine)	trimethylamine
ergosterol	tyramine
ergotamine	tyrosine
ergotaminine	uracil
ergothioneine	valine
	X-alkaloid (ergostetrin)

* The four alkaloids ergometrine, ergobasine, X-alkaloid and ergotocin are identical (see text)

The honour of the first person trying to analyze and isolate the active principles of ergot goes to the pharmacist Heinrich Wiggers in 1835 in Göttingen, Germany (Dann 1953). However, after numerous systematic botanical and chemical investigations no fundamental discovery was made.

The first pure alkaloid was described in 1875 by Tanret in France (Tanret 1875). The crystallized ergotinine was, however, almost inert. Sollmann and Brown (Sollmann & Brown 1905) studied in 1905 the circulatory effects in mammals after both intravenous and intramuscular injections of crude ergot. The results varied considerably because of differences in the preparations and hence the dosages of ergot. Even after destruction of the spinal cord the same pattern of a rapid drop of blood pressure followed by a prompt recovery of the blood pressure was noted, but only after intravenous injection of ergot and not after oral administration. The response to epinephrine (hypertension) was decreased by ergot. The adrenergic blockade by ergot is therefore first described by Sollmann (Sollmann & Brown 1905) and not by Barger as stated in his extensive monograph (Barger 1931). Barger and Carr (1906) obtained two impure fractions from ergotinine. The uterotonic activity was attributed to a single alkaloid, the so-called ergotoxine.

Ergotamine was developed as a new physiologically active agent in 1920 (Stoll 1920; Spiro 1921). Its uterotonic properties are easily lost during storing (Thompson 1935). At present, ergotamine is only used in the treatment of migraine and other vascular headaches. When inadvertently given during pregnancy it may cause fetal stress. A review of all side-effects of ergot alkaloids during pregnancy has been published elsewhere (de Groot et al. 1993b).

Uterine action after oral administration of extract of ergot (according to the British Pharmacopoeia) was monitored externally in 1927. It was found to be wholly inert, as was the extract according to the U.S. Pharmacopoeia (Bourne & Burn 1927). Ergotamine or ergotoxine exerted a prolonged action and were therefore considered to be ideal agents for use after delivery. However, it took four to ten minutes after intravenous injection before any uterotonic action was noted, twenty minutes after intramuscular injection and by mouth even thirty-five minutes or longer.

In their classic paper of 1932, Moir and Dale used the same technique for intra-uterine pressure recording as Schatz in 1872 (Schatz 1872) and Bourne

and Burn in 1927 (Bourne & Burn 1927): a sterilized bag was inserted in the puerperal uterus, connected by tubing to a mercury manometer and to a rotating drum with a recording device (Moir & Dale 1932; MacDonald 1982). When an aqueous extract of ergot was given by mouth to a postpartum woman, the effect appeared not only in a remarkably short time of four minutes, but also strikingly different as was seen after administration of ergotamine or ergotoxine. The contractions were more frequent (two or three to the minute), more regular, with greater amplitude and rise of the basal intra-uterine pressure than observed after administration of any other drug. Therefore it was concluded that another and more powerful uterotonic agent must be present. Indeed a watersoluble alkaloid was isolated in 1935 by the same group and henceforth called *ergometrine* (Dudley & Moir 1935).

The properties were described as follows: ".... the onset is sudden, and accompanied by pronounced 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. This stage lasts for about an hour, and is followed by a second stage, during which the uterus shows regular, vigorous, isolated contractions, continuing for an hour or more" Oral administration of 0.5 mg ergometrine

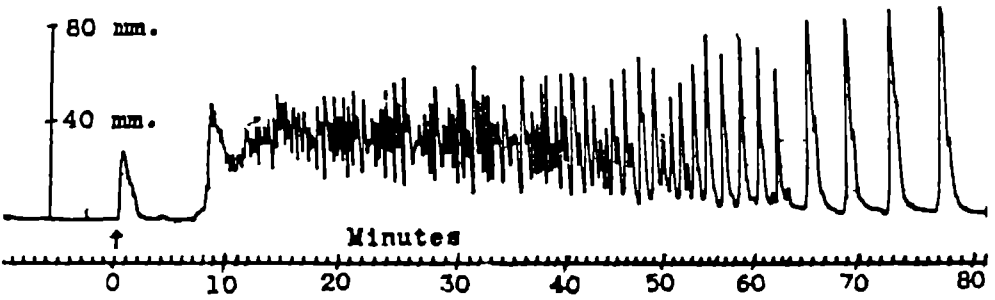


Figure 2 1 4 Tracing of uterine contractions made on sixth day of puerperium by intra-uterine bag method, showing the effect of 0 5 mg ergometrine by mouth The arrow shows moment of administration (Is Figure 1 from Dudley and Moir 1935) Reproduced with permission of British Medical Journal

provoked, after an interval of 6½-8 minutes, contractions identical with those produced by the watery extracts of ergot as described in 1932 (Moir & Dale 1932) (Figure 2.1.4). Therefore, the active substance of ergot extract must be ergometrine. After intramuscular or intravenous administration of ergometrine the sudden action was recorded after four and two minutes, resp.

Within a month, three other groups - two in the U.S.A. (Davis et al. 1935; Adair et al. 1935; Thompson 1935) and one in Switzerland (Stoll 1935) - described the same alkaloid, although by different names: ergotocin (Davis et al. 1935; Adair et al. 1935) ergostetrin (Thompson 1935) and ergobasine (Stoll 1935). The four alkaloids proved to be the same substance. In the United Kingdom it adopted the name ergometrine; a fifth name ergonovine was selected for use in the U.S.A.

Chemistry of ergometrine, its derivatives and bromocriptine

All naturally occurring alkaloids are derived from lysergic acid and contain a substituent at position 8 (Figure 2.2.1 p 52; Rall 1990). Two groups are described with different target organs, pharmacological properties and side-effects. Ergometrine is the simplest compound with a single amine-group as substituent. Upon hydrolysis, ergometrine yields lysergic acid and an amine; consequently it is designated as *amine alkaloid.* Methylergometrine is a semisynthetic amide derivative of d-lysergic acid. It contains an extra methyl-group in the substituent at position 8. (Methyl-)ergometrine has greater uterotonic than vasoconstrictive abilities (de Groot et al. 1993b) (see Chapters 2.2 and 2.3). The partial synthesis of ergometrine by Stoll and Hofmann (1938) was followed by the synthesis of lysergic acid diethylamide (LSD) in 1943 by Hofmann. It proved to be more toxic and less uterotonic than ergometrine. Within forty minutes after swallowing an overdosage, Hofmann himself experienced dizziness, unrest, difficulty in concentration, visual disturbances and "delusional insanity", as was described in the old epidemics of ergotism (Table 2.1.1). It was shown that the hallucinogenic activity resulted from serotonine (5-hydroxy-tryptamine)-antagonism (Hofmann 1970).

The *amino acid alkaloids* comprise the naturally occurring ergotamine and ergotoxine and the semisynthetic bromocriptine. Prolactin secretion inhibition is caused by the α-ergokryptine compound. The synthesis of bromocriptine (2-bromo-α-ergokryptine) in 1965 heralded the new era of dopamine receptor

stimulation. Interestingly, it is known that during epidemics of ergotism the milkproduction of nursing mothers and cows stopped. Ergot extracts were also used in the 19th century to treat amenorrhoea (Rall 1990)!

Management of the third stage of labour with ergot alkaloids

The World Health Organization (WHO) estimates that each year at least half a million (500,000) women die from causes related to pregnancy and childbirth (Royston & Armstrong 1989). Postpartum haemorrhage (PPH) is one of the most common causes of maternal death, amounting to 13% of all maternal deaths in developed and 33% in developing countries (van Dongen et al. 1991). The calculated Maternal Mortality Rate (MMR) on the British Isles in the 18th century was about 2,000 per 100,000 live births. William Smellie decribed PPH in 1751 as follows: "all women, when the placenta separates, and after it is delivered, lose more or less red blood from the quantity of half a pound to that of one pound or even two; but should it exceed this proportion and continue to flow without diminution, the patient is in great danger of her life" (Joyce & Lennon 1948). The MMR in the United Kingdom in 1930 was still 300/100,000 live births. Nowadays, in Western Europe and North-America this figure is about 8/100,000 live births (Royston & Armstrong 1989).

The tremendous decrease in MMR is due to improved socio-economic factors, introduction of antibiotics, blood transfusion facilities and oxytocic drugs. The active management of the third stage of labour and treatment of excessive blood loss in the so-called fourth stage of labour (period after expulsion of the placenta) by administering oxytocics has been described as "..... one of the enduring achievements of modern science" (Royston & Armstrong 1989).

After administering "secale luxurians" after birth, Schwenkfeldt in 1600 noted for the first time in history that ".... sanguinem sistere vulgus credit", i.e. ".... one believes it will stop the bleeding" (Bauer 1973). The "Guide to midwifery" from 1912 recommends an intramuscular injection of ergotine after the birth of the infant (Hart 1912).

The first application of ergometrine as a prophylactic drug is attributed to Browne in 1935, but it was published in 1947 (Flew & Gibber 1947). Ergometrine 0.5 mg was given intramuscularly to 500 consecutive normal cases as soon as the head was delivered. Results of blood loss are, however, not

given. It is only stated that no cases of manual removal of the placenta were seen.

Joyce and Lennon studied 156 cases with PPH between 1938-1947. They advocated that if PPH occurred before delivery of the placenta, 0.5 mg ergometrine should be given intramuscularly by ".... the midwife while awaiting the doctor's arrival" (Joyce & Lennon 1948). Shaw (1949) noted that the duration of the third stage was markedly reduced. Moreover, less blood transfusions were needed if a manual placental removal was done after prophylactic intravenous injection of ergometrine (54% vs 8%) (Shaw 1949). Daley (1951) is the first one who administered routinely 0.5 mg ergometrine intramuscularly in *normal* parturients (490 vs 510 controls) after crowning of the head. Blood loss was carefully measured. Significant reduction in duration of the third stage with four minutes and in blood loss of 70 mls was established. However, the most important finding was that the frequency of PPH -defined as blood loss > 560 mls- was significant less in the ergometrine group (9.2%) as compared to the control group (15.7%) (Daley 1951).

At present, evidence of the effectiveness of active management with oxytocic drugs is based on meta-analysis of randomized controlled trials. Prescribing any oxytocic drug routinely for the prevention of PPH resulted in significantly decreased blood loss, less blood transfusions, lower incidence of PPH (from 10-6%), shortened third stage of labour and decreased need of further administration of oxytocics (Prendiville et al. 1988a; 1988b; Elbourne 1988; McDonald 1993). No statistical differences in the incidence of PPH was found after administration of oxytocin, ergometrine or prostaglandins (Elbourne et al. 1988; Poeschmann 1991; Mc Donald 1993). However, it is very clear that ergometrine may provoke unpredictably severe hypertension, nausea, vomiting and many more side-effects due to its vaso-constrictive effects (de Groot et al. 1993b), sometimes leading to maternal deaths (Ringrose 1962). Moreover, there is ample evidence that both oral and parenteral ergometrine are not stable under humid, warm and light conditions (Walker et al. 1988; Hogerzeil et al. 1991; Hogerzeil et al. 1992; de Groot et al. 1994c; Hogerzeil et al. 1994). It was therefore concluded that the best choice for use in third stage of labour is *not* ergometrine but oxytocin (de Groot 1995a).

Conclusion

We may have come full circle: from the accidental poisoning with ergot alkaloids (ergotism), acceleration of labour, prevention and treatment of PPH to the knowledge of the severe side-effects and instability of ergometrine. Perhaps the time has come to abandon oral ergometrine from obstetrics and intravenous Methergin^{R} as prophylaxis in the third stage of labour. Primum non nocere.

2.2 Chemical background

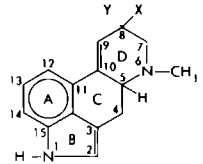
Ergot alkaloids can all be considered to be derivatives of the tetra-cyclic compound 6-methylergoline (Figure 2.2.1; Rall 1990). The naturally existing alkaloids of therapeutical interest are amide derivatives of *d-lysergic acid*, so called 9-ergolenes; they contain a substituent at position 8 and a double bond in ring D between C9 and C10. The substituent at position 8 can either be in the ß-configuration or in the α-configuration. The 8 H-atom is called 8α when it is *trans* to the 5-H and 8ß when it has a *cis* position in relation to the 5-H. Traditionally the α-isomer is distinguished from the ß-form by the prefix *iso* or by the suffix *inine*. Thus, the 8ß-configuration is called *d-lysergic acid* and the 8α-configuration, *d-isolysergic acid.* The substituent at position 8 forming d-lysergic acid is the working compound. Optical isomerism is due to the presence of two asymmetrical carbon atoms (position 5 and 8) in the lysergic acid portion of the molecule.

In combination with water and on exposure to light, in particular that of UV-frequency, H_2O can be added to the double bond between C-9 and C-10; 6-hydroxy derivatives are then formed: Lumi-derivatives. An acid environment facilitates this reaction (Rall 1990; Glover & Halki 1991). Furthermore, the ergot alkaloids are easily oxidized, with the *oxidation products* being coloured (Rall 1990).

Ergometrine(= ergonovine)(Figure 2.2.1) is an amide derivative of d-lysergic acid; it contains a double bond between C-9 and C-10 (ring D). Upon hydrolysis, ergometrine yields lysergic acid and an amine; consequently, it is designated as an *amine alkaloid.*
Methylergometrine (= methylergonovine) is a semisynthetic amide derivative of d-lysergic acid. It contains an extra methyl-group in the substituent of the ß-configuration at position 8 (Rutschmann & Stadler 1978; Rall 1990).

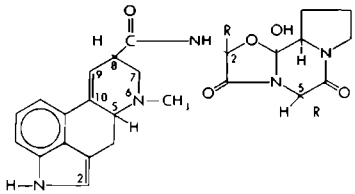
The enantiomers (optical isomers) are called ergometrinine and methylergometrinine. The naturally existing enantiomers are always present due to spontaneous epimerisation about the asymetric centre C8. However, the 8α-configuration *(-inine)* forms only a small part of the mixture (Rall 1990).

A AMINE ALKALOIDS AND CONGENERS



ALKALOID	X	Y
d-Lysergic acid	—COOH	—H
d-Isolysergic acid	—H	—COOH
d-Lysergic acid diethylamide (LSD)	$-C(=O)-N(CH_2CH_3)_2$	—H
Ergonovine (ergometrine)	$-C(=O)-NH-CH(CH_3)-CH_2OH$	—H
Methylergonovine	$-C(=O)-NH-CH(CH_2OH)-CH_2CH_3$	—H
Methysergide *	$-C(=O)-NH-CH(CH_2OH)-CH_2CH_3$	—H
Lisuride	—H	$-NH-C(=O)-N(CH_2CH_3)_2$
Lysergol	$-CH_2OH$	—H
Lergotrile †,‡	$-CH_2CN$	—H
Metergoline *,†	$-CH_2-NH-C(=O)-O-CH_2-$phenyl	—H

B AMINO ACID ALKALOIDS



ALKALOID §	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	$-CH(CH_3)_2$	$-CHCH_2CH_3$ (CH₃)
Bromocriptine ¶	$-CH(CH_3)_2$	$-CH_2CH(CH_3)_2$

* Contains methyl substitution at N 1
† Contains hydrogen atoms at C 9 and C 10
‡ Contains chlorine atom at C 2
§ Dihydro derivatives contain hydrogen atoms at C 9 and C 10
¶ Contains bromine atom at C 2

Figure 2.2.1 Natural and semi-synthetic ergot alkaloids; Reproduced with permission from Goodman and Gilman

Derivatives of l-lysergic acid (epimere at position 5) and d-isolysergic acid display relatively little biological activity. None of the other products of ergometrine display any biological activity (Rutschmann & Stadler 1978; Rall 1990).

The presence of the OH-group in the substituent at C8 in both ergometrine and methylergometrine makes glucuronidation a plausible metabolic pathway (Correia & Castagnoli 1984) (Figure 2.2.2). Indications of this pathway of metabolisation were obtained, but have not yet been validated. As literature gives no further information on glucuronidation of (methyl)ergometrine, this is still an issue to be investigated.

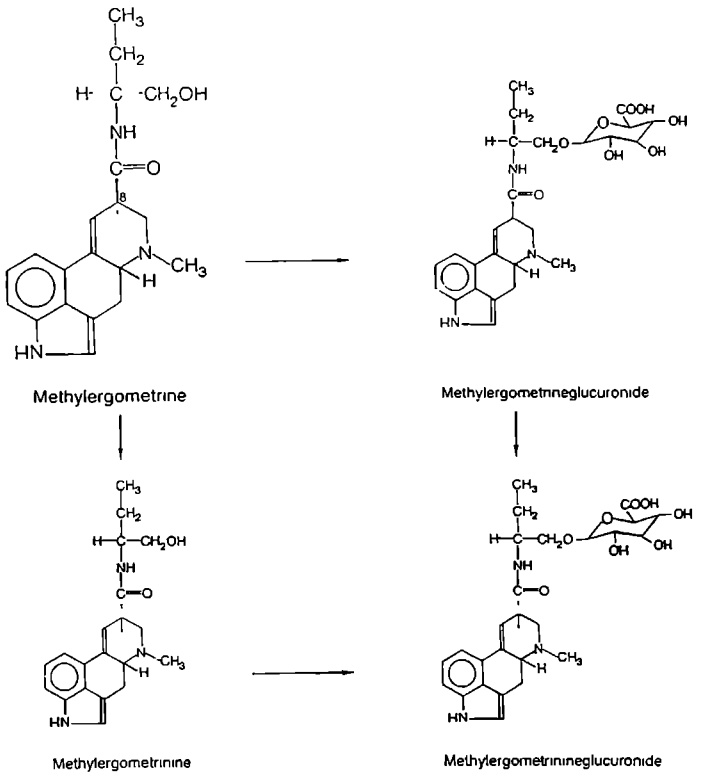


Figure 2.2 2 Glucuronidation of methylergometrine and its enantiomer methylergometrinine as possible metabolic pathway (TB Vree, personal communication)

2.3 Pharmacological properties

In general, ergot alkaloids act as partial antagonists at α-receptors and give a direct vasoconstrictive action. They mainly affect the dilated arterioles, induce contractions of uterine musculature, and provide a central stimulation of dopamine receptors (Müller-Schweinitzer & Weidemann 1978). Activity profiles for the vasoconstrictive and uterotonic properties of peptide alkaloids, dihydro-peptide alkaloids, lysergic acid amides, and lysergic acid alkaloids are given in Table 2.3.1 (Berde & Stürmer 1978; Leist & Grauwiler 1974).

In obstetrics, ergot alkaloid derivatives with specific uterotonic action and without vasoconstrictive properties are used in the management of the third stage. The vasoconstrictive action of (methyl)ergometrine (=ergonovine) is less than that of other ergot alkaloids (Table 2.3.1).

Ergometrine maleate and methylergometrine maleate are pharmacologically similar (Rall 1990; Glover & Halki 1991). Methylergometrine and ergometrine maleate decrease the postpartum blood loss by enhancing the muscle tone of the uterus, imposed by fast rhythmic contractions of the myometrium, the so-called tetany. As a by product, the myometrial blood vessels are compressed resulting in limited blood loss (van Dongen et al. 1991). Former studies have described the absorption rate of oral ergometrine and methylergometrine as rapid and complete (Rall 1990). Uterine action after oral administration of an ergot extract was described as early as 1927 (Bourne & Burn 1927). After *oral* administration of ergometrine a gradual ascent of the curve to the tetany level

Table 2.3.1 Activity profile of structural groups of ergot alkaloids

Activity profile	Vasoconstriction *(systemic)*	Uterotonic Contraction	Ergotism
Peptide alkaloids *[ergotamine]*	+++	++	+++
Dihydro-peptide alkaloids *[dihydro-ergotamine]*	++	±	±
Lysergic acid amides *[(methyl)ergometrine]*	±	+++	±
Lysergic acid alkaloids *[lysergic acid diethylamide (LSD)]*	±	++	++

(during intra-uterine pressure recording) was seen after 10 minutes. The tetany continued for one hour. The *intravenous* injection of ergometrine caused an instantaneous response after 15 to 20 seconds with an abrupt rise of the curve; 6.5 - 8 minutes after an intramuscular administration of ergometrine the same effect was seen (Moir & Dale 1932; Adair et al. 1935; Davis et al. 1935; Dudley & Moir 1935). A small dosage of ergometrine produced the fastest action when compared to other ergot alkaloids (Adair et al. 1935). Notwithstanding these properties, no information was found regarding the oral application of ergometrine or methylergometrine to prevent PPH (Prendiville et al. 1988a).

Although oral (methyl)ergometrine has been used for a long time, little pharmacokinetic data are available for both drugs (Kanto et al. 1976; Allonen et al. 1978; Mäntylä et al. 1978). A major reason for this has been the lack of analytical methods with sufficient sensitivity to measure low concentrations of both drugs in the plasma in the nanogram amounts which occur after the usual single therapeutic doses of 0.125-0.2 mg. No new data on the pharmacokinetics after oral administration for these drugs have been published since the late seventies (Mäntylä et al. 1978; Kanto et al. 1981). Chapter 4 describes pharmacokinetic data obtained with High Performance Liquid Chromatography (HPLC)-assay for oral (methyl)ergometrine in men and non-pregnant women.

Pharmacologic action of methylergometrine

Little is known about how (methyl)ergometrine achieves its oxytocic effect. Interaction with nifedipine suggests that the Ca^{++} channel of smooth muscle cells are of importance for this mechanism (Forman 1982). For oxytocin (OT), a receptor mechanism has been described. In contrast to OT, that has its own OT receptors on the uterus which increase during pregnancy, a specific (methyl)ergometrine receptor has never been described. Cibils and Hendricks (1969) studied the interaction between OT and (methyl)ergometrine by measuring the effect on pressure in postpartum uteri. They could not detect a major interference between these two drugs. They observed a relative lack of reaction to OT when the patients were premedicated with (methyl)ergometrine. Intra-amniotic infusion of methylergometrine did not show any uterine respons (Cibils & Hendricks (1969)). Daels (1974) described the existence of two different zones in the myometrium related to the embryologic origin of the

uterus: The innerzone, the *archemyometrium* (= rudimentary corpus uteri - oldest muscle layers) and the outerzone, *para- or neomyometrium* (see Chapter 1.3). Daels showed that in myometrium strips of non-pregnant, pregnant, and postpartum women the different layers had different contractile characteristics and different reactions to adrenaline and oxytocin. Tonic contraction in the inner layer occurred in postpartum myometrial strips after administration of adrenaline, whereas oxytocin affected the spontaneous motility of the postpartum inner layer only marginally. 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. (1975) suggested that methylergometrine affects the inner layer (*archemyometrium*) of the uterus in contrast to OT and prostaglandins (PGs) which are said to affect the outer muscle layer (*neomyometrium*) (Daels 1974; de Koning Gans et al. 1975; Saameli 1976).

Studies in the rabbit with concomitant medication showed antagonistic effects after administration of dihydroergotoxine, piperoxane, and phenoxybenzamin, but not after the administration of hexamethonium or atropine. This inhibitory action of the concomitant drugs was explained as being an α-receptor blockade of the medication (Saameli 1976). Saameli (1976) supports the concept that the oxytocic effect of ergot alkaloids and of (nor)epinephrine is due to stimulation of the same α-adrenoreceptors in the inner myometrial layer.

(Methyl)ergometrine is said to enhance the muscle *tone* of the uterus (van Dongen et al. 1991). De Koning Gans et al. (1975) suggested that the amplitude (A) and frequency (F) of contractions occur in the outer layer (the new uterus) while the (methyl)ergometrine affects the basal tone (BT) of the inner layer (old uterus). This might explain a certain constancy in the relation amplitude and frequency: a decrease of amplitude causes an increase of frequency (Chapter 5). Intensity (I) seems to have a maximum level. This 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.

(Methyl)ergometrine increases the basal tone. If an intensity-maximum exists, the amplitude of contraction has to decrease when basal tone increases. To explain it differently, an increase in basal tone, caused by (methyl)ergometrine, 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 (methyl)ergometrine.

2.4 Adverse Drug Reactions*

Adverse drug reactions (ADR) of ergot alkaloids especially of (methyl)ergometrine are reviewed. Many side effects after administration of ergot alkaloids have been described (Table 2.4.1). Ergot poisoning or ergotism (depression, nausea, slight giddiness, as well as pains in limbs and lumbar region) has mostly been observed within one hour of an intravenous injection of 0.5 mg ergotamine (Adair et al. 1935). Because of its severe vasoconstrictive component, ergotamine is contra-indicated during pregnancy and the active management of the third stage.

Nausea and vomiting occur quite frequently after administration of *oral* ergometrine (Mäntylä et al. 1978; Garcia et al. 1987; van Dongen et al. 1991). Cardiovascular side effects (brady- or tachycardia and hypertension) after both intramuscular and intravenous administrations of ergometrine are known (Browning 1974; Dukes 1991). Its vasoconstrictive effect is even used as a provocation test for coronary artery spasm susceptible patients (Goldberg 1983). One case of postpartum myocardial infarction probably induced by administration of 0.2 mg ergometrine maleate intravenously has been reported (Taylor & Cohen 1985). Bronchoconstriction (Louie et al. 1985), renal artery spasm (Fedotin & Hartman 1970), and segmental stenosis of a cerebral artery (violent headaches, convulsions, and mental confusion) (Henry et al. 1984) have been reported after intravenous administration of (methyl)ergometrine in postpartum women. Simultaneous intravenous administration of methylergometrine and oxytocin has been reported to result in severe postpartum hypertension, cerebral edema, and convulsions (Abouleish 1976). Puerperal psychosis has been described after both oral and intravenous administrations of ergometrine as a possible idiosyncratic reaction (Iff et al. 1989). Some authors claim that methylergometrine has less hypertensive side-effects and less influence on (not proven) decrease of postpartum prolactin levels than ergometrine, but the number of women examined in these studies are too small to draw any such conclusions (Del Pozo et al. 1975; Symes 1984).

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*Modified from De Groot ANJA, van Dongen PWJ, van Roosmalen J, Eskes TKAB. Ergotamin-induced fetal stress: review of side effects of ergot alkaloids during pregnancy - a case report- Eur J Obstet Gynec Reprod Biol 1993b; 51: 73-77.

Table 2 4 1 Adverse drug reactions of ergot alkaloids

Ergometrine		**Methylergometrine**	
• orally	ergotism	• orally	ergotism
	nausea, vomiting	• intravenously/	ergotism
	puerperal psychosis	intramuscularly	hypertension
	asthmatic attack	+ *oxytocin*	cerebral edema
	fetal death		arteriopathy
• intravenously/	ergotism		convulsion
intramuscularly	bradycardia, tachycardia		
	hypertension		
	coronary artery spasm		
	postpartum myocardial infarction		
	renal artery spasm		
	puerperal psychosis		
neonate	hypertonia, convulsion,		
	hyperthermia, respiratory failure		
Other ergot alkaloids			
Ergotamine	ergotism, hypothermia *(adult)*		
	reversible cerebral arteriopathy, claudication		
	placental abruption, fetal distress, fetal death		
Methysergide	damaging of heart valves		

Injections of ergometrine given inadvertently in neonates caused respiratory failure, hypertonia, and hyperthermia (Whitfield & Salfield 1980, Hirasing & Berger 1983) Fetal deaths are described after ingestion of ergometrine tablets and after administration of ergotamine (Treffers & Becker-Bloemkolk 1976, van Aken et al 1982, Au et al 1985), possibly in relation with placental abruption (Cattor & Wilkin 1966) If an ergot alkaloid is given during pregnancy, the administration of a ß-sympaticomimetic drug may prevent fetal stress or fetal death (Treffers & Becker-Bloemkolk 1976, Wong & Paul 1979) Ergot alkaloids should be handled with great care in obstetrics and only be used postpartum (de Groot et al 1993b)

Prophylactic use of ergometrine (injection) in the management of third stage was criticized by Ringrose (1962) In 1993, we also reported numerous side-effects for (methyl)ergometrine (de Groot et al 1993b) Due to its serious and unpredictable side-effects, its place among the oxytocics is controversial in prevention of postpartum blood loss

3 Stability under simulated tropical conditions*

Postpartum haemorrhage (PPH) is still one of the most common causes of maternal death, especially in third world countries (van Roosmalen 1988; Royston & Armstrong 1989; van Dongen et al. 1991). As in these countries emergency referral in case of severe bleeding is difficult to arrange, prevention and management of PPH at all levels of obstetric care is mandatory. For prevention and management of PPH the routine use of oxytocics in the postpartum period is advocated (Prendiville et al. 1988a). Drugs have to be stable to be used in tropical climates and the route of administration should be simple when used by untrained people.

The route of choice is by mouth. Among all oxytocic drugs only the ergot alkaloids are suitable for oral administration. Therefore, oral ergometrine and methylergometrine with favourable effects on both blood loss and maternal morbidity and mortality were regarded as possible treatments for use in tropical countries. Manufacturers usually do not investigate the stability of preparations under tropical conditions. They usually perform their tests in temperate climates. In third world countries, it is often practically and/or economically not possible to protect pharmaceutical preparations from the harmful effects of high temperatures and high relative humidity during transportation, storage and use. Recent stability studies of both ergometrine and methylergometrine injectable solutions show high extents of deterioration upon exposure to elevated temperatures and to light (L) (Walker et al. 1988; Hogerzeil et al. 1991; Hogerzeil et al. 1992). Moreover, large differences in potency and stability between the various brands and formulations seem to be more important than the differences between ergometrine or methylergometrine (Hogerzeil et al. 1994).

The aim of this investigation was to examine the stability of ergometrine and methylergometrine tablets to determine whether it is feasible to replace the parenteral route of oxytocics by orally administered drugs. The stability of the compounds have been assessed by using "shelf life" methodology to demonstrate whether the drugs can be transported and stored without loss of potency.

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*de Groot ANJA, Hekster YA, Vree TB, van Dongen PWJ. Ergometrine and methylergometrine tablets are not stable under simulated tropical conditions. J Clin Pharm Ther 1995b; 20: 109-113.

3.1 Material and methods

Study design

Definitions used in the study are given in Table 3.1.1. In the design of this study the recommendations laid down in "Protocol of the research of the stability of drugs in aqueous solutions" by the Dutch Society of Hospital Pharmacists (Anonymous 1992) have been used. We simulated 7 tropical conditions (Table 3.1.2).

Taking into account the known vulnerability of ergometrine and methylergometrine on exposure to light, all tablets were tested for light-induced degradation (Hartmann et al. 1982).

The following tablets were examined: ergometrine maleate 0.2 mg tablets BP88; batchnumber: 91 I 02/590E and containing 147μg free base and methylergometrine maleate 0.125 mg tablets; batchnumber: 2003; 95μg free base. Tablets were received in closed tins. During the storage tests the tablets were exposed to the intended conditions, in identical transparent tins. Each tin contained four tablets. For each sampling period (weeks 0-52), a different tin was used. One batch from each manufacturer was examined. To achieve acceptable statistical power, 4 tablets were assayed per storage condition per manufacturer. At weeks 0 and 52, 20 tablets per storage condition per manufacturer were investigated to improve the statistical power of the analysis. Tablet weight, integrity and colour were assessed prior to assay of drug content.

Table 3.1.1 Definitions used in the study

• **Stability**	The extent to which a product retains, within specified limits, and throughout its period of storage and use, (i.e. its shelf life) the same properties and characteristics it possessed at the time of its manufacture (USP 1994)
• **Shelf life**	The period of time during storage and use, at which the expected amount of active ingredient remains in the product
• **Batch**	A homogeneously produced number of drugs

Table 3.1.2 Definitions of simulated tropical conditions

Test	Storage condition			Notation
	Light exposure	*Temperature*	*Relative humidity (RH)*	
I	dark (D)	6-10°C	83-85%: ambient	D6/83
II	dark (D)	20°C*	75%**	D20/75
III	dark (D)	30°C*	45%**	D30/45
IV	dark (D)	30°C*	75%**	D30/75
V	dark (D)	40°C*	12-28%: ambient	D40/25
VI	dark (D)	40°C*	75%**	D40/75
VII	light (L)***	20-25°C#	20-35%: ambient	L20/30

* Specified within ± 2°C, ** Specified within ± 5%, *** Fluorescent white light, 450-650 nm, 1000 Lux, # Room temperature

Assay method

High Performance/Pressure Liquid Chromatography (HPLC) was used in preference to a radio-immunoassay. This method can differentiate between the active principle and its degradation products. The Radio Immuno Assay method, an other assay method is unable to make this distiction (Koskinen & Kleimola 1976; Sondack 1978; Tokunaga et al. 1983; de Groot et al. 1993a; de Groot et al. 1994c). In short the HPLC analysis that was used in this study was as follows. The column was 25 cm x 4.6 mm ID packed with Spherisorb 5-ODS (particle size 5 µm; Chrompack, Middelburg, Netherlands) with a guard column (75mm x 2.1mm ID) packed with 10 µm pellicular reversed phase (Chrompack, catalogue no 028653). An injection loop of 100 µl was used. The mobile phase consisted of a mixture of acetonitrile as solvent A and 0.067 M monobasic KH_2PO_4: 0.05% diethylamine H_20 buffer as solvent B; The mixture consisted of 60% of A and 40% of B. All reagents were of analytical grade (Merck,Darmstadt,Germany). The flow rate was 1.2 $ml.min^{-1}$. Detection wavelength was 240 nm. The retention time was 6.8 min, the capacity factor was 3.24; the analysis was carried out at room temperature. The detection limit of ergometrine and methylergometrine in water was 0.55 ng both at a signal to noise ratio of three. The inter-day variation was 1.2% for ergometrine and 2.2% for methylergometrine and the intra-day variation was 1.73% for ergometrine and 5.07% for methylergometrine. The data were analysed using a general linear model and a logistic regression model for ordinal response variables.

3.2 Results

The raw data are published in the World Health Organisation/Drug Action Programme WHO/DAP-research series (de Groot et al. 1994c). At t=0, the initial drug content of 20 tablets of each brand fulfilled the pharmaceutical requirements. The results of test I (least extreme condition) and test VI (most extreme condition) for both ergometrine and methylergometrine tablets are shown in Figure 3.2.1.

Ergometrine

The level of active ingredient in the product declines when stored under all conditions studied. Under refrigerated storage (D6/83), the least extreme condition, ergometrine remained stable for 3 weeks (content was 100.7% of stated amount; 0.148±0.014 mg/tablet) but at 7 weeks only 85.1%; 0.125±0.005 mg/tablet of the stated amount remained. When stored at 40°C and 75%RH in the darkness (D40/75), the most extreme condition, ergometrine was unstable with only 26.5% (0.039±0.008 mg/tablet) of the stated amount left after 3 weeks, and ≤ 1% (0.001±0.001 mg/tablet) after 52 weeks of exposure (Figure 3.2.1).

The influence of humidity was shown in the combination of test IV (D30/75), very humid, and test V (D40/25), hot and dry. At 30°C and 75%RH in the darkness (D30/75), only 23% (0.034±0.002 mg/tablet) of the stated amount remained after 21 weeks. At 40°C and 25%RH in the darkness (D40/25), 44.9% (0.066±0.010 mg/tablet) of the stated amount was left after 52 weeks. In these tests humidity had a greater influence on stability than temperature.

The influence of light was shown in combination of test II (D20/75) and test VII (L20/30). At 3 weeks of exposure the influence of light was stronger than of humidity with only 61.2% (0.090±0.010 mg/tablet) of the stated amount left test VII whereas test II showed still 70.7% (0.104±0.008 mg/tablet) of the stated amount. However, over a period of a year the influence of light was weaker than that of humidity showing only 15.6 % at 52 weeks in test II (D20/75) and still 44.2% in test VII (L20/30).

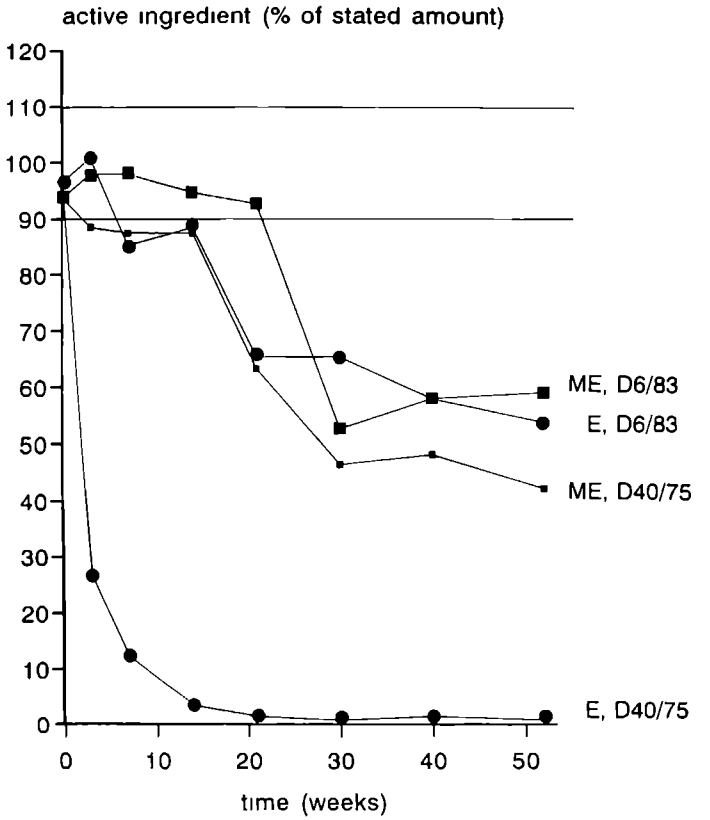

Figure 3 2 1 Stability of oral ergometrine and methylergometrine exposed to least (I) and most (VI) extreme conditions

E Ergometrine
ME Methylergometrine
D6/83 test I 6°C, 83% RH and darkness
D40/75 test VI 40°C, 75% RH and darkness

Methylergometrine

The drug was unstable under all conditions studied. Under refrigerated storage (D6/83), the least extreme condition, methylergometrine was stable for 21 weeks (92.6% of stated amount; 0.088±0.003 mg/tablet) but after 30 weeks it no longer fulfilled the pharmaceutical requirements (52.6%; 0.050±0.002 mg/tablet). At 40°C and 75%RH in the darkness (D40/75), the most extreme condition, the methylergometrine was unstable, with 63.2% (0.060±0.003 mg/tablet) of the stated amount left after 21 weeks, and ≤ 50% (0.040±0.002

mg/tablet) after 52 weeks (Figure 3.2.1).

Hardly any difference between test IV (D30/75) and test V (D40/25) was seen with respectively 49.5% (0.047±0.003 mg/tablet) and 51.6% (0.049±0.002 mg/tablet) of the active ingredient left after 52 weeks of exposure.

Under all conditions, the uncoated ergometrine tablets were far less stable than the coated methylergometrine ones. Instability rises with humidity (D30/75 or D40/75) and temperature (D40/25), for both ergometrine and methylergometrine. In the least extreme condition the coating did not seem to protect the compounds anymore from week 31 onwards (Figure 3.2.1).

During the tests, no differences in weight larger than 0.1 mg were noticed. Discolouration occurred in the tablets especially when stored under humid conditions. Growth of mould was observed on some tablets stored in humid conditions (tests II, IV and VI).

3.3 Discussion

Tablets

Drug stability is dependent on many product-related factors (Barends 1990; van der Vaart et al. 1990), i.e. the active ingredient, the excipients, the dosage form, the manufacturing process and the nature of the packaging. Methylergometrine tablets were included in our investigation because of the claims that methylergometrine shows less hypertensive side-effects and less influence on postpartum prolactin levels than ergometrine (Del Pozo et al. 1975; Symes 1984). When supplied by Unicef methylergometrine tablets are as cheap as ergometrine. The choice of manufacturer was made on ready availability of their products. Although ergometrine and methylergometrine are supposedly being produced on "market demand", in practice they are produced only once a year. Only one batch was available from each manufacturer. As only one brand of ergometrine and methylergometrine are generally distributed comparison between brands as recommended by Hogerzeil et al. (1994) was not possible in this study.

Sampling points in time

Long-term stability studies under "temperate climate" conditions normally last 5 years (Hartmann et al. 1982). The tablets in this study have been subjected to conditions that are more extreme. A shorter period of investigation (accelerated stability study) has been accepted as deterioration of tablet quality will appear sooner. The stability test was performed for a period of one year only as in actual practice in tropical countries tablets should not be stored after opening of the box for longer periods. Loss of potency by water absorption was expected to occur early (Bos 1990). Therefore, the sampling in the beginning of the experiment was done more frequently and eight samplings were done over the first 21 weeks (Anonymous 1992).

Under the least harmful storage conditions (D6/83) ergometrine and methylergometrine were not stable for more than 7 and 21 weeks, respectively. The results are alarming, indicating that careful storage of those products is critical when used in tropical conditions. Refrigerated storage may be necessary. Protecting the tablets from humidity by coating or special packaging may help as humidity seems to be more harmful than temperature. Light is not as damaging on tablets as on ampoules of the drugs (USP 1994).

Methylergometrine is substantially more stable than ergometrine even under test VI (D40/75).

Conclusion and recommendations

Both ergometrine and methylergometrine tablets are not stable under simulated tropical conditions. These tablets are the only oxytocic drugs given by mouth and therefore easy to administer when used by untrained people. However, because of their strong instability under the conditions studied, those preparations are not suitable for use as prophylactic agents of PPH. Moreover, pharmacokinetic data suggest that their absorption is also unreliable (de Groot et al. 1994a; 1994b).

4 Pharmacokinetics and bioavailability*

The most recent publications concerning the pharmacokinetic properties of (methyl)ergometrine and its degradation products date from the late seventies (Mäntylä et al. 1978; Mäntylä & Kanto 1981). These studies showed a favourable bioavailability (F≈60%) and a fast absorption in male volunteers. They did not show any correlation between the plasma level and the clinical effect of methylergometrine in postpartum women. In those studies a radio-immuno-assay (RIA) was used to establish the concentration and the absorption time of (methyl)ergometrine with its metabolites in both serum and urine. Metabolites in both plasma and urine could not be found via radio-immuno assay (RIA) due to the low concentrations. Because high performance liquid chromatography (HPLC) offers greater possibilities, a sensitive and selective HPLC analysis was developed to allow the pharmacokinetics of ergometrine to be followed. Ergometrine is the drug most often distributed in developping countries. Slight changes were made in the HPLC procedure in order to analyze the pharmacokinetics of methylergometrine.

First the drug assay will be described (Chapter 4.1). In Chapter 4.2, the various experiments of ergometrine and methylergometrine in men are described and data for methylergometrine in men and non-pregnant women are compared.

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*Excerpted from the following papers

de Groot ANJA, Vree TB, Hekster YA, van den Biggelaar-Martea M, van Dongen PWJ High performance liquid chromatography of ergometrine and prelimary pharmacokinetics in plasma of men. J Chromatogr Biomed Appl 1993a; 613: 158-161.

de Groot ANJA, Vree TB, Hekster YA, van den Biggelaar-Martea M, van Dongen PWJ, van Roosmalen J. Pharmacokinetics and bioavailability of oral ergometrine in male volunteers. Biopharm Drug Dispos 1994a; 15: 65-73.

de Groot ANJA, Vree TB, Hekster YA, van den Biggelaar-Martea M, van Dongen PWJ, van Roosmalen. Large variation in bioavailability of oral methylergometrine in human male volunteers. Drug Invest 1994b; 8(6): 345-361.

de Groot ANJA, Vree TB, Hekster YA, van den Biggelaar-Martea M, van Dongen PWJ, van Roosmalen J. Identical large variation in bioavailability of oral methylergometrine and ergometrine in male volunteers. J Appl Ther: accepted for publication 1995e.

de Groot ANJA, Vree TB, Hekster YA, van den Biggelaar-Martea M, van Dongen PWJ, van Roosmalen J. Comparison of bioavailability and pharmacokinetics of oral methylergometrine in men and women. Int J Clin Pharm Ther. 1995f; 33: 328-332.

4.1 Drug assay

The prophylactic use of oxytocic drugs such as oxytocin, ergometrine and methylergometrine reduces the risk of postpartum haemorrhage (PPH) as well as the need for further oxytocic therapy in the puerperium (van Dongen et al. 1991). The wide use of injectable ergometrine has become a point of discussion as the ampoule proves to be unstable under tropical conditions (Walker et al. 1988; Hogerzeil et al. 1991; 1992). Therefore, a project, supported by the World Health Organisation (WHO), has been started to assess the place of *oral* ergometrine in the prevention of PPH in third world countries.

Pharmacokinetic data for the pharmacologically similar ergot alkaloids ergometrine and methylergometrine are scarce (Rall & Schleifer 1985; Anonymous 1988a) and those which do exist are found in publications from the late seventies (Mäntyla et al. 1978; Mäntyla & Kanto 1981). In these studies, measurement of the compounds took place according to a Radio Immuno Assay method. The few studies dealing with the determination of ergot alkaloids in plasma employing HPLC either do not include ergometrine (Koskinen & Kleimola 1976; Edlund 1981; Smith & Molinaro 1988) or were developed to analyze the pharmaceutical formulation (Sondack 1978; Tokunaga et al. 1983).

The aim of this investigation was to develop a sensitive and selective HPLC analysis which could be used for a pharmacokinetic analysis of ergometrine.

4.1.1 Experimental

Drugs

Ergometrine maleate 0.2 mg (tablet = 0.147 mg free base) was obtained from Wolfs (Antwerpen, Belgium; batchnumber 91102). Ergometrine maleate 0.15 mg/ml FNA (injectable solution) was obtained from Medisch Spectrum Twente (Enschede, The Netherlands; batchnumber 93125020). The ergometrine batches fulfilled the requirements of a content uniformity test according to standard quality control criteria.

Chemicals

Analytical grade potassium dihydrogenphosphate and diethylamine were obtained from Merck (Darmstadt, Germany). Acetonitrile was obtained from FSA Laboratory supplies (Loughborough, UK).

HPLC analysis

The HPLC system consisted of a Spectra Physics SP 8775 autosampler (Spectra Physics, Eindhoven, The Netherlands), a SP 8800 Ternary HPLC pump (Spectra Physics), a fluorescence spectrophotometer F-1050 Hitachi (Merck, Amsterdam, The Netherlands), and an SP 4290 integrator (Spectra Physics). The column (25 cm x 4,6 mm ID) was packed with Spherisorb 5-0DS (Chrompack, Middelburg, The Netherlands), a guard column (75 mm x 2,1 mm ID) was packed with 10 μm pellicular reversed phase (Chrompack, Cat. no. 028653). An injection loop of 100μl was used. The mobile phase consisted of a mixture of 0.067*M* KH_2PO_4, 0.5 ml diethylamine in water (1:1) as solvent A and acetonitrile as solvent B. The mixture consisted of 65% A and 35% B. All reagents were of analytical grade. The flow rate was 1.2 ml/min.

Fluorescense detection was achieved at 315 nm excitation and 430 nm emission. The retention time was 5.26 min, the capacity factor was 4.54, and the analysis was carried out at room temperature.

Sample preparation

Plasma samples of 300 μl were deproteinated by acetonitrile 1:1 and centrifuged at 11,000g during 4 minutes. Of the clear supernatant, 100 μl was injected onto the column.

Calibration curves

Standard solutions were freshly made before each new set of runs. They were stable during a period of 14 days when kept at 4°C in the refrigerator. Calibration curves were constructed by adding variable quantities of the standard solution to blank plasma. The correlation coefficient was 0.99949 for ergometrine, and the equation $y = 33.32x + 0.408$ in the concentration range of 0.075 ng/ml to 5.0 ng/ml, where x is the concentration and y is peakheight, was used.

Concentration

The concentration of ergometrine was measured using a calibration curve where peak heights of the compound (y) were expressed *versus* spiked concentrations in plasma (x).

Quantitation limit, validation

The quantitation limit of ergometrine in plasma was 50 pg/ml at a signal-to-noise ratio of 3. The intra-day variability and inter-day variability are given in Table 4.1.2.1.

Subject

One male (45 year) volunteered for a pilot pharmacokinetic analysis of the oral and intravenous administration of ergometrine. The volunteer was screened for possible contra-indications (cardio-vascular disease and chronic obstructive lung disease). Bodyweight, height, blood pressure, haemoglobin level as well as liver and renal functions were recorded. During the experiments the blood pressure was monitored.

This study was approved by the Committee Experimental Research Involving Human Subjects (CEOM) of the University Hospital of Nijmegen.

Dosage

A single oral dose of ergometrine maleate 0.200 mg (=0.147 mg base; Wolfs) was given after a standard breakfast consisting of two sandwiches, no cheese, and unrestricted amounts of coffee or tea. For all tests, the time between the intake of breakfast and administration was at least one hour. One month later, 0.075 mg ergometrine maleate (=0.055 mg base; Medisch Spectrum Twente) was injected i.v. during one minute in the same volunteer.

Sampling procedures

Oral administration of ergometrine

Five ml blood samples were collected using an intravenous canula (Venflon ^{R} 1.0 mm 0D) at 0, 10, 20, 30, 60, 90, 180, 270, 360, 450 and 540 minutes after ergometrine administration.

Intravenous administration

In addition to the sampling times as described under oral administration, two extra samples were taken 3 and 5 minutes after the start of the injection.

After centrifugation of the blood samples, plasma samples were stored at - 20°C pending analysis.

4.1.2 Results

The intra- and inter-day variations are given in Table 4.1.2.1. Figure 4.1.2.1 shows the chromatograms of two plasma samples containing ergometrine concentrations of 1.95 ng/ml and 0.70 ng/ml as well as the chromatogram for blank plasma. Ergometrine is shown to be separated from endogenous compounds.

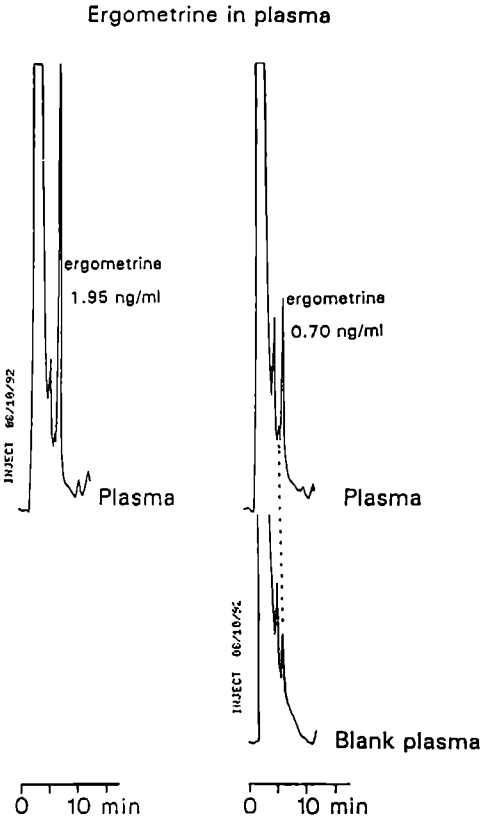

Figure 4.1.2.1 Chromatograms in human plasma samples

Table 4 1 2 1 Inter-day and intra-day coefficient of variation of ergometrine in human plasma

concentration (ng/ml)	Coefficient of variation (%) (n=4) Inter-day	Intra-day
3 76	1 68	2 99
1 89	2 11	2 68
0 43	5 14	1 96
0 10	6 10	3 05

Figure 4.1.2.2 shows the ergometrine plasma concentrations (ng/ml) versus time after oral administration of 0.2 mg ergometrine maleate and after intravenous administration of 0.075 mg ergometrine maleate in one male volunteer.

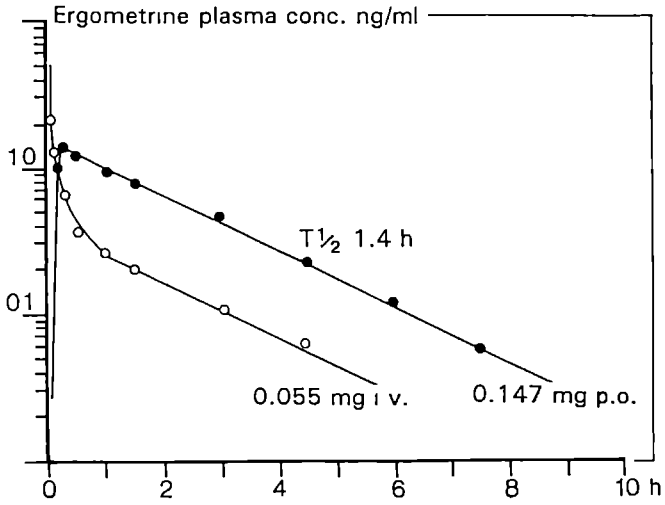

Figure 4 1 2 2 Ergometrine plasma concentration vs time curves of ergometrine after administration of an intravenous dose of 0 055 mg ergometrine base and after oral administration of 0 147 mg ergometrine base to the same male human subject

After oral administration, the compound is rapidly absorbed with a lag time of 5 minutes. A maximum plasma concentration of 1.32 $ng.ml^{-1}$ was reached after 12 minutes. The half-life of ergometrine is 1.4 hours in this volunteer. After the intravenous administration, the half-life was similar compared to the oral administration. The relative bioavailability of the oral administration was calculated to be 1.00. During the experiments no change in bloodpressure was observed.

4.1.3 Discussion

Ergometrine concentrations in plasma could be accurately measured using a HPLC method with fluorescence detection. With this analytical method, proper pharmacokinetics of oral and parenteral ergometrine can be described. The method is comparable to those reported for methylergometrine but avoids the extraction step (Edlund 1981). The limit of quantitation of 50 pg/ml is comparable to that of methylergometrine [20 pg/ml (Smith & Molinaro 1988) and 100 pg/ml (Edlund 1981)] and sufficient to carry out pharmacokinetic studies. The volunteer in this study took also part in the pharmacokinetic study of ergometrine with six male volunteers, the results of which are given in chapter 4.2.

4.2 Pharmacokinetic experiments

Ergometrine and methylergometrine belong to the group of oxytocic drugs which enhance uterine motility. As mentioned earlier (chapter 1.2.3) prophylactic use of such drugs in the third stage of labour reduces the risk of PPH and the need for further oxytocic therapy in the puerperium. The use of oxytocics in the postpartum period is advocated for the prevention and the management of PPH (Prendiville et al. 1988).

Because pharmacokinetic data for ergometrine and methylergometrine were scarce (Rall TW & Schleifer 1985; Anonymous 1988a) and mainly concerned methylergometrine (Mäntylä et al. 1978, Mäntylä & Kanto 1981), male volunteers were first studied to determine the pharmacokinetics for the oral administration of ergometrine. After the pharmacokinetic data of ergometrine in male volunteers showed a large variation in bioavailability (de Groot et al. 1994a), a comparable study was performed for methylergometrine in both men and (non-pregnant) women to investigate and compare the results with the previous data. When unfavourable pharmacokinetic results in men and non-pregnant women were found, no pharmacokinetic study in postpartum women was performed.

Thus we performed three series of experiments:

1. kinetics and bioavailability of oral ergometrine in male volunteers
2. kinetics and bioavailability of oral methylergometrine in male volunteers
3. kinetics and bioavailability of oral methylergometrine in non-pregnant female volunteers.

4.2.1 Methods

Drugs

Pure methylergometrine (reference substance 108) and ergometrine (reference substance 086) were obtained from Sandoz (Basel, Switzerland). Methylergometrine maleate as a 0.125 mg tablet Methergin^{R} (equivalent to 0.095 mg free base) was obtained from Sandoz (Nürnberg, Germany, batch number 3001).

Methylergometrine maleate 0.20 mg/ml (injectable solution; equivalent to 0.152

mg free base) was obtained from Sandoz (Uden, The Netherlands; batch number 475MFD920812). The injectable solution contained 93.3±6.5% of the claimed content (n=20).

Ergometrine maleate as a 0.2 mg tablet (equivalent to 0.147 mg free base) was obtained from Wolfs (Antwerpen, Belgium; batch number 91102). Ergometrine maleate 0.15 mg/ml FNA (injectable solution; equivalent to 0.110 mg free base) was obtained from Medisch Spectrum Twente (Enschede, The Netherlands; batch number 93125020). The injectable solution contained 99.2%±0.15 (n=20) of the claimed content.

The methylergometrine and ergometrine batches fulfilled the requirements of a content uniformity test according to standard quality control criteria.

Subjects

Twelve males and six non-pregnant women volunteered for the pharmacokinetic study. The subjects were screened for possible contra-indications (cardio-vascular disease and chronic obstructive lung disease). Bodyweight, height, blood pressure, haemoglobin level as well as liver and renal functions were recorded. Demographic data of the volunteers did not differ (Table 4.2.2.1a/b). They all had normal liver and renal functions. During the experiments, blood pressure was monitored. This study was approved by the Committee Experimental Research Involving Human Subjects (CEOM) of the Academic Hospital Nijmegen, Sint Radboud, The Netherlands.

Dosage

The oral and intravenous dosages of both drugs were administered according to a randomized cross-over design with an interval of at least 2 weeks between the administrations. Ergometrine and methylergometrine were administered to two different groups, each group contained six male volunteers. Only methylergometrine was administered to the six non-pregnant women.

A single oral dose of ergometrine maleate 0.200 mg was given. For the i.v. administration, 0.075 mg ergometrine maleate was injected. A single oral dose of methylergometrine maleate of 0.125 mg was given and for the i.v. administration 0.200 mg methylergometrine maleate was injected. Each volunteer received the drug in both forms of administration.

For all tests, the time between the intake of breakfast and dosing was at least one hour. The standard breakfast consisted of two sandwiches, no cheese, no butter and unrestricted amounts of coffee or tea.

Sampling procedures

Oral administration: Five ml blood samples were collected through an i.v.-canula (Venflon^R 1.0 mm OD) in tubes containing 0.5 mg Li^+ heparin at 0, 10, 20, 30, 60, 90, 180, 270, 360, 450, and 540 minutes after administration.

Intravenous administration: Intravenous injection took place during one minute in the arm which did not have the i.v. canula. In addition to the sampling times as described under oral administration, two extra samples were taken at 3 and 5 minutes after the start of the injection.

After centrifugation of the blood samples at 11,000 *g* for 4 min, plasma samples from both the oral and intravenous groups were stored at -20°C pending analysis. Care was taken that all of the intravenous dose was administered by cleaning the iv dosage line with 2 ml of 0.9% saline.

Drug assay

Methylergometrine and ergometrine in plasma was measured using an HPLC assay with fluorescence detection (Chapter 4.1).

Pharmacokinetic analysis

The pharmacokinetic parameters after intravenous administration were calculated using a two compartment model. After oral administration, it was not possible to calculate the distinct "distribution phase"; therefore, a one compartment model with lag-time was used for the oral data [MW\Pharm computer program Mediware^R, Groningen, the Netherlands] (Proost & Meyer 1992).

C_{max} is the maximum plasma concentration read from the fitted plasma concentration-time curve (r^2>0.98), and t_{max} the time at which C_{max} occurs. The $t_{1/2\beta}$ values were calculated from ln(2)/ß, where ß is calculated by log-linear regression analysis of the terminal log-linear phase. The $t_{1/2absorption}$ and $t_{1/2\alpha}$ were obtained by line feathering and linear regression analysis. Mean Absorption Time (MAT) was used as a measure of the rate of absorption and calculated as the difference between [MRT_{po}-t_{lag}] and MRT_{iv}. $AUC_{0-\infty}$ is the area under the

plasma concentration-time curve and was calculated using the linear trapezodial rule with extrapolation of t=∞, using Ct/ß with Ct being the last measured concentration. Total body clearance CL=Dose/$AUC_{0-\infty}$.
The bioavailability (F) is AUC_{oral}. $Dose_{iv}$/ AUC_{iv}.$Dose_{oral}$.
V_{ss} is the volume of distribution in steady state (V_{ss}=Dose.$AUMC_{0-\infty}$/$AUC_{0-\infty}^2$).

Analysis of variance was conducted according to standard procedures. The level of significance was defined at p≥0.05. The coefficient of variation (CV) was calculated as SD/mean x 100%.

4.2.2 Results

The mean demographic data of the volunteers are shown in Tables 4.2.2.1a/b. Individual values are presented in Appendix 1: Tables IV.1-IV.4, p 150-153. The only significant difference is the bodyweight for men and women in the methylergometrine study.

Table 4.2.2.2 summarizes the mean pharmacokinetic parameters after intravenous and oral administrations of methylergometrine in six male volunteers. There is no statistically significant difference in intrinsic pharmacokinetic parameters such as $t_{1/2ß}$, CL and V_{ss}.

Table 4.2.2.1a Mean demographic data ± SD for the two groups of male volunteers for **ergometrine** and **methylergometrine** (n=6).

	Ergometrine	Methylergometrine	Significance(p)
age (years)	41.3±7.1	35.7±12.5	0.36
weight (kilograms)	72.3±4.0	74.7±3.7	0.32
height (cm)	179±4.4	181±7.9	0.57
blood pressure			
systolic	122±2.6	119±4.9	0.30
diastolic	80 ± 5.8	78 ± 7.1	0.67

Table 4 2.2.1b Mean demographic data ± SD of six **male** and **female** volunteers for methylergometrine (n=6).

	Male	Female	Significance(p)
age (years)	35.7±12.5	41.2±5 3	0 34
weight(kilograms)	74.7±3.7	60.5±6.0	**0.001**
height (cm)	181±7.9	167±7.4	0.009
blood pressure			
systolic	119±4.9	114±10	0.31
diastolic	78 ± 7.1	71±7.0	0 11

Table 4.2.2.2 Mean pharmacokinetic parameters ± SD of **intravenous** (0.152 mg base) methylergometrine and **oral** (0.095 mg base) in male volunteers (n=6).

	Intravenous	Oral	Significance (p)
Dose (mg)	0.152	0.095	
F (%)	100	84.9±37.2	
t_{lag} (h)		0.33±0 09	
t_{max} (h)		0 68±0.22	
C_{max} (μg.L^{-1})		0.77±0.34	
t_{abs}* (h)		0.08±0.08	
$t_{1/2\alpha}$ (h)	0.19±0.27	-.-	
$t_{1/2\beta}$ (h)	1.85±0.28	2.08±0.43	0.31
MRT (h)	2.25±0.44	3.45±0.56	**0.0014**
MAT** (h)		0 87±0.72	
$AUC_{0-\infty}$*** (μg.h.L^{-1})	4.82±1.82	2.17±0.80	0.17
CL (L.h^{-1})	32 2±11.80	31.1±10.3	0 50
V_{ss} (L)	71 5±25.9	94.4±38.9	0.11

- - not detected, * model independent, ** one compartment model, *** calculated data, uncorrected for the dose

Bioavailability (F)	AUC_{oral} $Dose_{iv}/AUC_{iv}$ $Dose_{oral}$	see also p 84-86
t_{lag} (h)	lag time	
t_{max} (h)	the time at which C_{max} occurs	
C_{max} (μg L^{-1})	the maximum plasma concentration read from the plasma-concentration-time curve	
t_{abs} (h)	the half-life of absorption, calculated by least-square linear regression analysis	
$t_{1/2\alpha}$ (h)	the half-life of distribution, calculated by least-square linear regression analysis	
$t_{1/2\beta}$ (h)	the half-life of elimination, calculated by least-square linear regression analysis	
MRT_{po} (h)	the mean residence time AUMC/AUC after oral administration	
MAT (h)	the mean absorption time [MRTpo-t_{lag}] and MRT_{iv}	
$AUC_{0-\infty}$ (μg h L^{-1})	the area under the plasma-concentration-time curve extrapolated to infinite time	
CL (L h^{-1})	total body clearance = $Dose/AUC_{0-\infty}$	
V_{ss} (L)	the volume of distribution in steady state (V_{ss}= Dose $AUMC_{0-\infty}/AUC_{0-\infty}^2$)	

Figure 4.2.2.1 shows the ergometrine plasma concentrations (ng/ml) versus time curves after oral administration and after intravenous administration of ergometrine maleate in one representative male subject. After oral administration, the compound is rapidly absorbed after a lag-time of less than 0.5 minute. A maximum plasma concentration of 0.61 ng.ml^{-1} was reached after 85 minutes. The half-life of oral ergometrine is 2.0 hours in this volunteer. After the intravenous administration, the half-life was 1.6 hours. In this subject the relative bioavailability (F%) of the oral administration was calculated to be 103.8 (=103.8%).

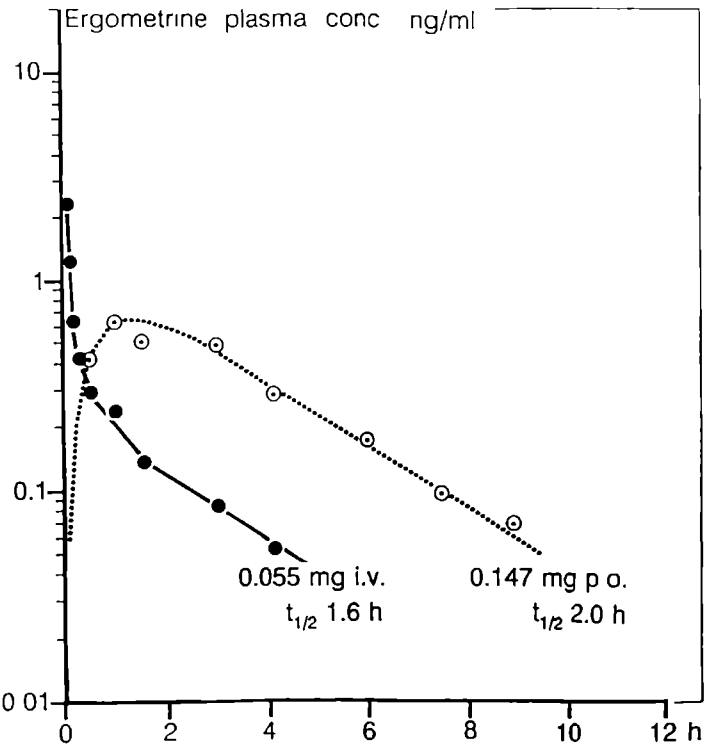

Figure 4 2 2 1 Ergometrine plasma concentrations (ng/ml) versus time curves after oral administration of 0 200 mg ergometrine maleate (=0 147 mg free base) and after intravenous administration of 0 075 mg ergometrine maleate (=0 055 mg free base) in one male subject

Figure 4.2.2.2 shows the methylergometrine plasma concentrations (ng/ml) versus time curves after oral administration and after intravenous administration of methylergometrine maleate in one representative male subject. After oral administration, the compound is rapidly absorbed after a lag-time of 10 minutes. A maximum plasma concentration of 0.67 $ng.ml^{-1}$ was reached after 24 minutes. After the intravenous administration, the half-life of methylergometrine is 2.31 hours. The half-life was similar to that of the oral administration, 2.7 (h). In this subject the relative bioavailability (F%) of the oral administration was calculated to be 0.80 (=80%).

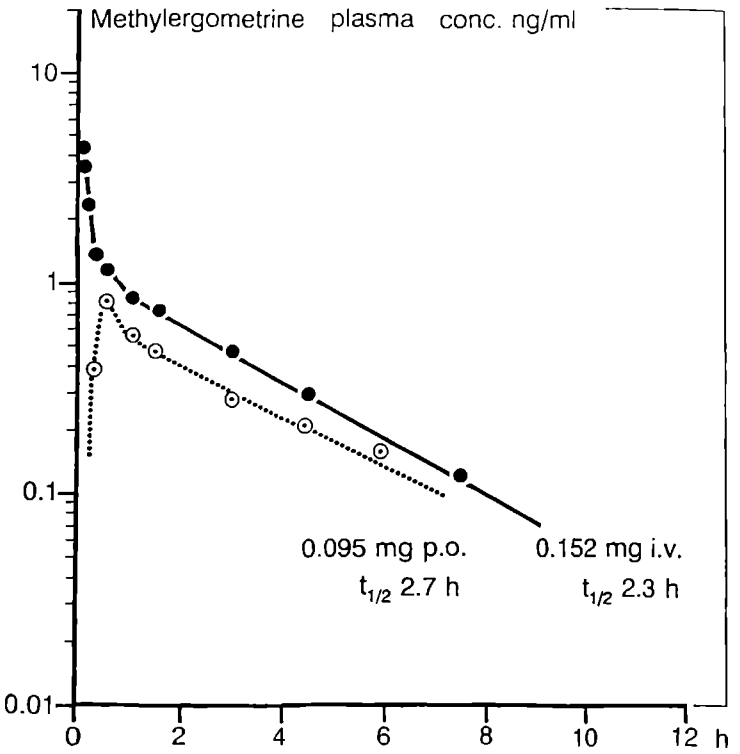

Figure 4.2.2.2 Methylergometrine plasma concentrations (ng/ml) versus time curves after oral administration of 0.125 mg methylergometrine maleate (=0.095 mg free base) and after intravenous administration of 0.200 mg methylergometrine maleate (=0.152 mg free base) in one representative male subject.

Figure 4.2.2.3 shows the methylergometrine plasma concentrations (ng/ml) versus time curves after oral administration and after intravenous administration of methylergometrine maleate in one representative female volunteer. In that female volunteer, a maximum plasma concentration of 1.28 $ng.ml^{-1}$ was reached after 38 minutes with a lag-time of 7 minutes. The half-life of oral methylergometrine was 1.5 hours. After the intravenous administration the half-life was 2.1 h. In this subject, the relative bioavailability (F%) of the oral administration was calculated to be 0.73 (73%).

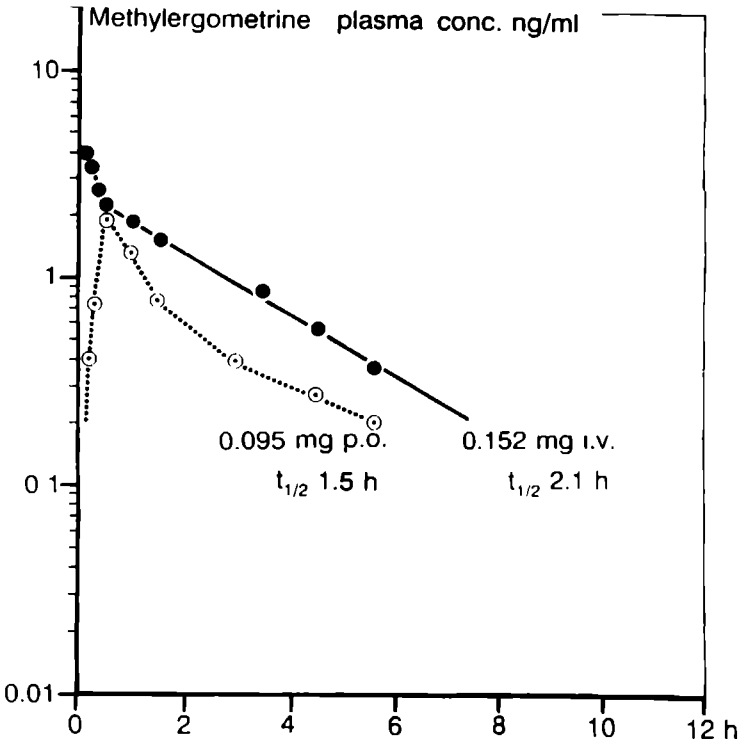

Figure 4 2 2.3 Methylergometrine plasma concentrations (ng/ml) versus time curves after oral administration of 0.125 mg methylergometrine maleate (=0.095 mg free base) and after intravenous administration of 0.200 mg methylergometrine maleate (=0 152 mg free base) in one representative female volunteer.

Table 4.2.2.3a summarizes the pharmacokinetic parameters in men for 0.055 mg ergometrine (base) and 0.152 mg methylergometrine (base). After intravenous administration, the pharmacokinetic profile can be described with a two-compartment model. As can been seen, there are no significant differences in these values.

Table 4.2.2.3a Mean pharmacokinetic parameters ± SD of intravenous administration for the two groups of male volunteers for **ergometrine** (0.055mg base) and **methylergometrine** (0.152mg base) (n=6).

	Ergometrine	Methylergometrine	Significance (p)
Dose (mg)	0.055	0.152	
$t_{1/2\alpha}$ (h)	0 16±0.20	0.19±0.27	≥0.8
$t_{1/2\beta}$ (h)	2.57±1.05	1.85±0.28	0.80
MRT (h)	2.90±1.38	2.25±0.40	0.30
CL ($L.h^{-1}$)	32.6±12.0	32.2±11.8	≥0.8
V_{ss} (L)	82.0±14.5	71.5±25.9	0.40
$V_{ss}.kg^{-1}$ ($L.kg^{-1}$)	-.-	0.96±0.36	

Abbreviations under Table 4 2 2.2 p 80

Table 4.2.2.3b Mean pharmacokinetic parameters ± SD of intravenous methylergometrine (0.152mg base) of six **male** and **female** volunteers (n=6).

	Male	Female	Significance(p)
Dose (mg)	0.152	0.152	
$t_{1/2\alpha}$ (h)	0.19±0.27	0.10±0.04	0.46
$t_{1/2\beta}$ (h)	1.85±0.28	1.94±0.34	0.64
MRT (h)	2.25±0.40	2.31±0.31	>0.8
CL ($L.h^{-1}$)	32.2±11.8	22.2±3.10	0.073
V_{ss} (L)	71.5±25.9	50.8±8.23	0.091
$V_{ss}.kg^{-1}$ ($L.kg^{-1}$)	0.96±0.36	0.84±0.12	0.43

Abbreviations under Table 4 2 2 2 p80

In Table 4.2.2.3b the same pharmacokinetic parameters for 0.152 mg methylergometrine (base) in the six female and six males are given. Again the pharmacokinetic profile following intravenous administration can be described with a two-compartment model. As can been seen, there is no significant difference except for trends in CL and V_{ss}.

Table 4.2.2.4a summarizes the pharmacokinetic parameters in men for 0.095 mg oral methylergometrine (base) and 0.147 mg ergometrine (base). After oral administration, the pharmacokinetic profile can be described with a one compartment model. The biovailability (F%) is subject dependent with the assumption that the total body clearance is similar after intravenous and oral administration. The lag-time 0.11±0.10 h for ergometrine, was significantly shorter than 0.33 ±0.09 h for methylergometrine

Table 4 2 2 4a Mean pharmacokinetic parameters ± SD of oral administration for the two groups of male volunteers for **ergometrine** (0.147mg base) and **methylergometrine** (0 095 mg base) (n=6)

	Ergometrine	Methylergometrine	Significance(p)
Dose (mg)	0 147	0 095	
F (%)	80 7±34 5	84 9±37 2	>0 8
t_{lag} (h)	0 11±0 10	0 33±0 09	**0.003**
t_{max} (h)	0 69±0 59	0 68±0 22	>0 8
C_{max} (µg L ^{1})	1 07±0 29	0 77±0 34	0 13
$t_{1\ 2abs}$* (h)	0 20±0 22	0 08±0 08	0 25
$t_{1/2\alpha}$ (h)	- -	- -	- -
$t_{1\ 2\beta}$ (h)	1 91±0 15	2 08±0 43	0 39
MRT_{po} (h)	3 08±0 53	3 45±0 56	0 27
MAT** (h)	1 26±0 90	0 87±0 72	0 43
$AUC_{0\ \infty}$*** (µg h L ^{1})	3 00±0 89	2 17±0 80	-
CL (L h ^{1})	36 5±12.1	31 1±10 3	0 41
V_{ss} (L)	98 9±36 6	94 4±38 9	>0 8
V_{ss} kg ^{1} (L kg ^{1})		1 26±0 50	-

Abbreviations under Table 4 2 2 2 p 80

In Table 4.2.2.4b the same pharmacokinetic parameters for 0.095 mg oral methylergometrine (base) in the six female and six males are given. Again the pharmacokinetic profile following oral administration can be described with a one compartment model. The elimination half-life ($t_{1/2\beta}$) was significantly longer in men than in women (p=0.0123). The lag-time for methylergometrine was significantly longer in men 0 33±0.09 h than in women 0.09±0.07 h (p=0.0004). The total body clearance was with 31.1±10.3 L.h^{-1} and 23.6±4.01 L.h^{-1} similiar for men and women, respectively. The volume of distribution was significantly larger in men than in women, 94.4±38.9 L vs 47 0±6.05 L (p=0.01).

Side-effects

After intravenous administration of 0.2 mg methylergometrine maleate, two men experienced a "weird" sensation, and another nausea Three women became dizzy after the methylergometrine injection, after oral dosing none of them experienced side-effects. Only one volunteer experienced nausea after administration of oral 0.2 mg ergometrine maleate.

Table 4 2 2 4b Mean pharmacokinetic parameters ± SD of oral methylergometrine (0 095 mg base) of six **male** and **female** volunteers (n=6)

	Male	Female	Significance(p)
Dose (mg)	0 095	0 095	
F (%)	84 9±37 2	96 4±27 5	0 56
t_{lag} (h)	0 33±0 09	0 09±0 07	**0.0004**
t_{max} (h)	0 68±0 22	0 97±0 74	0 39
C_{max} (µg l^{-1})	0 77±0 34	1 21±0 40	0 064
$t_{1/2abs}$* (h)	0 08±0 08	0 50±0 55	0 10
$t_{1\ 2\alpha}$ (h)	- -	- -	- -
$t_{1/2\beta}$ (h)	2 08±0 43	1 42±0 31	**0.0123**
MRT_{po} (h)	3 45±0 56	2 87±0 56	0 10
MAT** (h)	0 87±0 72	0 57±0 34	0 38
$AUC_{0\ \infty}$*** (µg h L^{-1})	2 17±0 80	3 49±0 70	-
CL (L h^{-1})	31 1±10 3	23 6±4 01	0 13
V_{ss} (L)	94 4±38 9	47 0±6 05	**0.01**
V_{ss} kg^{-1} (I kg^{-1})	1 26±0 50	0 78±0 05	0 039

Abbreviations under Table 4 2 2 2 p 80

4.2.3 Discussion

Oral methylergometrine has been proposed to be used in postpartum women. The aim of this study was to examine whether oral methylergometrine could be a possible alternative to injectable oxytocics used in the third stage of labour. Unexpectedly large variations in bioavailability and pharmacokinetics of oral ergometrine in male volunteers were found (de Groot et al. 1994a). The vast variability of pharmacokinetic parameters reported for ergometrine (de Groot et al. 1994a) was not reported in literature for methylergometrine (Rall & Schleifer 1985; Anonymous 1988a). These studies reported that methylergometrine had a fast gastro-intestinal absorption, and that about 60% of the orally administered dose reaches the systemic circulation (Mäntylä et al. 1978). The information was based on only two subjects.

However, this present study has shown an identically large variation in bioavailability of methylergometrine in men as for ergometrine. In men, the overall bioavailability was 80.7±34.5 % and 84.9±37.2% for ergometrine and methylergometrine, respectively. The variation was ≈40% CV. An identical variation in bioavailability was seen after oral administration of methylergometrine in women. After intravenous administration, the pharmacokinetic parameters of methylergometrine did not show any difference between men and women except for the V_{ss}, which was larger in men (p=0.091). This effect was more pronounced after oral administration of the drug (p=0.01). The oral administration showed more differences between the pharmacokinetic parameters in men and women. Men showed a longer lag-time (p=0.0004), a larger volume of distribution (p=0.001), and a longer $t_{1/2\beta}$ (p = 0.0123). The mean body weight of the men was significantly larger than that of the women (p=0.0010). Corrected for the body weight, the Vss did not differ between men and women after an intravenous administration of 0.2 mg methylergometrine maleate: 0.84±0.12 $L.kg^{-1}$ for women and 0.96±0.36 $L.kg^{-1}$ for men (p=0.4).However, after *oral* administration of 0.125 mg methylergometrine maleate, the $Vss.kg^{-1}$ remained larger in men 1.26±0.50 $L.kg^{-1}$ than in women 0.77±0.05 $L.kg^{-1}$ (p=0.0393).

After oral administration of the drug, absorption is subject dependent. The half-life of absorption ($t_{1/2abs}$) is the result of absorption and distribution

processes. Because it was not possible to calculate the "distribution phase" after oral administration, the one-compartment model was used for the data. Calculated by a one-compartment model $t_{1/2abs}$ data are underestimated as this model neglects the distinct distribution phase. Therefore we also calculated the mean absorption time (MAT). MAT is an alternative method to measure the rate of absorption and is model independent. MAT can be calculated from [MRT_{po} - t_{lag}] -MRT_{iv}. The MAT neither differed significantly in men between methylergometrine and ergometrine (p=0.43) nor between men and women (p=0.38) for methylergometrine. The intrinsic pharmacokinetic parameters such as $t_{1/2\beta}$, CL and V_{ss} in men and women depend on the drug and not on the route of administration (Table 4.2.2.4b).

In short, no real differences in pharmacokinetics were found in men between ergometrine and methylergometrine nor were differences between men and women for methylergometrine shown in this study. All these experiments showed large variations in bioavailability and pharmacokinetics.

As instability of (methyl)ergometrine tablets could influence the pharmacokinetic results, the drugs used in the experiments were tested for stability. The batches from which the tablets were taken fulfilled the content uniformity test's requirements. Therefore, instability of the used tablets was ruled out as a possible explanation for the large interindividual variations of bioavailability and lag time, after oral administration. The intravenous drug was stable and care had been taken that all of the dose was administered by cleaning the syringe with 2 ml of 0.9 % saline.

However, the purpose of administration of oral (methyl)ergometrine is to reduce postpartum blood loss. Therefore, a randomized trial has been set up to show whether a clinical effect despite possible varying pharmacokinetics could be demonstrated.

5 Pharmacodynamics*

Uterine activity can be stimulated during menorrhagia or the postpartum period. Ergot alkaloids were one of the earliest stimulants in obstetrics, applied as treatment or prevention of postpartum haemorrhage first noticed by Caspar Schwenkfeldt in 1600 (Barger 1931). In contrast to oxytocin and prostaglandins, ergot alkaloids can be given orally which has the advantage of easy drug administration. Pharmacokinetic and pharmacodynamic data on oral ergot alkaloids are, however, sparse.

Postpartum haemorrhage is responsible for 150,000 deaths worldwide a year (Kwast 1991b). About ninety-eight percent of which occur in developing countries (Royston & Armstrong 1989). In these countries active management of the third stage of labour with oxytocics is particularly advocated (WHO 1990). Intramuscular oxytocin, the standard care in the third stage, is not available to all women. Although not recommended by the manufacturer, oral use of methylergometrine maleate may be considered as an easy alternative. Before starting worldwide distribution of these tablets extensive study on the stability, pharmacokinetic and pharmacodynamic parameters and clinical effect had to be performed.

This study assessed simultaneously pharmacodynamic and pharmacokinetic parameters of oral and intravenous methylergometrine maleate on uterine muscle in six non-pregnant women at the second day of the menstrual cycle (CD 2) because at CD 2 the menstruating uterus resembles the uterus in the postpartum period (Hendricks 1966).

5.1 Material and methods

Subjects

Six non-pregnant women with regular menstrual cycles volunteered for the

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*Based upon the paper: de Groot ANJA, van Dongen PWJ, Vree TB, Eskes TKAB. Oral administration of methylergometrine shows a late and unpredictable effect on the non-pregnant human menstruating uterus. Eur J Obstet Gynecol Reprod Biol 1995d; 2: 101-107.

pharmacokinetic and pharmacodynamic studies with methylergometrine maleate. They were screened for possible contra-indications such as cardio-vascular disease, chronic obstructive lung disease, fibroids or uterine surgery, and should have had a tubal ligation to prevent any negative interaction with fertility.

This study was approved by the Committee Experimental Research Involving Human Subjects (CEOM) of the University Hospital Sint Radboud, Nijmegen, the Netherlands.

Intra-uterine pressure (IUP) recordings

Intra-uterine pressure was recorded using a fluid-filled sponge-tipped catheter (Hendricks 1966; Bengtsson 1968).

The portio vaginalis was cleansed and disinfected with iodine. The open-tip sponged catheter was inserted over a guiding tube. The uterus was manipulated as less as possible in order not to cause any interference with the uterine contractility pattern. A gauze (10x10cm) was left in the vagina while the catheter was fixed on the upper leg to prevent expulsion. The catheter was connected to a pressure-transducer, which was connected to a computer. The woman was in supine position during the registration. The pressure-transducer was fixed on the mattress being the level of the surface supporting the supine volunteer. Zero pressure was set at atmospheric pressure at this "mattress"-level (Faber 1992). The location of the catheter was controlled by asking the volunteer to cough. Proper intra-uterine position showed than a pressure elevation (about 10 mmHg).

Because presence of any foreign body in utero causes an increase of basal pressure level for at least 20 minutes (Braaksma 1970), we waited thirty minutes to allow the "cyclic-specific" pattern to develop and then started the study. After recording uterine activity at least 60 minutes after the insertion of the sponge-tipped catheter, methylergometrine maleate was administered either intravenously or orally. The registration ended when the catheter was expelled. If the catheter remained its position, it was removed after 5 h.
A transurethral catheter was inserted to provide continuous bladder drainage because filling of the bladder was reported to effect IUP (Braaksma 1970).

Digitalization of the signal (IUP)

The intra-uterine pressure signal was filtered by 0.65 Hz. Total noise with

shortened impulse was measured over 15 min (mean±SD = 0.442±0.084), which did not disturb the general activity pattern.
To obtain an accurate signal, the range of the mercury scale has been set on 0-150 mmHg.

Measurements were made using the DTX/plus pressure-transducer (Viggo-spectramed, Oxnard, California, USA) and a special developed amplifier before the signal was fed to a personal computer (DASH-8, Metrabyte). Special care has been taken for patient safety by a safety-chart. The software has been developed with Borland C^{++} (Scotts Valley, California, USA). Events were marked by special keys. Recordings were stored in files which were Microsoft Excel compatible. The resolution of the whole system was about 0.5 mmHg. The system was calibrated electronically and mechanically (mmHg).

Pharmacodynamics

Mechanical uterine activity was measured by IUP-recordings. Contractions were expressed in IUP-cycles. An IUP-cycle was defined as a transitory rise above the basal tone. To describe uterine activity, IUP-cycle specific parameters were distinguished: frequency (F), basal tone (BT), intensity (I) and amplitude (A=I-BT). The number of IUP-cycles in a 5 minutes' period were recorded and the mean value of F, BT and A of the IUP-cycles in each 5 minutes' period was calculated.

The mean values of these parameters (F, BT and A) during the thirty minutes' registration of the "cyclic-specific" pattern were regarded as base-line values and set at 100%. For each parameter the relative increase in a 5 minutes' period was expressed as percentage of base-line value and plotted versus time.

For each IUP-recording, the area under the curve (AUC) was calculated in time-intervals of 30 minutes and from the time of drug administration till 90 minutes after administration.

IUP-recordings

Registration took place at the 2^{nd} day of the cycle (CD 2) of two subsequent menstrual cycles to rule out a possible refractory period, i.e. uterine insensitivity to methylergometrine maleate. In addition four women were also examined when 0.2 mg methylergometrine maleate was injected on the third day of the menstruation of the second cycle (CD 3), i.e. 24 h after the oral test.

Drugs

Pure methylergometrine (reference substance 108) was obtained from Sandoz Pharma AG (Basel, Switzerland). Methylergometrine maleate (0.125 mg tablet Methergin^{R}; equivalent to 0.095 mg free base) was obtained from Sandoz Germany, Nürnberg; batch number 3001.

Methylergometrine maleate (0.20 mg/ml injectable solution; equivalent to 0.152 mg free base) was obtained from Sandoz, Uden, The Netherlands; batch number 475 MFD 920812.

These methylergometrine maleate batches fulfilled the requirements of standard quality control criteria.

Dosage

- For the assessment of the biovailability of methylergometrine maleate a cross-over design was used for the intravenous and oral administrations of methylergometrine maleate. An intravenous dose of 0.2 mg methylergometrine maleate was injected at CD 2 after a standard breakfast containing two sandwiches, no cheese and unrestricted amounts of coffee or tea by all subjects. The drug was administered at least one hour after insertion of the IUP-catheter. Care was taken that all of the intravenous dose was administered by cleaning the intravenous dosage-line with 2 ml 0.9% saline.

An oral dose of 0.5 mg methylergometrine maleate was given after a standard breakfast on the second day of the next menstrual cycle.

- An additional intravenous administration was administered in four women on CD 3, 24h after oral administration at CD 2.

Sampling

Oral administration

Blood samples of 5 ml were collected through an intravenous (i.v.) internal catheter (Venflon ^{R} 1.0 mm OD) in tubes containing 0.5 mg Li heparin at times: 0, 10, 20, 30, 60, 90, 180, 240 minutes.

Intravenous administration

Intravenous administration of methylergometrine maleate took place during one minute in the opposite arm where the Venflon was located. In addition to the sampling times as described under oral administration, two extra samples were taken at 3 and 5 minutes after the start of the injection.

After centrifugation of the blood samples at 11,000 g for 5 min, plasma samples from both the oral and intravenous groups were stored at - 20°C pending analysis.

Drug analysis

Drug analysis was performed by High Pressure Liquid Chromatography (HPLC) according to de Groot et al. (de Groot et al. 1994b).

Pharmacokinetic analysis

The pharmacokinetic parameters were calculated from a two-compartment model after intravenous administration and from a one-compartment model with a lag-time fitted to oral data [MW/Pharm computer program Mediware^R, Groningen, the Netherlands] (Proost & Meijer 1992). C_{max} is the maximum plasma concentration read from the fitted plasma concentration-time curve (r^2>0.98), and t_{max} the time at which C_{max} occurs. The $t_{1/2\beta}$ values were calculated from ln(2)/ß, where ß is calculated by log-linear regression analysis of the terminal log-linear phase. The $t_{1/2absorption}$ and $t_{1/2\alpha}$ were obtained by line feathering and linear regression analysis.

Mean Absorption Time (MAT) was used as a measure of the rate of absorption and calculated as the difference between [MRT_{po}-t_{lag}] and MRT_{iv}.

$AUC_{0-\infty}$ is the area under the plasma concentration-time curve and was calculated using the linear trapezodial rule with extrapolation of t=∞, using Ct/ß with Ct being the last measured concentration. The bioavailability (F) is AUC_{oral}. $Dose_{iv}$/ AUC_{iv}.$Dose_{oral}$. Total body clearance CL = F.Dose/$AUC_{0-\infty}$. V_{ss} is the volume of distribution in steady state (V_{ss} = F.Dose.$AUMC_{0-\infty}$/$AUC_{0-\infty}^2$). Analyses of variance were conducted according to standard procedures. The level of significance was defined at p = 0.05.

5.2 Results

Subjects

Six women entered the study. Their mean age was 38±5 year, mean weight 59±5 kg and a mean length of 167±6 cm (mean±SD). The blood pressure ranged between normal values; mean systolic pressure 113±11 mmHg, mean diastolic pressure 73±8 mmHg. They all had an normal sized uterus in a position of anteversion-anteflexion.

Pharmacokinetic results

Table 5.2.1 summarizes the mean pharmacokinetic parameters of 0.2 mg methylergometrine maleate after intravenous administration and of 0.5 mg after oral administration in the six women at CD 2. After intravenous administration the distribution half-life ($t_{1/2\alpha}$) was 0.09±0.04 h. The elimination half-life ($t_{1/2\beta}$) was 2.0±0.3 h. The total body clearance (CL) amounted to 22.0±2.7 $L.h^{-1}$ and the steady state volume of distribution (V_{ss}) was 50.5±5.8 $L.h^{-1}$. After oral administration of methylergometrine maleate the lag time was 0.30±0.08 h, the absorption half-life ($t_{1/2abs}$) was 0.14±0.12 h, the mean absorption time (MAT) was 0.40±0.35 h and the elimination half-life ($t_{1/2\beta}$) was 1.59±0.32 h. Total body clearance was 30.0±8.8 $L.h^{-1}$ and the volume of distribution was 68.6±24 L. The biovailability (F) was subject dependent and ranged between 47.7 and 94.6%, with the assumption that the total body clearance is similar after intravenous and oral administration. Large interindividual differences in C_{max} (53%CV), t_{max} (56%CV) and $t_{1/2abs}$ (85%CV) after oral administration were recorded. Two volunteers showed prolonged absorption and were left out in the calculation of the means.

Table 5.2.2 summarizes the pharmacokinetic parameters after additional intravenous administration of 0.2 mg methylergometrine maleate in four women when it was injected on CD 3 of the second cycle, i.e. 24 h after the oral administration. There is no difference in pharmacokinetic parameters after the intravenous dosage at CD 2 of the first menstrual cycle and at CD 3 of the second cycle ($p>0.05$). The individual pharmacokinetic parameters of methylergometrine maleate following intravenous and oral administrations are shown in appendix 2 Table V.1, p 154.

Table 5.2.1 Pharmacokinetic parameters (mean ± SD) of methylergometrine maleate after intravenous 0.2 mg (0.152 mg base) and oral 0.5 mg (0.380 mg base) administration in six female volunteers.

	Intravenous	Oral	Significance (p)
Dose (mg)	0.152	0.380	
F (%)		74.2±18.5	
t_{lag} (h)		0.30±0.08	
t_{max} (h)		0.75±0.40	
C_{max} ($\mu g.L^{-1}$)		3.88±2.19	
$t_{1/2abs}$ (h)		0 14±0.12	
$t_{1/2\alpha}$* (h)	0.09±0.04	-.-	
$t_{1/2\beta}$ (h)	2.0 ±0.3	1.6 ±0.3	0.0855
MRT (h)	2.3 ±0.4	2.8 ±0.4	0.0855
MAT** (h)		0.40±0.35	-
$AUC_{0-\infty}$ ($\mu g.h.L^{-1}$)	6.2 ±0.57	9.6 ±4.8	
CL ($L.h^{-1}$)	22.0±2.7	30.0±8.8	0.0607
V_{ss} (L)	50.5±5.8	68.6±24.0	0.1048

Bioavailability (F)	$AUC_{oral}.Dose_{iv}/AUC_{iv}$ $Dose_{oral}$
t_{lag} (h)	lag time
t_{max} (h)	the time at which C_{max} occurs
C_{max} ($\mu g\ L^{-1}$)	the maximum plasma concentration read from the plasma-concentration-time curve
$t_{1/2abs}$ (h)	the half-life of absorption, calculated by least-square linear regression analysis
$t_{1/2\alpha}$ (h)	the half-life of distribution, calculated by least-square linear regression analysis
$t_{1/2\beta}$ (h)	the half-life of elimination, calculated by least-square linear regression analysis
MRT_{iv} (h)	the mean residence time AUMC/AUC after intravenous administration
MAT (h)	the mean absorption time [MRTpo-t_{lag}] and MRT_{iv}
$AUC_{0\infty}$ ($\mu g\ h\ L^{-1}$)	the area under the plasma-concentration-time curve extrapolated to infinite time
CL ($L\ h^{-1}$)	total body clearance = Dose/$AUC_{0\infty}$
V_{ss} (L)	the volume of distribution in steady state (V_{ss} = Dose $AUMC_{0\infty}/AUC_{0\infty}^2$)

* one-compartment, ** model independent; -.- not detected

Table 5.2.2 Pharmacokinetic parameters (mean±SD) in four females

A Intravenous methylergometrine maleate (ME) (0.2 mg) **without** preceding oral ME

B Intravenous ME (0.2 mg) **with** preceding oral ME (0.5 mg).

	A	B	Significance (p)
$t_{1/2\alpha}$ (h)	0.09±0.04	0.05±0.02	0.14
$t_{1/2\beta}$ (h)	2.0 ±0.3	1.9 ±0.5	0 78
MRT_{iv} (h)	2.3 ±0.4	2.2 ±0.6	0.65
$AUC_{0\infty}$ ($\mu g.h.L^{-1}$)	6.2 ±0.6	7.0 ±3.1	0.55
CL ($L.h^{-1}$)	22.0±2.7	24 0±9.3	0.63
V_{ss} (L)	50.5±5 8	49.8±15.9	>0 8

Abbreviations see Table 5 2 1

Pharmacodynamic results, effect of methylergometrine maleate on IUP

When 0.2 mg methylergometrine maleate was injected intravenously on CD 2 of the first menstrual cycle, the frequency of uterine contractions and basal tone increased in all six women while the amplitude of the uterine contractions decreased. This effect lasted at least 90 minutes with a maximum effect at 30 minutes. The effect of 0.5 mg oral methylergometrine maleate on uterine activity on CD 2 of the second menstrual cycle in the same woman was much less marked than after the intravenous administration.

Figure 5.2.1 and 5.2.2 show an uterus well responding to both routes of administration and a uterus responding to intravenous but hardly to oral administration respectively. The best (volunteer 1) and worst (volunteer 2) responding registrations are shown.

Figure 5.2.1 shows the effect of methylergometrine maleate on IUP in volunteer 1. At the top of the figure the IUP-recordings after intravenous (*left panel*) and oral (*right panel*) administrations are given. At the bottom the mean values of F, BT and A of the IUP-cycles over 5 minutes' periods are shown.

The *left panel* shows the fast increase in frequency, basal tone and decrease in amplitude of uterine contractions after intravenous administration of 0.2 mg methylergometrine maleate. Within three minutes after the injection, the frequency of contractions increased with 350% to a maximum of 650% as percentage of the baseline frequency value. After 35 minutes the increase of frequency was reduced to 200% of the baseline value. The basal tone showed a fairly identical pattern with a maximum increase of 700% within 10 minutes after drug administration. Basal tone remained increased till 550% of its baseline value till 70 minutes after drug administration. The amplitude decreased to 30% of its baseline value within 10 minutes and remained reduced during further recording.

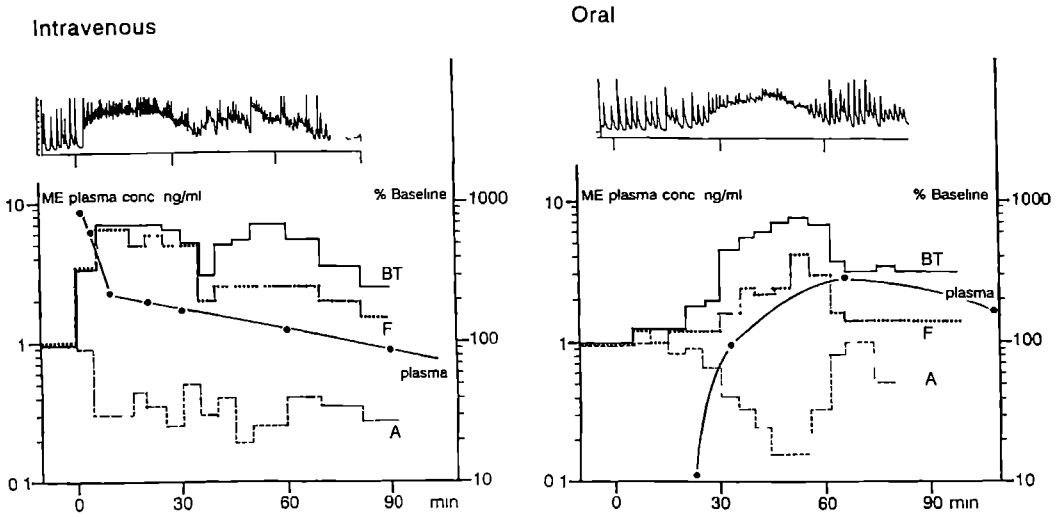

Figure 5 2 1 Effect of methylergometrine maleate (ME) after intravenous (0 2 mg) [*left*] and oral (0 5 mg) [*right*] administration in volunteer 1 At t=0, ME was administered.

Top-trace Effect on intra-uterine pressure

Bottom-trace Effect on frequency (F), basal tone (BT) and amplitude (A) The mean values of F, B and A during thirty minutes before drug administration were regarded as baseline values and set at 100%, the increase in a 5 minutes' period was expressed as % of baseline value and plotted versus time after intravenous (0 2 mg) ME and oral (0 5 mg) ME administrations

The *right panel* shows the late and less marked effect after oral administration of 0.5 mg methylergometrine maleate. An increase in frequency of 240% occurred 35 minutes after drug administration. A maximum increase of 320% of the baseline value was reached after 50 minutes. An increase in basal tone was seen after 30 minutes with maximum values of 700% after 50 minutes. The basal tone remained elevated compared to the baseline values. The amplitude decreased to 17% after 55 minutes, but returned to its baseline value 80 minutes after drug administration.

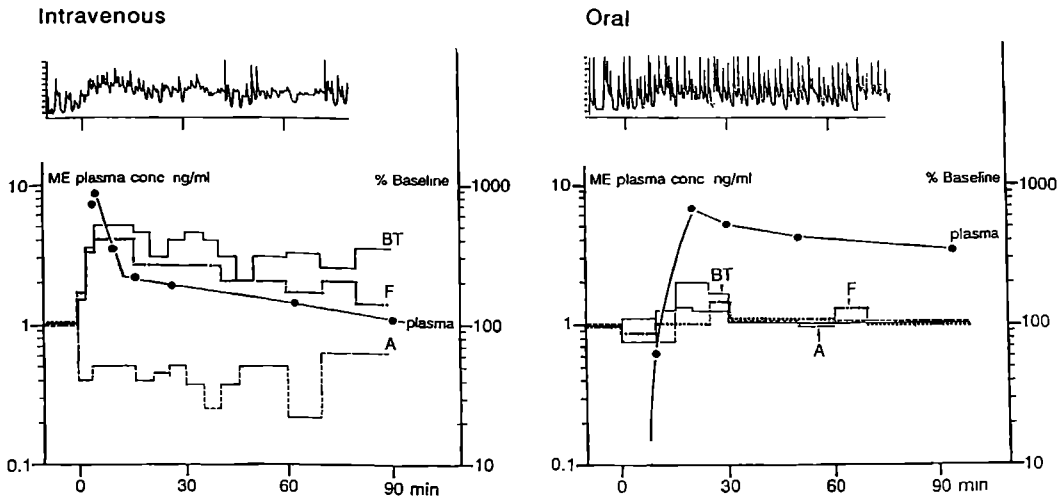

Figure 5.2.2 Effect of methylergometrine maleate (ME) after intravenous (0.2 mg) [*left*] and oral (0.5 mg) [*right*] administration in volunteer 2. At t=0, was administered.
For explanation of tracings, see Figure 5.2.1.

Figure 5.2.2 shows the effect of methylergometrine maleate on IUP in volunteer 2: she responded well to the intravenous dose but badly to the oral dose compared to volunteer 1. At the top of the figure the IUP-recordings after intravenous (*left panel*) and oral (*right panel*) administrations are given. At the bottom the mean value of F, BT and A of the IUP-cycles over 5 minutes' periods are shown.

The different responses to oral administration in volunteer 1 and 2 is shown clearly in the bottom-tracings (effect on F, BT and A) of Figures 5.2.1-2.

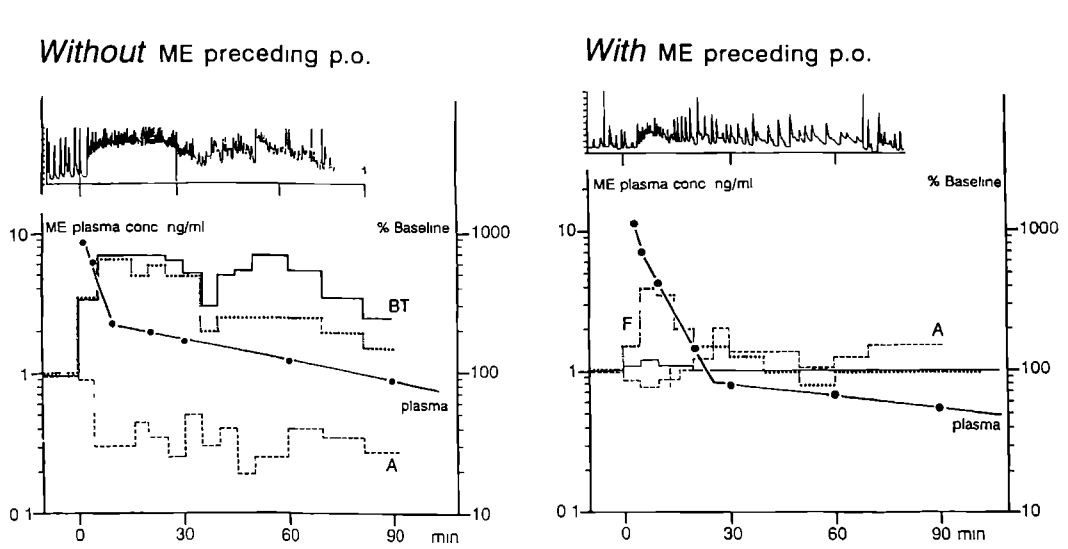

Figure 5.2.3 Effect of methylergometrine maleate (ME) after intravenous (0.2 mg) administration *without* preceding oral ME [*left*] and *with* preceding oral ME (0.5 mg) [*right*] in volunteer 1. At t=0, methylergometrine maleate was administered. For explanation of tracings, see Figure 5.2.1.

Figure 5.2.3 shows the effects of the intravenous dose on IUP *without* and *with* preceding oral methylergometrine maleate (0.5 mg) in volunteer 1. When 0.2 mg methylergometrine maleate was injected 24 h after the oral test, hardly any changes in BT, F and A of intra-uterine pressure were recorded.

Figure 5.2.4 illustrates the mean basal tone, mean frequency and mean amplitude in 5 minutes' periods after oral and intravenous administrations (A: *left panel*) and after intravenous administration at CD 2 and the day after an oral test CD 3 (B: *right panel*). The values used in the figure are the mean values of the 6 different volunteers. The figure clearly illustrates the different patterns in F, BT and A after intravenous or oral administrations (*left panel*). It shows also that there is hardly any uterine response to a 0.2 mg intravenous dose if this is preceded by an oral dose of 0.5 mg methylergometrine maleate 24 h before (*right panel*). The graphs are derived from the individual data shown in appendix 2 Tables V2-V5, p 155-158.

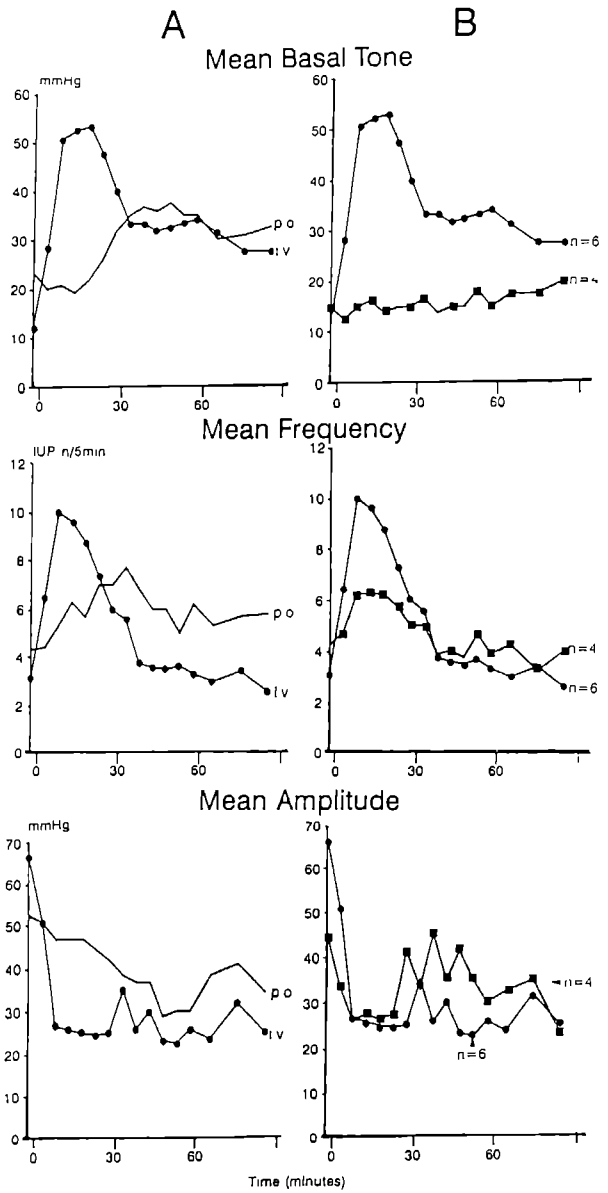

Figure 5 2 4

Mean basal tone (BT), mean frequency (F) and mean amplitude (A) of intra-uterine pressure (IUP)-cycles in a 5 minutes' period versus time At t=0, ME was administered

A left panel

The effect of intravenous (0 2 mg) and oral (0 5 mg) administrations of ME on mean BT (mmHg), mean F (number of IUP/5 minutes' period = IUP n/5min) and A (mmHg) of IUP-cycle in a 5 minutes period, in menstruating women (n=6)

B right panel

The effects of 0 2 mg ME on the same parameters are shown *without* (n=6) and *with* (n=4) 0 5 mg ME given orally 24 h before the intravenous administration

Table 5.2.3 shows the AUC of the individual IUP-recordings. When AUC 30 minutes before drug-administration ($AUC_{30\rightarrow0}$) is compared to AUC 30 minutes after drug administration ($AUC_{0\rightarrow30}$), a marked increase in AUC is seen after intravenous administration and hardly any after oral administration. After oral administration a (slight) change in AUC was seen in the period between 30 and 60 minutes after the intake of 0.5 mg methylergometrine maleate. When 0.2 mg methylergometrine maleate was injected 24 h after the oral test, the AUC was less marked than after the injection of 0.2 mg methylergometrine maleate at CD 2 of the first menstrual cycle and even less than after the oral administration of 0.5 mg methylergometrine maleate (Table 5.2.3). Table 5.2.3 has been derived from appendix V.6 (p 159-164).

Table 5.2.3 Area under the curve of IUP (AUC) during several time-periods in relation to intravenous (0.2 mg) and oral (0.5 mg) administrations of methylergometrine maleate (ME)

Volunteer		1	2	3	4	5	6
A		***Without* preceding oral ME**					
• Intravenous							
AUC	-30→0	726	843	1456	1320	339	682
AUC	0→30	2163	1329	2042	2384	580	943
AUC	30→60	1829	1352	1119	1479	651	914
AUC	60→90	1725	1311	857	1764	236	650
AUC	*0→90*	*5717*	*3992*	*3018*	*5627*	*1467*	*2507*
• Oral							
AUC	-30→0	640	1209	1077	1420	1062	1453
AUC	0→30	857	1240	1018	1320	953	998
AUC	30→60	1857	1307	1205	1851	1249	736
AUC	60→90	1358	1330	1216	1944	1244	1627
AUC	*0→90*	*4072*	*3883*	*3439*	*5115*	*3446*	*3361*
B		***With* preceding oral ME***					
• Intravenous							
AUC	-30→0	365	474	872	971	-	-
AUC	0→30	777	384	805	782	-	-
AUC	30→60	719	460	731	984	-	-
AUC	60→90	541	426	719	1294	-	-
AUC	*0→90*	*2037*	*1270*	*2255*	*3060*	-	-

AUC0→30 AUC (mean IUP multiplied by a defined time-period) over a time-period from 0 minutes till 30 minutes after drug administration, *Oral ME (0.5 mg) 24h before intravenous administration

Side effects

Three women experienced dizziness after intravenous injection, while all experienced abdominal cramps within 5 minutes after intravenous administration. After an oral dose three out of six experienced abdominal cramps approximately one hour after drug administration.

5.3 Discussion

This study demonstrates the feasability to assess the effects of uterine stimulation during human menstruation together with pharmacokinetic data. Although uterine stimulation is not frequently used to treat menorrhagia, this model may provide indirect evidence for the more important issue of postpartum haemorrhage. It is likely that the human uterus functions alike during menstruation and labour, i.e., to provide expelling force. This can be demonstrated by the intra-uterine pressure patterns which are similar in both situations (Hendricks 1966; 1968; Hein 1972). The same holds true for coagulating and fibrinolytic properties within the uterine cavity (Gerbasi et al. 1990; Yoshimura et al. 1992).

It is also our experience that the method used in this study, i.e. the sponge-tipped fluid filled catheter, is more reliable in the non-pregnant uterus than in the postpartum uterus because of increased degree of expulsion in the latter. In the postpartum uterus only transabdominal placed open-tip catheters provide reliable information. This procedure, however, encounters medical-ethical contra-indications when used just for research purposes. Micro-transducers at the catheter tip were not used because of possible artifacts (Åckerlund et al. 1978) and the impossibility of calibration during the recording (Braaksma 1971).

The most striking observation was the wide variation of bioavailability of oral methylergometrine maleate, which corresponds with the recently published data found in male volunteers (de Groot et al. 1994b); former data on methylergometrine (Saameli 1976) described only a fast absorption of methylergometrine tablets.

Uterine motility was reflected in basal tone, frequency, amplitude and AUC

of the IUP-cycle. The values of two $AUC_{-30\rightarrow 0}$ in the same volunteers in different tests were not similar which makes it irrational to compare $AUC_{0\rightarrow 90}$ after intravenous and after oral administrations within the same volunteer (e.g. volunteer 5). In one and the same volunteer F, BT and A showed quantitative variations at CD 2 of two subsequent menstrual cycles before drug administration took place. This explains why in one volunteer differences in $AUC_{-30\rightarrow 0}$ existed in the subsequent menstrual cycles. Volunteers 3, 5 and 6 (Table 5.2.3) had a higher BT before oral administration than before the injection of methylergometrine maleate. This explains why $AUC_{0\rightarrow 90}$ orally is larger than intravenously. The changes in BT, F, A and AUC after oral administration of methylergometrine maleate show a rather late and unpredictable stimulating effect on uterine motility. They reflect the same wide variation as observed in the pharmacokinetic data after oral administration.

The observation of the strongly diminished effect of intravenously administered methylergometrine maleate 24 h after oral administration suggests a long-lasting receptor blockade. It seemed as if the uterus was insensitive to the methylergometrine maleate-dose. The first dose may affect and change the uterine receptors for methylergometrine maleate. This could explain the insensitivity to the second dose of 0.2 mg methylergometrine maleate in postpartum uteri lasting 3 h, measured by external tocography, as reported by Müller & Stöker (1959) and observed in our experiments even 24 h after oral administration of 0.5 mg methylergometrine maleate. Methylergometrine maleate probably blocks α-receptors in the inner layer, specifically affecting the basal tone of this layer (Daels 1974; de Koning Gans et al. 1975; Saameli 1976).

Conclusion

Oral administration of methylergometrine maleate shows a late and unpredictable effect on the menstruating uterus in contrast to the fast and predictable effect of an intravenous dose.

A relation between plasma concentration and pharmacodynamic effect could not be demonstrated after oral administration. Therefore oral ergot alkaloids can not be advocated either for the treatment of menorrhagia or for postpartum haemorrhage.

6 Clinical effects

6.1 Survey of the management of the third stage of labour in the Netherlands*

The World Health Organization (WHO) advocates prophylactic oxytocic drugs to be administered to all women in the third stage of labour to reduce postpartum blood loss (WHO 1990). A survey in the United Kingdom in 1984 showed that the active management with Syntometrine and controlled cord traction is universal in those units with a third stage management policy, i.e. 98% of all units (Garcia et al. 1987; Prendiville et al. 1989).

The situation in the Netherlands is different in that there exists a strong belief that expectant management in low risk women is not worse than active management. Also, studies in Ireland (Begley 1990) and the United Kingdom (Thilaganathan et al. 1993) suggest that there still exists a need for a trial of oxytocin versus placebo in women at low risk for postpartum haemorrhage. One such study is in progress at present and conducted by Dutch midwives who are used to expectant management of the third stage.

We report here the results of a questionnaire sent to Dutch midwives and obstetricians to investigate the practices followed during the third stage of labour.

6.1.1 Methods

A questionnaire was mailed to Dutch midwives and obstetricians by a pharmaceutical industry (Ferring Ltd) making use of their mailing database. The respondent was asked whether he/she was a midwife or an obstetrician. Information was collected regarding the annual number of births in his/her practice and the number of colleagues in his/her practice.
The four questions are given in Table 6.1.1.1.

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*Based upon: de Groot ANJA, van Roosmalen J, van Dongen PWJ. Survey of the management of the third stage of labour in the Netherlands. 1995h; submitted.

Table 6.1.1.1 Questionnaire

1	Do you actively manage the third stage of labour?
	- as a routine
	- on indication
	- never
2	If you actively manage the third stage, which oxytocic do you use?
	- oxytocin 1st, 2nd, or 3rd choice?
	- ergometrine 1st, 2nd, or 3rd choice?
	- prostaglandin 1st, 2nd, or 3rd choice?
3.	Which dose of oxytocin do you use?
	- 1, 5, or 10 IU?
4	Which route of administration do you use?
	- intravenous, intramuscular, or intramyometrial?

In analyzing the results, each question was considered separately This means that percentages mentioned have been calculated from all those who responded the specific question.

6.1.2 Results

Of 1394 midwives, 406 (29%) returned the questionnaire. For the obstetricians, the response rate was higher: 47% responded (401) of the 855. The overall response rate was 35%, which is considered fairly good for a pharmaceutical mailing.

Fifty-five percent of the obstetricians used prophylactic oxytocics in the third stage as a routine; the other 45% only do so when indicated. As shown in Table 6.1.2.1 for the obstetricians, the drug of first choice was oxytocin (98.5%); ergometrine was used as second choice (49%), and prostaglandins was the third choice (29%). Only 10% of the midwives use prophylactic oxytocics in the third stage as a routine. As shown in Table 6.1.2.1, 98.5% of the midwives use oxytocin as the drug of first choice; ergometrine is the second choice (46%), while prostaglandins were used by 2% as the third choice

The most frequent route of administration was intramuscular; 80.5% of the obstetricians and 99% of the midwives prefer this route. The most frequent used dose was 5 IU of oxytocin; 75% of the obstetricians and 70% of the midwives administered this dose. Routine use of prophylactic oxytocics in the third stage of labour is not the standard of practice in the Netherlands as is shown in Figure 6.1.2.1.

Table 6.1.2.1 Management of the third stage of labour by Dutch midwives and obstetricians

		Midwives		Obstetricians	
Addressed		1394	%	855	%
Responded to 1 or more questions		406	(29.1)	401	(46.9)
Question 1					
• Active management of third stage		397		392	
- as a routine		39	(9.8%)	216	(55.1%)
- on indication		357	(89.9%)	174	(44.4%)
- never		1	(0.3%)	2	(0.5%)
Question 2					
• Choice of oxytocic		394		390	
- Oxytocin	1st choice	390	(98.5%)	384	(98.5%)
	2nd choice	2	(0.5%)	4	(1%)
	3rd choice	-	(0%)	1	(0.3%)
- Ergometrine	1st choice	4	(1%)	6	(1.5%)
	2nd choice	181	(46%)	192	(49.2%)
	3rd choice	4	(1%)	3	(0.7%)
- Prostaglandin	1st choice	0	(0%)	0	(0%)
	2nd choice	0	(0%)	29	(7.4%)
	3rd choice	8	(2%)	112	(28.7%)

( ): percentage calculated on the number of answers to the specific question

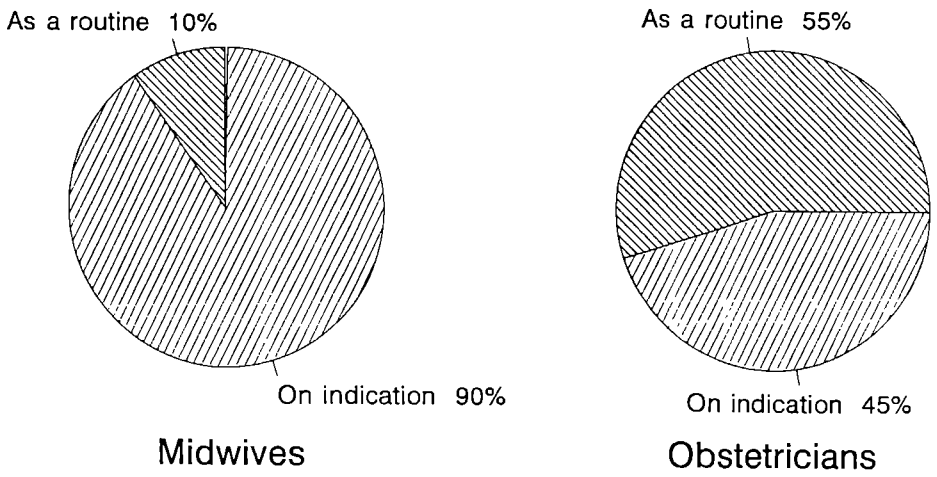

Figure 6.1.2.1 Use of oxytocic drugs in the third stage of labour in the Netherlands.

6.1.3 Discussion

The overall response rate of 35% is fairly good for pharmaceutical mailing, but selection of responders might take place. It is unknown which obstetricians or midwives responded and therefore bias may have occurred. The difference in management of 55% for obstetricians and 10 % for midwives with respect to use of prophylactic oxytocics as a routine is so striking, however, that the survey supports the statement that there are big differences between obstetricians and midwives in the management of the third stage of labour. Fifty-five percent of the obstetricians in the Netherlands tend to use prophylactic oxytocics as a routine as compared to only 10% of the midwives. But also among the obstetricians, no consensus exists as a large minority (45%) uses active management only on indication.

We conclude that in the Netherlands, routine prophylactic oxytocics is not the standard practice as is the case in the United Kingdom. The Netherlands, therefore, is one of the few places where one can still conduct randomized trials of oxytocics with a placebo. A placebo-controlled trial of oral ergometrine to reduce postpartum haemorrhage is presented in chapter 6.2.

6.2 A placebo-controlled trial of oral ergometrine to reduce postpartum haemorrhage*

PPH claims the lives of 150,000 women annually (Kwast 1991a). It is one of the most frequent causes of maternal mortality in the developing world (Kwast 1991b; Royston 1989). The prophylactic use of oxytocic drugs is generally advocated to prevent these tragedies (WHO 1990). At present, the best choice for prophylactic use in the third stage of labour is oxytocin (van Dongen et al. 1991; Mc Donald et al. 1993). On a world-wide basis, however, this standard of care is not available for all women who give birth. Not only are there logistic problems in some obstetric care settings in administering injections, such as oxytocin, there is also ample evidence that ampoules of oxytocin lack stability under tropical conditions (Walker et al. 1998; Hogerzeil et al. 1994). Stimulation of oxytocin by early breast suckling has been investigated as an alternative, but did not show reduction of postpartum blood loss (Bullough et al. 1989).

For prophylaxis, the only oral drugs available are ergometrine and methylergometrine. As described in Chapter 3, a world-wide distribution of (methyl)ergometrine tablets would entail logistical problems as the oral medication must be stable under tropical conditions. This issue has not yet been satisfactorily settled (de Groot et al. 1995b). Before the stability question is studied further, the prophylactic effectiveness of the oral ergometrine in reducing blood loss postpartum must be estabilished. We here report a randomized trial in which our primary hypothesis was that oral ergometrine will reduce postpartum blood loss by 30% as compared to a placebo. A lesser reduction of blood loss was considered to be of little use as its effects on maternal mortality and on the need for blood transfusions are probably negligible (Newton et al. 1961).

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*de Groot ANJA, van Roosmalen J, van Dongen PWJ, Borm GF. A placebo-controlled trial of oral ergometrine to reduce postpartum haemorrhage. 1995i; submitted.

6.2.1 Subjects and methods

Design

Basically the study is a double-blind multicentre trial of oral ergometrine versus placebo. Assuming a lognormal distribution for blood loss, it was estimated that a sample size of 140 per group was required to show a clinically relevant 30% reduction of blood loss with an error rate of 0.05 (two-sided) and a power of 0.80. To allow comparison with a standard prophylactic regimen, a third group receiving the standard intramuscular oxytocin was added, but for obvious reasons this could not be conducted in a blind manner. Thus, formal randomisation was conducted in a 2:2:1 design.

Randomization

The hospital pharmacy of the University of Nijmegen supplied numbered boxes containing 0.4 mg ergometrine maleate tablets, placebo tablets, or 5IU oxytocin according to a computer-generated randomisation list. Care was taken that no difference could be seen or heard between the packages of the tablets (whether ergometrine or placebo) and the oxytocin ampoules.

Recruitment

Two university hospitals (in Leiden and Nijmegen), a midwifery school (in Kerkrade) and independent midwives with a practice in the area of the university hospital of Nijmegen participated in the study. The study was approved by the medical ethical committees of the hospitals and the midwifery school. Informed consent was asked in early labour. Only women who did not develop exclusion criteria (Table 6.2.1.1) participated in the trial. They were assigned to either one of the groups just before the delivery of the baby's head. The same procedure was followed in home births.

Table 6 2 1 1 Exclusion criteria for participation in trial

1	The woman refuses to take part
2	Any cardiovascular disease (hypertension)
3	Multiple pregnancies
4	Non-cephalic presentation
5	Polyhydramnios
6	Tocolysis 2 hours prior to delivery
7	Anticoagulant therapy
8	Stillbirth
9	Antepartum haemorrhage
10	Chemical induction or augmentation (oxytocin, prostaglandins)
11	Instrumental/ Operative delivery
12	Anaemia Hb <6.8 mmol/L
13	Previous complication in the third stage

Management of the third stage was prescribed as follows:
(Prendiville et al. 1988a;b; Elbourn & Harding 1991)

1 Give tablets or injection immediately after birth.
2 When the mother feels contractions *or* when there are signs of separation, encourage maternal effort to adopt a position aiding gravity, i.e. standing upright, kneeling, squatting, or sitting on a bedpan. If necessary, place a flat hand on the mother's abdomen to act as a brace to aid pushing.
3 If the placenta does not deliver spontaneously, *wait* and reattempt the second step.
4 If haemorrhage occurs, administer additional oxytocics and remove placenta by other means, such as controlled cord traction.

Outcomes

Primary outcome of the study was the mean blood loss. PPH was defined as a loss of ≥500 ml blood loss (WHO 1990); and severe PPH as ≥1000 ml. Further use of oxytocics or other interventions were secondary outcomes of the study.

Assessment of blood loss

Measurement of blood loss by the gravimetric method (Wilcox et al. 1959) started immediately after birth. A "fresh" perineal pad was placed under the perineum to absorb blood or fluid. All gauzes and pads were collected in the hour following the delivery of the placenta and were weighed at the end of this period. The difference in weight of the material before and after the hour was calculated. A 100 gram increase in weight was considered to be equivalent to 100 ml blood (i.e. specific gravity is 1 g/ml). At delivery, some blood was usually spattered on the drapes and on the gowns of the attendants although attempts were made to minimize such losses. This gave a constant error of approximately 10% (Newton 1961). In addition, the placental interstices contain maternal blood (about 9% of placental weight). As systematic overestimations (amniotic fluid) and underestimations (blood loss) are likely to be distributed equally among the groups, no corrections have been made for them. In the midwifery school and in the hospitals, blood pressure was recorded just before birth and again 15, 30, 45, and 60 minutes after the delivery of the placenta.

6.2.2 Results

During the study period from July 1993 to July 1994, 371 women were assigned to the study: Kerkrade 61, Leiden 69, Nijmegen 23, and home births 218. Four women with exclusion criteria were entered erroneously (three forcipal extractions, one augmentation). They are considered as non-participants, leaving 367 women in the study (Table 6.2.2.1). Not all eligible women entered the trial. The main reason was that the woman wished a "natural childbirth" which would be disturbed by the prophylactic use of any drug. Age, parity, and labour characteristics of the parturients are comparable among the three groups (Table 6.2.2.1).

Blood loss, percentage of PPH, and the need for further oxytocics among the ergometrine, placebo, and oxytocin groups were not significantly different (Table 6.2.2.2).

Table 6 2 2 1 Details of parturients

	Ergometrine (n=146)	Placebo (n=143)	Oxytocin (n=78)
• **Demographic variables**			
Mean maternal age, years (SD)	30 (4)	30 (4)	30 (4)
Primiparous women (%)	48 (33%)	46 (32%)	27 (35%)
• **Labour**			
Length 1st stage, hours (range)	6 4(1-16 4)	6 8(1-16 7)	6 8(1 5-16 7)
Length 2nd stage, minutes (range)	22 (1-119)	23 (2-90)	25 (2-100)
Length 3rd stage, minutes (range)	15 (2-90)	14 (3-55)	11 (4-90)
Episiotomy (%)	40 (27%)	47 (33%)	23 (29%)
Birthweight, gms (SD)	3519 (443)	3498 (444)	3534 (410)

Table 6 2 2 2 Primary and secondary outcomes

	Ergometrine	Placebo	Oxytocin
• ***All parturients***	**n=146**	**n=143**	**n=78**
Mean blood loss, ml (SD)	476(340)	520(419)	499(454)
≥ 500 ml	54(37%)	55(38%)	25(32%)
≥1000 ml	12 (8%)	16(11%)	7(9%)
Use of further oxytocics	21(14%)	26(18%)	14(18%)
Third stage complications			
manual removal of placenta	2	0	1
requiring blood transfusion	1	3	2
• ***Primiparous women***	**n=48**	**n=46**	**n=27**
Mean blood loss, ml (SD)	585(417)	657(442)	562(459)
≥ 500 ml	25(52%)	26(57%)	12(44%)
≥1000 ml	7 (15%)	9(20%)	3(11%)
Use of further oxytocics	12(25%)	9(20%)	6(22%)
• ***Multiparous women***	**n=98**	**n=97**	**n=51**
Mean blood loss, ml (SD)	423(321)	455(394)	465(452)
≥ 500 ml	29(30%)	29(30%)	13(25%)
≥1000 ml	5(5%)	7(7%)	4(8%)
Use of further oxytocics	9(9%)	17(18%)	8(16%)

Table 6.2.2.3 Change in amount of blood loss compared to placebo group

	Ergometrine	Oxytocin
• ***All parturients***	-5% (-20% to +13%)*	-9% (-26% to +12%)
• ***Primiparous women***	-8% (-32% to +25%)	-20% (-44% to +15%)
• ***Multiparous women***	-5% (-22% to +19%)	-3% (-25% to +25%)

* 95% confidence intervals

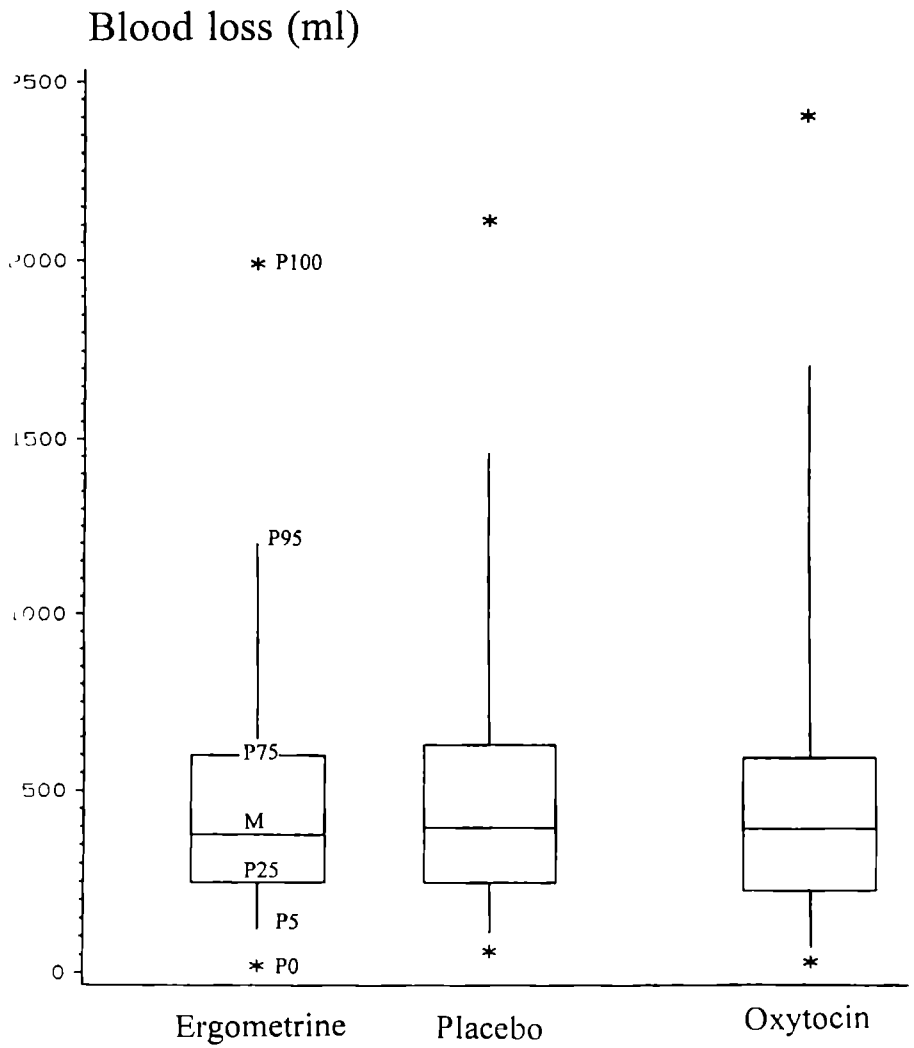

Figure 6.2.2.1 Effect of treatments on the amount of blood loss postpartum (ml)
Abbreviations M = median, P = Percentile (Box-plot)

The percentage of PPH (≥500 ml) amounted to 37%, 38%, and 32% among the three groups (Table 6.2.2.2) Ergometrine reduced blood loss by 5% (CI:-20% to +13%) as compared with placebo (Table 6.2.2.3). Oxytocin gave a reduction of 9% (CI:-26% to +12%).

Figure 6.2.2.1 shows the estimates for the effect of the treatments on the amount of blood loss. Blood pressure measurements were only recorded for the institutional births (n=149). Oral ergometrine showed no significant elevation of blood pressure.

6.2.3 Discussion

Routine use of oxytocics and active management of the third stage in low-risk women remains a controversial issue (Inch 1985; Anonymous 1986; Begley 1990; Thilaganathan et al. 1993) although WHO has recommended that the third stage should be managed actively in countries where access to hospital services is difficult or time consuming (WHO 1990). Easy alternatives to intramuscular oxytocin as early breast suckling have been examined but proved not effective (Bullough et al. 1989).

In the Netherlands, active management of the third stage of labour and routine use of oxytocics are not standard practice, especially not among midwives who attend most low risk pregnancies (de Groot et al. 1995h). The use of placebo was, therefore, not considered unethical. A study comparing oxytocin versus placebo is currently being conducted in Dutch midwifery practices.

Remarkable is the high rate of PPH in about one third of all three groups compared to 10% in Gilbert's study (Gilbert et al. 1987). This unexpected high rate of PPH was also noticed by McDonald et al. (1993) in their study on the effect of oxytocin alone versus Syntometrine. Part of the high incidence may relate to a study-induced higher accuracy in measuring blood loss. It is noteworthy that Gilbert (1987), but also McDonald et al. (1993) did not measure blood loss but only estimated the amount.

In our study, oral ergometrine gave only a small reduction in blood loss (5%). Especially in multiparous women, virtually no difference in blood loss was recorded among the three groups. Oral ergometrine does not seem to

reduce the frequency of severe PPH (≥1000 ml) contrary to McDonald's suggestion that this may be the main effect of prophylaxis (McDonald et al. 1987). Even the use of oxytocin intramuscularly showed little or no advantage in women at low risk for PPH. We could not confirm the reduction of blood loss by oxytocin im (5IU) in low risk women as described in the small study of Poeschmann et al. (1991).

As reported by others (Prendiville et al. 1988a; Poeschmann et al. 1991), parity and the presence of an episiotomy are determining factors in the amount of blood loss. These factors were equally divided among the three groups. Including these factors in the analysis did not change our results.

Conclusion

On the basis of our study, there is no reason to recommend oral ergometrine as an easy alternative to parenteral prophylactic drugs in the third stage of labour. It had too little demonstrable effect on blood loss after childbirth as compared to placebo. Until now, no other oral oxytocics are available for this purpose. Recently Irons et al. (1994) suggested nipple stimulation postpartum as an easy alternative to parenteral oxytocics for the third stage of labour. A reduction-trend in the amount of blood loss compared to placebo, was seen, but the difference was not significant. There is still a need for research into easy alternatives for active management of the third stage of labour.

7 Summary and conclusions

7.1 Summary

The objective of this thesis was to investigate the possibility of using oral ergometrine or methylergometrine to prevent postpartum haemorrhage (PPH) as an easy alternative to prophylactic parenteral drugs in the third stage of labour.

PPH is defined and its essentials in prevention and management are described (Chapter 1). Primary prevention of PPH is advocated at all levels of obstetric care. Intramuscular oxytocin as a prophylactic oxytocic drug has disadvantages in the active management of the third stage of labour. Oral medication is preferable to injections when world-wide use is contemplated. Only ergot alkaloids are suitable for oral administration for this purpose. The history of ergot alkaloids, which supplied the first uterotonics, is described. Their chemical background and pharmacological properties are summarized, and their adverse reactions to these drugs are reviewed (Chapter 2).

To be an alternative to prophylactic parenteral oxytocics, tablets should fulfill pharmaceutical, pharmacological, and clinical requirements. Data for these drugs had not yet provided conclusive evidence of their suitability. Therefore ergometrine and methylergometrine tablets were examined with regard to their stability under tropical conditions (Chapter 3), pharmacokinetics (Chapter 4), and pharmacodynamics (Chapter 5), and clinical effects (Chapter 6).

Chapter 1

Primary prevention of PPH is advocated at all levels of obstetric care. This implies that active management of the third stage is also recommended at the first, most peripheral, levels of obstetric care. Active management includes use of an oxytocic, early cord clamping, and active expulsion of the placenta. The oxytocic drug of choice is oxytocin, 5 IU, given intramuscularly.

Women with high risk factors for PPH (e.g. polyhydramnios, previous

complications in third stage, antepartum haemorrhage, prolonged labour, multiple pregnancies) should deliver in hospital. Timely ante partum referral is necessary. In these women, prevention and anticipatory management includes availability of intravenous treatment as well as active management with an oxytocic.

Evidence for the effectiveness of active management of the third stage in women at low risk for PPH is still not conclusive. Whether women delivering at home with easy accessability to hospital or those at low risk delivering in hospital should be actively managed remains controversial and is not supported by us until a clinical trial in this particular group of women has shown the effectiveness of active management. Guidelines for clinical practice are shown in the flow chart (Figure 1.2.4.1).

Because the menstruating uterus was used as model to simulate the process of placental separation in the pharmacodynamic study, Chapter 1.3 discusses our hypothesis that menstrual bleeding and placental separation are comparable. The endometrium, blood vessels, myometrium, and the coagulation factors are compared during menstruation and placental separation. There are no great differences between the non-pregnant endometrium and the decidua (postpartum). The differences in spiral arteries between the non-pregnant and pregnant state are striking. During menstruation, uterine contractions have probably no major role in haemostasis, whereas uterine retraction postpartum plays an important role in haemostasis postpartum. At local uterine level, changes in coagulation factors, increasing fibrinolytic capacity, and the function of platelets in haemostatic plug formation are comparable.

Chapter 2

Epidemics of ergotism occurred frequently in the Middle Ages. They were source of inspiration for artists and popularly known as "St. Anthony's Fire", resulting in gangrene, neurological disease, and death. It was caused by eating rye bread contaminated with the fungus *Claviceps purpurea*. In 1582 it was described that birth could be hastened by administering a few spurs of the secale cornutum. The dosage was, however, very inaccurate resulting in frequent uterine ruptures. The nickname of the preparation of "pulvis ad partum" was changed to "pulvis ad mortem". Therefore, after 1828 the ergot

alkaloids were no longer used during delivery but only as a measure to prevent postpartum haemorrhage.

From 1875 onwards, many derivatives of *ergot alkaloids* were found. Dudley and Moir isolated ergometrine in 1932. It proved to have a very specific uterotonic action. However, because of severe and unpredictable side-effects and the instability of the drug (this thesis), oral ergometrine is not the drug of choice for prevention of postpartum haemorrhage.

Chemical background and pharmacological properties are summarized and a review of adverse drug reactions is given.

Chapter 3

The stability of oral preparations of the two ergometrine compounds methylergometrine and ergometrine under tropical conditions was unknown and was, therefore, examined in this study.

The "shelf lives" of ergometrine and methylergometrine tablets were examined by exposing these to seven artificially controlled conditions. Samples were analysed by High Performance Liquid Chromatography at nine different sampling times over a period of one year to determine the content of ergometrine and methylergometrine. Under refrigerated storage (test I), less than 90% of the stated amount of active ingredient was found in the tablets after 14 weeks for ergometrine and 21 weeks for methylergometrine. When stored in the dark at 40°C with 75% Relative Humidity, the tablets fell below accepted specification criteria (= 90-110% of stated amount of active ingredient) within three weeks for ergometrine and 21 weeks for the coated methylergometrine tablets.

The stability of uncoated ergometrine was far less than that of coated methylergometrine tablets. Instability worsened under extreme humid and hot conditions, for both ergometrine and methylergometrine. From week 31 onwards, the coating did not seem to protect the compound anymore, irrespective of the condition of exposure.

Tropical conditions make the tablets unstable with humidity as the main adverse factor. Under all simulated conditions, both ergometrine and methylergometrine tablets were unstable.

Chapter 4

In 4.1 the assay method to measure (methyl)ergometrine in plasma is described. An isocratic high-performance liquid chromatographic method with fluorescence detection has been developed for the measurement of ergometrine in human plasma. The quantitation limit in plasma was 50 $pg.ml^{-1}$. An example of the plasma concentration-time curves after oral and intravenous administration of ergometrine in one volunteer is shown. This HPLC method makes it feasible to describe pharmacokinetic parameters for oral ergometrine.

In 4.2 the experiments are described. The aim of these experiments was to assess the pharmacokinetics and bioavailability of comparable doses methylergometrine and ergometrine (parallel design) in six male volunteers after an intravenous dose and an oral dose of the maleate (cross- over design). Further the pharmacokinetics and bioavailability of methylergometrine in six non-pregnant women were assessed and compared to the methylergometrine values in men (parallel design in gender).

After *intravenous administration*, the pharmacokinetic profile of methylergometrine and ergometrine can be described by a two-compartment model. No statistical differences between the pharmacokinetic parameters of both compounds in men were observed.

For methylergometrine and ergometrine the distribution half-life $t_{1/2\alpha}$ is 0.19±0.27 h, and 0.16±0.20 h ($p>0.8$), respectively; the elimination half-life ($t_{1/2\beta}$) is 1.85±0.28 h and 2.57±1.05 h ($p=0.80$), respectively; the total body clearance (CL) amounts to 32.2±11.8 $L.h^{-1}$ and 32.6±12.0 $L.h^{-1}$ ($p>0.8$); the steady state volume of distribution (V_{ss}) is 71.5±25.9 L. and 82.0±14.5 L. ($p=0.40$), respectively. In women, after intravenous administration of methylergometrine the distribution half-life $t_{1/2\alpha}$ is 0.10±0.04 h ($p=0.46$), the $t_{1/2\beta}$ is 1.94±0.34 h ($p=0.64$), the CL amounts to 22.2±3.10 $L.h^{-1}$ ($p=0.073$); and the V_{ss} is 50.8±8.23 L ($p=0.091$). The p-values between brackets show that the intrinsic pharmacokinetic parameters for methylergometrine were not statistically different between men and women.

After *oral administration*, the pharmacokinetic profile can be described with a one-compartment model. Except for the lag-time (t_{lag}), no statistical differences between the pharmacokinetic parameters of the compounds methylergometrine and ergometrine were present in men. The t_{lag} of methylergometrine and ergometrine after oral administration was subject

dependent. The average values for the two compounds were respectively 0.33±0.09 h and 0.11±0.10 h (p=0.003). For methylergometrine and ergometrine a large variation of bioavailability was observed 84.9±37.2% (43.8% CV) and 80.7±34.5% (42.7 %CV) (p>0.8), respectively.

However, differences, in the following intrinsic pharmacokinetic parameters for methylergometrine were noted between men and women. The t_{lag} in women was also subject dependent and was significantly shorter than the t_{lag} in men with a mean value of 0.09±0.07 h (p=0.0004). The $t_{1/2\beta}$ in women was shorter 1.42±0.31 h vs. 1.85 ± 0.28 (p=0.0123) and the steady state volume of distribution was smaller 47.0±6.05 L vs. 71.5 ±25.9 l (p=0.01). The mean $t_{1/2abs}$ was not significantly different 0.50±0.55 h (p=0.10).

In women mean value of bioavailability of methylergometrine was 96.4-±27.5% ranging from 63% and 138%, it was not significantly different from the value in men (p=0.56).

The experiments with oral administrations for both men and women show a large inter-individual variability in bioavailability.

From a pharmacokinetic point of view, the oral route of administration does not seem the most reliable way for accurate dosing to prevent postpartum haemorrhage.

Chapter 5

The objective was to study the pharmacodynamic and pharmacokinetic effect of oral and intravenous methylergometrine upon uterine motility during menstruation. Intra-uterine pressure was measured in six volunteers with a fluid- filled sponge-tipped catheter during menstruation. Methylergometrine maleate was given orally (0.5 mg) or intravenously (0.2 mg) in a cross-over design.

After intravenous administration, a fast increase of the frequency of uterine contractions and basal tone occurred with a decrease of amplitude, lasting at least 30 minutes. Oral administration had a longer latency time and a less marked effect on uterine motility. Pharmacokinetic data, such as the maximum plasma concentration (C_{max}), the time at which C_{max} is reached (t_{max}), and the half-life of absorption ($t_{1/2abs}$) also showed large individual variation after oral administration.

Oral administration of methylergometrine had an unpredictable and a late

effect on uterine motility in the menstruating uterus probably due to an unpredictable bioavailability in contrast with the fast and predictable effect after intravenous administration.

Chapter 6

Active management with oral ergometrine maleate 0.4 mg was compared with expectant management for the control of blood loss in the third stage of labour in women at low risk for postpartum haemorrhage (PPH).

The design of the study was a three-arm randomized trial in which 0.4 mg ergometrine maleate (2 tablets à 0.2 mg) was set off against a placebo, and both groups were compared to a standard oxytocin regimen of 5IU. The participants were women at low risk for PPH.

Of 367 parturients, 146 were randomized to ergometrine maleate 0.4 mg, 143 to the placebo and 78 to intramuscular oxytocin in a 2:2:1 design. Compared with the placebo, ergometrine reduced blood loss by 5% (-5%; Confidence interval: -20% to +13%). Oxytocin reduced blood loss by 9% (-9%; Confidence interval: -26% to +12%) as compared to the placebo.

Conclusion: Oral ergometrine has too little effect on blood loss after childbirth in order to be a good alternative to parenteral prophylactic management.

In short

- Primary prevention of PPH is advocated at all levels of obstetric care. This implies active management of the third stage of labour at the first and most peripheral levels of obstetric care where access to hospital services is difficult.
- Tropical conditions make (methyl)ergometrine tablets unstable.
- Pharmacokinetic experiments with oral (methyl)ergometrine show a large inter-individual variability in bioavailability for both men and women.
- Oral administration of methylergometrine had an unpredictable and late effect on uterine motility in the menstruating uterus probably due to inefficient bioavailability.
- Oral ergometrine has too little effect on blood loss after childbirth to be a good alternative for parenteral prophylactic management.

7.2 Conclusions

Oral (methyl)ergometrine is not an alternative to parenteral prophylactic oxytocic drugs in the active management of the third stage of labour. It is instable, its pharmacokinetic and pharmacodynamic properties are unpredictable and no clinical effect has been shown. All in all, the negative outcomes of the three studies on oral (methyl)ergometrine strengthen each other. To ameliorate a product's stability seems unlogical, if the same product shows unfavourable pharmacokinetics. All the more so, since the tablets do not show the wanted clinical effects.

Throughout history ergot alkaloids are known as powerful drugs. Epidemics of ergotism were frequently encountered in the Middle Ages; in obstetric practice their nickname has been "pulvis ad mortem" when used for augmentation or induction of labour (1928). Nowadays, the side effects of (methyl)ergometrine can still be severe. From the point of view of the (medical) adage "Primum non nocere", the use of (methyl)ergometrine as prophylactic drug is disputable.
It seems that the time has come to abandon oral ergometrine from obstetrics.

However, there is still no suitable alternative for the active management of the third stage of labour for women in developing countries. The research quest for easy alternatives should be continued. If not, maternal mortality will remain a catastrophal problem, costing 1,500 lives a day.

The conclusion drawn from our research project is two-fold:

- There is still no easy alternative for the active management of the third stage of labour.
- Because of unfavourable pharmaceutical and pharmacokinetic properties oral (methyl)ergometrine should be excluded from the medication list.

Samenvatting en conclusies

Samenvatting

De doelstelling van dit proefschrift was te onderzoeken of het gebruik van ergometrine en methylergometrine tabletten een eenvoudig alternatief zou zijn voor de profylactisch gebruikte parenterale medicatie in het derde tijdperk van de bevalling om fluxus of haemorrhagia postpartum (HPP) te voorkomen.

HPP wordt gedefinieerd en aandachtspunten voor de preventie en het beleid worden beschreven (Hoofdstuk 1). Er wordt toegelicht waarom primaire preventie van HPP op *elk* niveau van verloskundige zorg wordt bepleit. Intramusculaire toediening van oxytocine als profylactisch oxytocicum kent zijn nadelen bij gebruik in het actieve beleid van het derde tijdperk van de bevalling. Voor wereldwijd gebruik verdienen tabletten de voorkeur boven injecties. Van de oxytocica zijn alleen de ergot alkaloiden geschikt voor orale toediening. Ergot alkaloiden zijn de oudste uterotonica. De geschiedenis van de ergot alkaloiden wordt beschreven in Hoofdstuk 2.1. Hun chemische structuur, farmacologisch eigenschappen en bijwerkingen worden samengevat in Hoofdstuk 2.2-4.

Om als alternatief voor de parenterale profylactische oxytocica te kunnen dienen, moeten de tabletten voldoen aan farmaceutische, farmacologische en klinische eisen. Over deze gegevens was onvoldoende informatie.

Om deze reden werden (methyl)ergometrine tabletten onderzocht op stabiliteit onder tropische omstandigheden (Hoofdstuk 3), farmacokinetiek (Hoofdstuk 4), farmacodynamiek (Hoofdstuk 5) en klinisch effect (Hoofdstuk 6).

Hoofdstuk 1

Primaire preventie van HPP wordt bepleit op *elk* niveau van verloskundige zorg. Dit houdt in dat het derde tijdperk actief wordt geleid, ook in de eerste lijn en op de meest perifere niveaus van verloskundige zorg. Actief leiden van het nageboorte tijdperk houdt in dat profylactisch een oxytocicum wordt gebruikt, er vroeg wordt afgenaveld en de placenta aktief geboren wordt. Het te verkiezen oxytocicum is op dit moment oxytocine 5 IU intramusculair.

Vrouwen met hoge risico-factoren op het ontwikkelen van HPP (polyhydramnion, voorgaande complicaties van het nageboorte tijdperk, antepartum bloedingen, meerling zwangerschappen) dienen te bevallen in een ziekenhuis. Vroegtijdige antepartum verwijzing is noodzakelijk. Preventie en anticiperend beleid omvat bij deze vrouwen zowel actief leiden van het derde tijdperk als inbrengen van een infuus.

Tot op heden is het niet aangetoond dat actief leiden van het derde tijdperk bij vrouwen met een laag risico op het ontwikkelen van HPP nuttig is. Het blijft dan ook controversieel of vrouwen die thuis bevallen en voor wie een ziekenhuis makkelijk bereikbaar is, actief moeten worden geleid in het derde tijdperk. Actief leiden in een dergelijke situatie wordt door ons althans *niet* bepleit totdat een klinisch studie de effectiviteit van een dergelijke behandeling heeft aangetoond. Richtlijnen voor de praktijk van preventie van HPP worden gegeven in Figuur 1.2.4.1.

In Hoofdstuk 1.3 wordt de hypothese besproken waarbij de menstruele bloeding vergeleken wordt met de loslating van de placenta. Wij gebruikten de menstruerende uterus namelijk als model om de loslating van de placenta te simuleren in de farmacodynamische studie. Het endometrium, de bloedvaten, het myometrium en de stollingsfactoren worden tijdens menstruatie en loslating van de placenta vergeleken. Er zijn geen opvallende verschillen tussen het niet-zwangere endometrium en de decidua (postpartum). De verschillen in spiraal-arteriën in een niet-zwangere en zwangere uterus zijn daarentegen erg groot. Tijdens de menstruatie spelen uteruscontracties waarschijnlijk geen rol in de hemostase, terwijl retractie van de uterus postpartum wel essentieel is voor een goede hemostase. Op niveau van de uterus zijn veranderingen in stollingsfactoren, toenemende fibrinolytische activiteit en de functie van bloedplaatjes in de hemostatische prop-vorming vergelijkbaar.

Hoofdstuk 2

Ergotisme epidemieën kwamen frequent voor in de middeleeuwen. Ze golden als inspiratie bron voor kunstenaars en stonden bekend onder de naam "Het Antoniusvuur" of "Het Heilig vuur" leidend tot gangreen, neurologische ziekten en de dood. Antoniusvuur werd veroorzaakt door het eten van besmet (rogge-)brood met de schimmel Claviceps purpurea. In 1582 werd beschreven

dat de bevalling kon worden bespoedigd door toediening van enkele korreltjes van het secale cornutum. Onnauwkeurige dosering leidde echter tot vele uterus rupturen. Dit was dan ook de reden dat na 1828 de ergot alkaloiden slechts in het derde tijdperk ter preventie van HPP werden gebruikt en niet voor inductie of bespoediging van de baring.

Vanaf 1875 werden diverse derivaten van *Ergot alkaloiden* ontdekt. In 1932 werd door Dudley and Moir ergometrine geïsoleerd. Het bleek een zeer specifieke uterotone werking te bezitten. Echter, vanwege de ernstige en onvoorspelbare bijwerkingen en instabiliteit van de medicatie (dit proefschrift) is ergometrine *niet* het middel van voorkeur in de *preventie* van postpartum bloedingen.

De chemische structuur, farmacologische eigenschappen en bijwerkingen van ergot alkaloiden worden beschreven in Hoofdstuk 2.2-4.

Hoofdstuk 3

De stabiliteit onder tropische omstandigheden van ergometrine en methylergometrine tabletten was onbekend en werd daarom onderzocht.

De "shelf lives" van ergometrine en methylergometrine tabletten werden bepaald door de tabletten aan zeven kunstmatige omstandigheden bloot te stellen. De monsters werden geanalyseerd met behulp van High Performance Liquid Chromatography (HPLC) op negen verschillende bemonsterings tijdstippen gedurende een periode van een jaar. Daarbij werd de nog aktief werkzame hoeveelheid ergometrine of methylergometrine gemeten. Na veertien weken bewaard te zijn geweest in een gekoelde omgeving, werd minder dan 90% van de gemeten werkzame hoeveelheid teruggevonden bij de ergometrine tabletten, voor de methylergometrine tabletten was dit na 21 weken. Bewaard in het donker bij 40°C en 75% relatieve vochtigheid (Relatieve Humidity RH) voldeden de ergometrine tabletten na 3 weken al niet meer aan de farmaceutisch eisen (= 90-110% van de vermelde actieve component moet in het preparaat aanwezig zijn) en na 21 weken voldeden ook de "coated" methylergometrine tabletten niet meer aan deze eisen.

De stabiliteit van de non-coated ergometrine tabletten was duidelijk minder dan van de coated methylergometrine tabletten. Instabiliteit trad het sterkst op onder extreem vochtige en hete omstandigheden, zowel voor ergometrine als methylergometrine. Eenendertig weken na blootstelling aan een kunstmatige

bewaaromstandigheid leek de coating de methylergometrine tabletten niet meer te beschermen onafhankelijk van de specifieke kenmerken van deze bewaaromstandigheid.

Tropische omstandigheden leidden tot instabiliteit van de tabletten, waarbij de vochtigheid de meest schadelijke factor was. De coated methylergometrine tabletten waren stabieler in vochtige en hete omstandigheden dan de non-coated ergometrine tabletten. Onder alle gesimuleerde omstandigheden waren zowel de ergometrine als methylergometrine tabletten niet stabiel.

Hoofdstuk 4

Hoofdstuk 4.1 beschrijft de analyse methode voor de bepaling van (methyl)-ergometrine in plasma. Een isocratisch HPLC methode met fluorescentie detectie werd ontwikkeld voor de meting van ergometrine in humaan plasma. De detectie grens in plasma was 50 pg. ml^{-1}. Een voorbeeld van een plasmaconcentratie versus tijd-curve na toediening van orale en intraveneuze ergometrine wordt beschreven bij één vrijwilliger. De HPLC-methode maakte het mogelijk (methyl)ergometrine in humaan plasma aan te tonen.

Hoofdstuk 4.2 beschrijft de afzonderlijke experimenten. De doelstelling van de studies was om van methylergometrine en ergometrine (parallel design) de farmacokinetische eigenschappen te bepalen bij 6 mannen na orale en intraveneuze toediening in vergelijkbare doseringen (cross-over design). Daarnaast werden farmacokinetische eigenschappen en de biologische beschikbaarheid van methylergometrine bij zes niet-zwangere vrouwen bepaald en vergeleken met de waarden bij de mannen (parallel design in geslacht).

Na *intraveneuze toediening* kon het farmacokinetisch profiel van methylergometrine en ergometrine beschreven worden met een twee-compartimenten systeem. Er werden geen verschillen tussen farmacokinetische parameters van methylergometrine en ergometrine geconstateerd. Voor methylergometrine resp ergometrine was de distributie halfwaarde tijd $t_{1/2\alpha}$ 0.19±0.27 u, 0.16±0.20 u ($p>0.8$); de eliminatie halfwaarde tijd ($t_{1/2\beta}$) was 1.85±0.28 u, resp. 2.57±1.05 u ($p=0.80$); De totale klaring (CL) bedroeg 32.2-±11.8 $L.u^{-1}$, resp. 32.6±12.0 $L.u^{-1}$ ($p>0.8$); het steady state verdelings volume (V_{ss}) bedroeg 71.5±25.9 L. resp. 82.0±14.5 L. ($p=0.40$). Bij vrouwen was na intraveneuze toediening van methylergometrine de distributie halfwaarde tijd $t_{1/2\alpha}$ 0.10±0.04 u ($p=0.46$), de $t_{1/2\beta}$ 1.94±0.34 u ($p=0.64$), de lichaamsklaring

CL 22.2±3.10 $L.u^{-1}$ (p=0.073), en het verdelingsvolume V_{ss} 50.8±8.23 L (p=0.091). De p-waarden tussen haakjes laten zien dat de intrinsieke farmacokinetische parameters niet statistisch significant verschillend zijn tussen mannen en vrouwen.

Na *orale toediening* kon het farmacokinetisch profiel beschreven worden door een één-compartiment systeem. Bij mannen werden geen verschillen geconstateerd tussen methylergometrine en ergometrine behalve in de lag-tijd (t_{lag}). De t_{lag} van methylergometrine en ergometrine bleek persoons-afhankelijk te zijn na orale toediening; 0.33±0.09 u, resp 0.11±0.10 u (p=0.003). De verschillen in farmacokinetische eigenschappen tussen mannen en vrouwen waren echter wel groter. De t_{lag} bij vrouwen was eveneens persoonsafhankelijk en was significant korter dan t_{lag} bij mannen, gemiddelde waarde 0.09±0.07 u (p=0.0004). De $t_{1/2\beta}$ bij vrouwen was korter 1.42±0.31 u (p=0.0123) en het verdelingsvolume was kleiner 47.0±6.05 L (p=0.01). De gemiddelde $t_{1/2abs}$ was 0.50±0.55 u (p=0.10). Een grote variatie in biologische beschikbaarheid voor zowel methylergometrine als ergometrine werd aangetoond, namelijk 84.9±37.2% (43.8% CV) and 80.7±34.5% (42.7 %CV) (p>0.8). Bij vrouwen was de gemiddelde waarde van biologische beschikbaarheid van methylergometrine 96.4±27.5% variërend tussen 63% en 138%; dit was niet significant verschillend van de waarde bij mannen (p=0.56). De experimenten met orale methylergometrine en ergometrine lieten een grote interindividuele variatie in biologisch beschikbaarheid zien bij mannen voor beide preparaten. De experimenten met orale methylergometrine bij vrouwen toonden een vergelijkbare variatie in biologische beschikbaarheid aan. Uit farmacokinetisch oogpunt is de orale toedieningsweg geen betrouwbare route om (methyl)ergometrine nauwkeurig te doseren.

Hoofdstuk 5

De doelstelling van de studie was de farmacodynamische eigenschappen van intraveneus en oraal toegediende methylergometrine op de uterusactiviteit tijdens de menstruatie te bekijken, in combinatie met de farmacokinetiek. Hiertoe werd bij zes vrijwilligsters de intra-uteriene druk gemeten met een met vloeistof gevulde "sponge-tipped" druk-catheter tijdens de menstruatie. Methylergometrine maleaat werd oraal (0.5 mg) en intraveneus (0.2 mg) toegediend in een cross-over design.

Na intraveneuze toediening werd een snelle toename in frequentie en basale tonus van de uteruscontracties waargenomen terwijl de amplitude van de contracties verminderde. Deze verandering van farmacodynamische parameters duurde minimaal 30 minuten. Farmacokinetische gegevens, zoals de maximum plasma concentratie (C_{max}), de tijd waarop de C_{max} werd bereikt en halfwaarde absorptie tijd lieten sterke individuele variaties zien na orale toediening tussen de proefpersonen.

Men zou mogen concluderen dat orale toediening van methylergometrine een onvoorspelbaar en laat effect heeft op de uterusactiviteit van de menstruerende uterus, mogelijk door een onvoorspelbare biologische beschikbaarheid van het orale preparaat. Dit in tegenstelling tot het snel en voorspelbare effect dat na intraveneuze toediening van methylergometrine gezien wordt.

Hoofdstuk 6

Actief leiden van het derde tijdperk met orale ergometrine maleaat 0,4 mg werd vergeleken met het expectatieve beleid ter controle van het bloedverlies in het derde tijdperk van de bevalling van vrouwen met een laag risico op het ontwikkelen van haemorrhagia postpartum (HPP).

De studie werd opgezet als een drie-armige gerandomiseerde trial, waarbij 0,4 mg ergometrine maleaat (2 tabletten à 0,2 mg) werd vergeleken met een placebo en deze beide groepen een vergelijk mogelijk maakten met de standaard medicatie oxytocine 5 IU intramusculair.

Van de 367 deelneemsters werden 146 gerandomiseerd voor ergometrine maleaat 0.4 mg, 143 voor placebo en 78 voor intramusculaire oxytocine in een 2:2:1-design. Vergeleken met placebo, reduceerde ergometrine het bloedverlies met 5% (-5%; betrouwbaarheidsinterval: -20% tot +13%) Oxytocine reduceerde het bloedverlies met 9% (-9%; Betrouwbaarheidsinterval: -26% tot +12%) ten opzichte van placebo.

Conclusie Orale ergometrine heeft een te gering effect op het bloedverlies postpartum om een goed alternatief te zijn voor profylactisch parenteraal beleid.

Resumerend

- Primaire preventie van HPP wordt op *elk* niveau van verloskundig zorg bepleit. Dit impliceert actief beleid van het derde tijdperk in de eerste lijn en de meest perifere niveaus van obstetrische zorg, waar toegang tot ziekenhuis faciliteiten moeizaam is.
- Tropische omstandigheden leiden tot een instabiliteit van (methyl)-ergometrine tabletten.
- Farmacokinetische studies met orale (methyl)ergometrine tonen een grote interindividuele variatie in biologische beschikbaarheid aan voor zowel mannen als vrouwen.
- Orale toediening van methylergometrine gaf een onvoorspelbaar effect op uterusactiviteit, mogelijk door een inefficiente biologische beschikbaarheid.
- Orale ergometrine heeft een te gering effect op het bloedverlies postpartum om een goed alternatief te zijn voor de momenteel gebruikte profylactische parenterale medicatie.

Conclusies

Orale (methyl)ergometrine is geen alternatief voor parenteraal toegediende profylactische oxytocica in het actieve beleid van het derde tijdperk door aangetoonde instabiliteit, onvoorspelbare farmacokinetische en farmacodynamische eigenschappen en door afwezigheid van klinisch effect. De negatieve resultaten van de studies afzonderlijk versterken elkaar alleen nog maar in deze conclusie. Het heeft namelijk geen zin de stabiliteit van een middel te verbeteren als de farmacokinetiek te wensen overlaat. Temeer nu blijkt dat de tabletten ook niet het klinisch beoogde effect geven.

Door de geschiedenis heen staan de ergot alkaloiden bekend als zeer krachtige middelen. Heden ten dage kunnen de bijwerkingen van (methyl)ergometrine nog steeds zeer ernstig zijn. Vanuit het medisch adagium "Primum non nocere", is het gebruik van ergot alkaloiden als profylactisch middel discutabel.

Misschien is het tijd om orale ergometrine te schrappen uit het medisch verloskundig arsenaal?

Helaas is er nog steeds *geen* geschikt alternatief voor gebruik in het nageboortetijdperk voor vrouwen in ontwikkelingslanden. Onderzoek naar eenvoudige alternatieven zal gecontinueerd moeten worden. Anders zal moedersterfte een catastrofaal probleem blijven, dat dagelijks 1.500 levens kost.

De conclusie van de gehele studie is tweeledig:

- Er is nog steeds geen eenvoudig alternatief voor het gebruik van oxytocine bij het aktief leiden van het nageboortetijdperk.

- (Methyl)ergometrine tabletten voldoen vanwege onvoorspelbare stabiliteit en ongunstige farmacokinetische eigenschappen niet aan de huidige farmaceutisch eisen.

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Abstracts

de Groot ANJA, van Dongen PWJ, Vree TB, van Roosmalen J, Hogerzeil HV, Hekster YA Stability study on (methyl)ergometrine tablets

Presented (poster) at the first world congress on labor and delivery July 3-7, 1994, Jerusalem, Israel

de Groot ANJA, van Dongen PWJ, Vree TB, van Roosmalen J, Hekster YA Pharmacokinetics and bioavailability of oral ergometrine in male volunteers

Presented (poster) at XIV FIGO World congress at Montreal Canada 26-30 September 1994 Int J Gynecol Obstet 1994 46 (S1) 106

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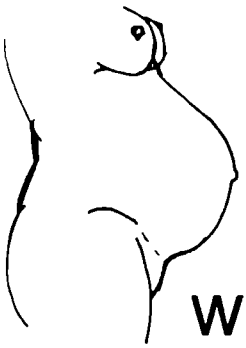
Curriculum vitae

De schrijfster van dit proefschrift werd geboren op 10 september 1964 in Nijmegen. Na middelbaar onderwijs te hebben afgerond op het Stedelijk Gymnasium te Nijmegen werd in 1982 de studie Geneeskunde aangevangen aan de Katholieke Universiteit te Nijmegen.

Na een wetenschappelijke stage in Dzodze (Ghana) en een co-schap sociale geneeskunde in Sengerema (Tanzania) werd in 1990 het arts-examen afgelegd. Als student was zij behalve bij het instituut voor ontwikkelings samenwerking tevens actief in enkele bestuurlijke taken.

De eerste stappen in de verloskunde werden gezet in januari 1991, toen zij als AGNIO in de maatschap gynaecologie/verloskunde van het Canisius-Wilhelmina Ziekenhuis begon. Na een korte periode als AGNIO werkzaam geweest te zijn in het AZN, begon zij de opleiding tot vrouwenarts in mei 1992 in het AZN (hoofd Prof Dr T.K.A.B. Eskes, Prof Dr R. Rolland). Zij was hier klinisch werkzaam tot januari 1994, waarna zij zich één jaar full-time aan onderzoek kon wijden. Momenteel vervolgt zij vanaf januari 1995 haar klinische opleiding in het Catharina ziekenhuis te Eindhoven (hoofd: Dr P.A. de Jong, Dr P.A. van Dop).



wij deden mee aan

het ergometrine project

helpt een tabletje ergometrine

het bloedverlies

na de bevalling verminderen?

Appendix 1. Tables concerning chapter 4: Pharmacokinetics

Table IV.1.a Demographic data of six **male volunteers** for **ergometrine**

Subject	1	2	3	4	5	6
age (years)	33	33	45	41	50	46
weight (kg)	73	70	72	67	79	73
height (cm)	181	184	178	175	173	183
BP* (mmHg)	120/70	120/80	120/80	125/88	120/82	125/80

*BP = blood pressure

Table IV.1.b Demographic data of six **male volunteers** for **methylergometrine**

Subject	1	2	3	4	5	6
age (years)	24	53	27	49	26	35
weight (kg)	75	79	79	73	72	70
height (cm)	180	173	194	183	173	184
BP* (mmHg)	120/80	120/80	125/80	120/88	110/70	120/70

*BP = blood pressure

Table IV.1.c Demographic data of six **female volunteers** for **methylergometrine**

Subject	1	2	3	4	5	6
age (years)	45	47	32	39	43	41
weight (kg)	61	70	60	65	55	52
height (cm)	162	172	165	176	156	171
BP* (mmHg)	100/60	120/80	130/75	110/75	110/65	115/70

*BP = blood pressure

Table IV.2.a Pharmacokinetic parameters of **ergometrine** after an intravenous dose of 0 055 mg (base) in six **male volunteers**

Subject		1	2	3	4	5	6
$t_{1/2\alpha}$	h	0 093	0 561	0 080	0 016	0 100	0 157
$t_{1/2\beta}$	h	1 830	2 180	1 587	3 53	2 103	4 213
MRT_{po}	h	1 986	2 177	1 524	4 436	2 416	4 825
$AUC_{0-\infty}$	µg h L^{-1}	1 34	1 68	0 98	1 75	1 14	2 49
CL	L h^{-1}	35 5	29 9	50 4	23 0	39 7	17 0
V_{ss}	l	70 4	64 8	76 87	102 0	96 0	82 1

Table IV.2.b Pharmacokinetic parameters of **ergometrine** after an oral dosis of 0 147 mg (base) in **six male volunteers**

Subject		1	2	3	4	5	6
Dose	mg	0 147	0 147	0 147	0 147	0 147	0 147
F	%	116	54 3	103 8	80 1	103 6	26 3
t_{lag}	h	0 147	0 008	0 007	0 28	0 151	0 084
t_{max}	h	0 84	0 11	1 41	1 34	0 23	0 21
C_{max}	µg L^{-1}	1 16	0 93	0 61	0 99	1 34	1 39
t_{abs}^{*}	h	0 18	0 015	0 55	0 36	0 010	0 087
$t_{1/2\alpha}$	h	- -	- -	- -	- -	- -	- -
$t_{1/2\beta}$	h	2 10	1 87	1 99	1 93	1 66	1 92
MRT_{po}	h	3 43	2 72	3 66	3 58	2 56	2 52
MAT**	h	1 297	0 593	2 129	1 136	0 007	2 389
$AUC_{0-\infty}$	µg h L^{-1}	4 17	2 44	2 70	3 76	3 15	1 75
CL	L h^{-1}	38 70	30 65	53 78	29 10	46 10	20 8
V_{ss}	L	116 9	82 63	154 5	81 2	110 1	48 23

\- not detected
* one compartment
** independent of model

Table IV.3.a Pharmacokinetic parameters of **methylergometrine** (0 152 mg i v) in **male volunteers** (Table 4 3 2-3)

Subject		1	2	3	4	5	6
$t_{1\,2\alpha}$	h	0 076	0 74	0 04	0 09	0 14	0 041
$t_{1\,2\beta}$	h	1 84	1 96	1 63	2 31	1 52	1 88
MRT_{iv}	h	2 30	2 54	1 87	2 92	1 70	2 17
$AUC_{0\,\infty}$	µg h L-1	4 74	8 11	2 96	4 07	4 05	3 63
CL	L h-1	30 4	17 65	49 7	33 9	21 5	39 8
V_{ss}	L	69 9	44 8	92 7	99 1	36 5	86 1

Table IV.3.b Pharmacokinetic parameters of **methylergometrine** (0 095 mg oral) in **male volunteers** (Table 4 3 2 4)

Subject		1	2	3	4	5	6
Dose	mg	0 095	0 095	0 095	0 095	0 095	0 095
F	%	103 6	22 2	81 9	80 0	85 4	136
t_{lag}	h	0 24	0 35	0 26	0 32	0 29	0 50
t_{max}	h	0 99	0 54	0 59	0 40	0 90	0 67
C_{max}	µg L^{-1}	1 00	0 50	0 47	0 67	0 65	1 35
t_{abs}	h	0 23	0 033	0 06	0 010	0 14	0 03
$t_{1/2\alpha}$	h	- -	- -	- -	- -	- -	- -
$t_{1/2\beta}$	h	1 62	1 87	2 28	2 69	2 37	1 65
MRT_{po}	h	2 91	3 09	3 64	4 22	3 91	2 91
MAT**	h	0 37	0 20	1 51	0 98	1 92	0 24
$AUC_{0\,\infty}$	µg h L^{-1}	3 07	1 13	1 52	2 03	2 16	3 10
CL	L h^{-1}	29 5	14 6	45 6	28 7	30 5	37 5
V_{ss}	L	69 1	39 3	153 3	111 7	103 9	89 2

\- not detected
* one compartment
** independent of model

Table IV.4.a Pharmacokinetic parameters of **methylergometrine** (0 152 mg i v) in **female volunteers**

Subject		1	2	3	4	5	6
$t_{1\,2\alpha}$	h	0 035	0 13	0 10	0 12	0 14	0 077
$t_{1\,2\beta}$	h	2 17	1 66	2 14	2 38	1 52	1 78
MRT_{iv}	h	2 67	2 12	2 80	2 55	1 70	2 04
$AUC_{0\,\infty}$	µg h L^{-1}	5 86	5 30	6 81	5 97	6 72	5 43
CL	L h^{-1}	22 7	26 6	17 6	20 5	21 5	24 2
V_{ss}	L	60 6	56 5	49 4	52 1	36 5	49 4

Table IV.4.b Pharmacokinetic parameters of **methylergometrine** (0 095 mg oral) in **female volunteers**

Subject		1	2	3	4	5	6
Dose	mg	0 095	0 095	0 095	0 095	0 19	0 19
F	%	98 6	138	73 1	63 0	90 5	115
t_{lag}	h	0 063	0 14	0 11	0 17	0 016	0 119
t_{max}	h	1 88	1 25	0 64	0 25	0 12	1 65
C_{max}	µg L^{-1}	0 76	1 36	1 28	1 05	3 83#	1 91#
t_{abs} *	h	1 26	0 49	0 14	0 010	0 016	1 06
$t_{1/2\alpha}$ *	h	- -	- -	-.-	- -	- -	- -
$t_{1/2\beta}$	h	1 26	1 29	1 54	1 96	1 40	1 06
MRT_{po}	h	3 70	2 71	2 55	3 00	2 06	3 19
MAT**	h	0 967	0 45	0 36	0 28	0 344	1 031
$AUC_{0\,\infty}$	µg h L^{-1}	3 61	4 39	3 11	2 36	7 61##	7 81##
CL	L h^{-1}	25 0	28 6	19 3	19 9	21 1	27 5
V_{ss}	L	45	53 0	42 9	56 2	42 7	42 2

For abbreviations see chapter 4

* one compartment
** model independent
# ## corrected for the dose
- - not detected

Appendix 2. Tables concerning chapter 5: pharmacodynamics

Table V.1.a Pharmacokinetic parameters of methylergometrine maleate (0 2 mg i v*) in six females

Subject		1	2	3	4	5	6
$t_{1\,2\alpha}$	h	0 035	0 065	0 13	0 10	0 061	0 14
$t_{1\,2\beta}$	h	2 17	1 61	2 14	2 38	1 69	1 78
MRT_{iv}	h	2 67	1 95	2 80	2 55	1 96	2 04
$AUC_{0\,\infty}$	µg h L^{-1}	5 86	6 11	6 81	5 97	6 90	5 43
CL	L h^{-1}	22 7	24 87	17 6	20 5	22 04	24 2
V_{ss}	L	60 6	48 6	49 4	52 1	43 14	49 4

Table V.1.b Pharmacokinetic parameters of methylergometrine maleate (0 2 mg i v) in four females 24h after the oral (0 5mg ME) test

Subject		1	2	4	5
$t_{1\,2\alpha}$	h	0 065	0 047	0 064	0 034
$t_{1/2\beta}$	h	2 29	1 79	2 22	1 27
MRT_{iv}	h	2 16	2 10	2 92	1 58
$AUC_{0\,\infty}$	µg h L^{-1}	3 72	8 48	10 5	5 17
CL	L h^{-1}	34 1	17 93	14 44	29 41
V_{ss}	L	73 1	37 65	42 12	46 40

Table V.1.c Pharmacokinetic parameters of methylergometrine (0 380 mg oral pure substance) in woman

Subject		1	2	4	5	3***	6***
Dose	mg	0 380	0 380	0 380	0 380	0 380	0 380
F	%	75 4	89 9	92 6	47 7	60 0	94 6
t_{lag}	h	0 32	0 16	0 31	0 39	0 28	0 43
t_{max}	h	1 12	0 24	0 80	0 45	4 46	2 94
C_{max}	µg L^{-1}	2 04	6 12	6 38	2 75	4 13	4 98
t_{abs}	h	0 24	0 010	0 15	0 007	4 24	1 73
$t_{1/2\alpha}$*	h	- -	- -	- -	- -	- -	- -
$t_{1/2\beta}$	h	1 73	1 97	1 10	1 63	4 21	1 73
MRT_{po}	h	3 17	3 01	2 11	2 75	12 48	5 44
MAT**	h	1 01	1 06	0 44	0 79	9 68	3 40
$AUC_{0\,\infty}$	µg h L^{-1}	7 00	15 6	13 82	5 45	10 22	11 76
CL	L h^{-1}	40 85	19 2	25 47	27 5	3 12	10 54
V_{ss}	L	102 2	54 4	40 41	64 4	19 0	26 88

* one compartment,** model independent *** absorption too long outliers?,
- - not detected For abbreviations see chapter 5

Table V.2 Mean values of Frequency, Basal Tone and Amplitude (A) in a 5 minutes' period after intravenous (0.2 mg) administration of methylergometrine maleate in six female volunteers.

	Frequency						Basal Tone						Amplitude					
Subject	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
Time *																		
0	2	3	4	2.5	3.5	4	10	10	25	20	0	10	100	80	50	100	35	35
5	7	5	8	4	8	7	35	35	30	40	10	20	90	40	25	105	10	35
10	13	6	8	11	10	12	70	50	60	65	20	40	30	40	10	60	5	15
15	13	6	7.5	12	7	12	70	50	65	65	20	45	30	40	10	55	10	10
20	10	4	7.5	12	9	10	70	45	70	65	25	45	45	30	10	50	5	10
25	12	4	5	9	7	7	65	30	70	60	25	35	35	35	7.5	45	10	15
30	10	4	4	7	5	6	50	30	60	55	15	30	25	40	20	30	15	20
35	10	4	4	6.5	3	6	30	40	40	50	10	30	50	30	20	30	60	20
40	4	4	3.5	5	3	3	50	40	30	40	10	30	30	10	20	20	60	15
45	5	3	3.5	4	3	3	55	20	40	40	10	25	40	30	10	30	50	20
50	5	3	3	4	3	3	70	20	40	40	5	20	15	40	20	20	25	20
55	5	3	3	4	3	4	70	20	30	50	5	25		40	15	20	15	
60	5	3	3	4	3	2	70	30	30	50	5	20	25	40	35	15	20	20
70	5	2.5	2.5	4	2	2	55	32	25	55	0	20	40	18		25	15	20
80	4	3	2.5	5	4	2	35	25	30	55	0	20	35	50	50	15	10	30
90	3	2	2.5	3	3	2	25	30	40	50	0	20	5	50	30	20	15	30

*Time after drug administration

Table V.3 Mean values of Frequency, Basal Tone and Amplitude (A) in a 5 minutes' period after intravenous (0.2 mg) administration of methylergometrine maleate in six female volunteers.

	Frequency						Basal Tone						Amplitude					
Subject	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
Time *																		
0	2.5	3.5	2.5	7	8	2.5	10	20	15	30	25	40	60	70	70	25	30	60
5	3	2.5	3	6	9	3	10	15	15	35	25	20	60	80	70	25	30	40
10	3	3	3	6	5	12	10	10	15	40	20	30	60	90	70	25	25	10
15	3	4	3	9	7	12	10	10	15	30	20	30	60	70	90	10	40	10
20	3	5	3	6	7	10	20	15	15	30	20	30	50	60	90	25	40	15
25	3	5	4	6	8	16	20	25	15	45	20	30	55	80	70	20	30	10
30	4	5	4	7	7	15	40	30	20	55	20	25	40	60	70	25	45	10
35	6	4	4	8	10	14	50	25	25	60	25	25	25	70	85	10	35	5
40	6	4	4	6	11	10	60	30	25	55	30	20	20	60	85	20	25	10
45	6	4	5	6	8	7	70	20	20	55	30	20	15	70	70	10	40	15
50	8	4	4	5	9	6	70	20	20	55	40	20	10	60	50	7.5	25	20
55	4	3	3	7	9	4	60	20	20	55	40	15	10	60	70	5	15	20
60	4	3	4	5	10	11	40	20	30	60	40	20	20	70	60	10	15	5
70	3	3	3.5	5	8	9	30	20	20	60	30	20	50	65	70	10	25	10
80	3.5	3	3.5	6	9	9	25	25	20	60	30	25	60	65	70	10	30	10
90	3	4	3.5	5	9	10	30	30	20	55	30	30	30	60	60	20	25	10

*Time after drug administration in minutes

Table V.4 Mean values of Frequency, Basal Tone and Amplitude in a 5 minutes' period in four female volunteers after intravenous (0 2 mg) administration of methylergometrine maleate (ME) *with* preceding oral (0 5 mg) ME

	Frequency				Basal Tone				Amplitude			
Subject	1	2	3	4	1	2	3	4	1	2	3	4
Time*												
0	3	4	5	5	10	10	20	20	40	60	30	50
5	3	6	4	6	10	5	20	15	35	30	25	45
10	3	7	7	8	15	10	20	15	30	30	10	35
15	8	6	4	7	20	10	20	15	35	30	15	30
20	7	6	5	7	15	5	20	15	40	25	10	30
25	4	7	4	8	15	5	25	15	50	30	10	20
30	3	5	4	8	10	5	25	20	80	50	10	25
35	-	4	4	7	-	5	25	20	-	60	10	30
40	2 5	4	3	6	10	0	25	20	55	90	10	25
45	-	3	3	6	-	0	20	25	-	70	10	25
50	2	4	3	6	10	5	20	25	55	70	15	25
55	-	5	3	6	-	5	20	30	-	70	15	20
60	1 5	5	3	6	10	0	20	30	40	50	10	20
70	2	5	3	7	10	0	20	40	50	60	10	10
80	2	3	3	5	10	0	20	40	60	60	10	10
90	-	4	3	5	-	0	20	40	-	50	10	10

*Time after drug administration in minutes

Table V.5 Mean±SD of the mean values of Frequency, Basal Tone and Amplitude in a 5 minutes' period in six females (A) excerpted from Table V 2 and V 3 and four females (B) Table V 4

	Frequency			**Basal Tone**			**Amplitude**		
	A ME IV	A ME po	B ME IV	A ME IV	A ME po	B ME IV	A ME IV	A ME po	B ME IV
Time*									
0	3 2±0 8	4 3±2 5	4 3±1 0	12 5±8 8	23 3±10 8	15 0±6	66 7±30 6	52 5±20	45 0±13
5	6 5±1 6	4 4±2 6	4 8±1 5	28 3±11 3	20 0± 8 9	12 5±6	50 8±37 9	50 8±22	33 8±9
10	10±2 6	5 3±3 5	6 3±2 2	50 8±18 5	20 8±12 0	15 0±4	26 7±20 9	46 7±31	26 3±11
15	9 6±3 1	6 3±3 7	6 3±1 7	52 5±18 6	19 2± 9 2	16 3±5	25 8±19 1	46 7±33	27 5±9
20	8 8±2 8	5 7±2 7	6 3±1 0	53 3±18 1	21 7± 6 8	13 8±6	25 0±19 5	46 7±27	26 3±12
25	7 3±2 9	7 0±4 7	5 8±2 1	47 5±19 7	25 8±10 7	15 0±8	24 6±15 7	44 2±28	27 5±17
30	6 0±2 3	7 0±4 1	5 0±2 2	40 0±17 6	31 7±13 7	15 0±9	25 0±8 9	41 7±22	41 3±31
35	5 6±2 5	7 7±3 9	5 0±1 7	33 7±13 7	35 0±15 8	16 7±10	35 0±16 4	38 3±33	33 3±25
40	3 8±0 7	6 8±3 0	3 9±1 5	33 7±13 7	36 7±16 6	13 8±11	25 8±18 0	36 7±29	45 0±35
45	3 6±0 8	6 0±1 4	4 0±1 7	31 7±16 3	35 8±21 5	15 0±13	30 0±14 1	36 7±28	35 0±31
50	3 5±0 8	6 0±2 1	3 8±1 7	32 5±22 7	37 5±21 4	15 0±9	23 3±8 8	28 8±22	41 3±26
55	3 7±0 8	5 0±2 4	4 7±1 5	33 3±23 2	35 0±19 5	18 3±13	22 5±11 9	30 0±28	35 0±30
60	3 3±1 0	6 2±3 4	3 9±2 0	34 2±22 9	35 0±15 2	15 0±13	25 8±9 7	30 0±28	30 0±18
70	3 0±1 2	5 3±2 6	4 3±2 2	31 2±21 3	30 0±15 5	17 5±17	23 6±9 9	38 3±27	32 5±26
80	3 4±1 1	5 7±2 8	3 3±1 3	27 5±18 1	30 8±14 6	17 5±17	31 7±16 9	40 8±28	35 0±29
90	2 6±0 5	5 8±3 0	4 0±1 0	27 5±17 2	32 5±11 7	20 0±20	25 0±15 5	34 2±21	23 3±23

*Time after drug administration in minutes

Table V.6.a *Area under the curve volunteer no1*

	Intravenous				*Oral*				*Intravenous* ***with*** *preceding oral ME*			
	ΣIUP AUC	**time period****	**mean IUP/sp**	**AUC 60sec**	**ΣIUP AUC**	**time period****	**mean IUP/sp**	**AUC 60sec**	**ΣIUP AUC**	**time-period****	**mean IUP/sp**	**AUC 60sec**
*Time**												
-20	26291	1200	21 9	2629	23066	1200	19 2	2306	12484	1200	10 4	1248
-10	27310	1200	22 7	2731	24382	1200	20 3	2438	15098	1200	12 6	1510
0	33560	1200	28 0	3356	29420	1200	24 5	2942	16198	1200	13 5	1620
2	4771	240	20	2386	31162	1200	26 0	3116	3128	240	13 0	1564
3	7072	120	59	7072					1388	120	11 6	1388
5	15120	240	63	7560					4102	240	17 1	2051
10	43657	600	72 8	8731					19444	600	32 4	3889
20	94462	1200	78 7	9446	33640	1200	28 0	3364	32663	1200	27 2	3266
30	94436	1200	78 7	9444	38040	1200	31 7	3804	32492	1200	27 1	3249
40	33952	600	56 6	7790	28887	600	48 1	5777	28869	1200	24 1	2887
45					35882	600	59 8	7176				
50	36312	600	60 5	7262	82366	1200	68 6	8237	27389	1200	22 8	2739
60	77504	1200	65 8	7750	76847	1200	64	7685	29975	1200	25 0	2998
70	69020	1200	57 5	6902	53004	1200	44	5300	27365	1200	22 8	2737
80					57409	1200	47 8	5741	21132	1200	17 6	2113
90									16477	1200	13 7	1648

* time after drug administration
** time-period expressed in number of sample-points
one sample point is 0 5 seconds

Table V.6.b *Area under the curve volunteer no2*

	Intravenous				*Oral*				*Intravenous* ***with*** *preceding oral ME*			
	ΣIUP AUC	**time period****	**mean IUP/sp**	**AUC 60sec**	**ΣIUP AUC**	**time period****	**mean IUP/sp**	**AUC 60sec**	**ΣIUP AUC**	**time-period****	**mean IUP/sp**	**AUC 60sec**
*Time**												
-20	36645	1200	30.5	3664				4835			15.8	1891
-10	21742	840	27.9	3624				4835				
0	33425	1200	25.9	3343	145055	3600	40.3	4835	37825	2400	15.8	1891
2	5062	240	20.9	2531				4441	2146	240	8.9	1073
3	3418	120	28.5	3418				4441	1337	120	11 1	1337
5	9135	120	76.1	9135				4441			14.3	1715
10	35219	600	58.7	7044	44408	1200	37.0	4441			14.3	1715
15					19836	600	33.1	3967				
20	69259	1200	57.7	6926	24864	600	41.4	4973	17150	1200	14.3	1715
30	56470	1200	47.1	5647	57011	1200	47.5	5701	13497	1200	11.2	1350
40	60146	1200	50.1	6015	51961	1200	43.3	5196	17773	1200	14.8	1777
50	49088	1200	40.9	4909	55950	1200	46.6	5595				
60	52092	1200	44.2	5298	48928	1200	40.8	4893	16110	980	16.4	1973
70	48566	1200	40 5	4857	51384	1200	42.8	5138	16416	1200	13.7	1642
80	53633	1200	44.7	5363	54166	1200	45.1	5417				
90	55138	1200	45.9	5514					18227	1200	15.2	1823

* time after drug administration
** time-period expressed in number of sample-points
one sample-point is 0.5 seconds

Table V.6.c *Area under the curve volunteer no3*

	Intravenous				*Oral*				*Intravenous* ***with*** *preceding oral ME*			
	ΣIUP AUC	**time period****	**mean IUP/sp**	**AUC 60sec**	**ΣIUP AUC**	**time period****	**mean IUP/sp**	**AUC 60sec**	**ΣIUP AUC**	**time-period****	**mean IUP/sp**	**AUC 60sec**
*Time**												
-20	62668	1200	52.2	6267	43016	1200	35.8	4302	35295	1200	29.4	3530
-10	56396	1200	47.0	5640	46587	1200	38.8	4659	36945	1200	30.8	3695
0	55653	1200	46 4	5565	39743	1200	33.1	3974	32341	1200	27.0	3234
2	9472	240	39.5	4736								
3	6603	120	55.0	6603								
5	14044	240	58.5	7022					14615	600	24.4	2923
10	41502	600	69.2	8300	38911	1200	32.4	3891	16823	600	28.0	3365
20	88478	1200	73.7	8848	38130	1200	31.8	3813	34056	1200	28.4	3406
25					18698	600	31.2	3740				
30	10984	155	70.9	8504	26323	600	43.9	5265	31108	1200	25.9	3111
40					48717	1200	40 6	4872	29784	1200	24.8	2978
50					49396	1200	41.2	4940	30155	1200	25.1	3016
60	44819	1200	37.3	4482	46421	1200	38.7	4642	27802	1200	23.2	2780
70	39140	1200	32.6	3914	46405	1200	38.7	4641	25578	1200	21.3	2558
80	34405	1200	28.7	3441	47131	1200	39.3	4713	30070	1200	25.1	3007
90	29311	1200	24.4	2931	52350	1200	43.6	5235	30656	1200	25.5	3066

* time after drug administration

** time-period expressed in number of sample-points
one sample-point is 0 5 seconds

Table V.6.d *Area under the curve volunteer no4*

	Intravenous				*Oral*				*Intravenous* ***with*** *preceding oral ME*			
	ΣIUP AUC	**time period****	**mean IUP/sp**	**AUC 60sec**	**ΣIUP AUC**	**time period****	**mean IUP/sp**	**AUC 60sec**	**ΣIUP AUC**	**time-period****	**mean IUP/sp**	**AUC 60sec**
*Time**												
-20	48307	1200	40 3	4831	54393	1200	45.3	5439	44498	1200	37.1	4450
-10	54542	1200	45 5	5454	62779	1200	52.3	6278	36848	1200	30.7	3685
0	55467	1200	46.2	5547	53335	1200	44 4	5334	35197	1200	29.3	3520
2	11808	240	49 2	5904								
3	4902	120	40.9	4902								
5	18021	240	75.1	9011								
10	46472	600	77.5	9294	56386	1200	47.0	5639	32181	1200	26.8	3218
20	84669	1200	70.6	8467	52624	1200	43.9	5262	30655	1200	25.5	3066
30	75992	1200	63.3	7599	49313	1200	41.1	4931	31129	1200	25.9	3113
40	57991	1200	48.3	5799	69966	1200	58.3	6997	36657	1200	30.5	3666
50	56744	1200	47.3	5674	79224	1200	66.0	7922	38127	1200	31.8	3813
60	62717	1200	52.3	6272	72926	1200	60.8	7293	43281	1200	36.1	4328
70	74283	1200	61.9	7428	78016	1200	65 0	7802	50379	1200	42.0	5038
80	71686	1200	59 7	7169	73428	1200	61 2	7343	54919	1200	45.8	5492
90	65712	1200	54.8	6571	81870	1200	68 2	8187	49933	1200	41.6	4993

* time after drug administration
** time-period expressed in number of sample-points
one sample-point is 0 5 seconds

Table V.6.e *Area under the curve volunteer no5*

	Intravenous				*Oral*			
	ΣIUP AUC	**time period****	**mean IUP/sp**	**AUC 60sec**	**ΣIUP AUC**	**time period****	**mean IUP/sp**	**AUC 60sec**
*Time**								
-20	16748	1200	14.0	1675	40302	1200	33.6	4031
-10	12135	1200	10.1	1214	42520	1200	35.4	4252
0	11768	1200	9.8	1177	44660	1200	37.2	4466
2	4882	240	20.3	2441				
3								
5	1044	360	2.9	348				
10	7225	480	15.1	1806	42827	1200	35.7	4283
20	26966	1200	22.5	2697	37827	1200	31.5	3783
30	32572	1200	27.1	3257	33680	1200	28.1	3368
35					21411	600	35.7	4282
40	31797	1200	26.5	3180	24355	600	40.6	4871
45					25398	600	42.3	5080
50	28100	1200	23.4	2810			42.3	
60	18241	1200	15.2	1824	53260	1200	44.4	5326
70	15389	1200	12.8	1539	53754	1200	44.8	5375
80	7045	1200	5.9	705	48314	1200	40.3	4831
90	5897	1200	4.9	590	47178	1200	39.3	4718

* time after drug administration

** time-period expressed in number of sample-points
one sample-point is 0 5 seconds

Table V.6.f *Area under the curve volunteer no6*

	Intravenous				*Oral*			
	ΣIUP AUC	**time period****	**mean IUP/sp**	**AUC 60sec**	**ΣIUP AUC**	**time period****	**mean IUP/sp**	**AUC 60sec**
*Time**								
-20	28182	1200	23 5	2818	64728	1200	53 9	6473
-10	23580	1200	19 7	2358	60722	1200	50 6	6072
0	14990	600	25 0	2998	48993	1200	40 8	4899
2	7093	240	29 6	3547				
3	2125	120	17 7	2125				
5	6621	240	27 6	3114				
10					46737	1200	38 9	4674
20	51399	1200	42 8	5140	35503	1200	30 0	3550
30	46013	1200	38 3	4601	37093	1200	30 9	3709
40	43869	1200	36 6	4387	30947	1200	25 8	3095
50	34416	1200	28 7	3442	31038	1200	25 9	3104
60	31293	1200	26 1	3129	26291	1200	21 9	2629
70	26482	1200	22 1	2648	28858	1200	24 0	2886
80	24979	1200	20 8	2498	37743	1200	31 5	3774
90	26523	1200	22 1	2652	40378	1200	33 6	4038

* time after drug administration
** time-period expressed in number of sample-points
one sample-point (sp) 0 5 seconds

Stellingen

behorende bij het proefschrift
"Safe motherhood - the role of oral (methyl)ergometrine
in the prevention of postpartum haemorrhage"
A N J A de Groot

1 Het derde tijdperk moet actief geleid worden, tenzij tweede-lijns zorg binnen 20 minuten bereikbaar is (dit proefschrift)

2 Ondanks het adagium in de geneeskunde "primum non nocere" is intraveneuze (methyl)ergometrine met haar mogelijk incidenteel dodelijke bijwerkingen nog steeds als profylactisch geneesmiddel geregistreerd (dit proefschrift)

3 Glucuronidatie is een aannemelijke metabole route van (methyl)ergometrine (dit proefschrift)

4 (Methyl)ergometrine lijkt zijn werkzaamheid uit te oefenen via een nog onbekende receptor op het archemyometrium (dit proefschrift)

5 Na een eerste dosering (methyl)ergometrine lijkt de receptor ongevoelig te worden voor een tweede dosering (dit proefschrift)

6 Nederland blijft een unieke locatie vanuit mondiaal verloskundig perspectief (dit proefschrift)

7 Objectieve beoordeling van wetenschappelijk versus ethisch belang is essentieel voor wetenschappelijk onderzoek

8 Patient-gebonden onderzoek dient te volgen op onderzoek bij vrijwilligers, waarbij de hoofdonderzoeker de eerste proefpersoon behoort te zijn

9 Goed klinisch onderzoek vraagt een leger van doorzetters

10 If you steal from another, it's plagiarism, if you steal from many it is research (Wilson Mizner)

11 Soms lijkt promoveren sneller te gaan dan het behalen van een golfvaardigheidsbewijs

12 Eskes knipt navelstrengen door maar knoopt enkele later weer aan onderzoek vast