COMPUTER METHODS AND PROGRAMS IN BIOMEDICINE 113 (2014) 15–22

journal homepage: www.intl.elsevierhealth.com/journals/cmpb

Potential drug–drug interactions in pediatric outpatient prescriptions for newborns and infants

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ARTICLE INFO

Article history:
Received 24 June 2013
Received in revised form
20 July 2013
Accepted 21 July 2013

Keywords:
Adverse drug reactions
Drug–drug interactions
National Health Insurance
Information technology
Patient safety

ABSTRACT

Objectives: To surveyed the quantities, types, and related information of potential drug–drug interactions (DDIs) and estimate the off-label use percentage of pediatric outpatient prescriptions for newborns and infants from the National Health Insurance Research Database (NHIRD) of Taiwan.

Background: Adverse drug reactions (ADR) may cause morbidity and mortality, potential drug–drug interactions (DDI) increase the probability of ADR. Research on ADR and DDI in infants is of particular urgency and importance but the related profiles in these individuals are not well known.

Methods: All prescriptions written by physicians in 2000 were analyzed to identify potential DDIs among drugs appearing on the same prescription sheet.

Results: Of a total of 150.6 million prescription sheets, with 669.5 million prescriptions registered in the NHIRD of Taiwan, six million (3.99%) prescription sheets were for 2.1 million infants with 19.4 million (2.85%) prescriptions. There were 672,020 potential DDIs in this category, accounting for 3.53% per prescription; an estimated one DDI in every three patients. The interactions between aspirin and aluminum/magnesium hydroxide were most common (4.42%). Of the most significant drug–drug interactions, the interaction of digoxin with furosemide ranked first (20.14%), followed by the interactions of cisapride with furosemide and erythromycin (6.02% and 4.85%, respectively). The interactions of acetaminophen and anti-cholinergic agents comprised most types of drug–drug interactions (6.62%).

Conclusion: Although the prevalence rates of DDIs are low, life-threatening interactions may develop. Physicians must be reminded of the potential DDIs when prescribing medications for newborns and infants.

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http://dx.doi.org/10.1016/j.cmpb.2013.07.016

1. Introduction

1.1. Background

Drug–drug interaction (DDI) is an important factor that may cause treatment failure or the development of side effects while the following adverse drug reaction (ADR) is major cause of increased mortality and morbidity. Fatal ADRs rank as the fourth to sixth leading causes of death in inpatients [1]. The death because of medical errors exceeded the number attributable to the eighth leading cause of death in the United States [2]. ADRs cause an estimated 5–6.5% of hospitalizations [1,3], and 2.5–4.4% of these originated from DDIs [4]. An estimated 1.46–35% outpatients may develop ADRs, and 13% of these cases may have serious drug reactions [5,6]. The findings of an investigation on DDIs using a sample database from the National Health Insurance Research Database (NHIRD) of Taiwan revealed the prevalence of potential DDIs to be 30%. Of all the potential DDI pairs, 9.9% of the pairs received a level 1 clinical significance classification, representing 3% of all prescriptions [7].

A systematic review of studies on ADRs in inpatient and outpatient children, and on ADRs causing hospital admissions indicated that the overall incidence of ADRs was 9.53% in inpatients, and severe reactions accounted for 12.29% of the total hospital admissions. The overall rate of pediatric hospital admissions due to ADRs was 2.09%. 39.3% of the ADRs causing hospital admissions were life-threatening reactions. In outpatient children the overall incidence of ADRs was 1.46% [6].

Not every healthcare provider can distinguish potential DDIs from ADRs, and take corrective measures accordingly. In a survey study, Glassman and his colleagues found that only 44% (ranging from 11 to 64%) of clinicians have correctly identified all drug–drug pairs [8]. A clinician's understanding of DDI can decrease the likelihood of ADR, safeguard patient safety, and avoid associated medicolegal problems.

1.2. Drug interactions and off-label medication used in infant

Research on ADR and DDI in infants, children and adolescents is of particular urgency and importance because this vulnerable group displays developmental, physiological, and psychological differences from adults. However, the DDI profiles in these individuals are not well known because related studies are lacking. Newborns and infants are more susceptible to diseases therefore parents and healthcare providers usually pay more attention to this population. Knowledge of their DDI profiles is, therefore, necessary to avoid subsequent ADRs when prescribing medications.

Before any medicine is authorized for use in humans, the product must have undergone clinical trials to ensure that it is safe, of high quality, and effective. However, medicines may not have received the same trials for use in children due to ethical and economic issues. Therefore, few newly developed medications included clinical trials on pediatric populations, and there is an absence of suitable, authorized medicines for children's use. As a consequence, the use of drugs outside the terms of the marketing authorization, known as off-label use, is quite common in pediatric pharmacotherapy. Studies have also revealed that the percentage of off-label drug use significantly associated with the risk of ADR [9,10].

The present study surveyed the quantities, types, and related information of prescriptions with potential DDIs for newborn and infant outpatients, and also evaluated off-label drug use related to DDI over a one year period.

2. Methods

2.1. Ethic statement

The confidentiality assurances were addressed by abiding the data regulations of the Bureau of National Health Insurance (BNHI), and institutional review board approval was waived.

2.2. Study population and National Health Insurance System in Taiwan

The population of Taiwan is 23,162,123 [11] with 23,074,487 insured by the National Health Insurance (NHI) program [12], a compulsory national health insurance system first implemented in 1995, and representing a nearly 99.6% enrollment rate. Several dozens of millions of health service claims are sent to the BNHI monthly where these undergo quality assurance checks by administrative staffs and are approved for payment under peer-review in a randomized sampling basis [13].

NHI claims for all prescriptions (including inpatients and outpatients) written by physicians (including general practitioners, specialists, dentists, and traditional Chinese physicians) are recorded in the National Health Insurance Research Database (NHIRD). A monthly updated NHI drug formulary forms the basis of reimbursements for hospitals and clinics, and over 21,000 pharmaceutical references have been validated by the Food and Drug Administration of the Department of Health. Due to redundancy of the pharmaceutical references, the lists of drugs have been re-classified according to the same formulations, regardless of the types of preparations. The revised drug formulary has 1600 pharmaceutical formulations. Healthcare facilities in Taiwan are classified into four types: medical centers, regional hospitals, local hospitals, and private practice clinics. They are defined by the scales, numbers of beds, and quality of medical and nursing care. For example, medical center should equip more than 500 beds with 22 clinical specialties while regional hospital should equip more than 250 beds. The categorizing task is managed by the Taiwan Joint Commission of Hospital Accreditation, a quasi-official body supported by the Department of Health of Executive Yuan of Taiwan. The rates of reimbursements differ due to the differing types of organizations which provide financial support to the hospitals.

The target study populations are newborns and infants. Newborns are those whose age younger than one month old while infants are age younger than 12 months old.