

Alcohol-associated rapid release of a long-acting opioid

Reason for posting: Palladone XL (hydromorphone hydrochloride) is a long-acting opioid for chronic pain relief in patients with persistent, moderate-to-severe pain. A recent pharmacokinetic study showed that co-ingestion of the drug with alcohol can accelerate release of the drug from its extended-release capsules. This has the potential to result in opioid overdose and serious side effects, including respiratory depression, coma and death (www.fda.gov/cder/drug/infopage/palladone/default.htm).

The drug: Hydromorphone has been available for pain relief for many years in other marketed drug products. The long-acting hydromorphone hydrochloride (Palladone XL) capsule was developed to allow slow release over 24 hours and once-daily dosing.

The recent pharmacokinetic study used a 4-arm crossover design to test 24 healthy adults in the fasted and unfasted state. In subjects who co-ingested a 12-mg Palladone capsule with 240 mL (8 ounces) of 40% ethanol the average peak hydromorphone concentration increased by almost 6 times compared with co-ingestion with water. One subject experienced a 16-fold increase. In some subjects, the peak plasma concentration after alcohol ingestion equivalent to two-thirds of a typical

serving of beer was almost twice that after water ingestion. The effects were more marked in the fasted state. No cases have yet been reported of injury resulting from this interaction.

Laboratory studies conducted at the time of licensing suggested that alcohol could accelerate the release of hydromorphone from Palladone capsules. It is possible that alcohol interacts with the capsule, causing it to break down and release too much hydromorphone into the blood at once (dose dumping). The capsules are made from 5 main ingredients: FD&C blue#2 (24-mg capsule only), red iron oxide (12-mg and 16-mg capsules only), gelatin, synthetic black iron oxide and titanium dioxide. Synthetic black iron oxide and FD&C blue#2 are ingredients in edible black ink.

There are other drugs that use the same capsular ingredients. For example, Apo-Doxepin and some formulations of nizatidine and temazepam contain synthetic black iron oxide, FD&C blue#2, gelatin and titanium dioxide. Each contains additives in addition to those listed for Palladone.

What to do: Palladone XL has been withdrawn from the US market. Although the interaction with alcohol described here may be specific to this drug, Health Canada has recommended that

Box 1: Slow-release opioids sold in Canada

- Hydromorph Contin (hydromorphone)
- Kadian SRC (morphine sulfate)
- M.O.S.-SR (morphine hydrochloride)
- M-Eslon (morphine sulfate)
- MS Contin SRT (morphine sulfate)
- Oxycontin SRT (oxycodone)
- PMS-Morphine Sulfate SR (morphine sulfate)
- Ratio-Morphine SR (morphine sulfate)
- Roxanol SR (morphine sulfate)
- Zomorph (morphine sulfate)

users of other slow-release opioids (Box 1) be warned of the potential for dose dumping if they consume alcohol. Health Canada has also requested that manufacturers of long-acting opioids submit data on the safety of their products when consumed with alcohol to the agency within the next 6 months.

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