Fair of face, foul of heart - cardiotoxicity and drug development

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Drug-related cardiotoxicity is difficult to predict in the early stages of drug development, and now may be the primary cause of drug withdrawals. Here we examine some of the main issues pertinent to cardiotoxicity and new drug development.

In a heartbeat

An understanding of cardiotoxicity and of the difficulties in predicting cardiotoxic potential requires some understanding of the molecular basis of the heartbeat. Cardiac cells spontaneously generate electrical currents which result in the repetitive contraction of the heart muscles that keeps us in circulation. This electrical activity results from the presence of specialised proteins (ion channels) which span the cell membrane and which can permit the passage of ions (electrically charged molecules). The movement of these ions can be measured as an electrical current, which has a characteristic pattern of voltage change known as an action potential. Action potentials produced in cardiac cells can be measured at the skin surface using an electrocardiogram (ECG). The ECG measurement is the sum of the action potentials in all cardiac cells. Synchronised electrical activity in cardiac cells causes cardiac muscle contraction, and this enables the heart to pump blood.

Change of heart

In normal patients the ECG shows a predictable pattern. Deviations from this pattern often indicate some form of cardiac insult, and may be predictive of cardiac problems. Hence, a commonly used measure of the potential for cardiotoxicity of a drug is the length of the interval between two well-defined points on the ECG trace, namely the QRS complex and the T wave. This interval is known as the QT interval.

A significantly prolonged QT interval may be associated with perturbations of the heartbeat, for example the potentially fatal cardiac arrhythmia known as torsades de pointes (TdP). The ion channels are the most likely molecular targets by which drugs could prolong the QT interval, by virtue of their causal involvement in cardiac electrical activity and their exposed (cell surface) location.

A number of cardiac ion channels have been identified. There is now evidence that the primary target for drug-induced TdP is an ion channel protein known as hERG, and it seems that all non-cardiac drugs with TdP potential interact with hERG. The classic example of a TdP-associated drug is terfenadine, an antihistamine which at one time was widely prescribed for hayfever. Only after it had been extensively used for several years did it become clear that terfenadine was associated with TdP and

sudden cardiac death. Eventually the drug was withdrawn. The observed side-effects of the drug are thought to be due to terfenadine interacting with the hERG channel.

Pharmaceutical heartache

The significance of drug-hERG interactions can be measured by the regulatory consequences and associated expenses. A non-cardiac drug with a TdP incidence of less than 0.1% can be removed from the market. For example, the pharmaceutical industry withdrew terfenadine (Seldane) even though it had an incidence of only 1/28,500 prescriptions, and grepafloxicin (Raxar) was withdrawn due to only seven cardiac-related deaths and three cases of TdP out of 2.7 million prescriptions.

The number of drugs associated with TdP continues to increase. In recent years a number of non-cardiac blockbuster drugs including cisapride (Propulsid), astemizole, grepafloxicin and terfenadine have been found to cause TdP and withdrawn from major markets. Other drugs such as sertindole (Serlect) and and ziprasidone (Zeldox) have either been withdrawn prior to marketing or required labelling changes that significantly restricted their use. Lidoflazine had its marketing authorisation application rejected because of QT effects.

Against this background it is not surprising that the regulatory authorities have introduced particular guidelines intended to aid detection of QT effects in new drugs. Currently the QT interval (or its derivation, the 'corrected' QT interval, QTc) is used as a surrogate for TdP, and as a general rule the regulatory authorities appear to require a comprehensive evaluation of QT effects to be carried out for new drugs. This has various implications for the design and expense of clinical trials (for example, it may be necessary to genotype any patients developing QT prolongation to identify any genetic risk factors such as those associated with long QT syndrome). Clearly these types of requirement will add to the length and cost of drug development, and therefore make it yet more imperative that drugs taken into expensive clinical trials should have the best possible chance of success.

Hence there is an urgent need for high-throughput screening (HTS) methods to provide detection of TdP prolongation potential early in the drug development process. Unfortunately, TdP itself is not amenable to most HTS techniques. In addition, TdP frequency is so low, usually less than 1/100,000, that it is unlikely to be detected even in clinical trials, which rarely involve more than 2-3,000 patients at most. For this reason, the TdP potential of drugs may not become manifest until the drug is being used in large populations, ie in the post-marketing phase. Therefore a surrogate marker for TdP is needed to identify drugs with TdP potential in the preclinical or clinical stages of drug development.

Currently QT or QTc prolongation is used as a TdP surrogate. However, it is by no means ideal; for example, the average QT increase of about 3% shown by terfenadine is within the daily QT variability often shown by individuals. Also, there may be incompletely understood drug-specific influences, in that two drugs with the same QT effect may have very different TdP potentials. Furthermore, while drugs that cause TdP prolong the QT interval, drugs that prolong the QT interval do not necessarily cause TdP. Therefore the use of QT as a TdP surrogate risks elimination of drugs which in fact would be perfectly safe. In addition, it may be that a proportion of cases of apparent drug-induced TdP have a significant genetic contribution, eg due to underlying mutations in the hERG gene.

At present, although QT is a poor predictor of TdP, the regulatory sentiment is such that drugs which show a QT effect in trials are likely to have more approval issues

than drugs which do not. This is in spite of evidence that QT prolongation does not necessarily mean that a drug is unsafe (of over 200 compounds associated with QT prolongation, over half are in clinical use in the UK). Hence the need for HTS or *in silico* systems that reliably predict drug-associated QT prolongation in patients.

The heart of the matter

The core issue then is that drug development is suffering from the current lack of HTS procedures capable of distinguishing between drugs which safely interact with hERG and drugs which interact dangerously, ie which will cause TdP. The main hurdle is the lack of a convenient TdP surrogate that can easily be measured in HTS formats. At present the *de facto* surrogate is QT, but, as we have seen, this is not a satisfactory solution.

Most HTS systems require tests to be carried out in cell culture. Routine cell-based screens for cardiotoxic potential have been facilitated by the cloning of the hERG gene, which can be functionally expressed in stable, cultured cell lines. This allows the assessment of drug-hERG interaction by monitoring the effect of the drug on the currents produced by hERG channels in cultured cells. However, this requires a sophisticated assay technique known as 'patch clamping', which isolates regions of the cell membrane containing hERG channels and measures changes in electrical potential difference. Use of this method in high throughput requires automation of patch clamping in array format, which is not widespread, although it appears to be becoming increasingly possible. If nothing else, such systems will allow the screening out of those drugs which have a clearly dangerous effect on QT, while allowing the further, qualified examination of those candidates with a low or intermediate QT effect.

However, the real prize will go to the enterprise which can develop a new TdP surrogate that is both meaningful (ie highly predictive of TdP in patients) and also amenable to high throughput formats. This may not be as simple as measurement or prediction of interaction with a given ion channel, as it is possible (for example) that there are unidentified factors in cardiac cells which affect the precise outcome of a drug-hERG interaction. As always, biology is not simple, but we should take heart from the exponential rate of technological progress, and we look forward to future developments in the field of TdP prediction, which shall surely be accelerated by the commercial rewards that await developers of an effective product in this field.

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