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NextDose

Development Version 2017

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Background

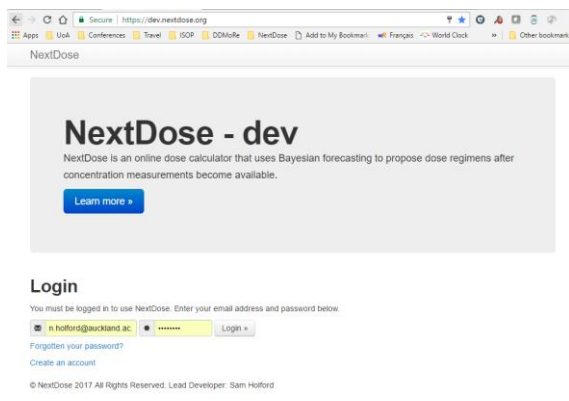


- NextDose is a free web based dosing tool
- <https://www.nextdose.org>
- NextDose has been in use at Auckland Starship and Auckland City hospital for all busulfan bone marrow conditioning since March 2012
- Currently used by 20 groups around the world
- Development version now available for testing

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Create an Account



The screenshot shows a web browser window with the URL <https://dev.nextdose.org>. The page title is "NextDose - dev". Below the title, there is a description: "NextDose is an online dose calculator that uses Bayesian forecasting to propose dose regimens after concentration measurements become available." A blue button labeled "Learn more" is visible. Below this, there is a "Login" section with the text "You must be logged in to use NextDose. Enter your email address and password below." There is a form with an email input field containing "n.holford@auckland.ac.nz", a password input field with masked characters, and a "Login" button. Below the login form, there are links for "Forgotten your password?" and "Create an account". At the bottom, there is a copyright notice: "© NextDose 2017 All Rights Reserved. Lead Developer: Sam Holford".

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Individual User Account



- Access to Demonstration Group patients
 - Can see patient details, doses, results
 - Cannot run new calculation
- Create new patients
 - Enter patient details, doses, run calculation
 - All details and results saved
 - Not visible to others (except NextDose admin)

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Enter a Medicine Name to Find a Demo Patient



Medicine	Dose	Date
Busulfan	M	19 Jun 1999
Warfarin	M	28 Nov 1986
Linezolid	M	12 Feb 1956
Tacrolimus	M	01 Jan 1952
Methotrexate	M	26 Mar 1997
Voriconazole	M	09 Feb 1965
Linezolid FirstDose	F	09 Aug 1949
Warfarin FirstDose	M	05 Dec 1946
Tacrolimus FirstDose	M	19 Jan 1954
Busulfan FirstDose	M	03 Jan 2014

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Create New Patient



Genotypes


Leave unchecked if unknown

- Genotype CYP2C9: *1/*1
- Genotype CYP2C9: *1/*3
- Genotype VKORC1: AA
- Genotype VKORC1: GA or GG
- Genotype CYP4F2: CC or CT
- Genotype CYP4F2: TT
- Genotype CYP2C19: Poor metaboliser
- Genotype CYP2C19: Normal metaboliser

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Enter Patient Details



NextDose **beta** About Help ▾ Nick Halford ▾

Find Patient

Enter Patient Details

Patient ID

Sex Male Female

Date of birth OR years

Family name

First/Other name(s)

Notes


This patient is just for demonstration/testing purposes

Group

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Add a Medicine



NextDose **beta** About Help ▾ Nick Halford ▾

Find Patient

Enter Patient Details

+ Add a new medicine ▾

NICK HALFORD ▾
DEMONSTRATION PATIENT
No medicines have been added to this patient yet.

Patient ID

Sex Male Female

Date of birth OR years

Family name

First/Other name(s)

Notes

This patient is just for demonstration/testing purposes

Group

Genotypes

Leave unchecked if unknown


- Genotype CYP2C9 *1/*1
- Genotype CYP2C9 *1/*3
- Genotype VKORC1 AA
- Genotype VKORC1 GA or GG
- Genotype CYP4F2 CC or CT
- Genotype CYP4F2 TT
- Genotype CYP2C19 Poor metaboliser
- Genotype CYP2C19 Normal metaboliser

Medicine dropdown: busulfan, methotrexate, tacrolimus, warfarin, linezolid, voriconazole

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Medicine Specific Observations



Enter Patient Details **Doses & Observations** **Results** **Print** **Delete**

03 Feb 2017 00:00 Height 178 cm

03 Feb 2017 00:00 Weight 85 kg

Observation type

Sample collection

Measured value

Lab no

Sample arrival

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Choose Model and Target



Find Patient

NICK HOLFORD (M)
DEMONSTRATION PATIENT
WARFARIN
03 Feb 2017 16:14

Patient Details | Doses & Observations | Results | Print | Delete

Calculation options

Model: PKPD Xue 2016

Target: 2 INR

Dose interval: 24 hours

Calculation comment: First Dose

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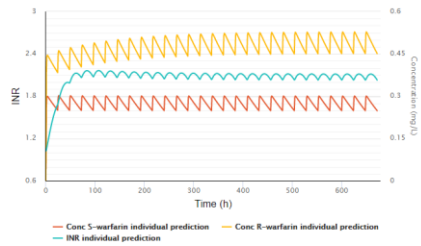
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Dependent variables used for calculation:

NextDose 1.5.0
Execution time: 15 s
Comment First dose
warfarin NextDose
694.2017-02-03-170248_inr_xue2016: Target INR = 2

Day 1 Predicted PO loading dose 17.7 mg
Day 1 Predicted PO maintenance dose 3.38 mg every 1 day

CAUTION: This is a prototype. Do not use for patient care.



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Enter INR Observations



Patient Details | Doses & Observations | Results | Print | Delete

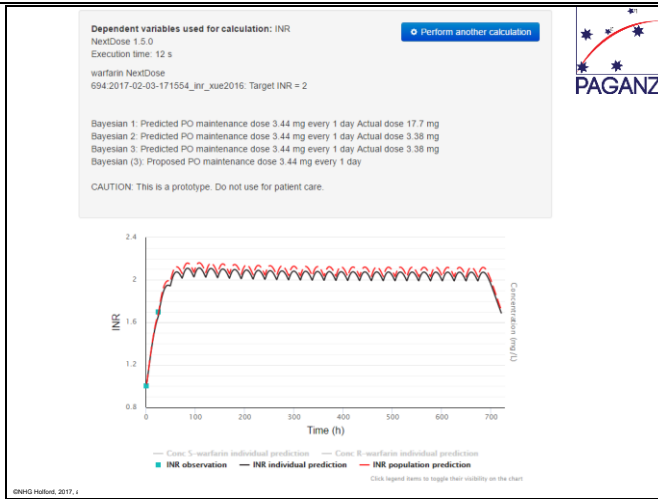
03 Feb 2017 00:00	Height	178 cm
03 Feb 2017 00:00	Weight	85 kg
03 Feb 2017 07:30	INR	1
03 Feb 2017 08:00	PO dose	17.7 mg
04 Feb 2017 08:00	PO dose	3.38 mg
04 Feb 2017 08:30	INR	1.7

Changes saved

Click a dose or observation row to edit. Or add a new dose or observation with the buttons below.

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Targets

- Concentration
 - Average SS
 - Time after dose at SS e.g. trough
- AUC
 - AUC 0-infinity
 - AUC dosing interval SS
- Biomarker
 - INR average SS
- Scaled Target e.g. SS trough/MIC

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Joint Models

- Concentration
 - Linezolid (total or unbound)
- Biomarker
 - Platelet count
- Target
 - AUCtss/MIC

Calculation options

Dependent variables Concentration:Total Platelets

Model

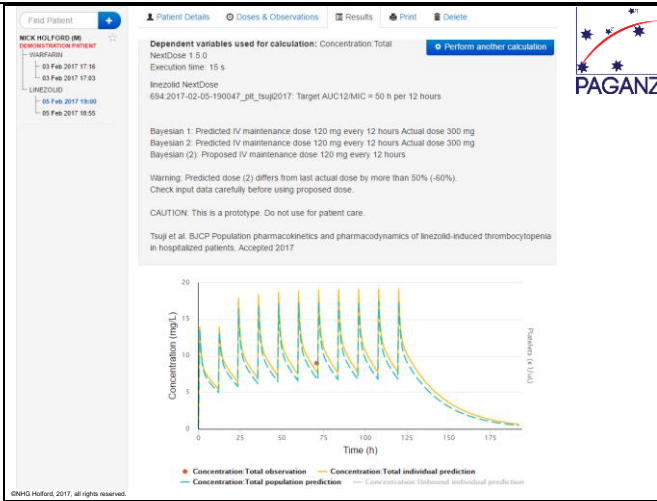
Target

Dose interval

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Evaluation

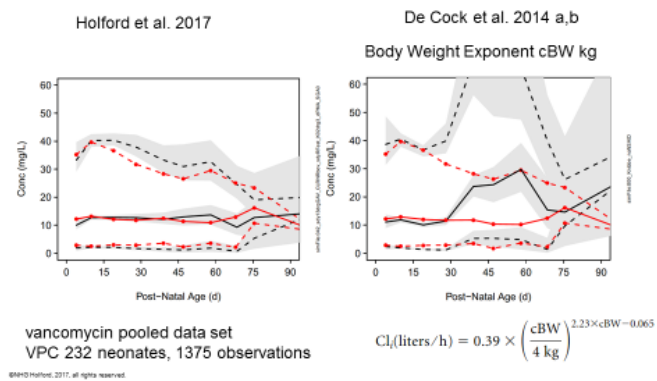
- Model Evaluation
 - External data set
 - Visual predictive check
- Predicted Dose Evaluation
 - Simulated data
 - Error in PK parameter estimates
 - Error in concentration prediction
 - Error in dose prediction

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Vancomycin



De Cock RF, Allegaert K, Brussee JM, Sherwin CM, Mulla H, de Hoog M, et al. Simultaneous pharmacokinetic modeling of gentamicin, tobramycin and vancomycin clearance from neonates to adults: towards a semi-physiological function for maturation in glomerular filtration. *Pharm Res.* 2014;31(10):2643-54.

De Cock RFW, Allegaert K, Sherwin CMT, Nielsen EI, de Hoog M, van den Anker JN, et al. A Neonatal Amikacin Covariate Model Can Be Used to Predict Ontogeny of Other Drugs Eliminated Through Glomerular Filtration in Neonates. *Pharm Res.* 2014;31(3):754-67.

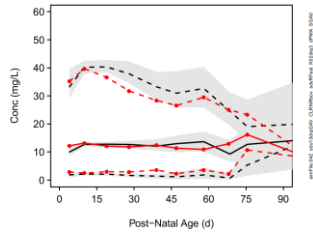
Janssen EJ, Valitalo PA, Allegaert K, de Cock RF, Simons SH, Sherwin CM, et al. Towards Rational Dosing Algorithms for Vancomycin in Neonates and Infants Based on Population Pharmacokinetic Modeling. *Antimicrob Agents Chemother.* 2016;60(2):1013-21.

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Vancomycin



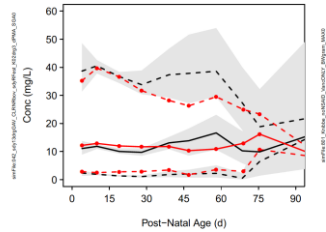
Holford et al. 2017



vancomycin pooled data set
VPC 232 neonates, 1375 observations

De Cock et al. 2014 a,b

Body Weight Exponent cBW g



$$Cl_r(\text{liters/h}) = 0.39 \times \left(\frac{cBW}{4 \text{ kg}} \right)^{2.23 \times cBW - 0.065}$$

One of the co-authors of the De Cock and Janssen papers told me the scale of weight for the body weight dependent exponent should be g not kg although this is not described in the original publication.

Changing the current body weight from kg to g improves the VPC but it is remarkable that a 1000 fold change in scale has less than a 3 fold impact on the predictions.

This brings into question the difficulty of evaluating models described in the literature without confirmation from the original authors that the model has been correctly described.

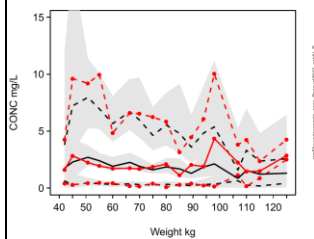
It is also remarkable that this size scaling method is largely insensitive to weight.

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Voriconazole

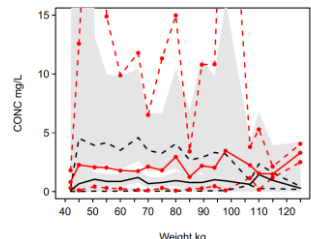


Pascual et al. 2012



Voriconazole pooled data set (Sydney & Lausanne)
VPC 609 patients, 2218 observations (healthy subjects excluded)

McDougall et al. 2016 a,b



Pascual A, Csajka C, Buclin T, Bolay S, Bille J, Calandra T, et al. Challenging recommended oral and intravenous voriconazole doses for improved efficacy and safety: population pharmacokinetics-based analysis of adult patients with invasive fungal infections. *Clin Infect Dis.* 2012;55(3):381-90.

Dolton MJ, Mikus G, Weiss J, Ray JE, McLachlan AJ. Understanding variability with voriconazole using a population pharmacokinetic approach: implications for optimal dosing. *J Antimicrob Chemother.* 2014;69(6):1633-41.

McDougall DA, Martin J, Playford EG, Green B. Determination of a suitable voriconazole pharmacokinetic model for personalised dosing. *J Pharmacokinetic Pharmacodyn.* 2016 a;43(2):165-77.
McDougall DAJ, Martin J, Playford EG, Green B. The Impact of Model-Misspecification on Model Based Personalised Dosing. *The AAPS Journal.* 2016 b;18(5):1244-53.

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Summary



- Try using the development version of NextDose
<https://dev.nextdose.org>
- We are looking for user feedback on both usability and technical features
- Bug reports (real bugs or unexpected behaviour) are encouraged