Management of immediate postcesarean section hemorrhage

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From Jan 1, 1982, to Dec 31, 1985, 33 (1.3%) of 2,545 women undergoing cesarean section experienced an immediate estimated blood loss >1,000 mL. In all cases, the etiology was uterine atony. Medical management was unsuccessful in 20 (60.6%) cases, and hysterectomy was necessary in ten. Conservative surgical management (hypogastric or uterine artery ligation or both) was used in 18 cases and was successful in ten (55.6%). Patients who responded to medical management had a mean estimated blood loss of 1,469 mL, compared to a loss of 2,120 mL, for those responding to ligation and a loss of 3,240 mL for those requiring hysterectomy ($P < 0.001$). Hysterectomy is the definitive procedure for the hemodynamically unstable patient with intractable obstetric hemorrhage if rapid bilateral uterine artery ligation fails. Hypogastric or uterine artery ligation is recommended for the hemodynamically stable patient who is desirous of future childbearing.

Postpartum hemorrhage occurs in approximately 5% of all deliveries; uterine atony and birth canal lacerations are the most frequent primary causes.^{1,2} Conventional treatment of uterine atony traditionally has consisted of fluid resuscitation, intravenous oxytocin, intravenous or intramuscular methylergonovine maleate, and uterine massage. Recently, 15-methyl-prostaglandin F2 alpha was reported¹ to be successful in treating 86% of women with severe postpartum hemorrhage that was unresponsive to conventional therapy. When medical therapy fails, uterine or hypogastric artery ligation, or hysterectomy, or both, becomes necessary.

Predisposing causes for uterine atony include high parity, overdistended uterus, abrupt or prolonged labor, general anesthesia, magnesium sulfate, and chorioamnionitis.^{1,2} In Hayashi and associates¹ study, most women with intractable uter-

ine atony had undergone operative delivery, with 49% having had a cesarean section.

The present study was limited to the management of women with intractable hemorrhage after cesarean section. Emphasis was placed on the effectiveness of bilateral hypogastric or uterine artery ligation.

Methods and materials

The hospital charts of women who had experienced hemorrhage at the time of cesarean section at Tripler Army Medical Center between Jan 1, 1982, and Dec 31, 1985, were reviewed. Hemorrhage was defined as an estimated blood loss >1,000 mL. During this time period, there were 13,781 deliveries, 2,545 (18.5%) of which were by cesarean section. All cases were managed by resident physicians under attending staff supervision.

The following data were analyzed: age, parity, fetal weight, estimated blood loss, etiology of hemorrhage, medical management, surgical management, and total amount and duration of oxytocin use during labor. Statistical analysis was performed using two-tailed Student's *t*-test, one-way analysis of variance, or chi-square test when appropriate.

Results

During the study period, 33 (1.3%) of the 2,545 cesarean section patients experienced obstetric hemorrhage >1,000 mL. All 33 women had been in labor, and uterine atony was thought to be responsible for the hemorrhage in all cases. All were treated with intravenous oxytocin and intramuscular methylergonovine maleate. In 18 cases, 1 mg of intramyometrial natural prostaglandin F2 alpha also was used. In 20 (60.6%) women, medical treatment was unsuccessful and surgery was performed (Table 1). In all cases, the decision to operate was made by the attending staff obstetrician.

The patients' mean $\pm$ SD age was 24 ± 4.5 years. There were 27 (1.8%) nulliparous women. The mean $\pm$ SD fetal weight was $3,527 \pm 752$ g. Eighteen (54.5%) women had received oxytocin to

induce or augment their labor. The mean $\pm$ SD duration of oxytocin administration during labor was 15.7 ± 10.6 hours, and the mean $\pm$ SD total amount of oxytocin infused was $7,113 \pm 9,384$ mU.

No woman was diagnosed as having chorioamnionitis, but six (18.2%) patients developed postpartum endomyometritis. In two multiparous, hemodynamically unstable women with blood loss in excess of 3,000 mL, immediate hysterectomy was performed. In one instance, hysterectomy was performed after a unilateral hypogastric artery ligation failed to control the bleeding. Hysterectomy was necessary in seven (46.7%) of the 15 cases with bilateral arterial ligations. Therefore, ten (30.3%) of the 33 women with immediate postcesarean section hemorrhage required hysterectomy.

The patient's mean $\pm$ SD age, parity, fetal weight, estimated blood loss, and amount and duration of oxytocin administration during labor for the three modalities of management are listed in Table 2. The means of the estimated blood loss were statistically significantly different; they were higher in women requiring surgical management, and higher still in those undergoing hysterectomy. The mean total amount of oxytocin administered during labor to women undergoing hysterectomy was 15,982 mU, which differs significantly from the mean of 4,809 mU infused to the 23 women who did not require hysterectomy ($P = .02$). Although patients with failed medical therapy delivered larger infants (mean $\pm$ SD, $3,709 \pm 676$ g) than those for whom medical treatment was successful (mean $\pm$ SD, $3,247 \pm 803$ g), this difference did not reach statistical significance ($P = .08$).

Discussion

Several factors, including dysfunctional labor and the use of oxytocin, have been associated with uterine atony.² Labor induction or augmentation with oxytocin occurred in 54.5% of the women in the present series. Patients who required hysterectomy received significantly more intrapartum oxytocin than those who responded to medical or conservative surgical management. A primary blunted response of the myometrium to oxytocin might have been responsible for the need to induce or augment labor, the uterine atony, and the failure to respond to conservative therapy. An alternate explanation is that the large amounts of oxytocin administered caused down regulations of its receptors, thus precluding further myometrial response.

Most cases of postpartum hemorrhage secondary to uterine atony respond to conventional therapy (intravenous oxytocin, intravenous or intramuscular methylergonovine maleate, and uterine massage).¹ Natural prostaglandin F2 alpha is metabo-

TABLE 1. SURGICAL PROCEDURES TO CONTROL POSTCESAREAN SECTION HEMORRHAGE.

Initial procedure	Number of patients	Patients requiring hysterectomy
Bilateral hypogastric artery ligation	10	5
Bilateral hypogastric and unilateral uterine artery ligation	2	1
Unilateral hypogastric and bilateral uterine artery ligation	1	0
Bilateral uterine artery ligation	2	1
Unilateral uterine artery ligation	2	0
Unilateral hypogastric artery ligation	1	1
Hysterectomy	2	2
Total	20	10

lized rapidly in the circulation. It has been found to be ineffective in the management of postpartum hemorrhage when administered intravenously or intramuscularly, but it is effective when injected directly into the myometrium.^{3,4} A prostaglandin analogue, 15-methyl-prostaglandin F2 alpha, is highly effective when administered intramuscularly in treating severe postpartum hemorrhage secondary to uterine atony.¹ In the present study, only 39.4% of women responded to medical therapy, which included intramyometrial prostaglandin F2 alpha. We can only speculate that a higher success rate might have been achieved if 15-methyl-prostaglandin F2 alpha had been used.

If medical management fails to control postpartum hemorrhage, hypogastric, ovarian, or uterine artery ligation or hysterectomy is required. In approximately 57% of women with intractable postpartum bleeding, conservative surgical procedures are unsuccessful.^{1,5,6} In the present study, bilateral hypogastric artery ligation failed to control bleeding in 6 of 12 patients. Clark and associates⁵ found that hypogastric artery ligation was ineffective in 60% of women with uterine atony that was unresponsive to medical therapy. Hysterectomy has been performed to control hemorrhage in approximately 1% of all women delivered by cesarean section.⁷ In the present series, hysterectomy was performed for hemostasis in 10 (0.39%) of the 2,545 cesarean section patients during the study period.

Necrosis of the pelvic organs after hypogastric artery ligation rarely occurs.⁶ Because of a network of anastomosing collateral vessels, adequate blood flow to the pelvic organs after such ligation usually is maintained. The main collateral blood supply comes from the middle sacral, lumbar, and superior hemorrhoidal vessels. To avoid anastomotic reversal of blood flow through the iliolumbar-lumbar and lateral sacral-middle sacral anastomoses,

TABLE 2. MEAN $\pm$ SD OF THE FACTORS STUDIED FOR PATIENTS RESPONDING TO MEDICAL MANAGEMENT OR CONSERVATIVE SURGERY AND FOR PATIENTS REQUIRING HYSTERECTOMY.

Factor	Medical therapy	Conservative surgery	Hysterectomy	P value
Patients (n)	13	10	10	
Age (yr)	25 $\pm$ 4	23 $\pm$ 5	25 $\pm$ 5	0.62
Nulliparity (%)	85	75	90	0.48
Fetal weight (g)	3,247 $\pm$ 803	3,943 $\pm$ 306	3,475 $\pm$ 866	0.08
Estimated blood loss (mL)	1,469 $\pm$ 545	2,120 $\pm$ 691	3,240 $\pm$ 1018	<0.001
Patients receiving oxytocin during labor (n)	6	7	5	
Duration of oxytocin administration (hr)	14.6 $\pm$ 10	10.4 $\pm$ 4.4	24.4 $\pm$ 12.9	0.06
Total amount of oxytocin (mU)	5,565 $\pm$ 6,200	4,161 $\pm$ 3,636	15,982 $\pm$ 14,189	0.07

ligation must be performed distally to the origin of the posterior division. Bilateral hypogastric artery ligation causes a 24% decrease in mean pressure within the hypogastric artery distal to the ligature and a 48% decrease in blood flow; the most significant change is that of an 85% decrease in pulse pressure.⁸ Thus, the hemodynamics of the distal arterial system more closely resemble those of a venous system, in which hemostasis by simple clot formation can occur.

A rapid and simple technique, ligation of the uterine artery as it ascends along the lateral margin of the uterus, with or without hypogastric artery ligation, was performed in seven cases in our series. Hysterectomy was performed in only 2 (28.6%) of these patients. This technique and ovarian artery ligation have been advocated^{7,9,10} in the conservative surgical management of obstetric hemorrhage. No significant complications have been identified on long-term follow up.^{9,11} Recanalization of the uterine arteries has been observed to occur in all cases.¹¹ In our institution, the attending obstetricians prefer ligation of the uterine artery over the ovarian. No ovarian artery ligation was performed in the present series.

Conclusions

This study, along with others,^{1,5,6} has demonstrated that conservative surgical control of intractable postpartum hemorrhage is possible in about half of cases. These procedures should always be attempted in the hemodynamically stable patient who desires future childbearing. In the hemodynamically unstable patient, a rapid bilateral uterine artery ligation may be performed. If it fails to control the bleeding, subtotal hysterectomy is the

fastest, safest, and most effective way to achieve hemostasis.

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The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the Department of the Army or the Department of Defense.

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†In pharmacodynamic studies (utilizing 10 mg of enalapril and lisinopril), ACE inhibition was significantly correlated to plasma renin activity and fall in diastolic blood pressure in normal volunteers.

— adapted from Ajayi et al, p 424²

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- Evaluation of the hypertensive patient should always include assessment of renal function. (See Dosage and Administration.)
- Angioedema has been reported with ACE inhibitors, including Zestril. (See Warnings.)

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Clinical significance has not been determined in hypertensive patients.

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INDICATIONS AND USAGE. Zestril is indicated for the treatment of hypertension. It may be used alone as initial therapy or concomitantly with other classes of antihypertensive agents. In using Zestril, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that Zestril does not have a similar risk. (See WARNINGS.) **CONTRAINDICATIONS.** Zestril is contraindicated in patients who are hypersensitive to this product. **WARNINGS.** **Angioedema:** Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including Zestril. In such cases, Zestril should be promptly discontinued, and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, eg, subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) should be promptly administered.** (See ADVERSE REACTIONS.) **Hypotension:** Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of use with Zestril in salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis. (See PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS.) In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of Zestril and/or diuretic is increased. Similar considerations apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion. **Neutropenia/Agranulocytosis:** Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of Zestril are insufficient to show that Zestril does not cause agranulocytosis at similar rates. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered. **PRECAUTIONS.** **General. Impaired Renal Function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including Zestril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of Zestril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when Zestril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of Zestril and/or discontinuation of the diuretic may be required. **Evaluation of the hypertensive patient should always include assessment of renal function.** (See DOSAGE AND ADMINISTRATION.) **Hyperkalemia:** In clinical trials hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 2.2% of hypertensive patients and 4.0% of patients with congestive heart failure. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in approximately 0.1% of hypertensive patients. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with Zestril. (See Drug Interactions.) **Surgery/Anesthesia:** In patients undergoing major surgery or during anesthesia with agents that produce hypotension, Zestril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion. **Information for Patients.** **Angioedema:** Angioedema, including laryngeal edema, may occur especially following the first dose of Zestril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician. **Symptomatic Hypotension:** Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patient should be told to discontinue the drug until they have consulted with the prescribing physician. All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with their physician. **Hyperkalemia:** Patients should be told not to use salt substitutes containing potassium without consulting their physician. **Neutropenia:** Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which may be a sign of neutropenia. **NOTE:** As with many other drugs, certain advice to patients being treated with Zestril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. **Drug Interactions. Hypotension—Patients on Diuretic Therapy:** Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with Zestril. The possibility of hypotensive effects with Zestril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with Zestril. If it is necessary to continue the diuretic, initiate therapy with Zestril at a dose of 5 mg daily, and provide medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS, and DOSAGE AND ADMINISTRATION.) When a diuretic is added to the therapy of a patient receiving Zestril, an additional antihypertensive effect is usually observed. Studies with ACE inhibitors in combination with diuretics indicate that the dose of the ACE inhibitor can be reduced when it is given with a diuretic. (See DOSAGE AND ADMINISTRATION.) **Indomethacin:** In a study in 36 patients with mild to moderate hypertension where the antihypertensive effects of Zestril alone were compared to Zestril given concomitantly with indomethacin, the use of indomethacin was associated with a reduced effect, although the difference between the two regimens was not significant. **Other Agents:** Zestril has been used concomitantly with nitrates and/or digoxin without evidence of clinically significant adverse interactions. No clinically important pharmacokinetic interactions occurred when Zestril was used concomitantly with propranolol or hydrochlorothiazide. The presence of food in the stomach does not alter the bioavailability of Zestril. **Agents Increasing Serum Potassium:** Zestril attenuates potassium loss caused by thiazide-type diuretics. Use of Zestril with potassium-sparing diuretics (eg, spironolactone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. **Carcinogenesis, Mutagenesis, Impairment of Fertility.** There was no evidence of a tumorigenic effect when lisinopril was administered for 105 weeks to male and female rats at doses up to 90 mg/kg/day (about 56 times* the maximum recommended daily human dose) or when lisinopril was administered for 92 weeks to (male and female) mice at doses up to 135 mg/kg/day (about 84 times* the maximum recommended daily human dose). *Based on patient weight of 50 kg. Lisinopril was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. It was also negative in a forward mutation assay using Chinese hamster lung cells. Lisinopril did not produce single strand DNA breaks in an *in vitro* alkaline elution rat hepatocyte assay. In addition, lisinopril did not produce increases in chromosomal aberrations in an *in vitro* test in Chinese hamster ovary cells or in an *in vivo* study in mouse bone marrow. There were no adverse effects on reproductive performance in male and female rats treated with up to 300 mg/kg/day of lisinopril. **Pregnancy. Pregnancy Category C:** Lisinopril was not teratogenic in mice treated on days 6-15 of gestation with up to 1,000 mg/kg/day (625 times the maximum recommended human dose). There was an increase in fetal resorptions at doses down to 100 mg/kg; at doses of 1,000 mg/kg this was prevented by saline supplementation. There was no fetotoxicity or teratogenicity in rats treated with up to 300 mg/kg/day (188 times the maximum recommended dose) of lisinopril at days 6-17 of gestation. In rats receiving lisinopril from day 15 of gestation through day 21 postpartum, there was an increased incidence in pup deaths on days 2-7 postpartum and a lower average body weight of pups on day 21 postpartum. The increase in pup deaths and decrease in pup weight did not occur with maternal saline supplementation. Lisinopril, at doses up to 1 mg/kg/day, was not teratogenic when given throughout the organogenic period in saline supplemented rabbits. Saline supplementation (physiologic saline in place of tap water) was used to eliminate maternotonic effects and enable evaluation of the teratogenic potential at the highest possible dosage level. The rabbit has been shown to be extremely sensitive to angiotensin converting enzyme inhibitors (captopril and enalapril) with maternal and fetal effects apparent at or below the recommended therapeutic dosage levels in man. Fetotoxicity was demonstrated in rabbits by an increased incidence of fetal resorptions at a dose of lisinopril at 1 mg/kg/day and by an increased incidence of incomplete ossification at the lowest dose tested (0.1 mg/kg/day). By whole body autoradiography, radioactivity was found in the placenta following administration of labeled lisinopril to pregnant rats, but none was found in the fetuses. There are no adequate and well-controlled studies in pregnant women. Zestril should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers:** Milk of lactating rats contains radioactivity following administration of ¹⁴C lisinopril. It is not known whether this drug is excreted in human milk.

Because many drugs are excreted in human milk, caution should be exercised when Zestril is given to a nursing mother. **Pediatric Use:** Safety and effectiveness in children have not been established. **ADVERSE REACTIONS.** Zestril has been found to be generally well tolerated in controlled clinical trials involving 2003 patients and subjects. The most frequent clinical adverse experiences in controlled trials were dizziness (6.3%), headache (5.3%), fatigue (3.3%), diarrhea (3.2%), upper respiratory symptoms (3.0%), and cough (2.9%), all of which were more frequent than in placebo-treated patients. For the most part, adverse experiences were mild and transient in nature. Discontinuation of therapy was required in 6.0% of patients. In clinical trials, the overall frequency of adverse experiences could not be related to total daily dosage within the recommended therapeutic dosage range. For adverse experiences which occurred in more than 1% of patients and subjects treated with Zestril or Zestril plus hydrochlorothiazide in controlled clinical trials, comparative incidence data are listed in the table below.

	Zestril (n = 2003) ¹ Incidence (discontinuation)	Zestril/Hydrochlorothiazide (n = 644) Incidence (discontinuation)	Placebo (n = 207) Incidence
Dizziness	6.3 (0.6)	9.0 (0.9)	1.9
Headache	5.3 (0.2)	4.3 (0.5)	1.9
Fatigue	3.3 (0.2)	3.9 (0.5)	1.0
Diarrhea	3.2 (0.3)	2.6 (0.3)	2.4
Upper Respiratory Symptoms	3.0 (0.0)	4.5 (0.0)	0.0
Cough	2.9 (0.4)	4.5 (0.8)	1.0
Nausea	2.3 (0.3)	2.5 (0.2)	2.4
Hypotension	1.8 (0.8)	1.6 (0.5)	0.5
Rash	1.5 (0.4)	1.6 (0.2)	0.5
Orthostatic Effects	1.4 (0.0)	3.4 (0.2)	1.0
Asthenia	1.3 (0.4)	2.0 (0.2)	1.0
Chest Pain	1.3 (0.1)	1.2 (0.2)	1.4
Vomiting	1.3 (0.2)	1.4 (0.0)	0.5
Dyspnea	1.1 (0.0)	0.5 (0.2)	1.4
Dyspepsia	1.0 (0.0)	1.9 (0.0)	0.0
Paresthesia	0.8 (0.0)	2.0 (0.2)	0.0
Impotence	0.7 (0.2)	1.6 (0.3)	0.0
Muscle Cramps	0.6 (0.0)	2.8 (0.6)	0.5
Back Pain	0.5 (0.0)	1.1 (0.0)	1.4
Nasal Congestion	0.3 (0.0)	1.2 (0.0)	0.0
Decreased Libido	0.2 (0.1)	1.2 (0.0)	0.0
Vertigo	0.1 (0.0)	1.1 (0.2)	0.0

¹Includes 420 patients treated for congestive heart failure who were receiving concomitant digitalis and/or diuretic therapy.

Clinical adverse experiences occurring in 0.3% to 1.0% of patients in the controlled trials and rarer, serious, possibly drug related events reported in uncontrolled studies or marketing experience included: **BODY AS A WHOLE:** Chest discomfort, fever, flushing. **CARDIOVASCULAR:** Angina pectoris, orthostatic hypotension, rhythm disturbances, tachycardia, peripheral edema, palpitation. **DIGESTIVE:** Abdominal pain, anorexia, constipation, flatulence. **METABOLISM:** Gout. **MUSCULOSKELETAL:** Joint pain, shoulder pain. **NERVOUS SYSTEM/PSYCHIATRIC:** Depression, somnolence, insomnia, stroke. **RESPIRATORY SYSTEM:** Bronchitis, sinusitis, pharyngeal pain. **UROGENITAL:** Oliguria, progressive azotemia, acute renal failure. **OTHER:** Blurred vision, pruritus, urinary tract infection, vasculitis of the legs. **ANGIOEDEMA:** Angioedema has been reported in patients receiving Zestril (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with Zestril should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.) **HYPOTENSION:** In hypertensive patients, hypotension occurred in 1.2% and syncope occurred in 0.1% of patients. Hypotension or syncope was caused by discontinuation of therapy in 0.5% of hypertensive patients. (See WARNINGS.) In patients with congestive heart failure, hypotension occurred in 5.0% and syncope occurred in 1.0% of patients. These adverse experiences were causes for discontinuation of therapy in 1.3% of these patients. **Clinical Laboratory Test Findings. Serum Electrolytes:** Hyperkalemia (See PRECAUTIONS.) **Creatinine, Blood Urea Nitrogen:** Minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 2.0% of patients with essential hypertension treated with Zestril alone. Increases were more common in patients receiving concomitant diuretics and in patients with renal artery stenosis. (See PRECAUTIONS.) Reversible minor increases in blood urea nitrogen and serum creatinine were observed in approximately 9.1% of patients with congestive heart failure on concomitant diuretic therapy. Frequently these abnormalities resolved when the dosage of the diuretic was decreased. **Hemoglobin and Hematocrit:** Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.4 g% and 1.3 vol% respectively) occurred frequently in patients treated with Zestril but were rarely of clinical importance in patients without some other cause of anemia. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia. **Other (Causal Relationship Unknown):** Rarely, elevations of liver enzymes and/or serum bilirubin have occurred. Overall, 2.0% of patients discontinued therapy due to laboratory adverse experiences, principally elevations in blood urea nitrogen (0.6%), serum creatinine (0.5%), and serum potassium (0.4%). **OVERDOSAGE:** The oral LD₅₀ of lisinopril is greater than 20 g/kg in mice and rats. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution. **DOSAGE AND ADMINISTRATION. Initial Therapy:** In patients with uncomplicated essential hypertension not on diuretic therapy, the recommended initial dose is 10 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 20-40 mg per day administered in a single daily dose. The antihypertensive effect may diminish toward the end of the dosing interval regardless of the administered dose, but most commonly with a dose of 10 mg daily. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. It is not, an increase in blood pressure should be considered. Doses up to 80 mg have been used but do not appear to give greater effect. If blood pressure is not controlled with Zestril alone, a low dose of a diuretic may be added. Hydrochlorothiazide, 12.5 mg has been shown to provide an additive effect. After the addition of diuretic, it may be possible to reduce the dose of Zestril. **Diuretic Treated Patients:** In hypertensive patients who are currently being treated with a diuretic, symptomatic hypotension may occur occasionally following the initial dose of Zestril. The diuretic should be discontinued, if possible, for two or three days before beginning therapy with Zestril to reduce the likelihood of hypotension. (See WARNINGS.) The dosage of Zestril should be adjusted according to blood pressure response. If the patient's blood pressure is not controlled with Zestril alone, diuretic therapy may be resumed as described above. If the diuretic cannot be discontinued, an initial dose of 5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.) Concomitant administration of Zestril with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium. (See PRECAUTIONS.) **Use in Elderly:** In general, blood pressure response and adverse experiences were similar in younger and older patients given similar doses of Zestril. Pharmacokinetic studies, however, indicate that maximum blood levels and area under the plasma concentration time curve (AUC) are doubled in older patients so that dosage adjustments should be made with particular caution. **Dosage Adjustment in Renal Impairment:** The usual dose of Zestril (10 mg) is recommended for patients with creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance > 10 mL/min < 30 mL/min (serum creatinine < 3 mg/dL), the first dose is 5 mg once daily. For patients with creatinine clearance < 10 mL/min (usually on hemodialysis) the recommended initial dose is 2.5 mg. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Renal Status	Creatinine-Clearance mL/min	Initial Dose mg/day
Normal Renal Function to Mild Impairment	> 30	10
Moderate to Severe Impairment	≥ 10 ≤ 30	5
Dialysis Patients	< 10	2.5†

†Dose or dosing interval should be adjusted depending on the blood pressure response. Rev E 12/88
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