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Cardiovascular disorders associated with naloxone monotherapy and in fixed-dose combination with opioids: Data from international safety surveillance

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ABSTRACT

Background: The widespread use of opioids has resulted in sharp rise of associated complications, particularly opioid-induced constipation (OIC). Opioid receptor antagonists have been proposed to treat OIC, but could precipitate rapid opioid withdrawal. As cardiovascular safety data are lacking, we assessed disproportionate reporting of adverse cardiac events associated with naloxone across large, international pharmacovigilance systems.

Methods: Post-marketing data from the World Health Organization (WHO) and FDA Adverse Events Reporting System (FAERS) were evaluated for naloxone and the synthetic opioids oxycodone and tilidine. The proportional reporting ratio (PRR), a measure of reporting frequency analogous to an odds ratio, was assessed. The primary outcome was reporting frequency of the MedDRA System Organ Class (SOC) 'Cardiac Disorders' for naloxone alone and in fixed-dose combination with opioids. Opioid mono-preparations served as quasi-experimental controls. A PRR greater than 2.0 was considered significant.

Results: In total, 14,827,374 million adverse drug event reports were reviewed. In WHO, there were 1757 reports of SOC cardiac disorders among 10,866 total reports for oxycodone (PRR 2.38 [95% CI 2.28–2.49, $\chi^2 = 1504$]). For oxycodone-naloxone, there were 43/453 reports of SOC cardiac disorders (PRR 1.45 [95% CI 1.09–1.92, $\chi^2 = 6.4$]). For the synthetic opioid tilidine there were 13/179 reports (PRR 1.13 [95% CI 0.67–1.91, $\chi^2 = 0.2$]) and for tilidine-naloxone, 30/505 reports (PRR 0.92 [95% CI 0.65–1.31, $\chi^2 = 0.2$]). In FAERS, the PRR for SOC cardiac disorders was 0.95 [95% CI 0.89–1.01, $\chi^2 = 2.1$] for naloxone (all administration routes) and 1.16 [95% CI 0.93–1.45, $\chi^2 = 1.3$] for naloxone (oral only). In comparison, the PRR was 1.66 [95% CI 1.63–1.69, $\chi^2 = 4278$] for oxycodone and 1.52 [CI 1.28–1.80, $\chi^2 = 1500$] for oxycodone-naloxone.

Conclusions: Available pharmacovigilance data do not suggest disproportionate reporting of adverse cardiovascular events for opioid antagonists used to treat OIC.

1. Introduction

Prescription and consumption of opioid analgesics has dramatically increased worldwide, with a particularly sharp rise in the United States [1,2]. With opioid use reaching historic highs, the frequency of adverse effects with these medications such as opioid-induced constipation (OIC) has risen in parallel. Current estimates indicate that nearly half of chronic pain patients on opioids experience OIC [3,4]. Opioid receptor antagonists mitigate this side effect, but have the potential to precipitate rapid opioid withdrawal with abrupt increase in blood pressure and heart rate. Sudden, unintended opioid withdrawal could therefore trigger adverse cardiovascular events including myocardial infarction, particularly in older subjects with coronary artery disease. A study of a large sample of patients on chronic opioids found that older age was a risk factor for OIC [5], creating a large population exposed to this theoretic cardiac risk. Furthermore, in a randomized controlled trial of alvimopan, a peripherally acting opioid receptor antagonist approved for OIC, an imbalance in cardiovascular events including myocardial infarctions was noted in comparison to placebo [6].

Beyond the single study of alvimopan, there is limited data available implicating abrupt opioid withdrawal to adverse cardiovascular complications. Moreover, randomized controlled trials of opioid antagonists may not be feasible in populations with low baseline cardiovascular risk and correspondingly low annual cardiovascular event rates [7]. Should a prospective trial be performed, it may be difficult to enrich the population through identification of opioid-dependent patients

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with established coronary artery disease. Lastly, there is the possibility of patient crossover since OIC would likely persist in the placebo arm. Given the biological plausibility of a potential cardiovascular danger posed by opioid antagonists and the paucity of randomized data, we analyzed pharmacoepidemiologic data for a signal of disproportionate reporting of adverse cardiovascular events associated with naloxone monotherapy and in fixed dose combination with opioids.

2. Methods

We evaluated all adverse event reports across drug surveillance databases for naloxone monotherapy (all administration routes) and naloxone in fixed-dose combination with opioids. Additionally, we evaluated adverse event reports associated with opioid monotherapy as a quasi-experimental negative control to determine the impact of the addition of naloxone to these agents. To capture adverse cardiovascular events we used the Medical Dictionary for Regulatory Activities (MedDRA) [8]. MedDRA is a clinically validated dictionary of adverse events, and is used by regulatory authorities for pre-marketing and post-marketing surveillance [9,10]. The MedDRA classifies adverse events by Systems Organ Class (SOC) pertaining to the major organ system affected by the reported adverse event. The term "SOC cardiac disorders" is a broad category that incorporates endocardial, myocardial and pericardial disorders, coronary artery disease, arrhythmias, heart failure, and other adverse cardiac signs and symptoms [11–13]. To assure broad capture of all potentially relevant adverse cardiovascular events related to opioid antagonist therapy we searched each database for events classified under "SOC cardiac disorders." This approach maximized sensitivity in capturing adverse cardiovascular events reported in association with the medications studied.

We used the proportional reporting ratio (PRR) to compare reporting of adverse events between drugs of interest. The PRR is defined as the proportion of spontaneous reports for a given drug that are linked to a specific adverse outcome divided by the corresponding rate for all other drugs combined [PRR = (event of interest drug / all events drug) / (event of interest all other drugs / all events all other drugs)] [14]. The PRR is analogous to an odds ratio with higher PRR values suggesting disproportionate reporting of the reaction of interest (eg. SOC cardiac disorders) relative to all other reported adverse reactions for that particular drug. A PRR is considered significant if it meets 3 empirically derived criteria: (1) an absolute PRR ≥ 2, (2) a χ^2 value ≥4 and (3) at least 3 unequivocal reports in the database analyzed [15,16]. The PRR is a validated screening tool for disproportionate reporting used by international regulatory authorities (eg. FAERS, European Medicines Agency — Eudra-vigilance system) [15,17]. The PRR has previously been utilized to assess differential reporting of adverse cardiac arrhythmic events among opioid agonists [18,19].

The Word Health Organization (WHO) international drug-monitoring program (VigiBase®) collects reports of adverse drug reactions from over 80 participating countries and is the largest pharamco-surveillance system in the world [20]. In addition, the system pools data from 10 countries with existing spontaneous adverse reaction reporting systems [21]. We evaluated individual case reports in the WHO database [21] to assess for reports of cardiac disorders associated with oxycodone (all administration routes) and oxycodone-naloxone in fixed dose combination. We also assessed tilidine, a low potency opioid similar to tramadol approved for use in Europe, as well as the tilidine-naloxone combination. All drugs were evaluated from market introduction through 2012 searching for reports classified under SOC cardiac disorders. Oxycodone and tilidine monotherapies served as quasi-experimental negative controls. Using count data from reports classified as SOC cardiac disorders and total case reports for each drug, we calculated PRR ratios for these medications.

The FDA Adverse Events Reporting System (FAERS) is a database of reported adverse events collected from patients, healthcare providers, and pharmaceutical companies through both the FDA-required post-marketing surveillance and the voluntary MedWatch® submission system [22]. Initiated in 1969, the FAERS system tracks individual safety reports, linking medications with unique case identifiers to eliminate multiple safety reports referring to the same adverse event. To complement our analysis of the WHO database, we analyzed cases in FAERS [23] to identify SOC cardiac disorders associated with naloxone, opioid monotherapies and fixed dose opioid combination products with naloxone. Analogous to our approach above, we assessed and calculated PRR values for SOC cardiac disorders for these medications in the FAERS database. For naloxone, we first assessed all administration routes composed of oral, sublingual, intravenous and intramuscular. Next, we evaluated oral naloxone separately as a proposed chronic treatment of OIC. In addition, we assessed oxycodone monotherapy, oxycodone-naloxone, buprenorphine, and buprenorphine-naloxone with opioid monopreparations serving as a quasi-experimental negative control versus the fixed dose combination product. Finally, we assessed cardiovascular disorders for alvimopan, an opioid antagonist previously found to have an excess number of cardiovascular events compared with placebo, as a quasi-experimental positive control.

3. Results

Between WHO and FAERS databases a total 14,827,374 million reports were evaluated. Fig. 1 displays a forest plot of the PRR values for SOC cardiac disorders for the opioid agonist monotherapies and in fixed-dose combination with naloxone in the WHO database. From 1998 to 2012 a total of 10,866 adverse drug reports (ADRs) for oxycodone were extracted, of which 1757 were categorized as SOC cardiac disorders. In the same timeframe, there were 414,531 reported SOC cardiac disorders among 6,104,511 total ADRs for all other medicinal products corresponding to a PRR of 2.38 [95% CI 2.28–2.49, $\chi^2 = 1504$] for oxycodone; above the significance threshold (2.0) conventionally assigned to the PRR measure. Following market introduction of oxycodone-naloxone, there were 453 ADRs of which 43 were categorized as SOC cardiac disorders. There were 290,430 reported SOC cardiac disorders and 4,428,967 total ADRs for all other medicinal products corresponding to a PRR of 1.45 [95% CI 1.09–1.92, $\chi^2 = 6.4$]. Following market introduction, 179 ADRs were recorded for tilidine of which 13 were SOC cardiac disorders compared to 502,664 reported SOC cardiac disorders of 7,831,403 total ADRs for all other medicinal products corresponding to a PRR of 1.13 [95% CI 0.67–1.91, $\chi^2 = 0.2$]. From market introduction of tilidine-naloxone, there were 505 total ADRs, of which 30 were reported SOC cardiac disorders compared to 497,684 reported SOC cardiac disorders out of 7,728,414 total ADRs for all other medicinal products corresponding to a PRR of 0.92 [95% CI 0.65–1.31, $\chi^2 = 0.2$].

Fig. 2 displays a forest plot of the PRR values for SOC cardiac disorders in the FAERS database. From 1984 to 2015, 6,995,971 ADRs were reported for all medicinal products of which 482,409 were cardiac disorders. During this period, there were 11,890 total ADRs for naloxone (all administration routes) and 778 reported SOC cardiac disorders corresponding to a PRR of 0.95 [95% CI 0.89–1.01, $\chi^2 = 0.1$]. For orally administered naloxone, there were 71 reported SOC cardiac disorders among 887 total ADRs corresponding to a PRR of 1.16 [95% CI 0.93–1.45, $\chi^2 = 3.2$]. There were 1118 total ADRs for oxycodone-naloxone of which 117 reported SOC cardiac disorders, corresponding to a PRR

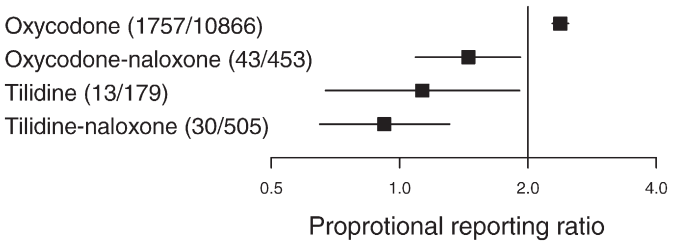

Fig. 1. Frequency of SOC cardiac disorders for oxycodone, oxycodone-naloxone, tilidine and tilidine-naloxone in WHO database.