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Proton pump inhibitors to be used more?

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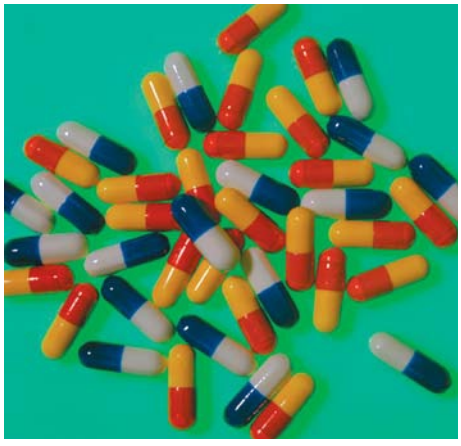
The negative news surrounding COX-2 inhibitors might increase the use of proton pump inhibitors (PPIs) in combination with conventional non-steroidal anti-inflammatory drugs (NSAIDs). PPIs are used to heal stomach and duodenal ulcers that can be caused by the use of NSAIDs.

Most NSAIDs have been used for many years and are important in the treatment of arthritis and other painful conditions. They inhibit cyclooxygenase-1 (COX-1) as well as -2 (COX-2) isoenzymes. Cyclooxygenase catalyses the formation of prostaglandins. COX-1 inhibition lowers stomach prostaglandin levels and is therefore associated with stomach ulcers and internal bleeding, whereas COX-2 enzyme mediates pain and inflammation.



High hopes

It was hoped that selective COX-2 inhibitors could provide the anti-inflammatory benefit of conventional NSAID with reduced gastrointestinal reactions. Coxibs, the newest class of NSAIDs that selectively inhibit COX-2, were developed and include celecoxib (brand name Celebrex), rofecoxib (Vioxx), valdecoxib (Bextra), parecoxib, lumiracoxib and etoricoxib.

Results of the VIGOR (Vioxx Gastrointestinal Outcomes research) study, released in March 2000, demonstrated that the incidence of serious gastrointestinal complications risk with Vioxx was reduced by 50% compared with the conventional NSAIDs naproxen. The study also indicated a risk of cardiovascular events versus naproxen.

In September 2004 however, Merck voluntary withdrew rofecoxib (Vioxx) from the market. This decision was based on a study showing an increased relative risk for confirmed cardiovascular events, such as heart attack and stroke, beginning after 18 months of the treatment in the patients taking Vioxx compared with those taking placebo.

Mid-February in the United States, an advisory panel at the Food and Drug Administration (FDA) voted to recommend that Vioxx be allowed back on the market under strict conditions including warnings to patients of the associated risks. The panel said other COX-2 inhibitors drugs should remain on the market. The FDA has still to decide.

A class effect?

Following Vioxx withdrawal, the European Medicines Agency (EMEA) and its scientific committee, the Committee of Medicinal Products for Human Use (CHMP) reviewed all available data on the cardiovascular safety of COX-2 inhibitors. These data indicate that an increased risk of heart attack and stroke could be a class effect of all COX-2 inhibitors.

'Based on these findings, the EMEA/CHMP is now providing further advice on these medicines', said Martin Harvey Allchurch, spokesperson at the EMEA, on the 8th March. Apart from rofecoxib (Vioxx), all COX-2 inhibitors remain on the market. 'However, prescribers and patients are advised that these products should not be used in patients with ischaemic heart disease or stroke. Caution is needed when COX-2 inhibitors are to be used in patients with risk factors of heart disease. These include high blood pressure, high cholesterol, diabetes and smoking. The cardiovascular risk may increase with duration of treatment and with high doses. The EMEA recommends that Doctors use the lowest effective dose of the COX-2 medicine for the shortest possible duration of treatment. The Europe-wide review is not final yet. The inquiry should be formally concluded in the coming months,' he added.

Enter PPIs

The concerns on COX-2 inhibitors might turn patients from selective COX-2 inhibitors to conventional NSAIDs combined with PPIs. However, in clinical practice, one third of people will not respond to a given NSAID, including a selective COX-2 inhibitor. In cases where the best treatment for an individual patient is a non-selective NSAID, concomitant administration of PPI might be an option in

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order to prevent gastrointestinal complications. In addition, even though studies show a significant reduction of gastrointestinal complications with selective COX-2 inhibitors, the risk was not eliminated.

Among the various PPIs, esomeprazole (Nexium, AstraZeneca) is one of the leading PPIs available on the market. Nexium is the first PPI developed as an isomer and it continues to establish an improved treatment standard. 'We know that people are moving away from COX-2 inhibitors,' said Maria Pierrou, gastrointestinal PR manager for AstraZeneca. Following the negative news on COX-2 inhibitors, 'It is quite probable that PPIs' sales, including Nexium's, will increase', she said. 'However, our message has not changed,' she added. 'We have always recommended that the use of PPIs should be considered with any NSAIDs, including COX-2 inhibitors. There is an enormous need for information but it is really up to the doctors and physicians to decide which medication is appropriate for each patient'.

Genotypic guidance for chemotherapy choices

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New research could explain how the anticancer drug paclitaxel induces apoptosis and how common tumor mutations induce resistance to paclitaxel [1]. Eileen White, Professor of Molecular Biology and Biochemistry at the Center for Advanced Biotechnology and Medicine, Rutgers University, Piscataway, USA and colleagues identify the proapoptotic protein BIM as a key player in apoptosis in epithelial tumors and in their response to paclitaxel. The use of proteasome inhibitors in tumors where the H-ras/MAPK pathway is activated, they report, overcomes the paclitaxel resistance of these tumors. 'What we find in the laboratory may not be reproduced in the clinic,' warns White, 'but it is worth trying. If our predictions hold up,' she adds, 'the general concept of designing combination chemotherapies based on individual tumor genotypes could rapidly gain acceptance.'

The importance of apoptosis

Acquired resistance to apoptosis is a common characteristic of cancer. Tumor cells not only proliferate faster than normal cells, they also fail to die when, for example, their DNA becomes mutated. Furthermore, defects in apoptosis help tumor cells to survive the onslaught of chemotherapy, which often works by inducing apoptosis.

Paclitaxel (Taxol), a natural anticancer agent that stabilizes microtubules, is known to induce apoptosis but how it does this and why tumors often become resistant to paclitaxel is poorly understood. White and her colleagues now suggest that paclitaxel induces apoptosis by inducing the accumulation of the proapoptotic protein BIM, a member of the BH3-only subfamily of BCL-2-related apoptosis signalling proteins. BIM and other BH3-only proteins are the most upstream regulators of apoptosis signalling in the BCL-2 family.

BIM and paclitaxel

In their paper [1], White and her colleagues show that BIM suppresses tumorigenesis in transformed BMK cells. Furthermore, paclitaxel induces BIM accumulation in these epithelial cells and BIM expression determines their sensitivity to paclitaxel *in vivo*.

'At the same time as we were doing this work, we were also trying to figure out how ras mutations, which are common in human tumors, affect responses to chemotherapy,' continues White. 'We discovered that H-ras/MAPK pathway activation suppresses paclitaxel-induced apoptosis in tumor cells by causing the phosphorylation and proteasome-dependent degradation of BIM.' It was like digging holes in two places and breaking through into the same hidden treasure store, she says.

This second discovery encouraged the researchers to test whether the proteasome inhibitor Velcade (Millennium Pharmaceuticals, Cambridge, MA, USA) could restore paclitaxel sensitivity to BMK cells containing an activated ras pathway. Their results indicate that this chemotherapeutic combination could indeed be beneficial.

Towards rational combination chemotherapy

'This research adds to our understanding of proapoptotic effects of BIM,' comments Kapil Bhalla, Professor of Oncology at the H. Lee Moffitt Cancer Center, University of South Florida, Tampa, USA. 'A cellular model like the one used here is unlikely to represent what happens in clinical epithelial cancers but it is a reasonable place to start.' A combination of a proteasome inhibitor and paclitaxel could be a very potent combination chemotherapy, says Bhalla, 'but only clinical studies will tell.'

Oncologist David Quinn, assistant professor of clinical medicine at the Keck School of Medicine, University of Southern California, LA, USA is also intrigued by the insights that White's results provide into how proteasome inhibitors and taxanes interact. When Velcade was first produced, says Quinn 'many researchers tried it out in the lab with other chemotherapeutic agents to see what effect it would have.' These somewhat random experiments uncovered a synergy between Velcade and taxanes and provided the basis for early clinical trials that are currently underway. Quinn himself is testing the drugs in combination in prostate cancer. 'Now we have these clues to how the combination might work, we will look in our patients for alterations in BIM expression,' he says.

White, meanwhile, hopes that her work will help to rationalize the design of combination chemotherapy approaches. 'Understanding how tumors are wired to commit suicide and how drugs induce cell suicide is going to be critical to improving combination chemotherapy,' she says. 'There are hopefully going to be far too many drugs to test this with that randomly, so we are going to need a rational approach that will allow us to develop chemotherapy based on individual tumour genotypes.'

Reference

1 Tan, T-T. *et al.* (2005) Key roles of BIM-driven apoptosis in epithelial tumors and rational chemotherapy. *Cancer Cell* 7, 227–238

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