Use of Secondary Intelligence™ to Predict Postural Hypotension in Humans Using Alpha-1A Adrenoceptor Binding Data

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Gilmer C, Abbasi M, Andrews S, Craven J, Ferreira S, Gupta V, Haslam G, Holbrook M, Hutchinson L, Islam B, Jo E, Lambert K, Pollard CE, Rosenbrier-Ribeiro L, Starkey J, Redfern WS. Quantitative Systems Toxicology & Safety, Certara UK Limited, Simcyp Division, Sheffield, S1 2BJ, United Kingdom.

ToxStudio®: Secondary Intelligence™ (V1.1)

Summary

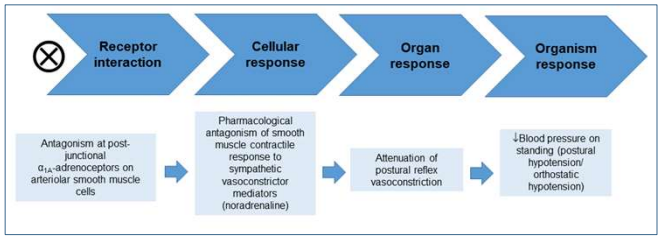
Secondary Intelligence™ is a new software tool for prediction of secondary pharmacology-related clinical side effects using quantitative analysis of expertly curated data on clinically used reference drugs, across a wide range of receptors[1]. The analysis comprises plots of the pharmacodynamically-effective unbound plasma concentration (C_u) of the reference drugs in humans divided by the *in vitro* K_i or IC_{50} of the drugs for their target receptors.

By comparing their C_u/K_i ratios at the α_{1A}-adrenoceptor with those of the reference drugs targeting this receptor for clinical efficacy, Secondary Intelligence™ correctly predicted an association with postural hypotension for 7/7 drugs, and a lack of it for 4/5 drugs.

Background

Postural hypotension (PH) is a characteristic clinical side effect of antagonism at the α_{1A}-adrenoceptor[2], as described in Figure 1.

Figure 1. Secondary Intelligence™ Mechanistic Safety Pathway for α_{1A}-adrenoceptor antagonism causing postural hypotension



The α_{1A}-adrenoceptor is frequently hit as an off-target receptor in secondary pharmacology screening[1]. The question arises: what ratio of unbound plasma concentration (C_u) to K_i is required for postural hypotension to become a risk?

Methods A: Reference drugs

The reference plot for α_{1A}-adrenoceptor antagonism was constructed from the C_u/K_i ratios (a measure of receptor occupancy) for 5 marketed drugs with α_{1A}-adrenoceptor as their primary target[3] and which are each associated with PH, using literature-curated data. The threshold for a high likelihood of interaction with α_{1A}-adrenoceptor is defined by the lowest C_u/K_i ratio of the reference drugs.

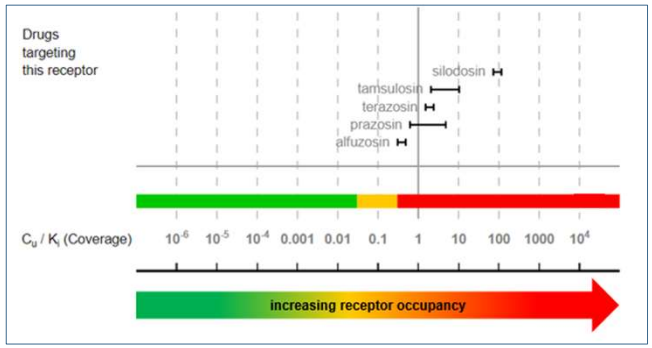
Methods B: Test drugs

To assess whether Secondary Intelligence™ could predict α_{1A}-adrenoceptor-mediated PH as a side effect, data on unbound C_{max} plasma concentrations (C_u) and K_i at α_{1A}-adrenoceptor were curated from the scientific literature for 7 drugs strongly associated with PH (PH-POS) and for 5 drugs with little or no association with PH in clinical use (PH-NEG).

A test drug is assessed against the reference drugs for a given receptor, and if its ratio of C_u/K_i is within the range of the reference set (or higher), it is considered to have a high likelihood of interaction with that receptor in clinical use.

Results

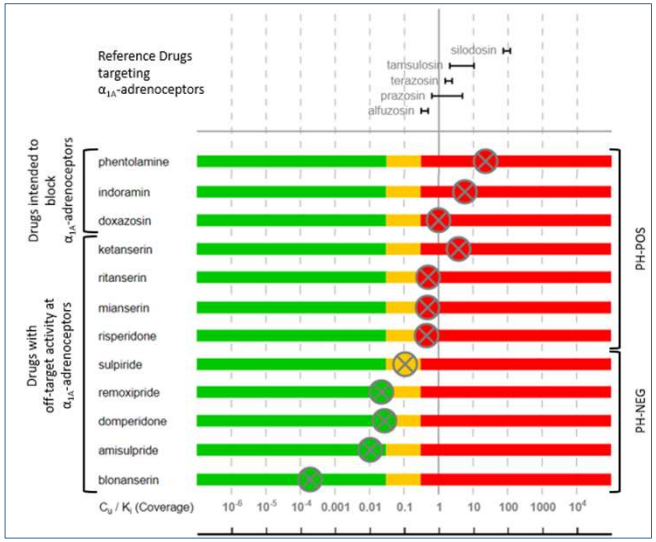
Figure 2. Data visualisation for α_{1A}-adrenoceptor antagonism in Secondary Intelligence™



- The C_u/K_i values for the reference drugs at α_{1A}-adrenoceptor range from 0.3 to 100. The threshold for a high likelihood of interaction is defined by alfuzosin; C_u/K_i = 0.3 (Figure 2).
- The PH-POS drugs, (doxazosin, phentolamine, indoramin, ketanserin, mianserin, ritanserin and risperidone) were correctly classified by Secondary Intelligence™ as having a high likelihood of interaction with α_{1A}-adrenoceptor in clinical use (C_u/K_i > 0.3; Figure 3). These drugs have a range of pharmacological activities, but none of their other receptor interactions is implicated in PH.
- The PH-NEG drugs (sulpiride, remoxipride, blonanserin, amisulpride and domperidone) were classified by Secondary Intelligence™ as having a low (C_u/K_i <0.03) or in one case (sulpiride), medium (0.03 < C_u/K_i <0.3) likelihood of interaction with α_{1A}-adrenoceptor in clinical use (Figure 3).

Results (cont.)

Figure 3. Likelihood of interaction at α_{1A}-adrenoceptor, assessed by Secondary Intelligence™ for 12 test drugs



Conclusions

Secondary Intelligence™ correctly predicted the presence or absence of postural hypotension risk in humans mediated by α_{1A}-adrenoceptor antagonism, for 11/12 drugs.

This implies that it would be able to achieve this for candidate drugs preclinically, using predicted clinical C_u values and measured K_i data at this off-target receptor, supporting better decision making.

These findings also provide confidence in the general approach used in Secondary Intelligence™.

References

- 1. Bowes J et al. 2012 Nature Reviews Drug Discovery 11: 909-922
- 2. Carruthers SG. 1994 Drug Safety 11:12-20
- 3. https://www.guidetopharmacology.org/

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