Universiteit
Leiden
The Netherlands

The role of glomerular filtration and active tubular secretion in predicting renal clearance of drugs in children using population pharmacokinetic and physiology-based pharmacokinetic modeling approaches: unspinning the yarn

Cristea, S.

Citation

Cristea, S. (2021, June 16). *The role of glomerular filtration and active tubular secretion in predicting renal clearance of drugs in children using population pharmacokinetic and physiology-based pharmacokinetic modeling approaches: unspinning the yarn*. Retrieved from https://hdl.handle.net/1887/3188573

Version:	Publisher's Version
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/3188573

Note: To cite this publication please use the final published version (if applicable).

Cover Page

Universiteit Leiden

The handle https://hdl.handle.net/1887/3188573 holds various files of this Leiden University dissertation.

Author: Cristea, S.
Title: The role of glomerular filtration and active tubular secretion in predicting renal clearance of drugs in children using population pharmacokinetic and physiology-based pharmacokinetic modeling approaches: unspinning the yarn
Issue Date: 2021-06-16

THE ROLE OF GLOMERULAR FILTRATION AND ACTIVE TUBULAR SECRETION IN PREDICTING RENAL CLEARANCE OF DRUGS IN CHILDREN USING POPULATION PHARMACOKINETIC AND PHYSIOLOGY-BASED PHARMACOKINETIC MODELING APPROACHES

Unspinning the yarn

Sînziana Cristea

Printing of this thesis was financially supported by the Leiden Academic Centre for Drug Research.

Cover design: Georgiana & Sergiu Popa

ISBN: 978-94-6332-756-5

The research described in this thesis was performed at the Systems Biomedicine and Pharmacology division of the Leiden Academic Centre for Drug Research (LACDR), Leiden University (Leiden, The Netherlands).

© S. Cristea, 2021
All rights reserved. No part of this thesis may be reproduced in any form or by any means without permission of the author.

The role of glomerular filtration and active tubular secretion in predicting renal clearance of drugs in children using population pharmacokinetic and physiology-based pharmacokinetic modeling approaches

Unspinning the yarn

Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof. mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op woensdag 16 juni 2021
klokke 16:15 uur

door

Sînziana Cristea

geboren te Suceava, Roemenie
op 11 juli 1988

Promotores:	Prof. dr. C.A.J. Knibbe
	Prof. dr. K. Allegaert (KU Leuven, Belgium)
Copromotor:	Dr. E.H.J. Krekels
Promotiecommissie:	Prof. dr. H. Irth, voorzitter
	Prof. dr. J.A. Bouwstra, secretaris
	Prof. dr. A.Rostami-Hodjegan
	Manchester University
	Prof. dr. S.N. de Wildt
	RadboudUMC
	Prof. dr. A. Vermeulen
	University of Ghent
	Prof. dr. M. Danhof
	Dr. J.G.C. van Hasselt

Table of contents

SECTION I	**BACKGROUND AND INTRODUCTION TO MODELING RENAL CLEARANCE OF DRUGS**	
Chapter 1	General introduction and scope	9
SECTION II	**POPULATION PHARMACOKINETIC MODELING TO GUIDE DOSING OF RENALLY EXCRETED DRUGS IN PRETERM NEONATES**	
Chapter 2	Amikacin pharmacokinetics to optimize dosing recommendations in neonates with perinatal asphyxia treated with hypothermia	23
Chapter 3	Larger dose reductions of vancomycin required in neonates with patent ductus arteriosus receiving indomethacin versus ibuprofen	37
SECTION III	**PBPK-BASED DOSING OF DRUGS CLEARED BY GLOMERULAR FILTRATION IN CHILDREN**	
Chapter 4	The predictive value of GFR-based scaling of pediatric clearance and doses for drugs eliminated by glomerular filtration with varying protein binding properties	55
SECTION IV	**ONTOGENY OF RENAL TRANSPORTERS AND ITS IMPACT ON RENAL CLEARANCE OF DRUGS IN CHILDREN**	
Chapter 5	The influence of drug properties and ontogeny of transporters on pediatric renal clearance through glomerular filtration and active secretion: a simulation-based study	91
Chapter 6	Estimation of ontogeny functions for renal transporters using a combined population pharmacokinetic and physiology-based pharmacokinetic approach: application to OAT3	117
SECTION V	**SUMMARY, CONCLUSION, AND PERSPECTIVES**	
Chapter 7	Summary, conclusion, and perspectives	137
Chapter 8	Nederlandse samenvatting	155
SECTION VI	**APPENDICES**	
	Curriculum vitae and list of publications	162
	Affiliations of authors	164
	Acknowledgements	167