

Physiologically based pharmacokinetic modeling to predict the pharmacokinetics of metformin, saxagliptin and dapagliflozin in normal and special patient populations

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BACKGROUND

There may be the need for combination of metformin with other antidiabetic drugs to adequately control hyperglycaemia. Dual or triple therapies with metformin such as combining it with saxagliptin or dapagliflozin or all three together could be an effective strategy. Saxagliptin and dapagliflozin demonstrate high efficacy and low risk in patients whose blood sugar is not adequately controlled by metformin alone. The study aimed to construct a physiologically based pharmacokinetic (PBPK) model in GastroPlus® to predict the pharmacokinetics of saxagliptin, dapagliflozin and metformin in different special populations towards enhancing treatment strategies for diabetes. The influence of the presence and absence of food in these populations while on these medicines was explored.

METHODOLOGY

The study utilised relevant physicochemical and physiological base data for input to a PBPK model to predict clinical outcomes of these antidiabetics in paediatrics, geriatrics and pregnant women, comparing this to normal age adults. This was carried out in simulated healthy, renal or hepatically impaired patients in fasted or fed situations. PBPK modeling and simulations were conducted using the advanced compartmental absorption & transit model in GastroPlus®. Modeling of single and population simulations were used to predict PK parameters for oral, immediate release dosage forms (metformin 500mg, saxagliptin 5mg and dapagliflozin 10mg). Clinical data was obtained from clinical studies and clinical trial reports. Other data such as physicochemical properties for input into the PBPK models, data for human physiology in fed and fasted state, ratio of blood-to-plasma and fraction unbound in plasma were experimentally conducted, obtained from literature or predicted. Statistical analysis of results was done using one-way ANOVA. P values of $p < 0.05$ were significant.

RESULTS

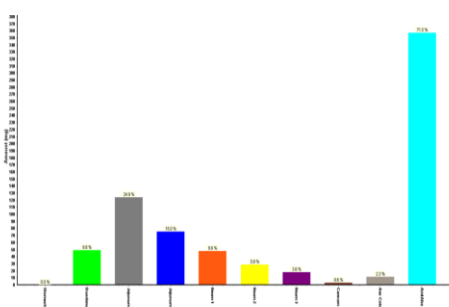


Fig 1: Regional compartmental absorption of metformin

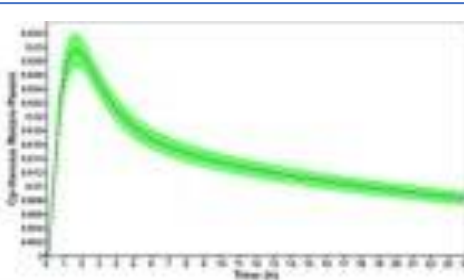


Fig 2: Simulated plasma concentration of dapagliflozin in healthy geriatric patients

Table 1: Modelled metformin pharmacokinetic data of different populations in the fasted state

	C _{max} (µg/mL)	T _{max} (h)	AUC _{0-∞}	AUC ₀₋₂₄	% Fa
Healthy adult	1.639E-3	1.04	5.083E-3	4.877E-3	71.42
Healthy geriatric	2.403E-3	1.28	8.932E-3	8.19E-3	70.33
Healthy pregnant patient	9.801E-4	1.2	3.344E-3	3.121E-3	73.85
Healthy paediatric	3.597E-3	1.12	0.01167	0.01117	71.43
Mild RI	1.285E-3	1.28	4.897E-3	4.496E-3	70.33
Moderate RI	1.349E-3	1.36	5.238E-3	4.8E-3	70.32
Severe RI	1.583E-3	1.44	6.242E-3	5.708E-3	70.30
End stage RI	1.922E-3	1.44	7.663E-3	6.994E-3	70.29
Cirrhosis=A	2.404E-3	1.28	8.932E-3	8.194E-3	70.33
Cirrhosis=B	3.63E-3	1.28	0.01357	0.01237	70.31
Cirrhosis=C	6.143E-3	1.28	0.02251	0.02062	70.30
Simple steatosis	1.475E-3	1.28	5.854E-3	5.347E-3	70.31
Nonalcoholic hepatitis	1.315E-3	1.36	5.155E-3	4.707E-3	70.32

* Renal impairment = RI, End stage renal disease = ESRD

- Age significantly influenced the pharmacokinetics of metformin, saxagliptin and dapagliflozin in both fed and fasted states.
- Single simulations in paediatric and geriatric populations with different stages of renal impairment and cirrhosis, steatosis, hepatitis, demonstrated that severe renal impairment and end stage renal disease (ESRD) significantly increased the AUC₀₋₂₄ of metformin.

RESULTS

- Fed conditions delayed T_{max} possibly due to slower gastric emptying time.
- Severe hepatic impairment (Cirrhosis C) significantly increased the AUC_{0-∞} and AUC₀₋₂₄.
- For saxagliptin, severe renal impairment and ESRD significantly increased AUC_{0-∞} and AUC₀₋₂₄. Cirrhosis A, B, C and simple steatosis significantly increased the AUC_{0-∞} and AUC₀₋₂₄.
- For dapagliflozin, mild, moderate and severe renal impairment significantly increased the C_{max} and AUC₀₋₂₄. Cirrhosis A, B, C, simple steatosis and non-alcoholic hepatitis significantly increased its AUC_{0-∞} and AUC₀₋₂₄.

CONCLUSION

There were some significant differences in fasted and fed conditions following oral administration of these drugs. The mechanism through which food can impact the pharmacokinetics of drugs is not fully understood especially in the paediatric population and requires further study. Cirrhosis A, B, C, simple steatosis and non-alcoholic conditions had no significant influence on the compartmental absorption of these drugs. Also fed and fasted conditions had no significant effect on compartmental absorption for the different populations. Regional absorption along the GIT for metformin shows significant absorption in the jejunum in comparison to other gastrointestinal regions.

REFERENCES

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