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Termination of pregnancy with reduced doses of mifepristone

World Health Organisation Task Force on Post-ovulatory Methods of Fertility Regulation

Abstract

***Objectives*—To compare the abortifacient efficacy and side effects of three doses of the antiprogestin mifepristone plus prostaglandin for termination of early pregnancy.**

***Design*—Randomised, double blind multicentre trial.**

***Setting*—11 departments of obstetrics and gynaecology and of family planning, mostly in university hospitals, in seven countries.**

***Subjects*—1182 women with an early pregnancy (menstrual delay of 7-28 days) requesting abortion.**

***Interventions*—Single doses of 200 mg, 400 mg, or 600 mg mifepristone followed, 48 hours later, by vaginal pessary of 1 mg of the prostaglandin E_1 analogue gemeprost.**

***Main outcome measures*—Outcome of treatment; duration and subjective amount of menstrual bleeding; side effects and complications; and concentrations of haemoglobin.**

***Results*—Outcome was similar with the three doses of mifepristone. Of the 1151 women with known outcome, 95·5% had a complete abortion (364 (93·8%) of those given 200 mg mifepristone, 368 (94·1%) of those given 400 mg, and 367 (94·3%) of those given 600 mg), 3·7% had an incomplete abortion (14 (3·6%), 15 (3·8%), and 14 (3·6%)), 0·3% had a missed abortion (three (0·8%), one (0·3%), and none), and 0·4% had a continuing live pregnancy (two (0·5%), two (0·5%), and one (0·3%)). Of the 43 women who had incomplete abortion, 23 underwent emergency uterine curettage (usually for haemostatic purposes) and three of these women were given a blood transfusion. The numbers of reported complaints, bleeding patterns, and changes in blood pressure and haemoglobin concentrations were similar with the three treatments.**

***Conclusions*—For termination of early pregnancy a single dose of 200 mg mifepristone is as effective as the currently recommended dose of 600 mg when used in combination with a vaginal pessary of 1 mg gemeprost.**

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Introduction

The antiprogestin mifepristone (RU 486; 11β-[p-(dimethylamino)-phenyl]-17β-hydroxy-17-[1-propynyl]estra-4,9-dien-3-one) has been registered for termination of early pregnancy in France and China since September 1988, in Great Britain since July 1991, and in Sweden since September 1992. In France and China mifepristone can be used for inducing abortion in pregnancies of up to seven weeks of amenorrhoea, while in Britain and Sweden it can be used in pregnancies of up to nine weeks of amenorrhoea. In all four countries the recommended treatment is a single dose of 600 mg mifepristone (three tablets of 200 mg) followed 36-48 hours later by a suitable prostaglandin analogue with uterotonic activity (such as a vaginal suppository of gemeprost or oral tablets of misoprostol), and this combination gives complete abortion in 95-96% of cases.[1] In the largest series reported to date efficacy was 95·3% among 15 709 women treated in France with vaginal gemeprost or intramuscular sulprostone as the prostaglandin.[2] The failures consisted of persisting pregnancies (1·2%), incomplete expulsion (2·8%), and women requiring a haemostatic surgical procedure (0·7%).

Several studies conducted on the pharmacokinetics of orally administered mifepristone indicate that concentrations of the antiprogestin in the blood do not increase proportionally with increasing oral doses.[3] This is probably because in humans mifepristone is bound to α_1 acid glycoprotein, which acts as a low affinity carrier protein. The carrying capacity of α_1 acid glycoprotein is limited so that plasma levels of mifepristone correlate with the concentration of this protein rather than the administered dose.[4] From these studies it seemed likely that the percentage of successful abortions achieved by a single dose of 600 mg mifepristone could be obtained with smaller doses of the antiprogestin. Support for this assumption is provided by studies conducted under the auspices of the World Health Organisation,[5,6] including a recent randomised multicentre trial in which five 25 mg doses of mifepristone given at 12 hour intervals were shown to be as effective as the recommended single dose of 600 mg.[7] Rodger and Baird administered single doses of 600 mg, 500 mg, and 400 mg of mifepristone and reported rates of complete abortion of 100%, 97%, and 90% respectively.[8] The number of women in each group was too small, however, to assess if the apparent downward trend was statistically significant.

The purpose of the present randomised, double

blind, multicentre trial was to compare the abortifacient efficiency and side effects of three single doses of mifepristone (200 mg, 400 mg, and 600 mg) followed 48 hours later by a vaginal pessary of 1 mg gemeprost in women with an early pregnancy.

Subjects and methods

Permission for the study was obtained from the WHO's Secretariat Committee on Research Involving Human Subjects and from the corresponding ethics committees of the 11 participating centres (Aberdeen, Edinburgh, Havana, Hong Kong, Ljubljana, Milan, Shanghai, Stockholm, Szeged, Tianjin, and Wuhan). Informed consent was obtained from all women taking part in the trial. The criteria used for selection of subjects were similar to those of our earlier studies.[6,7] Women requesting termination of pregnancy were recruited if they were in good general health and had a history of regular menstrual cycles (25-35 days) for at least three months before conception, a menstrual delay of 7-28 days, a positive urinary pregnancy test, and a normal intrauterine pregnancy as judged from clinical and ultrasound examinations. Women were excluded from the study if they were unsure about the date when their missed menstrual period should have started or about the date of onset of their last menstrual period; if their last menstruation did not start at the expected time or was abnormal in terms of duration or amount of flow; if they had an intrauterine device in situ, had used hormonal contraception during the cycle immediately before conception or during the conception cycle, or wished to start hormonal or intrauterine contraception before their first menses after abortion; or if there was a contraindication to the use of mifepristone or prostaglandin, a history or evidence of thromboembolism or liver disease, or regular use of prescribed drugs.

The planned sample size was 99 subjects per centre: this size was recommended by the task force's steering committee since it would permit detection (at the 0·05 level with 80% power) of a difference of 5% or more in success rate between 600 mg mifepristone (assumed to have 95% success rate) and the lower doses. A success rate lower than 90% was considered not to be clinically acceptable. At each participating centre women were randomly allocated to treatment with a single dose of 200 mg, 400 mg, or 600 mg mifepristone by a double blind method. Randomisation was done at WHO's headquarters using the random permutation block technique with block size of nine. The randomisation tables were passed to Roussel Uclaf (Paris, France), where the appropriate dose of mifepristone (one, two, or three 200 mg tablets) for each subject in the trial was dispensed in individually labelled medicine bottles. For the women receiving the lower doses two or one placebo tablets were added to the bottles so that they all contained three tablets.

All the subjects attended their clinic on the first day of the study, when they took their tablets in the presence of a member of the study team, who recorded the date and time. Two days later the women received a vaginal suppository of the prostaglandin E_1 analogue gemeprost, after which they remained under observation for at least four hours. During this time their blood pressure, temperature, pulse, and any complaints were recorded at hourly intervals, and medication for relief of pain or other symptoms was given as judged necessary. At the end of the observation period, a vaginal examination was made to remove any products of conception visible in the cervical canal or vagina. Subsequent follow up visits were scheduled at about one, two, and six weeks later. A fourth follow up visit was arranged if menstruation had not returned by the time of the six week visit. At each visit the women were asked about possible side effects and about the presence and amount of vaginal bleeding. Blood pressure, pulse, and a blood sample for measuring haemoglobin concentration were taken, and vaginal and ultrasound examinations were done if indicated.

As in our previous studies[6,7,9] the outcome of treatment was classified as complete abortion, incomplete abortion, missed abortion, or continuing live pregnancy on the basis of the subject's history, and clinical findings on pelvic examination, and if indicated, ultrasonography. All data were recorded on standardised forms and analysed at WHO headquarters, Geneva. Values given in the text and tables are arithmetic means and standard deviation unless stated otherwise. Comparisons between treatment groups and between outcome categories were made by the χ^2 test, χ^2 test for trend, Student's t test, or analysis of variance as appropriate. Repeated measures analysis of variance was used to assess the significance of differences in blood pressure and haemoglobin concentration and of changes in these parameters from pretreatment values within treatment group. Findings were considered statistically significant if they reached the 1% level.

Results

SUBJECTS

A total of 1182 subjects had been recruited when the trial was stopped: 99 women in each of eight centres; 91 in Ljubljana; and 149 and 150 in Aberdeen and Edinburgh respectively, where the sample size had been increased after the original target of 99 subjects had been reached more quickly than expected. The numbers of women who received 200 mg, 400 mg, and 600 mg mifepristone were 393, 393, and 396 respectively, but 14 women were excluded from the statistical analysis because they did not fulfil all of the admission criteria. These 14 women comprised nine who had a menstrual delay of less than seven days or more than 28 days (four, one, and four in the 200 mg, 400 mg, and 600 mg groups) and five whose average menstrual cycle lasted less than 25 days (one, one, and three in the three groups). All of these women had a complete abortion.

Table I shows the similar baseline characteristics of the women randomised to the three treatments: the women had a mean age of 28 and a mean weight of 57-58 kg; 742 of them had been pregnant before, and about two thirds of these had had one or more induced abortions; the mean menstrual delay was 17-18 days; the mean duration of amenorrhoea was 46 days; and the average diameter of the amniotic sac on ultrasound examination was 18-20 mm. The women in the three groups also had similar gynaecological histories (previous gynaecological surgery, past gynaecological infections, and occurrence of dysmenorrhoea) and obstetric histories (number and outcome of previous

TABLE I—*Baseline characteristics of women at 11 centres undergoing termination of early pregnancy with three different doses of mifepristone. Values are means (standard deviations)*

Characteristic	Dose of mifepristone		
	200 mg (n=388)	400 mg (n=391)	600 mg (n=389)
Age (years)	27·5 (6·2)	28·1 (6·6)	27·6 (6·2)
Weight (kg)	57·6 (8·7)	57·1 (8·1)	57·6 (9·4)
Height (cm)	163·3 (6·4)	163·1 (6·0)	163·6 (6·3)
Average length of menstrual cycles before conception (days)	28·7 (1·7)	28·6 (1·8)	28·7 (1·5)
Duration of last menses (days)	4·8 (1·2)	4·9 (1·1)	5·0 (1·2)
Number of previous pregnancies*	2·4 (1·5)	2·5 (1·4)	2·2 (1·3)
Menstrual delay (days)	17·1 (5·3)	17·2 (5·2)	17·6 (5·4)
Duration of amenorrhoea (days)	45·8 (5·3)	45·9 (5·4)	46·3 (5·5)
Diameter of amniotic sac (mm)	18·3 (7·3)	19·5 (8·1)	19·8 (7·9)

*Numbers of women who had been pregnant before: 242 in 200 mg group, 250 in 400 mg group, and 250 in 600 mg group.

pregnancies). There was also no difference between the three groups in the numbers of reported complaints related to pregnancy: 53% in each group reported nausea during this pregnancy, 44-46% reported breast tenderness, about 30% complained of fatigue, and 20-24% reported abdominal pain.

OUTCOME OF TREATMENT

Vaginal bleeding was induced in all but six of the 1168 women. (These six comprised one who was admitted to the study but who could not swallow the tablets and five who vomited immediately after taking the tablets and who had their pregnancy terminated the same day by vacuum aspiration.) About 57-63% of the women in each group started to bleed before administration of gemeprost. The women who started bleeding before receiving gemeprost did not differ from those who started bleeding after receiving gemeprost in height, weight, ponderal index, or in the interval between mifepristone and gemeprost treatments (about 48 hours). Among the women who started bleeding after gemeprost treatment the median interval between the prostaglandin's administration and the start of bleeding was about two hours and did not differ among the three treatment groups. Expulsion of identified products of conception occurred during the first four hours after gemeprost treatment in 807 of the subjects (267 (69·2%) 284 (73·4%), and 256 (66·7%) in the 200 mg, 400 mg, and 600 mg groups). In 308 of these 807 women the recorded time was 240 minutes because the expulsion had passed unnoticed and the products were found during the prescribed vaginal examination at the end of the four hours.

Table II shows that there was no difference among the three groups in the outcome of treatment. The slight increase in the numbers of complete abortions from 364 (93·8%) in the 200 mg group to 367 (94·3%) in the 600 mg group was not significant. In 23 of the 43 women classified as having an incomplete abortion curettage was done as an emergency procedure, usually for haemostatic purposes (three of these women were given a blood transfusion). In the remaining 20 incomplete abortions curettage was done electively because of a clinical or ultrasonographic suggestion of retained products: this diagnosis was confirmed in 16 of the women by histological examination of the curettings.

TABLE II—*Outcome of treatment of women in early pregnancy with three different doses of mifepristone at 11 centres*

	Dose of mifepristone					
	200 mg (n=388)		400 mg (n=391)		600 mg (n=389)	
	No (%)	95% Confidence interval of percentage	No (%)	95% Confidence interval of percentage	No (%)	95% Confidence interval of percentage
Complete abortion	364 (93·8)	91·4 to 96·2	368 (94·1)	91·8 to 96·5	367 (94·3)	92·0 to 96·7
Incomplete abortion	14 (3·6)	1·8 to 5·5	15 (3·8)	1·9 to 5·7	14 (3·6)	1·8 to 5·4
Missed abortion	3 (0·8)	0 to 1·7	1 (0·3)	0 to 1·8	0	
Continuing live pregnancy	2 (0·5)	0 to 1·2	2 (0·5)	0 to 1·2	1 (0·3)	0 to 0·8
Undetermined	5 (1·3)	0·2 to 2·4	5 (1·3)	0·2 to 2·4	7 (1·8)	0·5 to 3·1

The outcome for 17 women was undetermined. Six of these women either did not take the tablets or vomited them, and their pregnancies were terminated by vacuum aspiration. One subject took the tablets but requested a vacuum aspiration the next day. Two women refused the gemeprost pessary: one had a complete abortion while the other required an emergency curettage on the fourth day of the study because of heavy bleeding associated with an incomplete abortion. Six other women received both mifepristone and gemeprost and attended the follow up visit one week later, but they defaulted from attending further follow up visits and attempts to contact them failed. In each of these six subjects products of conception had been identified during the four hour observation period after gemeprost treatment. The remaining two undetermined outcomes concerned a woman who was admitted to another hospital with appendicitis two days after receiving gemeprost and who did not attend further follow up visits (ultrasound examination at the other hospital, however, confirmed that the abortion was complete) and one subject with an undiagnosed tubal pregnancy which ruptured about two weeks after treatment. If the women with undetermined outcome are excluded the overall success rate rises to 95·5% (95·0%, 95·3%, and 96·1% in the 200 mg, 400 mg, and 600 mg groups). When the outcome of treatment was analysed by the length of menstrual delay (≤14 days, 15-21 days, or 22-28 days) no difference was found in each of the three groups separately or overall.

Analysis of the individual results from the 11 participating centres indicated that there were no significant differences in outcome between treatment groups in any single centre. Between centres, however, the rates for complete abortions ranged from 88% to 100% for women given 200 mg mifepristone, from 82% to 100% for those given 400 mg, and from 88% to 100% for those given 600 mg. This variation approached significance in the 400 mg group ($p=0·05$) and was significant when the differences within treatments were pooled ($p<0·01$). When centres were ranked in terms of their rate of complete abortions three centres—Aberdeen, Hong Kong, and Wuhan—tended to have the lowest rates for the three treatments. In Aberdeen the relatively low overall success rate (91·2%) was because this centre had the highest proportion of cases with an undetermined outcome (seven of the study's total of 17 such cases). The low overall success rates in Hong Kong (87·6%) and Wuhan (86·9%) were related to the high proportion of cases classified as incomplete abortion in these two centres (8·2% and 11·1% respectively).

The duration of vaginal bleeding or spotting in women with a complete abortion was the same in subjects given 200 mg mifepristone (median 12 (range 4-71) days), 400 mg (12 (4-72) days), and 600 mg (12 (4-66) days). Duration of bleeding was significantly different between centres, ranging from a mean of 9·6 days in Milan to 17·8 days in Stockholm ($p<0·001$), but was not different between women of

TABLE III—*Haemoglobin concentrations (g/l) of blood samples taken at various times during study from women undergoing termination of early pregnancy with three different doses of mifepristone*

	Dose of mifepristone					
	200 mg		400 mg		600 mg	
	Mean (SD) concentration	No of subjects	Mean (SD) concentration	No of subjects	Mean (SD) concentration	No of subjects
At admission	125·0 (12·2)	387	124·4 (12·1)	391	123·9 (11·7)	389
Before gemeprost treatment	123·8 (11·9)***	384	124·1 (12·1)	388	123·0 (11·8)**	384
Follow up:						
One week	121·9 (12·2)***	379	121·5 (11·8)***	386	122·0 (11·4)***	377
Two weeks	122·9 (12·0)***	372	123·0 (11·8)	382	122·9 (11·8)	378
Six weeks	124·2 (11·9)	361	125·1 (11·7)	365	124·5 (11·6)	363

Significance of difference from value on admission: **$p<0·01$;***$p<0·001$.

TABLE IV—*Blood pressure (mm Hg) at various times after gemeprost treatment of women undergoing termination of early pregnancy with three different doses of mifepristone. Values are means (standard deviations)*

Time after gemeprost treatment (h)	Dose of mifepristone: 200 mg (n=386)	400 mg (n=387)	600 mg (n=384)	p Value†
	Systolic blood pressure			
0	109·9 (11·3)	109·8 (11·9)	109·3 (11·6)	
1	107·7 (11·7)***	108·5 (12·1)**	107·2 (10·6)***	0·48
2	106·9 (11·0)***	108·5 (11·6)	107·7 (11·6)**	0·07
3	108·4 (11·5)**	108·8 (12·1)	108·2 (11·5)	0·74
4	108·9 (10·9)	108·9 (11·1)	108·1 (11·3)	0·90
	Diastolic blood pressure			
0	68·3 (8·9)	68·7 (8·6)	68·1 (9·2)	
1	67·7 (9·0)	68·2 (9·1)	67·6 (8·7)	0·90
2	67·6 (8·6)	68·8 (8·7)	68·3 (8·8)	0·24
3	68·8 (8·9)	68·9 (9·3)	68·8 (8·6)	0·81
4	68·8 (8·2)	69·0 (8·9)	68·5 (8·6)	0·99

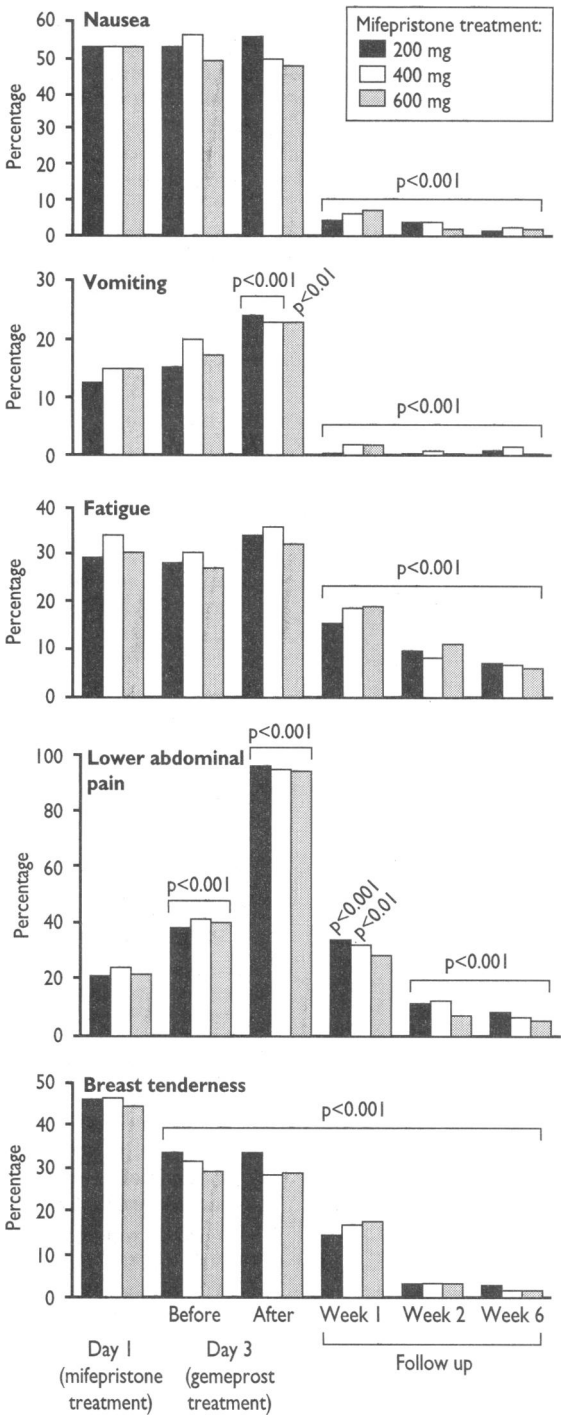
Significance of difference from value at 0 h: **p<0·01; ***p<0·001.
†Significance of difference between groups in change from value at 0 h (repeated measures analysis of variance).

Chinese origin and non-Chinese subjects. The amount of bleeding reported by the subjects was similar, being described as more or much more than normal menstruation by 290 (76%), 275 (71%), and 269 (69%) of the women in the 200 mg, 400 mg, and 600 mg groups respectively. There was also no difference between the three groups in the median time to the return of menses in women who had had a complete abortion (35-36 days). Of the five women who had not had their menses at the fourth follow up visit (two given 400 mg mifepristone and three given 600 mg), two were found to have become pregnant again.

SIDE EFFECTS AND COMPLICATIONS

Haemoglobin concentrations were similar in the three treatment groups at all times of sampling (table III). Concentrations were significantly lower just before gemeprost treatment than at admission in the 200 mg and 600 mg groups and were lowest at one week's follow up in all three groups. At that time the average levels were 2-3 g/l lower than on admission. Thereafter haemoglobin concentrations rose to pre-treatment values. During the first one to three hours after gemeprost treatment all three groups showed small and similar decreases in systolic blood pressure while diastolic blood pressure remained unchanged (table IV). All three groups also experienced highly significant decreases in pulse rate (by 3-4 beats/min) and increases of 0·1-0·2°C in body temperature after gemeprost treatment (p<0·001).

The figure shows the proportions of women who reported selected side effects during the course of the study. In addition to the complaints shown, data were also obtained on dizziness (which followed a pattern similar to that of vomiting) and other complaints (which remained constant at 2-5% throughout the study except just after gemeprost treatment, when it rose to 14-16% (partly due to the rise in diarrhoea from 0·1% on admission to 3·8% after gemeprost treatment)). Similar proportions of women in each of the three groups reported each complaint at any of the times during the study. Reports of nausea and fatigue were unaffected by mifepristone and gemeprost treatments but declined rapidly after the abortion had taken place. Vomiting and dizziness were unchanged by mifepristone treatment but increased slightly after gemeprost treatment (when nearly a quarter of the women vomited (94/386, 89/387, and 88/384 in the 200 mg, 400 mg, and 600 mg groups) and about one fifth reported dizziness (79/386, 71/387, and 73/384)) and then virtually disappeared. Lower abdominal pain had become more common by the third day of the study after gemeprost treatment (when about half of the women already had vaginal bleeding), and it became almost universal during the four hours of observation after gemeprost treatment (365/386, 362/387, and 362/384). Of the 1089 women who complained of lower abdominal pain at that time, 149 were given opioid analgesics (56 (14·5%), 44 (11·4%), and 49 (12·8%) women in the 200 mg, 400 mg, and 600 mg groups). A further 129 women were given non-opioid analgesics, most of them (108) receiving oral paracetamol. The centres differed considerably in the use of analgesic drugs: in five centres fewer than 5-10% of women received an analgesic preparation, and none received opioid medication, whereas in Aberdeen, Edinburgh, and Stockholm 50-60% of subjects received analgesia, about a half to two thirds of them receiving an opioid preparation. There were no differences between the three groups during follow up in the use of medication or in the treatment of complications. Antibiotics were given to 16 women for suspected pelvic or upper genital tract infections.



Percentages of women undergoing termination of early pregnancy with three different doses of mifepristone who reported side effects at various times during study. (Significant changes from value on Day 1 are marked with p values)

Discussion

The results of our randomised, double blind, multicentre trial confirm previous suggestions that the presently recommended dose of 600 mg mifepristone for the termination of early pregnancy could, when used in combination with the prostaglandin gemeprost, be reduced without loss of efficacy.[7,8] The rate of complete abortion achieved with 200 mg mifepristone was the same as that achieved with 600 mg. Moreover, in contrast to what has been reported after treatment with mifepristone alone,[2] doses less than 600 mg given in combination with gemeprost were not associated with a greater risk of the pregnancy continuing when the treatment failed. Although the limited data available are reassuring,[3] the teratogenic potential of mifepristone in humans remains unclear; hence the concern about pregnancies continuing if treatment fails and the recommendation that such pregnancies be terminated surgically.

The combined results for the treatments in our study (95·5% complete abortion, 3·7% incomplete abortion, and 0·8% missed abortion and continuing live pregnancies among women with known outcome) are similar to those reported for a large French series of 15 709 women given 600 mg (95·3%, 3·5%, and 1·2%) even though the maximum duration of amenorrhoea in the present study was 56 days compared with only 49 days in the French series.[2] Our present results are better than those achieved with 600 mg mifepristone in our earlier multicentre study (94·0%, 4·4% and 1·6% respectively).[7] This may reflect the increased experience of the investigators with this medical approach to terminating pregnancies. Doctors' anxiety and lack of experience were probably the reasons for the higher incidence of curettage for "incomplete" abortion in Hong Kong and Wuhan than in centres with similar populations of subjects such as Shanghai and Tianjin.

There were no differences among the three groups of women in the types and incidences of reported complaints and complications; in the time of onset, duration, and amount of vaginal bleeding; in the time until first menses; or in the reductions in haemoglobin concentrations. These results were virtually identical to those of our earlier multicentre trial,[7] with two exceptions: firstly, we did not observe changes in blood pressure after gemeprost treatment that were related to the dose of mifepristone given (the only clinically relevant changes occurred in three—or possibly seven —women, who experienced an episode of hypotension in the context of a vasovagal reaction that was probably provoked by dilatation of the cervix during expulsion of the products of conception); and, secondly, there was no difference between Chinese and non-Chinese women in the duration of vaginal bleeding (previously, Chinese women had reported longer bleeding). Our findings provide reassurance as to the safety of mifepristone plus prostaglandin for inducing abortion.

In keeping with our earlier conclusion,[7] we found no evidence that mifepristone caused any specific side effects or a significant increase in the complaints commonly associated with early pregnancy. The only significant change observed was a decrease in breast tenderness, as reported earlier.[7] As expected,[5] the uterine contractions and vaginal bleeding induced by mifepristone were associated with lower abdominal pain, which became almost universal after gemeprost treatment. At that time, 94·1% of the women complained of abdominal pain, and 12·9% were given opioid analgesics. The corresponding percentages in our earlier trial with 1 mg gemeprost were 86·6% and 6·0%.[7] The considerable differences between centres in the use of analgesic medication observed in this and our previous multicentre trials[6,7] were probably due to differences in the women's tolerance to pain or in the prevailing attitudes and practices of health care workers. In developing countries the availability and cost of strong analgesics may also play a role.[6] Whether reduced doses of gemeprost can lower the incidence and severity of abdominal pain and typical side effects of prostaglandin treatment (such as diarrhoea) without loss of efficacy is being studied currently.

In conclusion, this trial has shown that a single dose of 200 mg mifepristone is as effective as a single dose of 600 mg when used in combination with 1 mg gemeprost for the termination of early pregnancies. Further trials are currently investigating whether such a reduced dose of mifepristone is also effective in combination with other prostaglandins (particularly misoprostol, as suggested by a recent report[10]) or a lower dose of gemeprost and in longer pregnancies (of up to 35 days of menstrual delay).

Clinical implications

- The recommended dose of mifepristone for termination of early pregnancy is a single dose of 600 mg followed by a prostaglandin analogue
- The limited capacity of blood to transport mifepristone, however, suggests that lower doses should be equally effective
- In a multicentre trial of single doses of 200 mg, 400 mg, and 600 mg mifepristone used with a vaginal suppository of 1 mg gemeprost, the three doses gave equal rates of complete abortion with no difference in the rates of complications and side effects
- The presently recommended dose of mifepristone can be reduced without loss of efficacy when used with gemeprost

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Obesity as a determinant for response to antihypertensive treatment

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Abstract

***Objective*—To test the hypothesis that β blockers lower blood pressure more effectively than calcium entry blockers in obese hypertensive patients and that calcium entry blockers are more effective in lean patients.**

***Design*—Double blind, randomised controlled trial of treatment over six weeks.**

***Setting*—Tertiary referral centre.**

***Subjects*—42 white men with uncomplicated mild to moderate essential hypertension (World Health Organisation stage I or II); 36 completed the study.**

***Intervention*—Patients were randomised to metoprolol 50-100 mg twice daily or isradipine 2·5-5·0 mg twice daily for six weeks after a two week run in phase.**

***Main outcome measure*—Blood pressure after six weeks of treatment.**

***Results*—When stratified according to treatment and presence of obesity (body mass index $<$ or ≥ 27 kg/m^2), the mean (SD) fall in blood pressure in the β blocker group was 24 (13)/18 (10) mm Hg in obese patients and 18 (19)/12 (13) mm Hg in lean patients. In the calcium entry blocker group, the fall in blood pressure was 21 (15)/17 (6) mm Hg in lean patients and 18 (11)/8 (10) mm Hg in obese patients. After taking age and blood pressure before treatment into account there was a significant interaction between obesity and drug therapy ($p=0·019$) with a better diastolic blood pressure response to calcium entry blockers in lean patients and to β blockers in obese hypertensive patients.**

***Conclusion*—Obesity affects the efficacy of metoprolol and isradipine in reducing blood pressure.**

Introduction

Large scale prospective studies have shown that antihypertensive drugs prevent cardiovascular morbidity and reduce cardiovascular mortality.[1] β Blockers and calcium entry blockers are both recommended as first line treatment for hypertension[2] but there are no guidelines about which drugs lower blood pressure most effectively in patients with uncomplicated essential hypertension. Age has been claimed to be an important predictor of response to antihypertensive drugs, but other studies have not confirmed this initial hypothesis or its clinical implications.[4] Obesity, which is present in more than half of hypertensive patients, has been neglected as a potential determinant of response to treatment.[2]

Obesity has a major influence on the haemodynamic changes associated with hypertension.[5] Several studies indicate that obese hypertensive patients have a higher cardiac output and lower total peripheral resistance than lean patients at any given level of arterial hypertension.[6,7] Obese hypertensive patients seem to have increased sympathetic activity, which may be reduced with weight loss.[8] Different haemodynamic patterns in hypertensive patients have been suggested to be clinically relevant for treating hypertensive patients.[9] We therefore tested the hypothesis that a β blocker is more effective than a calcium entry blocker in obese patients and that a calcium entry blocker is more effective than a β blocker in lean patients. We reasoned that the putatively hyperdynamic circulation of obese patients would respond better to β blockade and that the increased peripheral vascular resistance in lean hypertensive patients might respond better to the smooth muscle relaxing effects of a calcium entry blocking drug.[10-12]

Subjects and methods

Patients referred to our hospital because of arterial hypertension were consecutively enrolled if they fulfilled all the study criteria. All patients were white men with mild to moderate essential hypertension who met World Health Organisation stage I or II criteria. Patients with secondary causes of arterial hypertension, congestive heart failure, clinical or electrocardiographic signs of coronary heart disease, second or third degree atrioventricular block, or concomitant diseases such as chronic obstructive lung disease, renal insufficiency, haematological diseases, or other conditions that could influence the resorption or metabolism of calcium entry blockers or β blockers, were excluded from the study.

In the single blind run in all subjects were given placebo for two weeks as a wash out. No other drugs were permitted throughout the whole study. To qualify for entry in the double blind treatment the patient's diastolic blood pressure had to be 95-109 mm Hg on two occasions during the wash out phase. All blood pressure measurements (before and during therapy) were obtained after the patient had rested for five minutes in a seated position. The people measuring blood pressure had been trained to use the mercury column sphygmomanometer. The appropriate cuff size to account for obesity was used. Forty two patients fulfilled the blood pressure criteria after the two week run in phase. Their mean (SD) casual blood pressure was 162 (12)/103 (8) mm Hg and their mean age was 49 (12) years.

After the run in phase patients were randomly assigned to treatment with either the calcium entry blocker isradipine 2·5 mg twice daily (n=20), or β blocker metoprolol 50 mg twice daily (n=22). If the diastolic blood pressure was more than 90 mm Hg after three weeks of treatment the dose was doubled. This was the case in seven patients randomised to receive β blockers and in six patients randomised to calcium entry blockers. Patients received no dietary guidelines (sodium restriction, weight loss programmes) throughout the study period. Blood pressure was monitored for six weeks. After six weeks venous blood samples were taken from each patient to measure serum concentration of the drug. Patients were unaware that blood was

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