Heart death risk cut by early warning drugs tests

July 14 2008

The likelihood of people dying because their medication has a side effect that affects the electrical activity of the heart is being reduced – thanks to a better understanding of why this happens and the development of tests to predict it.

The progress made on this topic will be discussed by leading scientists at The Federation of European Pharmacological Societies (EPHAR) 2008 Congress in Manchester on Monday, 14 July, 2008.

Many kinds of medicine are associated with this adverse drug reaction, which initially involves a slowing of the electrical recovery of the heart each time it beats – known as QT prolongation.

Although this effect is not in itself dangerous, in a small percentage of people, particularly those with existing heart problems, it may lead to a potentially fatal abnormal heart rhythm known as Torsades de Pointes (TdP).

The symposium at the University of Manchester will review how tests done before potential new medicines are given to patients can be used to assess the probability that a drug will lead to QT prolongation or to the actual risk (TdP).

Leading European researchers will meet at the conference, which is hosted by the British Pharmacological Society, to discuss what early testing is done, how the results are used, how good they are at predicting

effects on electrical activity in the human heart and what areas there may be for improvement.

Symposium organizer Dr Jean-Pierre Valentin of AstraZeneca R&D, Alderley Park, Cheshire, says that although significant progress has been made, which has decreased the number of old and new drugs carrying this cardiac safety risk, there is still more work to be done before strategies for assessing the risk are optimal.

He said: "The work being discussed is just one element of a discipline known as safety pharmacology. This involves determining which drug side effects could potentially be life-threatening and then trying to put in place tests that predict whether a given chemical might have one of these serious side effects in humans.

"By law, these tests must be done before a potential drug is first given to humans. In this way, the ultimate aim is to discover new medicines that can be developed rapidly and safely without causing any side-effects.

Dr Valentin continued: "Because the biology of the human body is so complex, no single group has the resources or breadth of knowledge to devise the best possible approach to predicting and preventing a given side effect. Rapid progress therefore needs academic and pharmaceutical company pharmacologists, doctors, government agencies and patients to collaborate as much as possible in order to share their knowledge and data. The symposium is just one mechanism for trying to achieve this.

Speaking specifically about TdP he said: "Until recently, the first indication that a drug carried a TdP risk was in patients, and, since it is a rare side-effect, this was only after millions patients had taken the drug.

"Although the low incidence of TdP might suggest relatively little need

for concern, some of the medicines causing TdP were only for minor treatments such as hay fever, in which case the safety risk of the drug far outweighed the benefit to the patient.

"Medicines for non life-threatening diseases that are known to cause TdP in man are no longer available, but for serious conditions, such as cancer, the risk of TdP is far lower than the risk of dying from cancer so the use of such drugs in still justified but requires very careful, additional monitoring by doctors.

"Therefore, the challenge is to be able to produce medicines for all health issues, irrespective of their severity, that carry no TdP risk. This is particularly important because of the large number of people with cardiovascular diseases that would increase their TdP risk - such as those with high blood pressure, high cholesterol and diabetes.

"The most important advance in understanding this side-effect was the realisation, based on the work of many scientists, that the fundamental cause is most likely to be the drug sticking to a particular protein in the heart.

"This information is crucial, since once this protein - known as hERG - was identified, tests could be developed that could be done in a test tube and were so simple that hundreds of different chemical structures could be tested in a working day. This massively increases the chances that the chemists making the potential drugs can find one that doesn't stick to hERG and therefore is unlikely to cause TdP.

"An important additional benefit from testing many compounds is that data for the activity of each compound can be fed into computer models that are 'trained' to predict the likely activity of compounds designed in a computer. This so-called 'virtual screening' allows thousands of compounds to be 'tested' per day.

"While these tests significantly reduce the risk that a new medicine will cause TdP, there are other factors. At this symposium we want in particular to assess how good our current tests are at predicting the outcome in man, and how best we can predict other drug effects leading to TdP. The learning points from the hERG and TdP story are important not just for this particular side-effect but for safety pharmacology in general."

The theme of drug safety will be continued at EPHAR 2008 on Monday, with Prof Pierluigi Nicotera, Director of the MRC Toxicology Unit, University of Leicester, delivering a plenary lecture titled 'Understanding Molecular Mechanisms of Cell Injury and Death: a Way to Improve Drug Safety and Design'.

Prof Nicotera said: "My research is focused on the mechanisms that decide death or survival of brain cells. The Unit is working to clarify which are the most relevant targets in disease processes regardless of the origin of disease – both common human diseases and diseases caused by toxic chemicals.

"By doing so we aim to understand common patterns of tissue responses to injury that can be targeted by new drugs. This could also lead to understand adverse drug reactions and cytotoxic processes occurring in organs following chemical exposure."

Source: University of Manchester