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Research Paper

MSBIS: A Multi-Step Biomedical Informatics Screening Approach for Identifying Medications that Mitigate the Risks of Metoclopramide-Induced Tardive Dyskinesia

Dong Xu [a,*], Alexandrea G. Ham [b], Rickey D. Tivis [c], Matthew L. Caylor [a], Aoxiang Tao [a], Steve T. Flynn [b], Peter J. Economen [b], Hung K. Dang [b], Royal W. Johnson [b], Vaughn L. Culbertson [d]

[a] Department of Biomedical and Pharmaceutical Sciences, College of Pharmacy, Kasiska Division of Health Sciences, Idaho State University, Meridian, ID 83642, USA
[b] College of Pharmacy, Kasiska Division of Health Sciences, Idaho State University, Meridian, ID 83642, USA
[c] Idaho Center for Health Research, Kasiska Division of Health Sciences, Idaho State University, Meridian, ID 83642, USA
[d] Department of Pharmacy Practice and Administrative Sciences, College of Pharmacy, Kasiska Division of Health Sciences, Idaho State University, Meridian, ID 83642, USA

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ABSTRACT

In 2009 the U.S. Food and Drug Administration (FDA) placed a black box warning on metoclopramide (MCP) due to the increased risks and prevalence of tardive dyskinesia (TD). In this study, we developed a multi-step biomedical informatics screening (MSBIS) approach leveraging publicly available bioactivity and drug safety data to identify concomitant drugs that mitigate the risks of MCP-induced TD. MSBIS includes (1) TargetSearch (http://dxulab.org/software) bioinformatics scoring for drug anticholinergic activity using CHEMBL bioactivity data; (2) unadjusted odds ratio (UOR) scoring for indications of TD-mitigating effects using the FDA Adverse Event Reporting System (FAERS); (3) adjusted odds ratio (AOR) re-scoring by removing the effect of cofounding factors (age, gender, reporting year); (4) logistic regression (LR) coefficient scoring for confirming the best TD-mitigating drug candidates. Drugs with increasing TD protective potential and statistical significance were obtained at each screening step. Fentanyl is identified as the most promising drug against MCP-induced TD (coefficient: −2.68; p-value < 0.01). The discovery is supported by clinical reports that patients fully recovered from MCP-induced TD after fentanyl-induced general anesthesia. Loperamide is identified as a potent mitigating drug against a broader range of drug-induced movement disorders through pharmacokinetic modifications. Using drug-induced TD as an example, we demonstrated that MSBIS is an efficient in silico tool for unknown drug-drug interaction detection, drug repurposing, and combination therapy design.

1. Introduction

Metoclopramide (MCP) is an antiemetic and gastrointestinal (GI) agent, and the only medication approved by the U.S. Food and Drug Administration (FDA) for the indication of gastroparesis. The mechanism of action is its dopamine (DA) receptor antagonistic activity which suppresses the effects of DA and promotes the release of acetylcholine (Ach) (Wijemanne et al., 2016). The increase of Ach level improves the symptoms of gastroparesis by speeding up stomach muscle movement and stomach emptying. Its antiemetic effect is the result of DA and serotonin (5-HT_3) receptor inhibition in the nausea and vomiting centers of the brainstem.

In 2009, the FDA placed a black box warning on the chronic use of MCP due to the increased risks and prevalence of tardive dyskinesia (TD). The term TD refers to the classic tardive dyskinesia (CTD), characterized by involuntary and repetitive movements of the extremities, lip smacking, grimacing, tongue protrusion, rapid eye movement or blinking, puckering and pursing of the lips, or impaired movement of the fingers. These symptoms are rarely reversible and there is no known treatment. Since the development of TD is related to the duration of the MCP therapy, the FDA recommends that patients not use MCP longer than three months.

Despite of the severe neurotoxicity, the pathophysiology of MCP-induced TD is still not fully understood. The causality has been hypothesized to be the DA-Ach imbalance resulting from blockade of DA receptors (Stahl et al., 1982). Studies have shown that MCP and other DA antagonists can cross the blood-brain barrier (BBB) and cause DA-Ach imbalance in the striatum (Rao and Camilleri, 2010; Massara et al., 1985; Jolliet et al., 2007). Elevated Ach levels have been observed in the striatal region of the brain in animal models (Bymaster et al., 1986; Damsma et al., 1990; Schulze-Delrieu, 1981). As a result, anticholinergic (AC) medications have been employed to correct the DA-Ach imbalance and have had some success in treating various types of drug-induced movement disorders, including akathisia and dystonia (Greene et al., 1988; Qiu and Lim, 2011; Wei et al., 2012; Waln and

* Corresponding author at: Department of Biomedical and Pharmaceutical Sciences, College of Pharmacy, Kasiska Division of Health Sciences, Idaho State University, 1311 E Central Dr., Meridian, ID 83642, USA.
E-mail address: xudong@isu.edu (D. Xu).

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Jankovic, 2013). However, in the case of drug-induced CTD, symptoms may persist or even exacerbate after AC medication co-administration (Brotchie et al., 2011; Rana et al., 2013). The American Academy of Neurology (AAN) has drawn no conclusion on AC therapy for TD treatment (Khouzam, 2015; Bhidayasiri et al., 2013). In light of these conflicting reports, our hypothesis is that not all medications with AC activity have appropriate mitigating effects on MCP-induced TD, particularly on CTD. It depends on how well a medication modulates the drug-induced DA-Ach imbalance. If the imbalance continues due to either insufficient or excessive Ach antagonism exerted by the secondary medication, not only will the TD symptoms persist, but also they will likely deteriorate. Therefore, there is a need to develop a systematic and efficient approach to screen and identify concomitant medications that can restore the delicate DA-Ach balance, and mitigate or even prevent MCP-induced TD. Here we present a multi-step biomedical informatics drug screening approach (MSBIS) that leverages informatics on bioactivity and post-market drug safety data for rapid discovery of effective secondary medications in the context of mitigating drug-induced TD toxicity.

2. Materials and Methods

We have developed a multi-step informatics approach to screen and identify concomitant drugs for mitigating toxicity induced by the primary drug. The overall workflow of the approach is illustrated in Fig. 1. Each of the screening steps is described below.

2.1. Ach Modulating Activity Scoring

Anticholinergics are a class of drugs designed to provide therapeutic benefits in a variety of disease states through inhibiting muscarinic Ach receptors in the CNS and peripheral systems. However, many medications outside the anticholinergics drug class may also elicit AC pharmacologic responses through off-target interactions. 120 medications have been classified to possess AC activity by clinicians (Hester, 2011). In the first screening step, we considered all 120 medications that encompass traditional anticholinergics/antimuscarinics as well as a large number of medications that are not regarded as traditional anticholinergics/antimuscarinics.

Our approach leverages the ever-increasing wealth of publicly available bioactivity and drug safety data. ChEMBL (Gaulton et al., 2012), the largest bioactivity database in the world, contains >1.5 million small molecules, 10,000 receptors, and 14 million bioactivity records. We have developed TargetSearch, an in-house bioinformatics web service (http://dxulab.org/software) to mine the vast amount of ChEMBL pharmacological data for relevant drug-receptor interactions including off-target polypharmacy (Xu et al., 2017). Here we used TargetSearch to score the anticholinergicity of the 120 drugs. The molecular structures of the 120 drugs were retrieved from DrugBank (Knox et al., 2011) and used as TargetSearch queries. ChEMBL was searched for either known bioactivity between a medication and 5 muscarinic Ach receptor subtypes (M1 – M5) or unknown off-target interactions via inferred structure-bioactivity relationships. If a query medication was found to have similar structure and chemical features to a bioactive molecule in the ChEMBL database, and this bioactive molecule had known bioactivity data associated with any of M1 to M5 receptors, we could infer that the medication would share similar bioactivity on the same receptors. The widely used extended connectivity fingerprint (Morgan) algorithm (Yildirim et al., 2007) was employed in the bioinformatics screening. A 10 μM bioactivity cutoff was used to ensure a higher level of confidence in identifying known and inferred relationships. When a hit was found, the receptor-specific AC scores were calculated from the Tanimoto coefficients reported by TargetSearch (Willett, 2006), which represents the drug's Ach modulating activity. The receptor-specific AC scores are in a [0, 1] range. A receptor-specific AC score of 1 indicated a medication had known bioactivity to a muscarinic Ach receptor whereas a score of 0 meant no known or inferred interaction was found. A score between 0 and 1 indicated that an inferred interaction was identified. The individual receptor subtype AC scores were averaged to give the mean AC score of a medication. This computational approach, illustrated in Fig. 2, essentially accounts for the pharmacodynamic interactions of a drug with muscarinic Ach receptors. It is fast, systematic, and has been shown to effectively capture drug off-target polypharmacy (Keiser et al., 2009) and measure drug-induced AC toxicity burden (Xu et al., 2017).

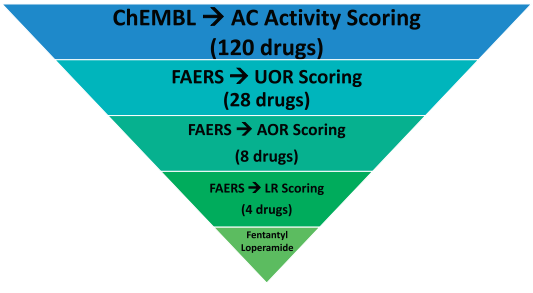

Fig. 1. The workflow of the MSBIS drug screening approach.

2.2. FDA Adverse Event Reporting System (FAERS)

An in-house FAERS relational database (January 2004 – June 2015) was used to detect and evaluate the drug-drug interactions between MCP and a secondary medication that lead to a decrease in MCP-induced TD incidences. FAERS is a public database for reporting adverse drug reactions (ADRs). It is one of the largest repository of ADR reports in the world, containing information voluntarily submitted by healthcare professionals, manufacturers, lawyers, and consumers in the United States (US) and other countries (Weiss-Smith et al., 2011). FAERS has been widely used in many post-marketing pharmacovigilance and drug safety research studies (Yue et al., 2014; Lorberbaum et al., 2016; Cortes et al., 2015; Kimura et al., 2015; Deepak et al., 2013; Oshima, 2011; Piccinni et al., 2011; Zhao et al., 2013).

To remove confounding by other TD-causing medications, an exclusion list of 26 TD-related drugs was compiled for this study. The drug exclusion list used in our FAERS queries is described in the Supplemental Materials.

2.3. Unadjusted Odds Ratio (UOR) Scoring

Based on data collected from FAERS, we calculated the UOR scores for each of the 28 selected drugs to assess the preliminary MCP-induced TD risk mitigating potential. The UOR (also known as reporting odds ratio) is a widely used method in adverse drug event signal detection (Rothman et al., 2004). It has been employed extensively in many published studies based on FAERS data (Zhao et al., 2013; Fujimoto et al., 2014; Hoffman et al., 2013; Yoshimura et al., 2013). A UOR (>1.0) indicates an increase of adverse drug events whereas a UOR (<1.0) signals a reduction of adverse drug events. Here we applied a much more stringent UOR cutoff (<0.09) to identify drugs with strong TD-mitigating indication.

The UOR score is defined as $\frac{a/b}{c/d}$, where *a, b, c,* and *d* are the number of safety reports under a background of MCP treatment, in which patients had undergone additional drug treatment ('Drug B') leading to a specified outcome: *a* is the number of safety reports in patients received drug B, such as a drug with AC activity, and had the TD adverse event; *b* is the number of safety reports in which patients received drug B and did not have the TD adverse event; *c* is the number of safety reports in which patients did not receive drug B and had the TD adverse event; and *d* is the number of safety reports in which patients did not receive drug B and did not have the TD adverse event (Table 1).

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