Premarin Induced Ischemic Colitis

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Özet: *PREMARIN'E BAĞLI İSKEMİK KOLİT*

Oral kontraseptiflere (östrojen ve progesteron) bağlı iskemik barsak hastalığı literatürde oldukça sık oranda rapor edilmiş olmakla beraber Premarin'e (equine konjuge östrojen) sekonder intestinal iskemi nadiren bildirilmiştir. Burada Premarin kullanımına bağlı olarak gelişmiş 3 iskemik kolit vakası sunulmaktadır. Premarin'in oluşturduğu iskemi oral kontraseptiflerle gelişen iskemik kolitin tersine sadece kolonda lokalizasyon göstermekte, cerrahi tedavi gerektirmemekte, kronik yahut kronik intermittent gidişle seyredebilmekte, ilaç kullanımının devamına rağmen geri dönebilmekte ve nonspesifik abdominal veya kolonik semptomlar gösterebilmektedir.

Anahtar Kelimeler: İskemik Barsak Hastalığı, Premarin

Summary: *There are numerous literature reports of oral contraceptive-induced (estrogen and progesterone) ischemic bowel disease. However, premarin-induced (equine conjugated estrogen) intestinal ischemia has rarely been reported. We describe 3 cases of Premarin-induced ischemic colitis. In contrast to oral contraceptive-induced ischemic colitis, Premarin-induced ischemia is restricted to the colon, does not require surgical therapy, can have a chronic or chronic intermittent course, may be reversible in spite of continued usage of premarin, and may present with nonspesific abdominal and colonic symptoms.*

Key Words: Ischemic Bowel Disease, Premarin.

The clinical entity of oral contraceptive-induced colonic ischemia was first described by Boley et al. in 1963 (1). Ischemic bowel disease is generally considered a condition of the elderly, and is usually associated with underlying vascular disease. However, ischemic bowel disease does occur in otherwise helathy younger patients. The patients are primarily women on oral contraceptives consisting of estrogen plus progesterone (4-9). Only 2 cases of ischemic bowel disease in the setting of oral contraceptives with progestational agents alone (2,3) and 4 with estrogen replacement in the form of Premarin (conjugated equine estrogen) have been reported (4,10,11). We report an additional 3 cases of Premarin-induced ichemic bowel disease.

CASE 1

E.N. is a 47 year old white woman referred to The Johns Hopkins Hospital in November 1991 for hemoccult positive stool and episodic diarrhea. Her past history was significant only for total abdominal hysterectomy and bilateral salpingo oophorectomy (TAH + BSO) for a large right ovarian tumor and leiomyomata in January 1990. The patient was placed on Premarin 0.625 mg. daily (3 weeks on and 1 week off) 1 month postoperatively as postmenopausal therapy. On presentation the physical examination was normal. Evaluation included stool examination for ova and parasites, Clostridium difficile toxin, and culture all of which were negative. Colonoscopic examination revealed patchy erythema and granular mucosa in the proximal sigmoid colon. Biopsies from this area showed erosions with pseudomembranes, congestion, and edema but no evidence of chronic inflammation of crypt distortion. The histopathologic appearance strongly favored ischemic injury. Consequently, Premarin was stopped and the patient's diarrhea resolved and stool guaiac became negative for occult blood. Repeat colonoscopy performed 2 months after discontinuation of Premarin

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revealed no macroscopic or microscopic evidence of sigmoid ischemia.

CASE 2

C.C. is 35 year old white woman admitted to Francis Scott Key Medical Center in August 1991, for severe abdominal pain and rectal bleeding. Her past history was significant for TAH + BSO for endometriosis and an appendectomy in 1988. The patient's only medication was Premarin 0.625 mg. daily (25 days on and 5 days off) which was begun in 1988 after surgery. One day prior to her admission, the patient complained of severe crampy abdominal pain associated with nausea, watery diarrhea, followed by 3 episodes of biright red blood per rectum. Her physical examination revealed mild abdominal tenderness in the midabdomen and left upper quadrant. Rectal examination revealed hemoccult positive brown stool. Laboratory examination revealed a WBC of 11,300 with normal differantial, and normal coagulation parameters. Stool examination for ova/parasites, Clostridium difficile toxin and culture were negative. Abdominal plain films were normal.

On the second hospital day, colonoscopic examination revealed a 40 cm segment of extremely friable, erythematous, and edematous mucosa in the descending colon. Biopsies taken from this area showed hemorrhage, necrosis and neutrophilic infiltration interpreted as ischemic injury. A small bowel series performed 6 days after onset of symptoms was normal. The patients symptoms resolved within 24 hours of admission, and she has remained asymptomatic for past 10 months while remaining on Premarin.

CASE 3

W.K. a 49 year old white woman was hospitalized at Camden-Clark Memorial Hospital in Parkersburg, West Virginia in May 1991 with complaints of severe, crampy, left lower quadrant pain and bloody diarrhea. The patient reported a 3 1/2 year history of intermittent diarrhea with up to 8-10 watery bowel movements a day and an episode of rectal bleeding 3 years prior to admission. In 1984 she underwent TAH + BSO for dysfunctional uterine bleeding. Premarin 0.625 mg daily in a cyclical manner (25 days on and 5 days off) was prescribed in 1985. Physical examination was remarkable for tenderness in the left lower quadrant. Stool for ova and parasites, Clostridium difficile toxin, leukocytes, and culture were negative. Colonoscopy revealed focal segmental, denuded mucosa from the mid-descending colon to mid-sigmoid with ulceration, edema, and exudate associated with stellate and linear ulcers. Biopsies from these areas showed patchy edema and hemorrhage of the lamina propria with focal necrosis and neutrophil infiltrate which was felt to be compatible with ischemia. Barium enema and small bowel series were normal. Premarin was discontinued in October 1991 and her symptoms resolved. The patient is symptom free 9 months after hospital discharge.

DISCUSSION

The association between oral contraceptives (estrogen and progesterone) and ichemic bowel disease is well recognized (4-9). Characteristically, patients present with acute, severe, abdominal pain followed by the development of bloody diarrhea. There are 3 main forms of estrogen-induced ischemic colitis which include a) infarcted bowel requiring colonic resection, b) stricture formation, and c) transient or reversible ischemia (12). The distribution of injury is usually segmental, but may involve the entire colon. Also, patents with small bowel ischemia caused by oral contraceptives have been reported (13-16). Birth control-induced ischemic colitis can be caused by arterial occlusion (13,15,17,18) or venous occlusion (16,19). The watershed areas of mesenteric vascular supply, specifically the splenic flexure and rectosigmoid, are most commonly involved.

Interestingly, the number of reported cases of oral contraceptive-induced colitis has been decreasing over time and their clinical characteristics has been changing (Table 1). Current cases have followed a generally more benign course not requiring bowel resection as seen in earlier reports. Although physician awarness of complications of these medications as well as the lack of novelty of this association may provide some explanation of the change in frequency of recent reports, the decrease in estrogen dose used in oral contraceptives in the last decade may be a more important factor. Decreased dosage of estrogen may also account for the change in character of recent reports.

On the other hand, Premarin, a mixture of equine conjugated estrogens, has not been frequently associated with ischemic bowel disease. The clinical presentation and course of patients with Premarin-induced ischemic bowel disease seems to be different in several respects from oral contraceptive induced ischemia. Our patients and the 4 literature cases (see details in Table 2) were all successfully managed medically in contrast to the more frequent need for surgical treatment in patients on oral contraceptives. Also, in the previous literature reports of birth control pill-induced ischemic colitis, the onset of clinical symptoms was acute and severe requiring immediate management. In contrast, 2 of our 3 cases had chronic symptoms. Patient 3 had a chronic intermittent colitis of 3 1/2 years duration with 2 separate attacks of rectal bleeding with continuous Premarin use, and Case 1 had 18 months of colonic symptoms before presentation.

The previous literature suggests that symptoms resolve in days to weeks with discontinuation of estrogen compounds. In distinction, Premarin-induced colitis appeared to often resolve in spite of continual drug use. For instance, in Case 2 despite the continuation of Premarin, the patient remained asymptomatic after the initial attack spontaneously resolved. In Case 3, the first of 2 separate attacks of severe colitis resolved without Premarin discontinuation. Finally, as demonstrated by Case 1, the clinical presentation can be nonspecific with mild episodic diarrhea and hemoccult positive stool suggesting that Premarin-induced colitis may occur much more commonly than is currently appreciated.

Previously a positive correlation was found between the dose of estrogen in birth control pills and the risk of vascular thrombosis(22). Consequently, the infrequency of reported Premarin induced cases may reflect both the smaller number of patients on this therapy as well as the lower estrogenic activity in Premarin (0.625 mg of oral Premarin has 1/7 the equivalent estrogenic activity of the usual estrogen dose in oral contraceptives). Also, symptoms of colitis in 2 of our patients were mild and not thought to be related to Premarin until the acute presentation. The difference in clinical presentation between Premarin and oral contraceptive induced ischemia may also be related to the difference in estrogenic activity among compounds.

Table I, Literature review of Ischemic Colitis or Enterocolitis Caused by Oral Contraceptives*

No. of Cases	Cases with Transient Ischemia	Cases with Infarction	Date of Report	Reference No.
17	2 (17%)	15 (83%)	1963-1973	16
41	15 (37%)	26 (63%)	1963-1980	18
9	8 (91%)	1 (9%)	1980-1992	4,5,10

* References 16 and 18 are large literature reviews of all published cases in the designated time periods as noted above. References 4,5, and 10 are the only published reports presenting cases in the last decade.

Concerning potential mechanisms of the birth control pill and Premarin related ischemic bowel disease, in a study performed among postmenopausal women, a 289% increase was found in the incidence of hypercoagulability by antithrombin and heparin-antithrombin activity in the conjugated estrogen treated group (Premarin 1.25mg daily in a cyclic schedule) compared to the control group (20).

In addition, hypercoagulabilty, as documented by thromboelastography and appearance of fibrin monomers has been reported with the use of Premarin, but this increased clotting tendency with Premarin is less pronounced than with oral contraceptive agents (21). Specifically, alterations in the thrombin generation test and antithrombin III activity were not as evident with Premarin as the changes noted with oral contraceptive therapy. Also, hypercoagulability is not related to the duration of estrogen therapy (20), and when estrogen treatment is discontinued patients revert to pretreatment patterns (20,21).

Finally, with the aging of the American population and the increasing popularity of Premarin usage in post-menopausal women, the frequency of ischemic colitis with Premarin will most likely rise. In this regard, physicians administering Premarin should consider coagulation status testing in all patients especially those with a personal or family history of hypercoaguability before prescribing this agent and consider following patients on Premarin with similar testing, as well as dispensing the lowest effective estrogen dose. Also, physicians should have a high index of suspicion that nonspecific abdominal and colonic symptoms may be Premarin-induced colonic ischemia.

Table II. Cases of Premarin Induced Ischemic Colitis*

Pt No	Age (yrs)	Symptoms	Colonic Location	Duration of Hormonal Therapy Prior to Symptoms	Duration of Symptoms Prior to Presentation	Time to Resolution	Outcome (Transient or Resection)	Follow-up	Ref No.
1	50	abd. pain bloody diarrhea	transverse	6 mo.	1 day	na	transient	well	B
2	41	abd. pain bloody diarrhea	dis. trans. to poximal descening	3 mo.	2 day	1 day	transient	well	I
3	38	melena abd. pain	descending and sigmoid	2 yr.	na	4 days	transient	well	H
4	50	melena abd. pain	descending	10 yr.	na	1 week	transient	well	H
5	47	hemocc. (+) stool. episodic diarrhea	sigmoid	21 mo.	18 mo.	2 days	transient	well	JHH**
6	35	abd. pain hematochzia	descending	3 yr.	1 day	1 day	transient	well***	JHH
7	49	abd. pain bloody diarrhea	descending and sigmoid	6 yr.	3.5 yr.	2 day	transient	well	JHH

* ALL patients were on Premarin for physiologic or surgical induced menopause (cases 5,6,7 took Premarin 0.625 mg/day; case 2 took 1.25 mg/day; cases 1,3,4 dose not reported)
** JHH = The Johns Hopkins Medical Institutions
*** Patient well on 1 year follow-up visit despite continuation of Premarin

KAYNAKLAR

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