Fresh, functional human tissues and the prediction of drug safety

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Vascular safety

Intact, functional coronary arteries dissected from human heart samples, mounted on wire myographs for measurement of isometric force.

Changes in blood flow and vascular tone can greatly affect cardiac function; even a brief reduction in coronary blood flow can induce dysfunction of the heart.

Shown opposite is an example of the concentration-dependent coronary artery vasoconstriction caused by 5-hydroxytryptamine (‘5-HT’ or ‘serotonin’).

Respiratory safety

Current in vivo experiments for the assessment of drug-mediated changes in minute volume, tidal volume and respiratory rate may not reflect the most common causes of respiratory side-effects, which are often due to changes in airway resistance or compliance.

Human isolated bronchi or precision-cut lung slices are an excellent model to assess the effects of test compounds on airway resistance.

The image opposite shows the constriction observed to the mucaricin agonist carbachol over a period of 32 minutes, in a human precision-cut lung tissue airway.

Gastrointestinal safety

Isolated mucosa from the small or large intestine mounted in Ussing chambers allows measurements of bi-directional ion transport. This can be a useful predictor of gastrointestinal adverse drug effects such as secretory diarrhoea.

The example data trace shows the effect of cholera toxin (known to cause diarrhoea) on short-circuit current passing across human isolated colon. Cholera toxin increases the secretion of chloride ions into the lumen of the gut, sodium ion follows, leading to the movement of water into the gut.

Summary

Preclinical human tissue assays can be successfully used to help predict clinical adverse effects. Data generated may contribute to the determination of therapeutic index by correlating a measured biological effect with drug concentration in target or surrogate tissue. Whilst assays such as these do not completely replace existing safety tests, they can contribute to a platform of evidence that increases the probability of clinical success and reduces the risk that species differences will go undetected. The considerable untapped resource of residual tissues has the potential to contribute significantly to the 3Rs.

References

2. Defined as procedures involving ‘exisions or partial excisions’ Hospital Episode Statistics, Admitted Patient Care 2011-12 in England.
3. A comparison of respiratory abnomalities identified in clinical trials Murphy, D.J. Regulatory Toxicology and Pharmacology (2014) 69, 135-140.