J. Med. Toxicol. (2012) 8:83–85
DOI 10.1007/s13181-011-0208-9

ARTICLES YOU MIGHT HAVE MISSED

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Published online: 26 January 2012

Keywords Drug smuggler · Cannabinoid receptors · Bisphosphonate · Vitamin K antagonists

Erenberg ES, Kamphuisen PW, Sijpkens MK et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. Circulation 2011;124:1573–1579.

Background: New generation anticoagulation agents are gaining popularity over the existing conventional vitamin K antagonists. Rivaroxaban (direct factor Xa inhibitor) and dabigatran (direct thrombin inhibitor) have less food and drug interactions and do not require regular INR monitoring. However, one major limitation is the lack of a specific reversal agent in case of hemorrhage or emergent surgery. In an animal study, prothrombin complex concentration (PCC) reversed the effect of rivaroxaban. Whether dabigatran anticoagulation can be reversed by PCC administration remains unclear.
Research Question: This study aims to evaluate the potential utility of PCC in reversing the anticoagulation effect of rivaroxaban and dabigatran in healthy volunteers.

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Methods: A double-blind, randomized, placebo-controlled, crossover trial was conducted with 12 healthy male volunteers. Each volunteer received either dabigatran or rivaroxaban for 3 days. After the last dose on day 3, subjects received an infusion of either PCC or normal saline. Blood was obtained at baseline, just prior to experimental treatment infusion, and then serially over 24 h for the following studies: prothombin time (PT), endogenous thrombin potential (ETP), activated partial thromboplastin time (aPTT), ETP lag time, thrombin clotting time (TT), and ecarin clotting time (ECT). After an 11-day washout period, each subject received the other anticoagulation agent following the above protocol.
Results: Compared to placebo, PCC completely normalized the PT prolongation and ETP decrease induced by rivaroxaban and sustained the normalization for 24 h. PCC did not reverse the anticoagulation effects (aPTT, ETP lag, TT, or ECT) by dabigatran. Several minor self-limited bleeding adverse events (epistaxis, gingival bleeding, and hematoma at IV site) were noted among the participants.
Conclusion: In 12 healthy volunteers, PCC readily reversed the anticoagulation effects of rivaroxaban but not the anticoagulation induced by dabigatran.
Critique: This is a first human trial of addressing the major limitation of the new class of anticoagulation drugs. Clinical applicability of the finding is limited by the small number of subjects, single procoagulation agent, study dose, and the use of surrogate marker of bleeding. However, the results of this study are encouraging that anticoagulation by rivaroxaban may be reversible with PCC.
Implication for Toxicologists: A growing number of patients with atrial fibrillation are being prescribed new generation anticoagulation drugs that eliminate the complexity of prescribing and taking warfarin. But for toxicologists, we are faced with a dilemma—how to reverse the action of these new

drugs for patients with major bleeding. Although the study is not definitive, it is a step forward towards a clinically relevant answer.

Benedetti F, Amanzio M, Rosato R et al. Nonopioid placebo analgesia is mediated by CB1 cannabinoid receptors. Nat Med 2011;17(10):1228–1230.

Background: Prior research in the neurobiology of pain has shown that placebos can activate endogenous opioids following conditioning with opioid and non-opioid analgesics. The endocannabinoid system is implicated in the placebo activation.
Research Question: To assess the effects of the CB1 cannabinoid receptor antagonist, rimonabant on placebo responses in opioid and non-opioid conditioned subjects
Methods: Six groups of healthy human volunteers underwent a pain challenge test with a tourniquet on four or five nonconsecutive days. Group 1 (control) did not receive any pharmaceutical treatment. Group 2 was given only rimonabant 90 min before the tourniquet test on days 2 and 4. Group 3 (opioid conditioned) received morphine on days 2 and 3 and received placebo on day 4. Group 4 underwent the same procedure as group 3, but received rimonabant with the placebo on day 4. Group 5 (non-opioid conditioned) underwent the same procedure as group 3, but received ketorolac to assess the placebo effect in non-opioid conditioned subjects. Group 6 underwent the same procedure as group 5, but received rimonabant with placebo on day 4.
Results: Rimonabant had no effect on pain tolerance in and of itself. Placebo increased pain tolerance in subjects previously treated with either morphine or ketorolac. Rimonabant blocked the placebo response in the NSAID group, but not the opioid group.
Conclusion: CB1 cannabinoid receptors play a role in the non-opioid placebo response seen with NSAID use.
Critique: This study does not establish the site of action of rimonabant nor does it account for other non-opioid, non-cannabinoid neurotransmitters involved in placebo effects. This study does suggest cannabinoid receptors may have a role in non-opioid-mediated pain control.
Implication for Toxicologists: This study provides additional evidence of the CB1 receptor's role in analgesia and highlights the potential for developing a new non-opioid analgesic, which may potentially decrease the demand for prescription opioids.

Schilcher J, Michaelsson K, Aspenberg P. Bisphosphonate use and atypical fractures of the femoral shaft. N Engl J Med 2011;364(18):1728–1737.

Background: Although bisphosphonates are commonly prescribed to patients with osteoporosis to reduce their risk of fractures, several studies suggest that bisphosphonates may increase the risk of stress fractures (atypical femoral fractures). However, these studies did not take into account other prevalent medications in this patient population.
Research Question: To investigate whether atypical femoral fractures are associated with bisphosphonates or other common medications.
Methods: This report utilized both an observational cohort and case–control study design. National health registries were accessed to identify cases of stress fractures, demographics, and medical information.

Observational cohort study: All women over 55 years of age were included in the cohort (1.5 million) based on data from Statistic Sweden. Age-adjusted relative risk (RR) and absolute risk of stress fractures were estimated from the calculated age-stratified incidence of stress fracture with and without bisphosphonates use.

Case–control study: The National Swedish Patient Register was accessed to identify patients with atypical femoral fractures ($n=59$) using a consensus definition provided by the American Society for Bone and Mineral Research. Two hundred sixty-three patients with non-stress fractures served as the control group. Information on medication history and their use (duration and last use) was obtained though the Swedish Prescribed Drug Register.
Results: Cohort study: Of 1.5 million women, 83,311 received bisphosphonates and 46 of 59 cases of stress fractures were found in this population. Bisphosphonates had an age-adjusted RR of 47.3 (95% CI 25.6–87.3) for stress fracture and corresponding absolute risk of five cases per 10,000 patient-years. Higher RR for stress fracture was also associated with two or more year of use (67.0, 95% CI 35.8–125.8) and time of last use less than 1 year (42.9, 95% CI 22.9–80.4).

Case–control study: Seventy-eight percent of the case patients received bisphosphonates compared to 10% of the control group, corresponding to multivariable-adjusted odds ratio of 33.3 (95% CI 14.3–77.8). The risk of stress fracture was 50-fold higher in patients with more than 2 years of use. Use of glucocorticoids or proton-pump inhibitors did not alter the association between bisphosphonate use and stress fractures.
Conclusion: Bisphosphonates use was highly prevalent among the patients with stress fractures. However, the absolute risk of developing stress fractures appear far smaller compared to the magnitude of benefits from preventing fractures in patients with osteoporosis.
Critique: The authors report an association between long-term (>2 years) use of bisphosphonates and stress fractures using a large population-based studies but a causal relationship is difficult to study from observational cohort or case–control study. Although a large number of patients with stress fractures were exposed to bisphosphonates, it is unclear if there was a dose-dependent relationship or an association to

the severity of osteoporosis itself. Interestingly, larger number of stress fractures occurred within 1 year of stopping the medication (42 out of 46 cases among the users) compared to the duration of bisphosphonate use (39 out of 46 cases). This brings to question why bisphosphonates were stopped and whether a similar association would be present if the drug was continued. Moreover, the Swedish Prescription Drug Register data is only available after 2005. It remains unknown if any other drug exposure prior to 2005 may have contributed to the overall finding. Finally, the study population consists of homogenous group of women that limits the generalizability of the findings to other more diverse population.

Implication for Toxicologists: Although there is an association between stress fracture and bisphosphonate use, it is difficult to determine a causal relationship. Patients should be made aware of the potential risk of stress fracture versus the benefit of bisphosphonates use.

Sormaala MJ, Salonen HM, Mattila VM et al. Feasibility of abdominal plain film images in evaluation suspected drug smuggler. Eur J Radiol. 2011.

Background: Suspected bodypackers often present to the hospital under police custody for evaluation of concealed drug contraband. Abdominal radiographs have long been considered the first-line diagnostic tool in this process, but have received little scrutiny of effectiveness. Complications with undue morbidity might occur in patients with undetected contraband.

Research Question: To evaluate inter-radiologist interpretation error and reliability of plain radiographs in detecting concealed substances in the gastrointestinal tract.

Methods: This is a retrospective chart review of abdominal radiographs for suspected bodypackers at a single institution during an 8-year period. The radiographs were reviewed by two separate study radiologists and interpreted as either clearly positive or negative for smuggled drugs. The two new reports and the original interpretations were compared. Customs was contacted to determine the number of drug packets retrieved from individuals with positive radiographs.

Results: During the study period, 224 suspected bodypackers underwent imaging with 279 radiographs (some patients with multiple radiographs). Two-hundred three (73%) were read as negative by all three radiologists and 35 (13%) were interpreted as positive by all three radiologists. In 41 (14%) of cases, there were disagreement among the radiologists. The kappa value for inter-observer variability was 0.7.

Conclusion: In 86% of cases, there was consensus among all three radiologists, but there was disagreement in 14% of cases. The authors recommend further study with low-dose CT to better assess equivocal studies as missing a single case may be consequential.

Critique: There are several limitations to the study. It was unclear if the two study radiologists were blinded to the original interpretation. The authors were unable to follow those subjects with a negative radiographic interpretation; thus, no mechanism for identifying the occurrence of false negatives. Subsequently, determining accurate sensitivity and specificity of abdominal plain films from this study is impossible. There is no comment on false-positive readings. Additionally, the authors do not provide any data to support their recommendations for using CT imaging.

Implication for Toxicologists: The study suggests that abdominal radiographs may be insufficient to screen bodypackers. Further studies are warranted to determine the optimum imaging that will assure the public health goals of both patient safety and prevention of illicit drug entry into the community.