Cancer Chemother Pharmacol (1999) 43: 427–434

ORIGINAL ARTICLE

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A pharmacokinetic model and the clinical pharmacology of cis-platinum, 5-fluorouracil and mitomycin-C in isolated pelvic perfusion

Received: 20 February 1998 / Accepted: 25 September 1998

Abstract *Purpose*: An isolated pelvic perfusion technique using multiple agents was used both in patients with unresectable recurrent pelvic neoplasms and as a preoperative therapy for advanced pelvic malignancy. *Methods*: The technique consisted of vascular occlusion via transfemoral balloon catheters, circulation and drug infusion using standard hemodialysis technology, and a 45-min isolation period. Blood and urine samples were analyzed for the levels of cis-platinum (17 patients, 21 courses of therapy, 50–100 mg/m^2, infusion 0–10 min), 5-fluorouracil (12 patients, 14 courses, 1500 mg/m^2, infusion 1/3 dose 0–1 min, 2/3 dose 1–20 min) and mitomycin-C (11 patients, 14 courses, 10–20 mg/m^2, infusion 10–20 min). An empirical, four-compartment pharmacokinetic model was developed to establish drug distribution curves for the pelvic and systemic circulations and to yield valid estimates of the pharmacokinetic parameters. *Results*: Pelvic isolation of drug was demonstrated by the pelvic-systemic drug exposure ratios of 6.0:1 for cis-platinum, 8.4:1 for 5-fluorouracil and 9.0:1 for mitomycin-C. Isolation at the L3-4 interspace resulted in minor urine drug elimination during isolation (cis-platinum 7.2% of drug, 5-fluorouracil 2.4% and mitomycin-C 2.5%). Because drug infusion was limited to the first 20 min of isolation, drug levels at the end of the isolation period were reduced to the extent that no extracorporeal drug removal mechanism was needed. *Conclusion*: These pharmacokinetic results indicate that this isolation technique has the potential to provide increased therapeutic indices and is a suitable system for evaluating fast-acting highly toxic experimental drugs to human pelvic cancers which are poorly responsive to conventional clinical protocols.

Key words Pharmacokinetics · Pelvic perfusion · Clinical pharmacology

This work was supported in part by CORE grant P30 CA13943, by NIH/NCI grant 5T32CA-09656-05 and by the Providence College Fund to Aid Faculty Research.

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Introduction

Isolated regional perfusion of chemotherapy dates back to 1958 when Creech et al. reported the use of an extracorporeal circuit to deliver a high concentration of drug to a regional arterial/venous circuit of the extremity. This technique permits regional delivery of drug at far higher concentrations than achievable by systemic therapy only (Collins 1989). The pharmacokinetics of pelvic perfusion with dose levels of cis-platinum and 5-fluorouracil were established in the 1980s (Wile et al. 1985; Wile and Smolir 1987). This methodology is currently being used in patients with unresectable recurrent pelvic cancer (Turk et al. 1993) or as a preoperative therapy for advanced pelvic malignancy (Wanebo et al. 1996) using a multiple agent protocol (cis-platinum, 5-fluorouracil and mitomycin C) at the higher end of the dosage levels.

The acquisition of blood samples during the isolated perfusion period to establish drug pharmacokinetics is limited by the complexity of the surgical procedure and the low volume of the isolated pelvic blood (estimated at 15% of the total circulation). Thus an empirical, four-compartment pharmacokinetic model suitable for commercial spreadsheets was developed. This model fits the limited experimental drug concentrations during the isolation period and gives good approximations for the drug distribution curves and other pharmacokinetic parameters of interest. This report presents the mathematical basis of this pharmacokinetic model, and

Table 1 Data on patients undergoing isolated pelvic perfusion

	Cis-platinum	5-Fluorouracil	Mitomycin C
Number of patients with pharmacokinetic data	17	12	11
Patients with recurrent rectal carcinoma	13	10	10
Patients with liposarcoma of retroperitoneum	1	0	0
Patients with Dukes' C adenocarcinoma	1	1	1
Patients with Dukes' SCCA anus	2	1	0
Number of courses of therapy monitored	21	14	14
Number of initial courses of therapy	11	9	9
Number of subsequent courses of therapy	10	5	5
Dosage levels (mg/m^2)	50–100	1500	10–20
Period(s) when drug was delivered during the 45-min isolation period	Continuous infusion 0–10 min	1/3 dose as bolus at $t = 0$ min, 2/3 dose as infusion 0–20 min	Continuous infusion 10–20 min

the resulting pharmacokinetics for the three chemotherapeutic agents.

Materials and methods

Patients with unresectable recurrent pelvic cancer or resectable advanced pelvic malignancy underwent isolated pelvic perfusion for a 45-min period. Patient characteristics and dosage regimens are presented in Table 1. The isolation technique (Fig. 1) incorporated transfemoral access, vascular balloon occlusion and extracorporeal circulation (250 ml/min) using standard hemodialysis technology and proximal thigh tourniquets (Turk et al. 1993). The balloon occlusion catheters (#8) were inserted via the femoral artery and vein to a level of approximately 2 cm above the bifurcation of the aorta and inferior to the vena cava (usually at L3-4) and monitored by on-table fluoroscopy. The perfusion cannulas were inserted via the same vessels and attached to an extracorporeal circuit; the advantage of the circuit was tested by dye injection. A renal dialysis machine was used to provide flow at 250–300 ml/min under nonoxygenated and normothermic conditions. Proximal thigh tourniquets were inflated to 100 mm Hg above systolic pressure during perfusion.

All drugs were infused during the first 20 min (Table 1). Pelvic and systemic blood samples were obtained from the venous perfusion cannula and the subclavian vein catheter at 5, 10, 15, 20, 30 and 45 min during isolation and 3 min after the end of isolation. The urine was collected during the isolation period. Its total volume was recorded and a sample was obtained for drug analyses. Where feasible, tissue samples were also obtained and analyzed for platinum content. Most tissue samples were taken immediately after the end of pelvic isolation. An effort was made to obtain tissue samples including tumor from perineal recurrence sites, as well as muscle in subcutaneous tissue and in perfused portions of pelvis or proximal thigh. However, one patient had tumor tissue samples taken at various time-points during and after pelvic isolation to follow the time-course of platinum tissue distribution. Samples were stored at −20 °C until analyzed. High performance liquid chromatographic methods were used to obtain the drug levels of 5-fluorouracil (Darnowski et al. 1985) and mitomycin C (Hartigh and Oort 1981). Samples were assayed for platinum content using conventional three-electrode d-c argon plasma emission spectroscopy (Forastiere et al. 1988).

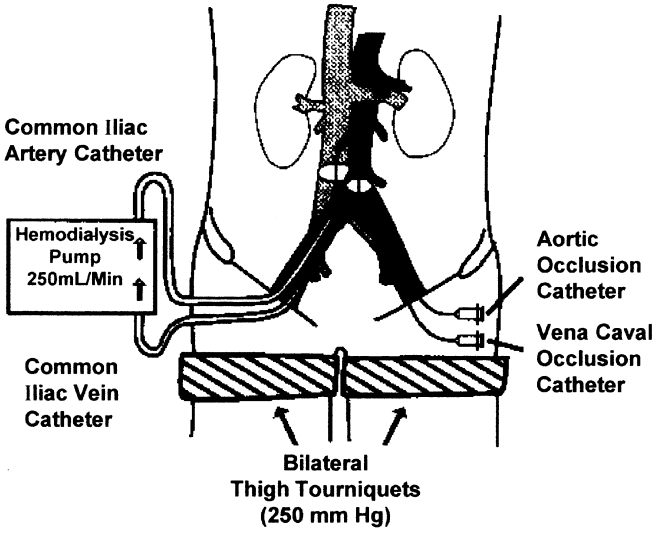

Fig. 1 Isolated pelvic perfusion incorporating transfemoral access and vascular isolation, and the extracorporeal circuit using standard hemodialysis technology

Experimental blood drug concentrations were fitted with the following empirical, four-compartment pharmacokinetic model to obtain the drug distribution curves in the isolated and systemic circulations and to obtain valid approximations for the pharmacokinetic parameters of interest.

Pharmacokinetic model

Figure 2 presents the four compartment scheme of our pharmacokinetic model for isolated pelvic perfusion. The drug is infused at a constant rate (zero order kinetics) into a pelvic volume of distribution compartment which includes the isolated serum volume and the "quickly equilibrated" local intercellular water. The drug leaves this compartment by two routes. During drug infusion when the concentration gradients are high and favorable, there is a major leak (first order kinetics) from the isolated pelvic circulation to the nonisolated systemic circulation (systemic volume of distribution compartment). The use of major and minor leaks from the pelvic to systemic systems is mathematically necessitated by the shape of the systemic drug distribution curve which increases during drug infusion and then decreases after the drug infusion period. The major leak mathematically accounts for the drug increase in the systemic system during drug infusion. The minor leak is incorporated into the following pelvic and systemic clearance terms. There is a first order kinetic clearance during the whole isolation period to a pelvic clearance compartment which incorporates the processes of tissue distribution, blood cell distribution, metabolism and a minor leak to the systemic compartments. In addition, during isolation there is a first order clearance from the systemic volume of distribution to a system clearance compartment which incorporates the processes of tissue and blood cell distribution, metabolism and excretion. The following mathematical model uses empirical approximations for the kinetic equations and it rapidly fits the experimental drug concentrations in the pelvic and systemic circulation during the isolated pelvic perfusion period. The mathematics and resulting drug distribution curves can be conveniently setup on commercial spreadsheets.

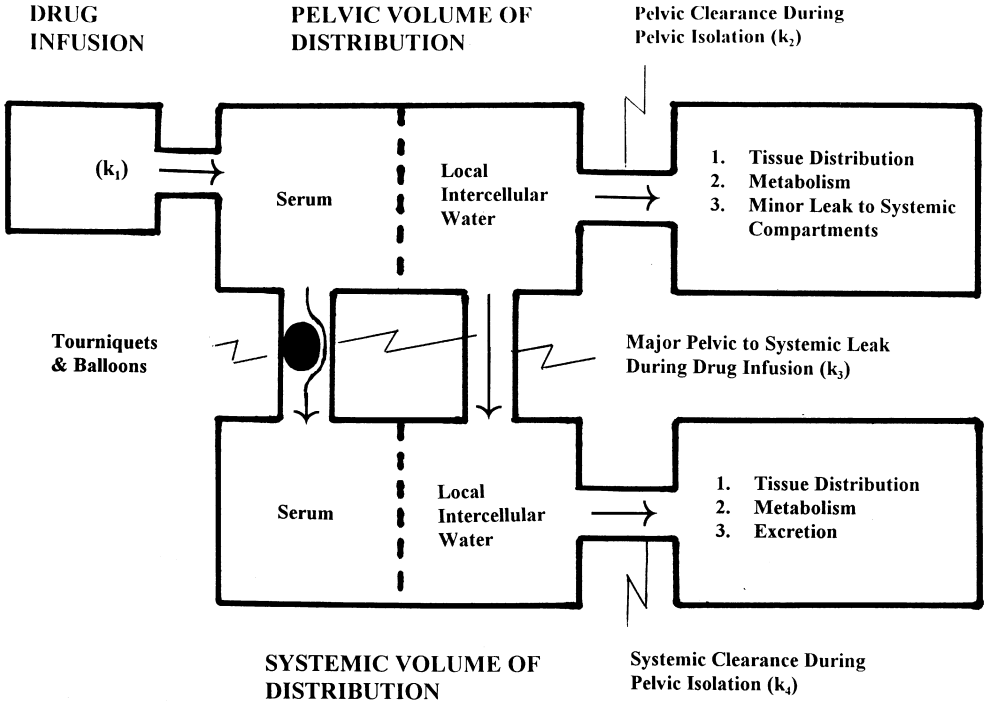

Fig. 2 Four compartment pharmacokinetic model for drug distribution during the 45-min isolated pelvic perfusion period

Definition of kinetic terms

$[\,]$ is the concentration of drug (e.g. μg/ml)

$$\text{Rate}_{\text{pelvic input}} = (\partial[\,]/\partial t) = k_1 = (\Delta[\,]/\Delta t)$$
$$\text{Rate}_{\text{pelvic clearance}} = -(\partial[\,]/\partial t) = k_2[\,]$$
$$\approx -(\Delta[\,]/\Delta t) \approx k_2[\,]_{\text{pelvic ave}}$$
$$\text{Rate}_{\text{pelvic leak}} = -(\partial[\,]/\partial t) = k_3[\,]$$
$$\approx -(\Delta[\,]/\Delta t) \approx k_3[\,]_{\text{pelvic ave}}$$
$$\text{Rate}_{\text{systemic clearance}} = -(\partial[\,]/\partial t) = k_4[\,]$$
$$\approx -(\Delta[\,]/\Delta t) \approx k_4[\,]_{\text{systemic ave}}$$

The approximations for the three first order kinetic rates are evaluated in 1-min increments for simplicity.

$[\,]_0$ is the drug concentration at beginning of minute

$[\,]_f$ is the drug concentration at end of minute

$\Delta[\,]_{\text{change}}$ is the change in drug concentration during the minute period $= [\,]_f - [\,]_0$

$[\,]_{\text{ave}}$ is the average drug concentration during the minute period $= [\,]_0 + \Delta[\,]_{\text{change}}/2$

Derivation of the equation for the drug concentration change in the pelvic compartment

Since $\Delta t = 1$, $(\Delta[\,]/\Delta t)$ will be abbreviated as $\Delta[\,]$.

$\Delta[\,]_{\text{pelvic input}} = k_1$ during drug infusion period

$\Delta[\,]_{\text{pelvic input}} = 0$ after the drug infusion period

$\Delta[\,]_{\text{pelvic clearance}} = k_2[\,]_{\text{pelvic ave}}$ during the pelvic isolation period

$\Delta[\,]_{\text{pelvic leak}} = k_3[\,]_{\text{pelvic ave}}$ during drug the infusion period

$\Delta[\,]_{\text{pelvic leak}} = 0$ after the drug infusion period

Mass balance equation during drug infusion period

$$\Delta[\,]_{\text{pelvic change}} = \Delta[\,]_{\text{pelvic input}} - \Delta[\,]_{\text{pelvic clearance}} - \Delta[\,]_{\text{pelvic leak}}$$
$$\Delta[\,]_{\text{pelvic change}} = k_1 - k_2[\,]_{\text{pelvic ave}} - k_3[\,]_{\text{pelvic ave}}$$
$$\Delta[\,]_{\text{pelvic change}} = k_1 - k_2\{[\,]_0 + \Delta[\,]_{\text{pelvic change}}/2\} - k_3\{[\,]_0 + \Delta[\,]_{\text{pelvic change}}/2\}$$

Rearranging terms

$$\Delta[\,]_{\text{pelvic change}} + k_2\Delta[\,]_{\text{pelvic change}}/2 + k_3\Delta[\,]_{\text{pelvic change}}/2 = k_1 - k_2[\,]_0 - k_3[\,]_0$$

$$\Delta[\,]_{\text{pelvic change}}\{1 + k_2/2 + k_3/2\} = k_1 - k_2[\,]_0 - k_3[\,]_0$$

$$\Delta[\,]_{\text{pelvic change}} = \{k_1 - k_2[\,]_0 - k_3[\,]_0\}/\{1 + k_2/2 + k_3/2\}$$

Thus the change in the pelvic drug concentration at the end of the 1-min period can be calculated using the initial concentration and the kinetic constants. After the drug infusion period, the equation simplifies to:

$$\Delta[\,]_{\text{pelvic change}} = -k_2[\,]_0/\{1 + k_2/2\}$$

Derivation of the equation for the drug concentration change in the systemic compartment

During the drug infusion period, the drug from the pelvic leak is the drug input to the systemic compartment. The kinetic rate equations use drug concentrations, not drug amounts. Thus the systemic drug input per minute during drug infusion is equated to

the pelvic leak per minute by multiplying by the ratio of volumes of the two compartments.

$$\Delta[]_{\text{systemic input}} = -\Delta[]_{\text{pelvic leak}} \times \{\text{Volume}_{\text{pelvic compartment}} / \text{Volume}_{\text{systemic compartment}}\}$$

$$\Delta[]_{\text{systemic input}} = -k_3[]_{\text{pelvic ave}} \times \{\text{Volume}_{\text{pelvic compartment}} / \text{Volume}_{\text{systemic compartment}}\}$$

which becomes

$$\Delta[]_{\text{systemic input}} = -k_3[]_{\text{systemic ave}}$$

during the drug infusion period, and

$$\Delta[]_{\text{systemic input}} = 0$$

after the drug infusion period; also

$$\Delta[]_{\text{systemic clearance}} = k_4[]_{\text{ave}}$$

during the pelvic isolation period.

Mass balance equation during drug infusion period

$$\Delta[]_{\text{systemic change}} = \Delta[]_{\text{systemic input}} - \Delta[]_{\text{systemic clearance}}$$

$$\Delta[]_{\text{systemic change}} = k_3[]_{\text{systemic ave}} - k_4[]_{\text{systemic ave}}$$

$$\Delta[]_{\text{systemic change}} = k_3\{[]0 + \Delta[]_{\text{systemic change}}/2\} - k_4\{[]_0 + \Delta[]_{\text{systemic change}}/2\}$$

Rearranging terms

$$\Delta[]_{\text{systemic change}} - k_3\Delta[]_{\text{systemic change}}/2 + k_4\Delta[]_{\text{systemic change}}/2 = k_3[]_0 - k_4[]_0$$

$$\Delta[]_{\text{systemic change}}\{1 - k_3/2 + k_4/2\} = k_3[]_0 - k_4[]_0$$

$$\Delta[]_{\text{systemic change}} = \{k_3[]_0 - k_4[]_0\}/\{1 - k_3/2 + k_4/2\}$$

After drug infusion period, equation simplifies to

$$\Delta[]_{\text{systemic change}} = -k_4[]_0/\{1 + k_4/2\}$$

The calculations for this model can be easily arranged in a spreadsheet using a two-dimensional array of 45 rows for the 1-min kinetic periods and individual columns for the calculations of the concentrations such as $[]_{\text{drug input}}$, $[]_0$, $[]_{\text{increase}}$, $[]_{\text{final}}$, $[]_{\text{ave}}$ and $[]_{\text{drug outputs}}$ for both the pelvic and systemic compartments.

The inputs into this mathematical model for each course of therapy are total patient serum volume, percentage of blood supply isolated (15%), the drug infusion rate constant, k_1, and the drug infusion period. Note that with 5-fluorouracil, two drug infusion constants were used, i.e. k_1 (one-third of the dose during the first minute) and k_1' (two-thirds of the dose from the 1–20-min time period). Pharmacokinetic curves for the isolated pelvic circulation and the nonisolated systemic circulation are then manually fitted to the experimental, time-dependent drug concentrations by optimizing four dependent variables. The first is the volume of distribution ratio (i.e. total volume of compartment to serum volume) which primarily fits the magnitudes of the pelvic and systemic serum drug concentrations, a concept similar to the "extrapolated volume of distribution" used with the pharmacokinetics of bolus drug administration (Wagner 1975). The volume of distribution ratios for both the pelvic and systemic compartments are assumed to be equal. The second dependent variable is the first order rate constant, k_3, for the "pelvic leak" to the systemic circulation during drug infusion. This parameter sets the relative levels of pelvic to systemic drug concentrations. The last two dependent variables are the first order rate constants, k_2 and k_4, for the clearance processes from the pelvic and systemic compartments, respectively. These latter parameters determine the decrease in drug levels in the pelvic and systemic circulations after drug infusion and during isolation. The fitting of the experimental concentration-time data was done visually by changing one or more of the four dependent variables within a spreadsheet and observing the effect on the resulting pharmacokinetic curves (with respect to the experimental points) displayed in the same spreadsheet

Pharmacokinetic parameters for the blood can be easily evaluated from this model. The parameters of interest are (1) the pelvic and systemic exposures (area under the time-concentration curve, AUC) during isolation and their ratio which gives the time-averaged enhancement of drug concentrations in the isolated circulation, (2) the maximum pelvic drug concentrations, (3) the pelvic half-life after drug infusion and during isolation and (4) the percentage of drug leaking from the pelvic to the systemic circulation during drug infusion (i.e. the major leak to the systemic compartment). The AUC during isolation was calculated in 1-min intervals using the trapezoidal rule.

Results and discussion

Figures 3–5 illustrate the optimum fits of the pharmacokinetic curves (solid lines) to the experimental data for single courses of therapy for each drug. Since the experimental data vary over more than an order of magnitude, these fits were more efficiently performed visually rather than using a "least squares" type of mathematical routine. The resulting curves are very reasonable fits from such a simple model which assumes equilibrium in the compartments where multiple dynamic processes are going on. Also, curves and pharmacokinetic data can be obtained using this model from very limited experimental data (i.e. three or more points). Table 2 presents the pharmacokinetic parameters of interest for each drug. Pelvic isolation was achieved as indicated by a sixfold pelvic-systemic drug exposure ratio of for cis-platinum and eight- to ninefold ratios for 5-fluorouracil and mitomycin-C. Wile et al. (1985) reported a similar ratio of 7.8 for 5-fluorouracil and a smaller ratio of 2.8 for cis-platinum using their hyperthermic pelvic perfusion technique. The low drug concentrations in the systemic circulation relative to the pelvic drug concentrations are related more to a large systemic volume (85% of total blood supply) rather than a low drug leak

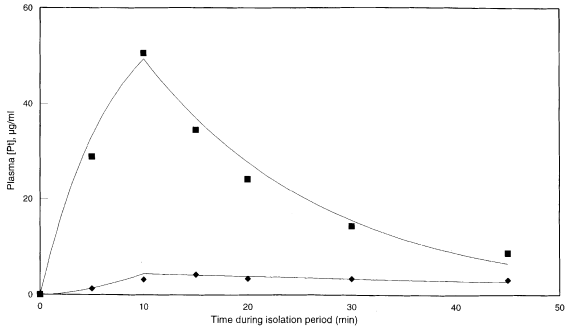

Fig. 3 Plasma platinum levels during the 45-min isolated pelvic, perfusion period. Cis-platinum (200 mg) was infused during 0–10 min (dose 100 mg/m^2). Experimental points: □ isolated pelvic region, + nonisolated systemic region; *solid lines* are fitted curves from the pharmacokinetic model

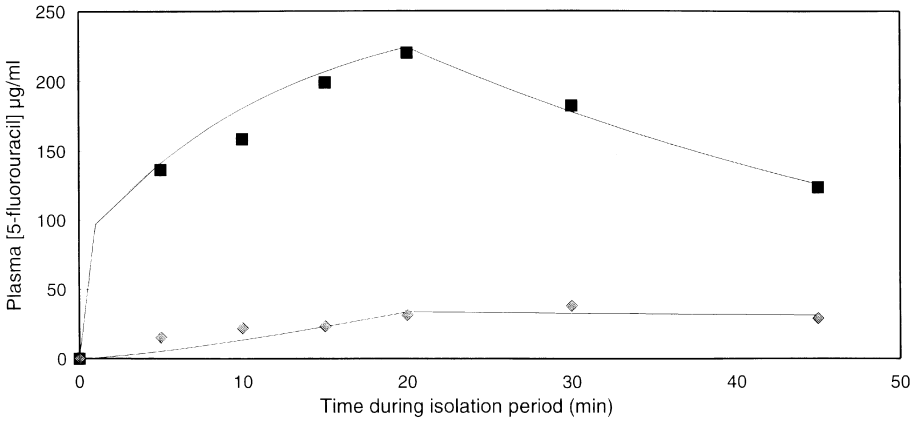

Fig. 4 Plasma 5-fluorouracil levels during the 45-min isolated pelvic perfusion period following a 1000 mg bolus at $t = 0$ and 2000 mg infused during 0–20 min (total dose 1500 mg/m^2). Experimental points: □ isolated pelvic region, + nonisolated systemic region; *solid lines* are fitted curves from the pharmacokinetic model

since the major leak during drug infusion was evaluated as 30–40% of the dose.

The evaluation of the total drug leak from the isolated pelvic circulation to the systemic circulation cannot be fully determined with the limited experimental set of drug concentrations. However, the major portion of this leak during the drug infusion period, where drug concentration gradients are favorable, is evaluated from k_3. The minor portion of the leak after drug infusion and during isolation cannot be directly evaluated. This minor leak appears as an additional kinetic term in the summation of first order kinetic processes incorporated in the clearance kinetic constants, k_2 and k_4. This inclusion of the minor leak terms in the clearance kinetics can be illustrated if one compares the well-established half-lives for cis-platinum from ordinary bolus and short-term infusions (30–40 min), (DeConti et al. 1973; Pratt et al. 1981) with that of this technique's pelvic half-life (15 ± 1 min) and systemic half-life (106 ± 11 min). Thus, the additional leak term decreases the pelvic clearance half-life and increases the systemic clearance half-life. Calculations have been performed to evaluate the order of magnitude of this minor leak and, assuming that the ordinary clearance terms have a kinetic constant with a half-life of 30 min, this minor leak is approximately one-fourth of the major leak during drug infusion. Thus, the overall drug leak would be in the 40–50% range.

The percentage of blood isolated (i.e. 15%) was our best estimate of the isolated blood volume between the bilateral thigh tourniquets and the aortic and vena occlusion balloons, given the physiology of the average human. An error in this parameter only reflects on one of the pharmacokinetic parameters of interest, the percentage of the drug leaking from the pelvic to the systemic compartment during drug infusion. Thus, the isolation of a greater percentage of the blood supply isolated would lower the percentage of drug leaking from the pelvic to the systemic compartments. These conclusions were verified by calculations using a blood supply isolation of 25%.

The maximum pelvic drug levels with our dosage protocol are higher than those reported previously. The maximum pelvic cis-platinum serum level of 37 µg/ml is threefold higher than that reported by Wile and Smolir (1987) for one patient receiving 50 mg cis-platinum with hyperthermic pelvic isolation perfusion, a dose two- to threefold lower than our dosage range. Our level is also more than twice the maximum serum levels reported for short-term i.v. infusions of 100 mg/m^2 for 6- and 15-min periods (Vermorken et al. 1984). The maximum mitomycin C level is three- to fourfold higher than those

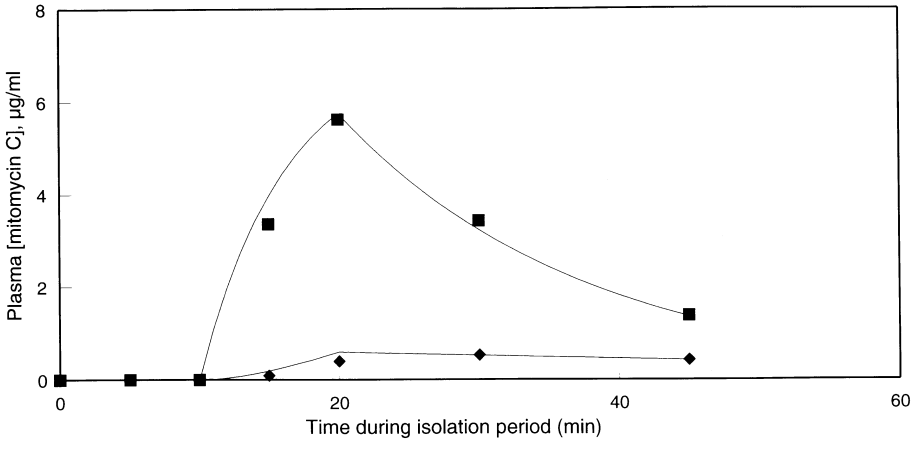

Fig. 5 Plasma mitomycin C levels during the 45-min isolated pelvic perfusion period. Mitomycin C (30 mg) was infused during 10–20 min (dose 15 mg/m^2). Experimental points: □ isolated pelvic region, + nonisolated systemic region; *solid lines* are fitted curves from the pharmacokinetic model

Table 2 Pharmacokinetic parameters for isolated pelvic perfusion

Parameter	Cis-platinum		5-Fluorouracil		Mitomycin C	
	Mean (±SE)	No. of values	Mean (±SE)	No. of values	Mean (±SE)	No. of values
Plasma pelvic to systemic exposure[a] ratio during isolation	6.0(±0.6):1.0	21	8.4(±0.8):1.0	14	9.0(±1.3):1.0	14
Plasma drug concentrations						
Maximum pelvic concentration	37(±4) μg/ml[b]	21	317(±45) μg/ml	14	5.3(±0.8) μg/ml	14
Pelvic concentration at end of isolation	5.7(±0.6) μg/ml	17	156(±19) μg/ml	14	1.0(±0.2) μg/ml	13
Concentration 3 min after end of isolation	4.3(±0.5) μg/ml	17	100(±12) μg/ml	14	0.6(±0.1) μg/ml	13
% drug eliminated in urine during isolation	7.2(±1.3)%	8	2.4(±0.6)%	10	2.5(±0.2)%	3
Pelvic plasma half-life after drug infusion and during isolation	15.3(±0.8) min	21	27(±3) min	14	9.8(±0.7) min	14
Percentage of drug leading from pelvic to systematic compartment during drug infusion	38(±2)%	21	35(±2)%	14	30(±3)%	14
Ratio of the volume of distribution to plasma volume[c]	4.7(±0.3):1.0	21	11.9(±0.9):1.0	14	7.2(±0.7):1.0	14

[a] Exposure defined as the area under the time-concentration curve, i.e. AUC
[b] The platinum concentration was directly measured by emission spectroscopic methodology. The cis-platinum concentration was calculated by multiplying the platinum concentration by a factor of 1.5 (i.e. the ratio of the molecular weight of cis-platinum to the atomic weight of platinum)
[c] The volume of distribution is the sum of the plasma volume and the volume of the local intercellular water in which the drug quickly equilibrates (a concept similar to the "extrapolated volume of distribution" used with the pharmacokinetics of bolus drug administration)

reported for bolus or short-term infusions at 20 mg/m^2 (Hartigh 1983; Reich 1979). The maximum 5-fluorouracil levels for our 20-min bolus/infusion protocol were sevenfold higher than those reported by Wile et al. (1985) for five patients receiving 1 g 5-fluorouracil with hyperthermic pelvic isolation perfusion – again, dosages two- to threefold lower than our dosage range. Our levels were also threefold higher than those reported for bolus administration at one-third the dose (Fraile et al. 1980; Heggie et al. 1987).

Drugs were infused during the first 20 min of isolation and the pelvic drug concentrations at the end of the isolation period were within the range reported for bolus or short-term infusions. Concentrations had decreased by a factor of nine from peak values to levels 3 min after the end of infusion for cis-platinum and mitomycin C, and by a factor of three for 5-fluorouracil (Table 2). Thus, no extracorporeal drug removal mechanism was needed.

The pelvic clearance half-lives from our isolation procedure (Table 2) are readily interpretable. As stated above, the cis-platinum half-life decreased to 15 min because of the additional leak from the isolated circulation. The half-life of mitomycin C of 10 min is of the order of that reported as $t_{1/2}\alpha$ for bolus or short-term infusion (Reich 1979, den Hartigh 1983). The half-life for 5-fluorouracil is threefold higher than that reported for bolus administration, probably due to the combination of a longer infusion period and a lower rate of metabolism in the isolated circulation due to the exclusion of the liver (Fraile et al. 1980; Heggie et al. 1987). The extended infusion period does give a longer half-life as shown by a comparison with a previous isolated pelvic perfusion protocol using dual boluses at the 0 and 22-min marks. The half-lives were 13.6 ± 2.5 min ($n = 6$) for this previous protocol and these are of the order of those reported in the literature.

Isolation by the balloon catheters was at the L3-4 interspace and thus the blood supply to the kidney was not included in the isolated pelvic circulation. This minimized nephrotoxicity, especially from cis-platinum. This closure resulted in minor urine drug eliminations during isolation (cis-platinum 7.2% of drug, 5-fluorouracil 2.4% and mitomycin-C 2.5%). Included in the complications of the procedure were technical issues such as disruption of the aortic balloon occlusion catheter during the perfusion. The catheter was changed without incident; the patient suffered leukopenia after perfusion. It is not clear whether the release of chemotherapeutic agents into the aorta and the branches was responsible as several patients had leukopenia after perfusion. Other complications included femoral artery injury in a patient with severe arteriolosclerosis, aborting the second perfusion, and reconstruction of a severely atheromatous femoral artery. Perfusion was extremely well tolerated and all patients were discharged by postoperative day 3. Leukopenia occurred in approximately 75% of patients, and was counteracted by filgrastim which was begun on postoperative day 2.

Tissue platinum levels were less than 1 μg/g of fresh tissue for fatty tissue and 1–5 μg/g for non-fatty tissue. Platinum tissue levels followed those in the blood, i.e. reaching a maximum and then decreasing by the end of isolation. Maximum tissue platinum in the pelvic area (3–5 μg/g) was fourfold higher than that in the systemic

Table 3 Summary of kinetic rate constants during isolated pelvic perfusion

Rate constant	Mean ± SD	*n*	Time period (min)
Cis-platinum			
Drug infusion k_1	4.8 ± 2.0 mg/l-min	21	0–10
Pelvic clearance k_2	0.48 ± 0.01 min^{-1}	21	0–45
Pelvic leak k_3	0.13 ± 0.06 min^{-1}	21	0–10
Systemic clearance k_4	0.008 ± 0.0068 min^{-1}	21	0–45
Mitomycin C			
Drug infusion k_1	1.4 ± 1.3 mg/l-min	14	10–20
Pelvic clearance k_2	0.076 ± 0.020 min^{-1}	14	10–45
Pelvic leak k_3	0.10 ± 0.05 min^{-1}	14	10–10
Systemic clearance k_4	0.022 ± 0.008 min^{-1}	14	10–45
5-Fluorouracil			
Drug infusion (1/3 dose) k_1	212 ± 113 mg/l-min	14	0–1
Drug infusion (2/3 dose) k_1'	24 ± 11 mg/l-min	14	1–20
Pelvic clearance k_2	0.028 ± 0.010 min^{-1}	14	0–45
Pelvic leak k_3	0.051 ± 0.018 min^{-1}	14	0–20
Systemic clearance k_4	0.0044 ± 0.0025 min^{-1}	14	0–45

region. The levels at the end of isolation (1–2 μg/g) are of the order of those reported in the literature for comparable tissues (LeRoy et al. 1979; Litterst et al. 1979).

There were no statistically significant differences between the pharmacokinetics for the initial course of therapy and those for subsequent courses for all three drugs. There was no effect during isolation on the endogenous plasma levels of magnesium, iron, copper or zinc in either the pelvic or the systemic circulation other than minor dilution effects due to fluid replacement (<5%).

The pharmacokinetic results of this study indicate that there is significant enhancement of pelvic drug levels with isolated pelvic perfusion indicating its potential to increase the therapeutic index and clinical efficacy. Table 3 presents a summary of the kinetic rate constants from the pharmacokinetic evaluation of the three drugs in our isolated pelvic perfusion protocol. This system would seem to be ideal for evaluating fast-acting highly toxic experimental drugs to human pelvic cancers against which treatment protocols show limited clinical success.

The pharmacokinetic modeling using empirical approximations for the kinetic rate equations is a convenient and novel way of fitting data using relatively simple mathematics and commercially available spreadsheets. It is easily adapted to other multicompartment schemes and when data is fitted visually, it gives a direct feel for the pharmacokinetic consequences of the different kinetic constants.

Acknowledgements The following students at Providence College assisted in this research: Leslie (Kelly) Cousens, Shelia Fitzpatrick, Jerry Brito, Kara Merkle and Katie Campbell. Thanks are extended to Elizabeth Kill and the personnel at the Chemistry and Materials Laboratories of Texas Instruments, Inc., Attleboro, MA 02703, for permission to use their plasma emission spectrometers and for their invaluable technical assistance. Special acknowledgement for technical support is given to Nancy Marshall who operated the hemodialysis pump unit during the perfusion. Audrey Levy, Physician's Assistant Certified (PA-C), is thanked for her pre- and postoperative care of the patients, and her interaction with the perfusionist regarding drug dosage. Ms. Marshall and Levy are at Roger Williams Medical Center.

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