Reformulated OxyContin®: an interview with Dr. Paul Coplan, Executive Director, Risk Management and Epidemiology, Purdue Pharma

Published on August 29, 2013 at 7:18 AM

Interview conducted by April Cashin-Garbutt, BA Hons (Cantab)

What is OxyContin® and what is it used for?

OxyContin contains oxycodone, which is an opioid agonist. It is used for the management of moderate to severe pain when a constant opioid analgesic is needed for a prolonged period of time.

OxyContin is not to be used:-

- for acute pain
- for mild pain or pain that is not expected to persist for an extended period of time
- as an as-needed (prn) analgesic
- in the first 24 hours following surgery for patients not previously taking the drug - this is because its safety in this setting has not been established
- for postoperative pain unless the patient is already receiving chronic opioid therapy prior to surgery, or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time.

What were the problems with original OxyContin® and why was it necessary to develop reformulated OxyContin®?

OxyContin contains oxycodone, a Schedule II controlled substance which can be abused in a manner similar to other opioid agonists legal or illicit.

Purdue chose to reformulate OxyContin in order to make it more difficult to manipulate for certain types of misuse and abuse (injection and inhalation).

What did the reformulation development process involve?

The reformulation process began in early 2001. Initially, Purdue began reformulating OxyContin to include Opioid Antagonists. The first attempt was with Naloxone, a combination of Oxycodone and Naloxone and that started in 2002. That was suspended due to safety concerns primarily involving the Naloxone getting released when it was not supposed to.

The next program began in 2004 with Naltrexone that was also suspended due to safety concerns.

The current reformulation effort began in 2005 using Polyethylene oxide as the ingredient to make the pill harder to crush or dissolve. That went through two FDA advisory committees before it got approved.

The first FDA advisory committee was in May of 2008 and then the subsequent one was in September of 2009. The product was then approved in April 2010; roughly nine years after the efforts for reformulation began.

In October 2010 there was another FDA advisory committee, a third one, this one was to discuss the design of the post marketing studies. The question was: what is a good way to measure the effects of abuse deterrent formulations to assess whether or not they are working?

There were three steps done preapproval to ensure that the product had adequate characteristics to be considered abuse deterrent.

The first step was the laboratory extraction procedures which we call in vitro testing. That involves testing it under various conditions of physical force, crushing force; various heat characteristics; various pH environments; various solvent environments; looking at how the formulation withstood various types of physical mechanisms to extract the active substance. That was the first step.

The second step involved testing the pharmacokinetics of the reformulated product in people. Normally, we test how the drug is absorbed and what the blood levels are and so in this case we tested it in people. We looked at absorption levels for people, for example, people who snorted the crushed reformulated product. This is a crushed *original* product to see if there were differences in the blood levels that were absorbed after snorting the reformulated or the original version. That was the second step.

The third step involved drug liking studies, whereby people who were established abusers of oxycodone were asked to abuse the reformulated version and the original version of OxyContin and to evaluate their liking of the two formulations. In addition, there were other types of objective measures such as pupil dilation size etc.

Those three sets of studies were submitted to the FDA prior to approval and then there was a post-approval commitment to conduct studies in the real world to assess the effects of the abuse-deterrent formulation in the community in a post marketing environment.

How does the abuse potential of reformulated OxyContin® differ from original OxyContin®?

In the first step we found that extraction was much more difficult. It was not impossible, but it was much more difficult.

The product was reformulated to be bioequivalent for patients. It had to deliver the same amount of analgesic substance, which is oxycodone, to patients who were taking the pill orally.

With the original formulation, people used to crush it for snorting or crush it and dissolve it for injecting or chew the whole tablet, so that what would normally be a twelve-hour release upon chewing would become something that would be absorbed in a short amount of time.

So, all of those three routes involved breaking down the tablet to get around the extended release mechanism and then people who were intent on abusing it would inject it, snort it or swallow it.

What we found in the second phase of testing, which was the pharmacokinetic assessment, was that the blood levels were roughly equivalent for patients. Individuals who took the pill orally as a whole tablet had similar levels of delivery of the analgesic substance with original and reformulated OxyContin as indicated by blood levels of oxycodone, but the crushed tablets of reformulated OxyContin were absorbed more slowly than that of original OxyContin. That's because even after the most extensive crushing procedure, there were still medium-size pieces of the tablet that led to a delayed absorption effect.

Regarding the injecting route of abuse, people were not able to inject it because they were not able to prepare it for injecting due to the gummy substance that forms with water that impedes putting it into a syringe.

In the last step of preapproval testing, patients substantially disliked the new formulation compared to the old formulation.

Please can you outline the post marketing studies?

In the post marketing studies we conducted eleven studies. Six of those were originally a post marketing requirement for FDA. Five of them were additional studies that did not quite meet the criteria that the FDA uses for formal post marketing studies, but nevertheless provided very useful information that complemented and provided context for the formal studies.

Although we designed the post-marketing program to assess changes in abuse of OxyContin before the FDA

published a guidance document on developing abuse–deterrent formulations of opioid analgesics, the pre-approval and post-approval programs for OxyContin were consistent with the FDA guidance document.

The results of the 11 post-marketing studies to date indicate that 9 studies demonstrate a strong reduction in abuse or diversion of OxyContin, one study has data that is limited in timeframe but has shown only a small effect to date, and one study had substantial changes in prescribing practices occur during the study period so the effect of reformulation cannot be discerned from other changes. Each study included comparison opioid analgesic groups to differentiate between the general trends over time for prescription opioid abuse versus those that were specific for OxyContin.

What we found is that rates of abuse in the comparator groups remained flat, or in some cases increased (for example, for ER oxycodone) whereas the rates of abuse of OxyContin declined by around 40% to 50% on average with a range of between 30% and 70% depending on which study we looked at.

Three of the studies have been published in journal articles: one paper assessed changes in abuse among people being assessed for treatment at substance abuse treatment centers, one paper assessed changes in abuse using calls to poison centers and a national surveillance system of drug diversion events, and one using the national Poison Data System.

Another of the studies evaluated changes in the number of deaths reported to the company. Every company has an adverse event reporting system by which they collect adverse event that occur in association with their products and people are encouraged to report such adverse events to the company. Before the introduction of the new formulation, Purdue received a fairly steady number of fatal adverse event reports. The reported number of fatal adverse events was On average, about 30 deaths per 3-month period among approximately 500,000 people prescribed OxyContin every month in the US. After the introduction of reformulated OxyContin, the number of deaths reported to Purdue decreased 60% to 70% by the second year after introduction while the number of people prescribed OxyContin was approximately 495,000 per month.

Other studies suggested the pattern of abuse has changed. For example, we conducted a study in in a rural Appalachian area of Kentucky where moonshine was a big issue and has been an area with a lot of prescription opioid abuse. The study was conducted among a group of people who frequently injected prescription opioids and assessed how their abuse of opioids changed after reformulated OxyContin was introduced. We figured it was a worst-case scenario test of the abuse-deterrent formulation.

In the study interview, people abusing prescription opioids were asked what their preferred drug was before the new formulation was introduced and 76% said their preferred drug for abuse was OxyContin. Several months after reformulated OxyContin was introduced, only 0.6% of people in the study said their preferred drug of abuse was reformulated OxyContin.

Will it still be necessary to monitor all patients receiving reformulated OxyContin® for signs of abuse?

Yes. The results of the post-marketing studies indicate that abuse of OxyContin has gone down substantially, and that reformulated OxyContin is less abused than original OxyContin, especially by injecting and insufflation ("snorting"); however, the new formulation is designed to be bioequivalent for patient use and there still is a possibility that people may abuse it by taking it orally. Therefore it is important to still monitor people taking reformulated OxyContin, as it is for any other opioid analgesic.

How does the safety and efficacy of reformulated OxyContin® compare to original OxyContin®?

The efficacy is bioequivalent. The peak blood concentration after taking a pill (called Cmax) and the time it takes for the blood concentrations to peak (Tmax) are equivalent for original and reformulated OxyContin, indicating that the new formulation delivers the analgesic substance equivalently.

From the safety perspective, they generally have equivalent safety profiles. There is one new adverse event that emerged in the post-marketing surveillance of OxyContin; the excipient that is used to make the tablet harder, polyethylene oxide, is harder to swallow. Instructions to patients have therefore been added to ingest the tablet with sufficient water to swallow.

A question has been how to get the pain-relieving benefits of opioids for patients but reduce the abuse and therefore, maximize the benefit-to-risk balance of using prescription opioids. What is exciting about abuse-deterrent formulations of opioids is that they can preserve patient access to the analgesic benefits but deter abuse by non-patients.

Do you expect to have to make any further adjustments to reformulated OxyContin®?

The Greek philosopher Heraclites said "nothing is permanent except change". This applies to the abuse and misuse of prescription opioids too, and therefore we remain constantly vigilant to understand what needs to be done to make our products safer for patients and for society.

Currently, our efforts are focused on developing abuse-deterrent formulations of other prescription opioids. We are not currently looking at improving the formulation because it seems to be working well.

What are Purdue Pharma's plans for the future?

We have three large programs. One is to move our existing product portfolio of opioid analgesics towards abuse-deterrent formulations. A second is to develop new molecular entities to treat pain that have a different safety profile to opioids. A third is a research program to evaluate and demonstrate the efficacy and safety of long-term opioid use.

One development program in Phase 3 is a combination of extended-release oxycodone and naloxone, called Targiniq, that intended as an abuse-deterrent formulation for the treatment of moderate to severe chronic pain. Naloxone is an opioid receptor antagonist that can block the high experienced from an opioid agonist such as oxycodone, especially when the opioid agonist is injected or snorted. However, during oral ingestion naloxone is metabolized by the liver so that it does not interfere with the analgesic effects of oxycodone. In addition,in Europe they use Targiniq to manage constipation because in European studies there has been a reduction in the level of constipation associated with Targiniq relative to ER oxycodone.

Where can readers find more information?

www.purduepharma.com

About Dr. Paul Coplan

Paul Coplan is Executive Director and the head of the Risk Management and Epidemiology department at Purdue Pharma. He is also adjunct assistant professor in Epidemiology at the University of Pennsylvania School of Medicine.

He has a Doctor of Science degree in Epidemiology from Harvard University, an MBA from Wharton Business School, a Master of Science in Public Health and Nutrition from the University of Massachusetts and a BS Honors in Biochemistry and Physiology from the University of Witwatersrand.

He has published over 50 peer-reviewed journal articles, worked on the successful approval of 8 pediatric and 1 adult vaccines and 7 drugs over the past 17 years in drug development research at Merck, Wyeth, Pfizer and a non-profit HIV prevention drug development organization, and has conducted studies in 15 countries.

He is the co-chair of the Benefit-Risk Assessment Communication and Evaluation Special Interest Group of the International Society of Pharmacoepidemiology and the Chair of the Metrics Subteam for the REMS Program Companies that are implementing the Class REMS for ER/LA Opioid Analgesics.