Chapter 1
Pharmacokinetic Aspects of Regional Tumor Therapy

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1.1 Introduction

The aim of a safe and efficient drug therapy is to direct the agent as near as possible to its target where it generates its maximum pharmacological effect while keeping side effects at a minimum.

Contrary to effects of a drug on the organism (pharmacology), the organism itself exerts an effect on the fate of a drug in man in a time-dependent manner. This pharmacokinetic fate comprises absorption, distribution, metabolism, and complete elimination from the body (ADME).

Although these processes are rather complex and determined by various endogenous and exogenous factors, pharmacokinetic parameters for each single drug are available. Table 1.1 gives an overview for the most relevant parameters for clinical evaluation.

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Table 1.1 Clinical relevant pharmacokinetic parameters [1]

PK parameter	Dimension	Relevance
$t_{1/2}$zp	Time	Transfer from blood to deep compartment
$t_{1/2}$el	Time	Elimination half-life from the body
C_{max}	Concentration/volume	Peak concentration in blood or tissue
t_{max}	Time	Time to reach C_{max}
AUC	Concentration/volume × time	Area under concentration–time curve
Cl_{tot}	Volume/time	Total body clearance
V_d	Volume	Volume of distribution

The concentration of a drug in the target organ can be increased by using special applications such as regional drug administration. By changing the actual physiological conditions of the target organ (for instance by occlusion of a blood vessel), regional administration increases the absorption rate of the chemotherapeutic agent from the blood into tumor tissue. As a consequence, blood flow is decreased through the affected organ, and tissue-extraction rate is accelerated or increased.

So regional administration combined with a temporary occlusion of the supplying vessels is a valuable therapeutic option, especially for the chemotherapeutic treatment of liver tumors and liver metastases, respectively.

1.2 Hepatic Blood Flow (Q_{hep})

The perfusion of the liver is a main factor of the regional administration. Hepatic blood flow is the sum of portal vein (1050 mL/min) and common hepatic artery (300 mL/min) blood flow. Therefore Q_{hep} is about 1500 mL/min (≈ 90 L/h).

1.3 Hepatic Extraction Rate (E_{hep})

E_{hep} is calculated as follows by the arterial and venous drug concentration during liver passage.

$$E_{hep} = \frac{conc_{arterial} - conc_{venous}}{conc_{arterial}} = Cl_{freedrug} \times conc_{freedrug}$$

E_{hep} ranges from 0.0 (=no extraction) to 1.0 (=complete extraction). An E_{hep} of 0.8 indicates the elimination and metabolism of 80% of the drug entering the liver leaving 20% of the administered drug to exit the liver through the liver veins.

1.4 Hepatic Clearance (Cl_{hep})

Cl_{hep} is defined as the volume of blood passing through the liver that is cleared from a compound per time. Hepatic clearance is based on the whole-body clearance minus the renal clearance and the mostly quantitative not relevant non-hepatic, non-renal clearance by other organs (e.g., the skin or lung). Cl_{hep} depends on the blood flow through the liver, the liver cell mass, and the activity of drug-metabolizing enzymes. It is the product of E_{hep} and the blood flow through the organ (Q_{hep}).

$$Cl_{hep} = Q_{hep} \times E_{hep}$$

Considering the hepatic extraction of a drug, its tissue penetration does not only depend on physiological conditions (as already mentioned) but also on the physicochemical properties of the molecule as well. Besides the drug there are some other factors with impact on the hepatic clearance (see Table 1.2).

Table 1.2 Factors that have an influence on E_{hep} of a drug

Parameter	Mechanism
Blood flow	Distribution rate
Tissue uptake	Absorption mechanism (diffusion, active transport)
Protein binding	Intravascular depot
Liver diseases	Altered vascularization, dysproteinemia
Cytostatic	Physicochemical properties (lipophilicity, pk value, ionization) Metabolism (phase I and II)
Occlusion method	Means and duration of occlusion, amount of particles

Table 1.3 Pharmacokinetic parameters (after i.v. administration) of cytostatic agents that are suitable for intra-arterial administration due to their first-pass effect [4–7]

Drug	V_d [L]	Cl_{tot} [L/min]	$t_{1/2}$ [h]	Metabolism
Doxorubicin	≈1500	1.2	30	Liver
Epirubicin	≈2000	1.2	35	Liver
5-fluorouracil	16	2.0	0.3	Ana-, catabolism
Irinotecan	200–400	0.5	15	Liver
Mitomycin C	≈50	1.1	0.6	Blood metabolites
Pt-agents	30 (UF*)	0.04	150	Blood metabonates
Gemcitabine	85	0.8–1.5	0.5–1.5	Liver, leucocytes
Carmustine	250	≈4.2	1.5	Metabonates
Paclitaxel	800	2200	50	Liver

**UF* ultrafiltrate

Despite their chemical heterogeneity, a number of different cytostatic agents can be used for regional intra-arterial treatment (see Table 1.3). The most important assumption for the drug is a so-called first-pass metabolism or first-pass effect. Per definition first-pass effect is the sum of all processes (distribution and metabolism) occurring during the first liver passage of a drug before the drug reaches systemic blood circulation and becomes available in the whole body. New investigational approaches

represent the combination of HAI irinotecan plus 5-fluorouracil, oxaliplatin, and intravenous cetuximab or bevacizumab [2, 3].

By comparing the intra-arterial/intravenous AUC ratio, chemoembolization leads to a therapeutic advantage (TA), calculated as follows:

$$\mathrm{TA} = \frac{\dfrac{\mathrm{AUC}_{\mathrm{hep}}}{\mathrm{AUC}_{\mathrm{blood}}}\,\text{i.a.}}{\dfrac{\mathrm{AUC}_{\mathrm{hep}}}{\mathrm{AUC}_{\mathrm{blood}}}\,\text{i.v.}}$$

In comparison to i.v. administration, decreasing hepatic perfusion results in a higher regional distribution rate.

$$\mathrm{RA} = 1 + \frac{\mathrm{Cl}_{\mathrm{tot}}}{Q_{\mathrm{hep}} \times \left(1 - E_{\mathrm{hep}}\right)}$$

Regional application combines decreasing side effects and higher levels of toxicity (increased apoptosis rate) [8]. The RA gets more intense the faster the cytostatic distributes into the tissue and the higher its extraction rate from the body.

1.5 Pharmacokinetic Data Using Degradable Starch Microspheres (DSM)

A successful embolization can be characterized by comparing the main pharmacokinetic parameters with data obtained after conventional administration. $\mathrm{AUC}_{\mathrm{last}}$ and C_{max} are the most suitable values for calculating the shift of the drug's concentration from the blood to the tissue.

Depending on the chemotherapeutic agent, the administration of DSM leads to a decrease of systemic circulation from 20 to 60%. It is the most important requirement that the chemotherapeutic does not bind to DSM or red blood cells [9].

So far most of the studies concerning pharmacokinetic data of cytostatic agents after the embolization of the common hepatic artery used DSM. The findings in Table 1.4 from several studies show between 19 and 98% reductions in plasma drug concentrations. The reduced systemic drug exposure may be seen as an increased first-pass extraction during the prolonged time of the drug in the occluded target area. The higher

Table 1.4 Mean reduction of plasma AUC in patients with HCC using DSM

Drug	Tumor type	AUC decrease (%)	*N*	References
Mitomycin C	Primary and secondary liver cancer	33	87	[10, 13–17]
Doxorubicin	Primary and secondary liver cancer	19	5	[18, 19]
Carmustine (BCNU)	Primary and secondary liver cancer	62	5	[11]
Fotemustine	Primary and secondary liver cancer	53	4	[20]
5-FU	Primary and secondary liver cancer	38	8	[21]
Floxuridine	Colorectal liver metastasis	34	3	[16]
Cisplatinum	Colorectal liver metastasis	38	4	[22]
Cisplatinum and sodium thiosulfate	Head and neck cancer	98	6	[23]

first-pass extraction of the drug in the target compartment will lead to a lower dose of drug reaching the systemic circulation and subsequently to fewer side effects [10, 11]. Besides the chemotherapeutics given in Table 1.4, one of the most currently irinotecan is administered intra-arterial after chemoembolization as well [12]. Irinotecan (CPT-11) is a pro-drug and needs to be activated in the body. The drug shows poor affinity to the responsible enzyme (human carboxy esterase), therefore only small amounts of the pharmacologic active metabolite SN-38 are formed (about 10% of the parent compound). This activation can be improved by regional administration to the liver leading to higher amounts of SN-38 in the blood and tissue.

Numerous investigations characterized the combination of mitomycin C (MMC) with different amount of DSM. The AUC ratio is relatively consistent from 0.55 to 0.80 as can be seen in Table 1.5. Administration of 60 mg DSM did not show any effect, obviously this amount was too low for any occlusion of blood vessels.

More data about the distribution of other cytostatic agents into tumor and healthy tissue using DSM in animals and patients are in Tables 1.6 and 1.7. Table 1.6 gives an overview of experimental findings in animals.

Table 1.5 Average AUC ratio, measured as peripheral plasma AUC of MMC with and without DSM in patients with HCC

DSM [mg]	MMC (mg/m^2)	*N*	AUC ratio	95% CI	References
360	15	36	0.74	0.62–0.87	[10]
360	10	6	0.70	0.55–0.88	[13, 15]
900	5–10	11	0.61	0.47–0.80	[13, 15]
540	3	7	0.73	0.62–0.86	[15]
900	9	10	0.55	n.s.	[14]
360	10	3	0.80	n.s.	[16]
450–900	18	14	0.55	n.s.	[17]
60	20	7	No effect	n.s.	[24]

n.s. not specified

Table 1.6 Ratio of cytostatic drugs in tumor and healthy liver tissue (with and without DSM) in vivo (rat, rabbit)

			Tumor/liver ratio[a]		
Species	Tumor type	Drug	Without DSM	With DSM	References
Rabbit	Liver	5-FU	0.63	3.59	[25]
Rat	Liver	5-FU	0.38	2.25	[26]
Rat	Liver	Doxorubicin	1.3	8.3	[27]
Rabbit	Liver	Doxorubicin	0.25	1.24	[28]
Rabbit	Liver	Doxorubicin	0.4	1.01	[29]
Rat	Liver	Tauromustine	0.47	2.16	[30]
Rabbit	Liver	Carboplatin	0.94	6.81	[31]
Rat	Lung	Carboplatin	1.19	2.11	[32]
Rat	Liver	Docetaxel	0.67	1.38	[33]

[a]Substance-dependent measurements, intervals from 15 to 480 min

Table 1.7 presents data of human biopsy samples indicating that DSM leads to an increased uptake of drug into tumor tissue. Intra-arterial application of DSM and a cytotoxic drug leads to an increased drug concentration in the tumor compartment as well as DSM-induced increase of tumor versus normal tissue drug concentration ratio.

1.6 Further Chemoembolization Tools

Besides DSM other materials for chemoembolization have been developed recently. In transarterial chemoembolization (TACE) DSM, polyvinyl alcohol polymers, Gelfoam, and gelatin-based microspheres (Embosphere) are used to keep systemic circulation of a chemotherapeutic at a minimum. Polyvinyl alcohol polymers and superadsorbent polymer microspheres (SAP, HepaSphere®, QuadraSphere®) can be loaded with a compound to become drug-eluting beads (DEB, DEBDOX, DEBIRI). In the following

Table 1.7 Mean ratio of drug concentration in tumor and healthy liver tissue (with and without DSM) in patients with secondary liver cancer or oral cancer

		Tumor AUC		Tumor/liver ratio			
Drug	Tumor type	Without DSM	With DSM	Without DSM	With DSM	*N*	References
99mTc-DTPA 2 mCi	Secondary liver cancer	0.87 ± 0.4 (10^{-7} × CPM s/pixel) After 3 min	1.11 ± 0.5 (10^{-7} × CPM s/pixel) After 3 min	0.33 (10^{-7} × CPM s/pixel) After 3 min	0.35 (10^{-7} × CPM s/pixel) After 3 min	5	[16]
FUdR 0.15 mg/kg	Secondary liver cancer	5.9 ± 4.4 (nmol/g) After 5 min	17.1 ± 9.4 (nmol/g) After 5 min	0.16 ± 0.09 (nmol/g) After 5 min	0.63 ± 0.13 (nmol/g) After 5 min	14	[34]
DDP 25 mg/m^2	Secondary liver cancer	0.67 ± 0.5 µg/mL After 15 min	3.03 ± 1.6 µg/mL After 15 min	0.68 ± 0.6 µg/mL After 15 min	0.93 ± 0.1 µg/mL After 15 min	8	[22]
DDP 150 mg/m^2 + STS 9 g/m^2	Oral cancer	19.8 ± 4.7 µmol/L × h	89.6 ± 31.3 µmol/L × h	n.s.	n.s.	6	[23]

n.s. not specified

Table 1.8 Effects of different permanent embolization materials on maximum plasma concentrations in animals

Drug	Species	Material	Tumor type	Reduction of C_{max} in plasma	References
Carboplatin	Rabbit	Embosphere	Liver	84% after 30 min	[35]
	Rabbit	DEBDOX	Liver	82% after 20 min	[36]
Doxorubicin	Rabbit	QuadraSphere	Liver	54% after 10 min	[37]
Irinotecan SN-38	Sheep	DEBIRI	Lung	80% after 10 min No effect	[38]
Irinotecan SN-38	Rabbit	DEBIRI	Liver	48% from 10 to 60 min 34% after 2 h	[39]

Tables 1.8, 1.9, 1.10, and 1.11, various agents used for chemoembolization and their effect on maximum plasma concentrations of antineoplastic drugs as well as corresponding tumor concentrations and tumor/liver ratios in animals and patients are listed.

Combination of DSM or other occlusion agents and chemotherapy i.a. reduced systemic exposure to chemotherapy in animals and patients manifested not only in pharmacokinetic parameters but also in reduced hematological toxicity [10]. Comparative pharmacokinetic studies between various occlusion agents still need to be investigated in further studies. In conclusion, chemoembolization with DSM and other agents is a valuable therapeutic option in palliative and neo-adjuvant medicine as evident in the following chapters.

HAI administration of superparamagnetic nanoparticles makes it possible to visualize the distribution mechanism from

Table 1.9 Effects of different permanent embolization materials on concentration in tumor tissue and on tumor/liver ratios in animals

Drug and embolization material	Tumor type	Species	Mean tumor concentration i.a. [µg/g]	Mean tumor concentration i.a. with embolization [µg/g]	Tumor/liver ratio i.a.	Tumor/liver ratio i.a. with embolization	References
Carboplatin 5 mg/kg (Embosphere)	Liver	Rabbit	4.01	20.33	1	2.5	[35]
Doxorubicin 11.25 mg (DEBDOX)	Liver	Rabbit	58	239.5	n.s.	n.s.	[36]
Doxorubicin 5 mg (DEBDOX)	Liver	Rabbit	n.s.	26.1	n.s.	17.8–16.1	[40]
Doxorubicin 4 mg (QuadraSphere)	Liver	Rabbit	153.4	196.5	n.s.	n.s.	[37]
Irinotecan 12 mg (DEBIRI) SN-38	Liver	Rabbit	0.497 0.062	0.872 0.351	n.s.	n.s.	[39]

n.s. not specified

Table 1.10 Effects of different permanent embolization materials on maximum plasma concentrations in patients

Drug	Material	Tumor type	Mean AUC reduction	References
Doxorubicin 25–100 mg/m^2	DEBDOX	Untreated large/multifocal HCC patients	57% after 0–7 days (compared to conventional TACE)	[41]
Doxorubicin 25–75 mg/m^2	Drug-eluting SAP-microspheres	Unresectable HCC patients	58% after 0–3 h (compared to conventional TACE)	[42]
Oxaliplatin 25–100 mg	HepaSphere	Colorectal liver metastasis and intrahepatic cholangiocarcinoma patients	45% after 0–7 days (compared to FOLFOX)	[43]

Table 1.11 Effects of different permanent embolization materials on concentration in tumor tissue and on tumor/liver ratios in patients

Drug/ embolization material	Tumor type	Tumor AUC		Tumor/liver ratio		References
		Control	With embolization	Control	With embolization	
Oxaliplatin 25–100 mg OEM (HepaSphere)	Colorectal liver metastasis and intrahepatic cholangiocarcinoma patients	n.s.	n.s.	1.08–1.38 (FOLFOX i.v.)	1.27–71.2	[43]
Doxorubicin 75–150 mg DEBDOX	Unresectable HCC patients	n.s.	5.0 μM mean level after 8 h 0.65 μM mean level after 32–36 days	n.s.	n.s.	[44]

the blood to the liver by magnetic resonance imaging. Besides, these particles are capable of drug targeting as a drug carrier [45]. The role of Kupffer cells in drug distribution into the liver has been discussed recently [46].

Another alternative chemotherapy strategy comprises HAI plus chemoembolization plus administration of liposomal drug preparations. This has been investigated for paclitaxel [47] and fluorouracil [26] in tumor-bearing rats.

The advantage of transarterial chemoembolization (TACE) combined with drug-eluting beads (DEB) versus conventional TACE treatment has been discussed to show a lower associated toxicity, due to reduced systemic drug circulation [48].

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