Cancer Chemother Pharmacol (2005) 55: 318–322
DOI 10.1007/s00280-004-0895-x

ORIGINAL ARTICLE

James F. Belliveau · Elisabeth Arevalo · Hank Griffin
Harold J. Wanebo

Isolated pelvic perfusion: plasma pharmacokinetics depend primarily on drug dosage and not the type of drug

Received: 8 September 2003 / Accepted: 24 June 2004 / Published online: 15 January 2005

Abstract *Purpose*: Comparison of the pharmacokinetics of four drugs with the isolated pelvic perfusion protocol showed linear relationships between drug dosage and two isolated pelvic plasma parameters, mean AUC (pelvic exposure, μM min) and the mean maximum pelvic drug level (μM). It appears that the pharmacokinetics are sufficiently defined as to predict plasma distribution curves for an additional drug with this protocol. Recent FDA approval of oxaliplatin allowed an evaluation of this premise. *Methods*: Linearity of drug dosage with maximum drug levels and exposure (AUC) in the isolated pelvic plasma yields initial estimates of these parameters for additional drugs. Use of an empirical, four-compartment pharmacokinetic model (Wanebo and Belliveau in Cancer Chemother. Pharmacol. 43:427, 1999) allowed the generation of predictive plasma distribution curves. These curves were established by optimizing the initial estimates of maximum drug levels and exposure along with estimates of two additional parameters (half-life of pelvic clearance and pelvic to systemic exposure ratio) from experimental data of the four drugs pharmacokinetically characterized. *Results*: Calculated plasma distribution curves for oxaliplatin matched the experimental curves from the first three patients receiving oxaliplatin therapy, given the experimental ranges of pharmacokinetic parameters seen with the initial four drugs. *Conclusion*: These results give an overall picture for the plasma pharmacokinetics during the isolation period for the isolated pelvic perfusion protocol. Enough experimental data have been accumulated for five drugs to establish a simple pharmacokinetic model (Wanebo and Belliveau in Cancer Chemother Pharmacol 43:427, 1999) and interdrug relationships (i.e., this report) which can be used to predict reasonable plasma distribution curves for additional drugs with this protocol.

Keywords Pharmacokinetics · Pelvic perfusion · Clinical pharmacology

J. F. Belliveau (✉) · H. Griffin
Departments of Chemistry and Biochemistry, Providence College, 549 River Avenue, Providence, RI 02918, USA
E-mail: bells@providence.edu
Tel.: +1-401-8652238
Fax: +1-401-8651438

E. Arevalo
Department of Biology, Providence College, 549 River Avenue, Providence, RI 02918, USA

H. J. Wanebo
Division of Surgical Oncology, Roger Williams Medical Center/ Boston University School of Medicine, Providence, RI 02908, USA

Introduction

Creech et al. [2] in 1958 were the first to report an isolated regional perfusion protocol in which an extracorporeal circuit was used to deliver a high concentration of drug to a regional arterial/venous circuit of the extremity. At our institution, Roger Williams Medical Center, an isolated pelvic perfusion protocol has been used for 11 years both in patients with unresectable pelvic neoplasms [8] and as a preoperative therapy for advanced pelvic malignancy [10]. The pharmacokinetics of four drugs used in this protocol had been determined (cisplatin, mitomycin C, 5-fluorouracil and Adriamycin) prior to this year. The pharmacokinetics of three of these drugs were published [9] along with a curve-fitting algorithm based on a pharmacokinetic model for isolated pelvic perfusion. This report presents a comparison among the pharmacokinetics of the four drugs which enabled the generation of plasma distribution curves for the recently approved oxaliplatin (Eloxatin) in the United States. Oxaliplatin has subsequently been used in three courses of therapy and the predicted versus experimental plasma distribution curves are compared.

Materials and methods

Patients with unresectable recurrent pelvic cancer or resectable advanced pelvic malignancy underwent

isolated pelvic perfusion for an isolated period of 60 min. Protocol parameters, patient characteristics and dosage regimens for the initial four drugs used are presented in Table 1. The isolation technique incorporated transfemoral access, vascular balloon occlusion and extracorporeal circulation (300 ml/min, currently using an open heart-lung pump with oxygenation and hyperthermia capabilities).

All drugs were infused during the first 25 min. Pelvic and systemic blood samples were obtained at 5, 10, 15, 20, 30, 45 and 60 min during isolation and 3 min after the end of isolation. Samples were stored at −20°C until analyzed. High-performance liquid chromatographic methods were used to obtain the drug levels of 5-fluorouracil [3] and mitomycin C [5]. Samples were assayed for platinum content (cisplatin and oxaliplatin) using conventional three-electrode d-c argon plasma emission spectroscopy [4]. Adriamycin was analyzed with a UV/visible spectrophotometric method (article in preparation).

Experimental blood drug concentrations were fitted with an empirical, four-compartment pharmacokinetic model [9] to obtain the drug distribution curves in the isolated and systemic circulations and to obtain valid approximations for the pharmacokinetic parameters of interest (see Appendix 1).

Results

Comparison of the plasma pharmacokinetic parameters among the four drugs (cisplatin, mitomycin C, 5-fluorouracil and Adriamycin) showed a linear relationship with two parameters in the isolated pelvic plasma circuit. Figure 1 presents the mean area under the time–concentration curve (AUC) (pelvic exposure, μ*M* min) and the mean maximum pelvic drug level (μ*M*) as a function of dosage (μmol/m^2) for each of the four drugs. A log–log plot was used because the dosage spanned four orders of magnitude (45–11,531 μmol/m^2). Excellent linearity was found for the maximum drug levels ($r^2 = 0.9994$) and the pelvic exposures ($r^2 = 0.9983$). This linearity has been reported in abstract form [1]. These results indicate that the plasma clearance of drugs in the isolated circuit is, to a first approximation, due to normal body processes and not to the type of drug. Our range of drugs spanned inorganic complexes to organic compounds of varying polarity.

Table 1 presents a summary of the results for the four drugs with isolated pelvic perfusion. Of particular interest are the data on the maximum pelvic drug levels and pelvic exposures. The differences between the mean experimental maximum drug level and the calculated maximum drug level from the linear equation (Fig. 1) was less than 12% for the four drugs. The differences between experimental and calculated pelvic exposures were less than 24% for the four drugs. The calculated parameters were within the range of experimental values for the individual courses of therapy.

Given the relationships in Fig. 1, it was possible to determine reasonable plasma clearance curves for a new drug with the isolated pelvic perfusion protocol. Oxaliplatin has recently been approved for use in the United

Table 1 Patient data and pharmacokinetic results on the initial four drugs

	Mitomycin C	Adriamycin	Cisplatin	5-Fluorouracil
No. of courses of therapy	4	2	8	13
No. of patients	4	2	6	11
Cancer types				
Recurrent rectal	3	0	3	10
Recurrent ovarian	0	0	1	0
Recurrent prostrate	0	1	0	0
Anal sarcoma	0	1	1	0
Adenocarcinoma	1	0	0	1
SCCA of anal canal	0	0	1	0
Period of drug infusion (min)	10	15	15	20
Dose (μmol/m^2)	45	138	333	11,531
Pelvic drug levels, maximum (μ*M*)				
Mean, experimental	16	46	106	2,100
Mean, calculated	17	47	102	2,337
% difference—calculated vs experimental	9.1	−2.1	−3.8	11.3
Range, experimental	10–24	38–54	49–166	1,631–2,731
Pelvic exposure, AUC (μ*M* min)				
Mean, experimental	323	1,066	2,900	73,106
Mean, calculated	398	1,175	2,747	83,381
% difference—calculated vs experimental	23.3	−10.2	−5.5	14.1
Range, experimental	208–430	803–1,329	1,399–4,803	57,257–9,4980
Pelvic clearance, $t_{1/2}$ (min)				
Mean	12	12	22	28
Range	9–15	11–12	15–40	16–50
Exposure (AUC) ratios—pelvic to systemic				
Mean	6.7	5.9	5.6	7.8
Range	4.8–9.0	3.6–8.2	3.0–11.1	3.3–10.7

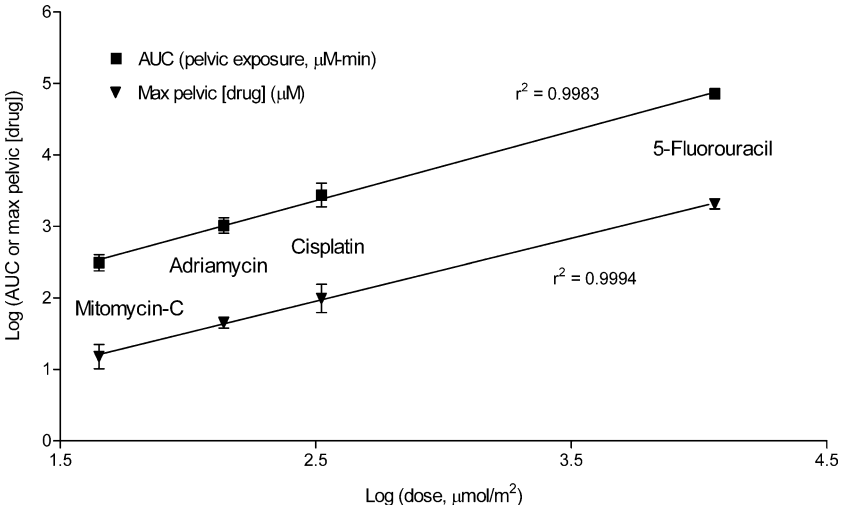

Fig. 1 Linearity of drug dose with mean pelvic exposures (*filled squares*) and mean maximum pelvic drug concentrations (*filled triangles*). Error bars are ±SD

States and would be an ideal substitute for cisplatin, given its reported greater anticancer effect in colon cancer [6, 7]. The initial dosage level was chosen equivalent to that of cisplatin on a weight basis (i.e., 100 mg/m^2). Toxicities will be evaluated at this dosage level and it is hoped that the dosage can be escalated to an equivalent dose on a molar, not weight, basis (333 μmol/m^2 or 132 mg/m^2). The linear relationships of Fig. 1 were used to calculate initial values for the maximum pelvic drug level and pelvic exposure for this new drug in micrograms per milliliter. Thus it is expected that the maximum oxaliplatin pelvic plasma level would be about 30 μg/ml and the pelvic exposure would be on the order of 800 μg min/ml.

To generate predictive plasma distribution curves, a pharmacokinetic curve-fitting algorithm [9] was used to calculate pelvic and systemic plasma drug levels during the isolated perfusion period optimizing four pharmacokinetic parameters (see Appendix 1). In addition to the maximum pelvic drug level and pelvic exposure values from the linear relationships, final plasma distribution curves were also fitted to a $t_{1/2}$ plasma clearance lifetime of approximately 20 min and pelvic to systemic exposure ratios of approximately seven, given the pharmacokinetic data of the initial four drugs (Table 1).

Figure 2 gives the calculated pelvic and systemic plasma distribution curves. Also included are the experimental distribution curves for the first three

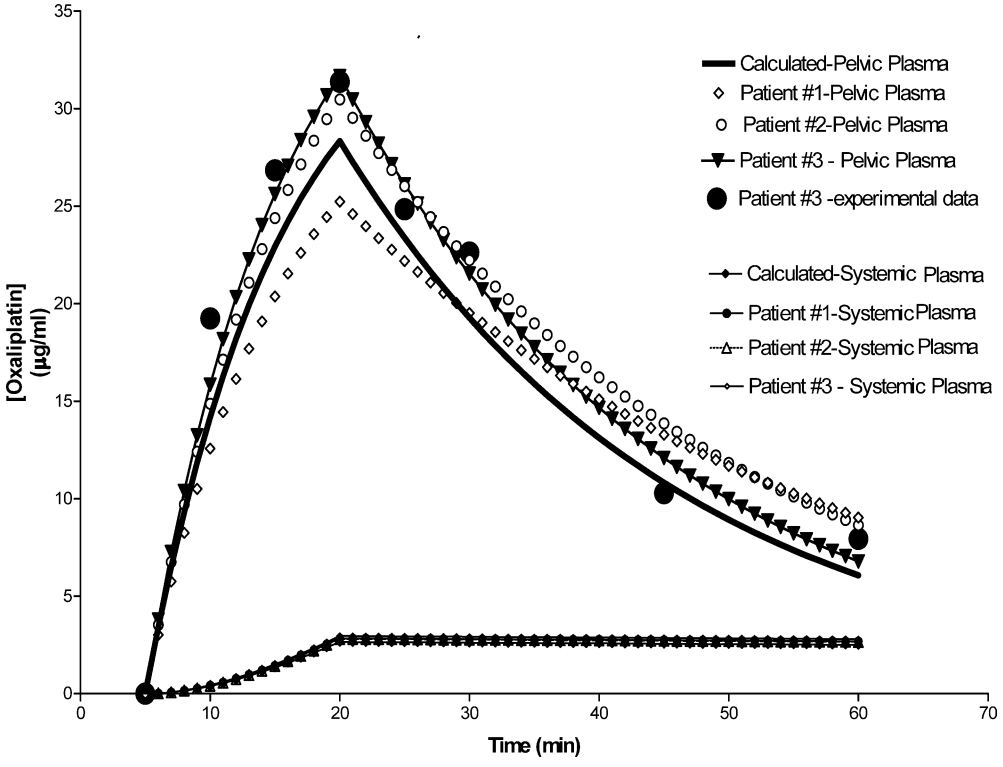

Fig. 2 Calculated and experimental oxaliplatin plasma distribution curves during the isolation period. Experimental data for patient no. 3 are shown (*filled circles*)

Table 2 Calculated and experimental pharmacokinetic parameters for oxaliplatin

	Pelvic level, maximum (mg/l)	Pelvic exposure (mg min/l)	Pelvic clearance, $t_{1/2}$ (min)	Exposure ratio (pelvic/systemic)
From calculated linear relationships	32.2	809		
From the predicted distribution curve	28.3	840	18	7.1
Patient no. 1	24.7	863	27	6.9
Patient no. 2	30.5	971	22	7.8
Patient no. 3	31.4	939	18	7.1

Table 3 Linear least squares slope and intercept data for five versus four drugs

Curve	No. of drugs	No. of points (means)	Slope ± SD	Intercept ± SD	r^2
Log $[drug]_{max}$	Four	Four	0.879 ± 0.016	−0.244 ± 0.043	0.999
	Five	Five	0.878 ± 0.014	−0.237 ± 0.037	0.999
Log (exposure)	Four	Four	0.973 ± 0.029	0.927 ± 0.079	0.998
	Five	Five	0.968 ± 0.038	0.961 ± 0.103	0.995

patients receiving oxaliplatin therapy. Visibly, the upper isolated pelvic plasma distribution curves matched closely whereas the lower three systemic distribution curves overlapped to where they could not visibly be separated. Table 2 presents calculated and experimental parameters for oxaliplatin.

Discussion

The calculated pelvic distribution curve (Fig. 2) closely matched the experimental curves for the first three patients. Also, the calculated versus experimental values for four pharmacokinetic parameters were quite close (Table 2), given the experimental ranges of the initial four drugs (Table 1).

There was a negligible difference between the linear relationships established with all five drugs for drug dosage versus mean AUC (pelvic exposure, μM min) and the mean maximum pelvic drug level (μM) and the four-drug relationships (Table 3). The differences between the four- and five-drug slopes and intercepts were well within the standard deviations of these parameters.

The linear relationships of drug dosage versus AUCs and the maximum pelvic drug levels were unexpected. However, on reflection, since the aqueous plasma compartment is the initial site of drug input and the therapeutic concentrations are below the drug solubility limits, it is reasonable that the drugs are handled identically in this compartment. Thus, differences in plasma pharmacokinetic parameters among drugs would be due to the different dose levels.

These results give an overall picture for the plasma pharmacokinetics during the isolation period for the isolated pelvic perfusion protocol. Enough experimental data has been accumulated for five drugs to establish a simple pharmacokinetic model [9] and interdrug relationships (i.e., this report) which can be used to predict reasonable plasma distribution curves for additional drugs with this protocol. The authors believe that the effect of plasma drug parameters being primarily due to drug dosage and not drug type has not been documented in the literature for any other drug delivery protocol.

Acknowledgements The following student at Providence College assisted in this research: Eddie Martucci. This work was supported in part by the CORE grant P30 CA13943 and the NIH/NCI grant 5T32CA-09656-05, and by the Providence College Fund to Aid Faculty Research.

Appendix 1

A four-compartment pharmacokinetic model was developed by our group for isolated pelvic perfusion [9]. 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 non-isolated systemic circulation (systemic volume of distribution compartment). There is also 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 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.

Curve fitting of patient data 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, k_1, and the drug infusion period. Pharmacokinetic curves for the isolated pelvic circulation and the non-isolated systemic circulation are then 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. 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 parameters 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.

Pharmacokinetic parameters can be easily evaluated from this model. The parameters of interest are (i) the pelvic and systemic exposures (AUC) during isolation and their ratio which gives the time-averaged enhancement of drug concentrations in the isolated circulation, (ii) the maximum pelvic cisplatin concentrations, (iii) the pelvic half-life after drug infusion and during isolation and (iv) the percentage of cisplatin leaking from the pelvic to the systemic circulation during drug infusion.

Generation of predictive distribution curves for new drugs The inputs to generated predictive plasma distribution curves for oxaliplatin were the same as above, using parameters for an average patient. The curves were fitted to optimize four parameters, the maximum pelvic drug level and pelvic exposure values from the linear relationships, a $t_{1/2}$ plasma clearance life-time of approximately 20 min and pelvic to systemic exposure ratios of approximately seven. The latter two parameters were established from the combined pharmacokinetic data of the initial four drugs, especially the closely related cisplatin data (Table 1).

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