Supplemental material

Methodologies for Population Pharmacokinetic Modeling of Target-Site Drug Exposure: A Narrative Review of Current Strategies

Clinical Pharmacokinetics

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Table S1. Characteristics of population pharmacokinetic models describing plasma and target-site concentrations using rate constants.

Model	Target-site	Drug	Number of patients	Patient population	Connection plasma to target-site	Notes
Piva (2019) [1]	CSF	Daptomycin	9	Adult patients with external ventricular drainage and ventriculostomy-related meningitis	One transfer rate constant	
Le Tilly (2021) [2]	CSF	Trastuzumab	21	Patients with leptomeningeal carcinomatosis of HER2+ breast cancer	Transfer rate constants, the rate constant from serum to CSF is a zero-order transfer rate	
Blassman (2019) [3]	CSF	Vancomycin	21	Adult critical care patients with proven or suspected external ventricular drain (EVD)-associated ventriculitis	Transfer rate constants	
Breilh (2001) [4]	Lung tissue	Ciprofloxacin	38	Patients undergoing lung surgery for bronchial epithelioma	Transfer rate constants	
Rietveld (2024) [5]	Peritoneal fluid	Irinotecan and active metabolite SN-38	18	Adult patients with colorectal cancer and extensive peritoneal disease without other extra-abdominal metastases	Absorption rate constant	
Ferron (2008) [6]	Peritoneal fluid	Oxaliplatin	24	Patients treated for primary or recurrent peritoneal carcinomatosis with debulking surgery and hyperthermic intraperitoneal chemotherapy	Absorption rate constant	
Valenzuela (2011) [7]	Peritoneal fluid	Oxaliplatin	30	Adult patients with peritoneal carcinomatosis without extra-abdominal metastasis who underwent cytoreductive surgery	Absorption rate constant	
Siebinga (2023) [8]	Salivary gland, kidney, liver, tumor and other tissues	[^{177}Lu]Lu-PSMA-617	10	Patients with low volume early stage metastatic prostate cancer	Transfer rate constants	

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Table S2. Characteristics of population pharmacokinetic models describing plasma and target-site concentrations using intercompartmental clearance.

Model	Target-site	Drug	Number of patients	Patient population	Connection plasma to target-site	Notes
Helfer (2022) [9]	CSF, muscle and subcutaneous tissue	Ceftaroline	21	12 healthy male volunteers [10]) and 9 neurosurgical patients who required the insertion of an EVD [11]	Intercompartmental clearance into the tissue (Q_{in}) and intercompartmental clearance out of the tissue (Q_{out})	Data from 2 studies [10,11]
Li (2023) [12]	CSF	Linezolid	22	Post-operative neurosurgical patients with indwelling ventricular or operative site catheters	Intercompartmental clearance and the transfer multiplier between plasma and CSF compartments	
Luque (2014) [13]	CSF	Linezolid	11	Intensive care unit (ICU) patients with a proven or suspected CNS infection and an external central nervous system drainage present	Intercompartmental clearance	
Li (2019) [14]	CSF	Meropenem	15	Postoperative neurosurgical patients with indwelling drain tube and diagnosed with an intracranial infection	Intercompartmental clearance	
Li (2018) [15]	CSF	Norvancomycin	22	Post-operative neurosurgical patients with an indwelling catheter in the operational area/ventricle and a diagnosis of intracranial infection	Intercompartmental clearance	
Lamminsalo (2019) [16]	CSF	Oxycodone	30	Adult female patients undergoing elective gynecological surgery with planned post-operative epidural analgesia	Intercompartmental clearance	
Haug (2013) [17]	CSF	Semagacestat	20	Healthy male volunteers	Intercompartmental clearance	Data from Bateman et al. [18]
Wittau (2011) [19]	Colon tissue	Ertapenem	38	Adult patients requiring open or laparoscopic surgery at the colon and/or rectum	Intercompartmental clearance	Data of 15 patients from Wittau et al. [20]

Ullah (2023) [21]	Dialysate fluid	Meropenem	6	Patients undergoing automated peritoneal dialysis without peritonitis	Intercompartmental clearance and a transit compartment for the transfer from plasma to dialysate fluid	
Komatsu (2022) [22]	Liver tissue	Flomoxef	43	Patients undergoing elective surgical resection of hepatic lesions	Intercompartmental clearance	
Al Jalali (2023) [23]	Peritoneal dialysate (PDS)	Ceftazidime/avibactam	8	Adult patients undergoing automated peritoneal dialysis	Intercompartmental clearance and a scaling factor	
Ikawa (2008) [24]	Peritoneal fluid	Biapenem	19	Patients undergoing abdominal surgery for the relief of inflammatory bowel disease	Intercompartmental clearance	
Garbez (2022) [25]	Peritoneal fluid	Caspofungin	11	ICU patients with secondary peritonitis and septic shock	Intercompartmental clearance	
Ikawa (2008) [26]	Peritoneal fluid	Imipenem (IPM), meropenem (MEPM), and doripenem (DRPM)	29 (10 IPM, 8 MEPM, 11 DRPM)	Postoperative abdominal surgery patients	Intercompartmental clearance	
Garbez (2021) [27]	Peritoneal fluid	Micafungin	12	ICU patients with secondary peritonitis and septic shock	Intercompartmental clearance	
Carrié (2024) [28]	Peritoneal fluid	Piperacillin/tazobactam	45	Adult patients on the surgical and trauma ICU with a suspected or documented intra-abdominal infection while treated by open abdomen vacuum assisted closure (OA/VAC)	Intercompartmental clearance	
Van Os (2024) [29]	Subcutaneous adipose and skeletal muscle tissue	Lefamulin	12	Healthy volunteers	Intercompartmental clearance	Data from Zeitlinger et al.[30]
Al Jalali (2021) [31]	Subcutis and muscle interstitial space fluid	Ceftolozane/tazobactam	8	Healthy male volunteers	Intercompartmental clearance	

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Table S3. Characteristics of population pharmacokinetic models describing plasma and target-site concentrations using an effect compartment

Model	Target-site	Drug	Number of patients	Patient population	Connection plasma to target-site	Notes
Chambers (2019) [32]	Bone	Ertapenem	10	Patients undergoing elective joint arthroplasty or elective lower limb amputation	Equilibration rate constant and ratio between plasma and bone concentrations	
Hannam (2023) [33]	CSF	Celecoxib, valdecoxib and rofecoxib	10	Healthy adult volunteers	Equilibration rate constant and transfer factor	
Valle (2005) [34]	CSF	HTB (metabolite of triflusal)	23	Healthy volunteers	First-order equilibration rate constant and CSF-plasma partition coefficient	Data of 8 patients from Ramis et al. [35]
Kip (2018) [36]	Intracellular peripheral blood mononuclear cells (PBMCs)	Miltefosine	51 (29 children, 22 adults)	Colombian cutaneous leishmaniasis patients	Intracellular distribution rate constant and steady-state intracellular-to-plasma ratio	
Franken (2022) [37]	Intracellular PBMC	Tacrolimus	184	Adult kidney transplant recipients with whole-blood and intracellular tacrolimus concentrations measured at 3 months post-transplantation	Intracellular distribution rate constant and steady-state whole-blood to intracellular ratio	
Peterson (2020) [38]	Skin tissue	Vancomycin	59	Pediatric patients undergoing posterior spinal fusion or ventriculoperitoneal shunt placement	Equilibration rate between plasma and skin and partition coefficient	

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Table S4. Characteristics of population pharmacokinetic models describing plasma and target-site concentrations with the target-site as part of the peripheral or central compartment.

Model	Target-site	Drug	Number of patients	Patient population	Connection plasma to target-site	Notes
Riccobene (2016) [39]	Epithelial lining fluid (ELF)	Ceftaroline	50	Healthy adult subjects	Part of the central compartment with a partition coefficient accounting for the distribution into ELF	
Van Hasselt (2016) [40]	ELF	Imipenem	165	Healthy volunteers, subjects with renal impairment and elderly subjects	Time-independent penetration coefficient	Data from 4 studies [41–43]
Lakota (2020) [44]	ELF	Omadacycline	613	Healthy adults, patients with end-stage renal disease, and patients with uncomplicated urinary tract infections, community-acquired bacterial pneumonia, or acute bacterial skin and skin structure infection	Proportionality term	Based on data from a previous model [45], additional phase 1 studies [46–48] , a phase 1b study [49], and phase 3 studies [50–52]
Hanberg (2018) [53]	Subcutaneous adipose tissue	Meropenem	10	Critically ill patients receiving extracorporeal membrane oxygenation treatment	Plasma peripheral compartment with the fraction unbound in subcutaneous adipose tissue	
Bue (2020) [54]	Subcutaneous tissue	Piperacillin	10	Patients requiring continuous renal replacement therapy (CRRT)	Scaling factor	

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