Today, low molecular weight heparins (LMWHs) are more and more commonly used. They are about to replace standard heparin in certain circumstances. The pharmacokinetics of intraperitoneal standard heparin are well known in continuous ambulatory peritoneal dialysis (CAPD), but data concerning LMWHs are lacking. The present study investigated the pharmacokinetics of intraperitoneal LMWHs in a single dose and compared them with the subcutaneous route in CAPD patients. The study enrolled 8 CAPD patients with a mean age of 47 ± 14.14 years. All patients had 40 mg enoxaparin added to their night exchange on one day. Blood samples were drawn just before instillation and at 2, 4, 8, 12, 18, and 24 hours after instillation for determination of plasma anti-factor Xa activity. After two days of washout, the same patients were given enoxaparin 40 mg subcutaneously, and blood samples were drawn at the same time points. Although no plasma factor Xa activity was seen after intraperitoneal administration, subcutaneous administration resulted in increased plasma factor Xa activity. We conclude that a single dose of intraperitoneal enoxaparin did not cause any change in plasma anti–factor Xa activity. That finding may be due either to an insufficient dose or to nonabsorption.

Key words
Continuous ambulatory peritoneal dialysis, fibrin, heparin, anti–factor Xa, low molecular weight heparin

Introduction
For certain drugs, the intraperitoneal route is frequently preferred to obtain systemic or local effects in patients on continuous ambulatory peritoneal dialysis (CAPD). Insulin is among the drugs most commonly administered intraperitoneally (1). Heparin and antibiotics are also administered intraperitoneally for treatment of peritonitis. Additionally, heparin is given to CAPD patients intraperitoneally when fibrin particles are observed in the dialysate (2–4).

Today, low molecular weight heparins (LMWHs) are more and more commonly used. They are about to replace standard heparin in certain circumstances. Owing to their lower molecular weight, LMWHs exhibit pharmacokinetic properties that are different from those of standard heparin. Because of higher bioavailability rates and longer half-lives, LMWHs are administered once or twice daily by the subcutaneous route.

Data concerning the pharmacokinetics of intraperitoneal LMWHs in CAPD patients are limited. In previous case reports, intraperitoneal LMWH in high doses has been reported to yield systemic anticoagulation (5,6). But experience emerging from single-case reports is unlikely to be generalized. Knowing the pharmacokinetics of intraperitoneal LMWH is crucial for the good management of CAPD patients. In the present study, we investigated the pharmacokinetics of single-dose intraperitoneal and subcutaneous LMWH in CAPD patients.

Patients and methods
Our study enrolled 8 CAPD patients with a mean age of 47 ± 14.14 years. The mean duration of peritoneal dialysis was 34 ± 18.24 months. The underlying causes
of renal failure were hypertension \((n = 4)\), Alport syndrome \((n = 2)\), pyelonephritis \((n = 1)\), and diabetes mellitus \((n = 1)\). Residual renal function was negligible in all patients. Patients who had experienced peritonitis within the last 6 months and patients with coagulation disorders were excluded. Written informed consent was obtained from all patients.

During the study, all patients were using 2 L of 2.27% dextrose peritoneal dialysis solution (Dianeal: Baxter Healthcare Corporation, Deerfield, IL, U.S.A.) containing enoxaparin 40 mg for the night exchange (8 hours). Blood samples were drawn just before instillation of the enoxaparin exchange and at 2, 4, 8, 12, 18, and 24 hours after instillation for determination of plasma anti–factor Xa activity.

After two days of washout, the same patients were given 40 mg enoxaparin subcutaneously, and blood samples were drawn at the same time points.

Specimens were collected in 3.2% trisodium citrate tubes (whole blood:anticoagulant ratio of 9:1). Within 1 hour of venipuncture, the mixture was centrifuged at 3000 rpm for 20 minutes at 20°C. All samples were stored at –50°C until the day of analysis.

The pharmacokinetics of LMWH were assessed by determining anti–factor Xa activity. Plasma anti–factor Xa activity was measured using an STA-Staclot Heparin (1) kit (Diagnostica Stago, Asnières, France). The pharmacokinetics analyses were performed using the Pharmacologic Calculation System computer program [PHARM/PCS, Version 4.0, based on (7)]. The two-way Friedman variance analysis test was applied for statistical analysis, and \(p < 0.05\) was considered significant.

**Results**

Peak plasma anti–factor Xa activity was attained 2 – 4 hours after subcutaneous administration of LMWH. Anti–factor Xa activity was within the therapeutic range in all patients given subcutaneous LMWH. After 8 hours, plasma anti–factor Xa activity was undetectable in all but 3 patients. Figure 1 presents the mean plasma anti–factor Xa activity–time profile after subcutaneous enoxaparin.

Peak anti–factor Xa activity \((C_{\text{max}})\) after 40 mg subcutaneous enoxaparin was 0.78 ± 0.09 IU/mL, and time to peak activity \((t_{\text{max}})\) was 3.25 ± 0.37 hours. Elimination half-life \((t_{1/2})\) was 3.95 ± 0.51 hours. Table I summarizes the pharmacokinetic parameters.

In all patients given intraperitoneal LMWH, plasma anti–factor Xa activity was undetectable.

**Discussion**

We detected no plasma anti–factor Xa activity after a single 40-mg dose of enoxaparin administered intraperitoneally.

Few publications address intraperitoneal LMWH administration. Schrader et al. (5) reported that they treated a CAPD patient with deep vein thrombosis by adding intraperitoneal LMWH to each exchange (dose: Kabi 2165, 8000 anti–factor Xa units). Anti–factor Xa activities were 0.5 – 0.8 IU/mL during the first 3 months, and 1.15 – 1.35 IU/mL at the end of the third month. Kleta et al. (6) used LMWH intraperitoneally in a 2-year-old CAPD patient for anti-thrombotic prophylaxis. They added 40 mg enoxaparin to one of two dialysate bags each day and obtained a sufficient prophylactic level (0.4 – 0.5 IU/mL).

In our study, in contrast to the two case reports, we detected no anti–factor Xa activity in plasma after

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean±SEM</th>
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<tbody>
<tr>
<td>(C_{\text{max}}) (IU/mL)</td>
<td>0.78±0.09</td>
</tr>
<tr>
<td>(t_{\text{max}}) (hours)</td>
<td>3.25±0.37</td>
</tr>
<tr>
<td>(t_{1/2}) (hours)</td>
<td>3.95±0.51</td>
</tr>
<tr>
<td>(\text{AUC}_{(0-24)}) (IU·h/mL)</td>
<td>5.40±1.54</td>
</tr>
<tr>
<td>(\text{AUC}_{(0-\infty)}) (IU·h/mL)</td>
<td>5.95±1.45</td>
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</table>

SEM = standard error of the mean; \(C_{\text{max}}\) = maximum concentration; \(t_{\text{max}}\) = time to maximum concentration; \(t_{1/2}\) = elimination half-life; \(\text{AUC}_{(0-24)}\) = area under the curve, from 0 to 24 hours; \(\text{AUC}_{(0-\infty)}\) = AUC, from 0 to infinity.
a single 40-mg dose of enoxaparin administered intraperitoneally. A previous study at our institution showed that intraperitoneal administration of LMWH did not affect total plasma levels of tissue factor pathway inhibitor (8). Failure to detect plasma anti–factor Xa activity may result from nonabsorption of LMWH (unlike standard heparin) or administration of a dose insufficient to elevate plasma activity beyond the sensitivity of the detection method. Our findings suggest that, when the intraperitoneal route is preferred for anticoagulation in CAPD patients, plasma anti–factor Xa activity should be carefully monitored.

Single-dose subcutaneous enoxaparin administration resulted in adequate anti–factor Xa activity, but in prolonged clearance \( [t_{\text{max}}: 3.95 \pm 0.51 \text{ hours}] \) in CAPD patients. Goudable et al. (9) found that the elimination of LMWH (CY 216) was about 1.5 times slower in patients with moderate renal insufficiency than in healthy subjects. Cadroy et al. (10) studied clearance of LMWH in healthy subjects and in patients with renal failure. The Cadroy group showed that the elimination of LMWH was delayed in patients with renal failure as compared with elimination in healthy subjects.

Our result is consistent with previous reports. Unlike the case with standard heparin, renal clearance (non saturable mechanism) plays a major role in the clearance of LMWH. If LMWHs are prescribed for CAPD patients, close monitoring of anti–factor Xa activity is required.

In our study, we gave a single dose of LMWH and did not adjust the heparin dose with regard to patient weight. Additionally, individual variations in the pharmacokinetics of LMWH may have influenced our result owing to our small sample size. But, with the same CAPD patients, we obtained the expected effect after subcutaneous administration of the drug, even though we detected no plasma anti–factor Xa activity after intraperitoneal administration.

**Conclusion**

Our study indicates that whether the subcutaneous or intraperitoneal route is used for LMWH administration, plasma anti–factor Xa activity should be carefully monitored for therapeutic drug level.

**References**


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PART TWO

Clinical Experiences
Peritoneal sclerosis is one of the most important complications of peritoneal dialysis (PD) treatment. Encapsulating peritoneal sclerosis (EPS) represents the most advanced stage of that disease and has a high mortality. No therapy of choice has been established for sclerosing peritonitis, although many have been proposed, with variable results. Tamoxifen has been successfully used in the treatment of patients with fibrosing diseases, mainly retroperitoneal fibrosis. Our purpose in the present study was to investigate whether treatment with tamoxifen in PD patients with peritoneal sclerosis has a beneficial effect.

Among more than 450 patients treated in our program since 1980, 23 were diagnosed with peritoneal sclerosis. Of those 23, 9 were treated with tamoxifen [20 mg every 12 hours: tamoxifen group (TG)] for a mean period of 14.5 ± 7 months (range: 6 – 30 months). The other 14 patients received no treatment and were considered the control group (CG). Both groups were similar in demography and peritoneal antecedents. Follow-up was longer in CG than in TG (mean: 47 months vs. 29 months), but the difference did not reach statistical significance. Mild thrombopenia in 1 patient was the only toxic effect observed with the use of tamoxifen. In CG, 4 patients developed EPS and died—3 of them during the first 6 months after diagnosis. No patient treated with tamoxifen developed EPS. Overall mortality was significantly higher in CG (71% vs. 22%, p = 0.03). Although follow-up was longer in CG, half the patients in that group died during the first 2 years after diagnosis.

Our experience suggests that treatment with tamoxifen of patients diagnosed with peritoneal sclerosis diminishes the related complications and significantly reduces mortality, at least in the short- to mid-term. However, a prospective therapeutic trial is required to confirm our results.

Key words
Tamoxifen, peritoneal sclerosis

Introduction
Peritoneal fibrosing syndrome includes a spectrum of changes present in peritoneal dialysis (PD) patients. Those changes range from a thickened peritoneum to encapsulating peritoneal sclerosis (EPS). Encapsulating peritoneal sclerosis is a rare and serious complication of PD with a high mortality rate (1,2). Gandhi et al. (3) described the first case in relation to PD in 1980. More cases were later reported in PD patients and were shown to be associated with a number of factors, including severe or recurrent peritonitis, prolonged duration of PD, treatment with beta-blockers, and use of chlorhexidine or acetate. However, the causes of EPS remain unknown.

The presenting symptoms are often vague, including weight loss, abdominal pain, anorexia, loss of ultrafiltration capacity, and, in advanced cases, small-bowel obstruction. To avoid the fatal consequences of EPS, early diagnosis is mandatory. No preventive treatments are known. Several post-diagnosis measures have been proposed: total parenteral nutrition; steroids or immunosuppressive drugs, or both; and surgery. Good results have been reported only sporadically (4,5).

Tamoxifen is an antiestrogenic drug that has been shown to be useful in the treatment of other fibrosing diseases such as desmoid tumors (6), idiopathic retroperitoneal fibrosis (7), and sclerosing mesenteritis (8). Recently, the first case of successful treatment with tamoxifen in 1 PD patient with EPS has been described (9).

Our purpose in the present study was to investigate whether tamoxifen has beneficial effects in the treatment of PD patients diagnosed with peritoneal sclerosis.

Patients and methods
We included in the study all patients who had been diagnosed with sclerosing peritonitis since 1980 in our PD unit. The criteria used to establish the diagno-
sis of sclerosing peritonitis included clinical and functional data, radiologic signs, and anatomic signs (2). To be able to compare the outcome of patients treated with tamoxifen, we established two groups: the tamoxifen group (TG) included patients who were diagnosed with sclerosing peritonitis and treated with tamoxifen, and the control group (CG) included patients who were diagnosed with sclerosing peritonitis and received no treatment.

Statistical analysis
Data are expressed as mean ± standard deviation, and \( p < 0.05 \) was considered statistically significant. Comparison of proportions between groups was performed using the chi-square test. The Student \( t \)-test was used to compare means.

Results
Among more than 450 patients treated in our PD unit since 1980, 23 were diagnosed with sclerosing peritonitis. Of the 23, 9 patients were treated with tamoxifen (20 mg every 12 hours) for a mean period of 14.5 ± 7 months (range: 6 – 30 months). The other 14 patients received no treatment and were considered the control group.

Table I shows the characteristics of the patients. No significant differences were found between groups. No toxicity was observed in relation to tamoxifen treatment, except in 1 patient who developed mild thrombocytopenia (90×10^3/µL) that resolved with a tamoxifen dose reduction.

In 10 cases (3 TG; 7 CG), clinical and functional data were used to diagnose sclerosing peritonitis. Radiologic signs were used to make the diagnosis in 16 cases (8 TG, 8 CG), and pathology findings were diagnostic in 10 cases (4 TG, 6 CG). The causal factors related to sclerosing peritonitis were severe peritonitis (6 TG, 8 CG), recurrent peritonitis (1 TG, 4 CG), hemoperitoneum (1 TG, 1 CG), and unknown (1 TG, 1 CG).

Two patients developed sclerosing peritonitis after PD withdrawal (1 TG, 1 CG). All other patients discontinued PD after diagnosis. In TG, 5 patients were transferred to hemodialysis, 2 were transplanted, and 2 died. In CG, 2 patients were transferred to hemodialysis, 2 received a transplant, and 10 died. Follow-up was longer in CG than in TG (47 ± 58 months vs. 29 ± 15 months), but the difference did not reach statistical significance.

Complications related to sclerosing peritonitis (abdominal abscess, intestinal occlusion) were less frequent in TG (1 case) than in CG (7 patients). No patient treated with tamoxifen developed EPS during 29 months of follow-up. On the other hand, 4 patients in CG developed EPS and died—3 of them during the first 6 months after diagnosis. Overall mortality was significantly higher in CG than in TG (71% vs. 22%, \( p = 0.03 \); Figure 1). In CG, 10 of 14 patients died, 4 of them as a consequence of complications of sclerosing peritonitis. In TG, 2 of 9 patients died, neither of them in relation to sclerosing peritonitis. In CG, half the patients died during the first 2 years after diagnosis. In CG, mortality grew during the first 3 years (to 85% from 37%); in TG, mortality remained at 22% during the same period.

Discussion
Treatment with tamoxifen of PD patients diagnosed with sclerosing peritonitis prolongs patient survival, at least in the short- to mid-term. No therapy of choice has been established for patients with sclerosing peritonitis. Transfer to hemodialysis is always required. Withdrawal from PD is mandatory to avoid the persistence of pathogenic factors. However, withdrawal has been reported to possibly exacerbate the disease process (intestinal adhesions progress), because inflammatory reactions often persist after PD discontinuation (10). Withdrawal permits regression of peritoneal fibrosis only in its early stages. If the peritoneal catheter is removed, the situation of a “dry” peritoneum may lead to new fibrin deposition. Recently, some authors (11) have proposed preservation of the peritoneal catheter and periodic irrigation of the peritoneal cavity for 6 – 12 months to prevent intestinal adhesions.

Many other therapies have been proposed, with variable results. Steroids or immunosuppressive drugs, total parenteral nutrition, and surgery (alone or in various combinations) have been associated with increased patient survival in cases of sclerosing peritonitis. However, only limited series or sporadic cases have been reported. Junor et al. (4) first described the successful use of steroids with azathioprine or cyclosporin in patients with sclerosing peritonitis, showing much better outcomes in treated patients than in patients receiving no treatment. Selgas et al. (12) also reported an apparent beneficial effect of renal transplantation in patients with sclerosing peritonitis. Surgery is dif-
The postoperative complications are numerous, and mortality is high (13). Bhandari et al. (5) recommended the use of immunosuppressive therapy before surgery, because prior drug treatment may reduce the adhesions. Total parenteral nutrition alone has no beneficial effects (14); it should be used in combination with steroids or surgery, or both.

Recently, the use of tamoxifen was reported in one PD patient with EPS (9). Tamoxifen has been used in the treatment of estrogen receptor–positive breast cancers. The successful use of tamoxifen was first described in 1985 by Kinzbrunner et al. (6) to treat desmoid tumor, a type of benign fibrotic tumor. Later, Clark et al. (7) reported good results after treating retroperitoneal fibrosis with tamoxifen. The negative estrogen-receptor status of many of the tumors successfully treated with tamoxifen supports the idea that other mechanisms of action may be at work. Tamoxifen inhibits protein kinase C (a phosphorylator of proteins) and calmodulin; it also reduces the production of epidermal growth factor. However, the mechanism of action of tamoxifen on peritoneal sclerosis has yet to be elucidated.

Mortality from peritoneal sclerosis is extremely high, specially if encapsulation is present. More than 60% of deaths occur within the first few months after diagnosis. Success with tamoxifen on other fibrotic

| TABLE I | Patient characteristics |
|-----------------|-----------------|-----------------|-----------------|
|                | Control (n = 14) | Tamoxifen (n = 9) | p Value |
| Sex (M/F)      | 6/8             | 4/5             | NS             |
| Age (years)    | 41.8 ± 17       | 52.7 ± 16       | NS             |
| Time on PD (months) | 63.9 ± 30     | 53.6 ± 34       | NS             |
| Duration of follow-up (months) | 47.4 ± 58 | 29 ± 20 | NS             |
| Peritoneal function at baseline |                      |                  |                |
| Ultrafiltration (mL) | 962 ± 387      | 861 ± 252       | NS             |
| D/P creatinine   | 0.73 ± 0.1      | 0.67 ± 0.1      | NS             |
| Urea MTC (mL/min) | 25.2 ± 10       | 22.1 ± 7        | NS             |
| Creatinine MTC (mL/min) | 3.1 ± 7   | 10.2 ± 4        | NS             |
| Last data on peritoneal function |                      |                  |                |
| Ultrafiltration rate (mL)^a | 703 ± 355       | 694 ± 381       | NS             |
| D/P creatinine   | 0.77 ± 0.1      | 0.7 ± 0.1       | NS             |
| Urea MTC (mL/min) | 19.4 ± 5        | 17.3 ± 5        | NS             |
| Creatinine MTC (mL/min) | 12.7 ± 4   | 9.7 ± 4         | NS             |
| Mayor abdominal surgery before PD | 1             | 1               | NS             |
| Mayor abdominal surgery on PD | 2             | 1               | NS             |
| Hemoperitoneum   | 6               | 3               | NS             |
| Patients with previous peritonitis | 13            | 8               | NS             |
| Accumulated peritoneal inflammation days | 15.5 ± 10    | 13.2 ± 9        | NS             |
| Catheter withdrawal with cloudy effluent during last peritonitis | 8             | 7               | NS             |
| Peritoneal resting | 6             | 5               | NS             |

^a Using a high glucose concentration (at least one 3.86% dextrose exchange daily).

M/F = male/female; NS = nonsignificant; PD = peritoneal dialysis; D/P = dialysate-to-plasma ratio; MTC = mass transfer coefficient.
processes led us to try the medication in our PD patients with peritoneal sclerosis. In our experience, tamoxifen has a low incidence of complications (mild thrombopenia in 1 case in the present study) and may be considered a safe drug. It reduces the complications related to peritoneal sclerosis, and, to mid-term at least, protects against development of EPS. No patient treated with tamoxifen in our series developed EPS. In contrast, 4 patients who received no treatment developed encapsulating disease.

In the current series, the overall mortality rate was significantly higher in CG than in TG (71% vs. 22%). Although follow-up was longer in CG, 50% of patients in that group died during the first 2 years of follow-up, many of them as a consequence of peritoneal sclerosis. Those findings indicate that patients treated with tamoxifen have a better clinical outcome, at least during the period studied. In our experience, tamoxifen is an effective choice for the treatment of peritoneal sclerosis, but the optimal duration of the treatment must be defined by controlled studies.

Conclusions
Our experience suggests that treatment with tamoxifen in patients diagnosed with peritoneal sclerosis may be beneficial and should be considered. The drug diminishes the complications related to the disease and significantly reduces the mortality rate, at least in the short- to mid-term. The small size of our series limits interpretation of the results, but the great difference found between the treatment group and the control group has encouraged us to design a prospective controlled trial with larger series.

References

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