

events, including one liver transplant and six deaths. However, it has not yet been determined whether these can be attributed to the drug. Glaxo Wellcome are now examining the data to determine their future course of action.

Troglitazone has not been removed from the market either in the USA or in Japan, but Warner-Lambert and Sankyo in the USA, and similarly Sankyo in Japan, are revising the product labelling to recommend more-frequent blood testing and to monitor liver function. Warner-Lambert believe that the avail-

able data do not support a suspension of troglitazone sales and that some of the reports of liver dysfunction are a result of the heightened awareness following a label change in October. On the news of this suspension, Warner-Lambert's shares plunged \$25.88 to \$114.00, while Glaxo Wellcome's stock appeared unaffected.

The timing of this news prior to the SMR symposium led to inevitable questions being raised concerning the safety of rosiglitazone with respect to liver damage. Smith was able to reassure his

audience that no adverse liver effects have been seen with rosiglitazone. He emphatically pointed out that 'these drugs should be treated separately' because, despite the mode of action the thiazolidinediones share, there are also many differences between them, including metabolism and excretion rates.

The \$1 billion peak worldwide sales value predicted for these antidiabetics remains a glittering prize for some of the industry's major players.

*Simon Fenwick*

## A first for selenium in high blood pressure

Researchers in the USA have developed a novel group of compounds based on selenium, which they say may have therapeutic use as orally active drugs for treating high blood pressure without interfering with the CNS. The fact that selenium is a crucial component of the drug could also help improve understanding of this trace element in general health and disease.

Biochemist Sheldon May of the Georgia Institute of Technology and colleagues at Mercer University (Atlanta, GA, USA) have described a group of antihypertensive compounds known as the phenylaminoalkyl selenide compounds [*J. Pharmacol. Exp. Ther.* (1997) 283, 470–477].

The team has used rational design methods to create derivatives of their original lead compound (developed in the mid-1980s) and focused on minimizing absorption into the CNS and improving resistance to digestive enzymes in order to boost oral activity and reduce side-effects. 'We think our antihypertensive compounds are the first where biological activity is a consequence of the unique chemistry and biochemistry of selenium', explains May.

### Toxicity concerns

Although the researchers first discovered the original compound in the 1980s, concern about the potential toxicity of selenium and the ready availability of

other antihypertensive drugs effectively precluded further development. However, recent findings about the potential physiological importance of selenium have led to renewed interest in such compounds.

There is evidence that selenium, which is an antioxidant, may play a crucial role in diseases as diverse as cancer, heart disease, arthritis and AIDS because of its involvement in numerous enzymic processes.

Working with Dr Stanley Pollock (Mercer University), May's team has tested their phenylaminoalkyl selenides on a strain of rats that spontaneously develops high blood pressure and they confirmed the antihypertensive effects of the compounds. 'We now have clear evidence that these molecules act on the peripheral nervous system and allow the blood vessels to relax sufficiently so that blood flow increases', May explains.

The team also found that a hydroxylated version has minimal effects on behaviour, so it is probably not interfering with the CNS of the test animals. 'Our analytical ICP/MS (mass spectrometry) data directly corroborate the behavioural results on restricted CNS permeability', explains May, which is important for avoiding many of the side effects associated with other antihypertensive drug leads. May also emphasizes that the drug is orally active – an antihypertensive that

needs to be injected would not be commercially viable and would be an inconvenience for patients.

May's compounds are therapeutically active at concentrations several orders of magnitude less than their toxic dose. No detrimental side effects are observed in the animals, but additional preclinical work is needed before the team can apply for testing in humans.

### Industry collaboration

May and his colleagues would like to establish a collaboration with a pharmaceutical company to study these compounds further. However, they do not necessarily see these particular derivatives as being developed into prescription drugs. 'The real value of these antihypertensive compounds may be to show how we might make selenium-containing therapeutic agents for other diseases'. Selenium deficiency has been linked to survival rate in HIV infection and also to mutation of otherwise benign viruses, which can then cause heart damage in experimental animals.

The compounds have, of course, now been patented.

*David Bradley*

*e-mail: [Bradley@enterprise.net](mailto:Bradley@enterprise.net)*

*Web: [http://homepages.](http://homepages.enterprise.net/bradley/elem1.html)*

*[enterprise.net/bradley/elem1.html](http://enterprise.net/bradley/elem1.html)*