Case Study: The link between animal and human research in developing medicines

Bringing medicines to *life*

Just 12% of all potential medicines make it to market[i] and one of the main reasons for this is safety-related issues flagged during nonclinical (animal) and clinical (human) research[ii]. Unless a medicine can demonstrate that its benefits outweigh any possible safety risk for humans it cannot be brought to market.

In order to determine the effectiveness and safety of medicines in development, scientists use a wide range of methods including nonclinical research with animals, which must be carried out before clinical trials on humans. Animal tests provide important information on how a medicine will act in a whole organism. However, animals and humans can behave differently in research trials due to a range of factors including their physical make up and the way tests can be administered. Therefore it is important that the industry evaluates the animal models which are used in medicine development, so we carry out the most appropriate tests, using the minimum number of animals necessary, and can be confident in the information they provide as a basis for human trials.

At present, there is not one single, accepted method to assess the ability of animal tests to predict outcomes in humans or potential safety hazards. Therefore, seven[iii] ABPI member companies came together to create the Animal Model Framework for evaluating the ability of animal trials to predict human outcomes[iv]. The group have recently used this framework to particularly investigate the ability of studies in dogs to predict heart-related safety concerns of potential new medicines in humans[v].

Companies shared data on 113 small molecule compounds across therapeutic areas from dog cardiovascular safety studies, and phase I human trials, importantly, taking into account the dose given.

The results of this study suggest that dog cardiovascular studies do provide important evidence for evaluating potential medicine safety, and for medicine development decision making. However, limitations of the model were also identified.

- The results showed that there was good agreement between dog and human studies for the effects of medicines on part of the heartbeat called QTc. Changes in QTc can disturb the rhythm of the heart, and are a key adverse drug reaction which will almost certainly lead to the termination of medicine development if identified. Therefore it is key for patient safety and medicine development decisions that any such effects are identified as early as possible in development. The study showed that if there was no effect of the drug in the dog there was very unlikely to be an effect in the human study and conversely if there was an effect of the drug in the dog, there was a reasonable chance of there being an effect in humans.
- In contrast, there was less agreement between dog and human studies of medicine effects on other cardiovascular parameters such as heart rate and blood pressure. This may be due to differences in the effect of the medicine between species, differences in how blood pressure measurements are made between species, or differences in the number of dogs and humans tested.
- Importantly, the dose exposure was a key factor in determining the agreement between dog and human studies for all parameters – using higher doses in dogs increased the sensitivity of the tests (i.e. more real safety signals were identified), but decreased specificity (i.e. more adverse events were detected in dogs which were not found in humans).

Overall, this study demonstrates the significant value of some components of the dog cardiovascular model in predicting outcomes in humans but also highlights the complexity of decision making in medicine development, which must depend on multiple sources of evidence, and take into account complex factors around species differences and dose exposure.

i Munos, B. (2009) Lessons from 60 years of pharmaceutical innovation, Nat. Rev Drug Discovery 8, 959-968.

ii Cook, D., Brown, D., Alexander, R., March, R., Morgan, P.,Satterthwaite, G., and Pangalos, M. N. (2014). Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework. Nat. Rev. Drug Discov. 13, 419–431
Kola, I., and Landis, J. (2004). Can the pharmaceutical industry reduce attrition rates? Nat. Rev. Drug Disc. 3, 711–715.

iii AstraZeneca R&D, GlaxoSmithKline, Novartis Pharma, Amgen, Janssen Research and Development, Eli Lilly and company, Pfizer Inc.

iv Valentin, J.-P., Bialecki, R., Ewart, L., Hammond, T., Leishman, D., Lindgren, S., Martinez, V., Pollard, C., Redfern, W., and Wallis, R. (2009b). A framework to assess the translation of safety pharmacology data to humans. J. Pharm. Tox. Meth. 60, 152–158.

v Ewart L, Aylott M, Deurinck M, Engwall M, Gallacher DJ, Geys H, Jarvis P, Ju H, Leishman D, Leong L, McMahon N, Mead A, Milliken P, Suter W, Teisman A, Van Ammel K, Vargas HM, Wallis R, Valentin JP (2014) The Concordance between Nonclinical and Phase I Clinical Cardiovascular Assessment from a Cross-Company Data Sharing Initiative. Toxicol. Sci. 142(2):427-35.

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