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Estimation of total prescription weights of active pharmaceutical ingredients in human medicines based on a public database for environmental risk assessment in Japan

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ABSTRACT

The distribution of active pharmaceutical ingredients (APIs) in prescription medicines for human consumption in Japan was estimated using the public database of the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB). From the latest NDB, 2058 APIs were identified, and the prescription weight exceeded 1 tonne/year for 711 APIs. Of these, 298 APIs were selected for further analysis after removing 413 APIs that were not covered by current environmental risk assessment (ERA) directives or were combination products. Among the 298 APIs, 43 were relatively newly branded APIs that have been available on the Japanese market since 2001 or later and have no generic drugs, and only 5 of the branded APIs are used by more than 1% of the population. When prescription data from the 47 prefectures in Japan were analyzed, prescription weights for 257 of the 298 APIs were the highest in Tokyo, probably because of its large population. Though it has both advantages and limitations, this novel method based on a non-profit public database can provide a transparent, unbiased and cost-effective solution for the estimation of the environmental exposure of generic and branded human medicines distributed with prescriptions in Japan.

1. Introduction

Information on the manufacturing amount or sales statistics of human medicine is imperative for the prediction of the total amount of APIs emitted to the environment and for the estimation of the expected introduction concentration (EIC) or the predicted environmental concentration (PEC) as indicated in current directives for environmental risk assessment (ERA) of human medicines in the US (FDA, 1998), EU (EMA, 2006) and Japan (MHLW, 2016a). In Japan, however, information on the manufacturing amount is not generally made public by pharmaceutical companies, and sales statistics provided by marketing research companies are not available for free, and processes for the investigation and data sources are not always transparent. Especially when a patent of an API marketed by a single pharmaceutical company is expired and generic drugs containing the same API provided by multiple manufacturers are commercially available on the market, it becomes more difficult to estimate the total amount of the API derived from multiple commercial products.

The National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB) was initiated by the Ministry of Health, Labour and Welfare (MHLW) in 2009 to provide “big data” for electronic prescription-derived information on various health care services provided by the National Health Insurance in Japan, and the prescription volumes of human medicines are described in the NDB (Okamoto, 2014). Because the public health insurance system for the whole nation is well established and the level of digitized prescriptions is high in Japan, the NDB contains more than 95% of all health insurance claims in Japan, which makes the NDB quite a useful and

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reliable data source for policymakers and researchers (Ministry of Health, Labour & Welfare (MHLW, 2017a). Since 2011, the NDB, which includes detailed personal information, has been disclosed to a limited number of researchers due to security reasons, and a popularized public database is required for effective utilization by citizens. Under these circumstances, MHLW, after extracting summary data from the NDB (MHLW, 2017a), published the first version of NDB Open Data Japan (NDB-ODJ) on the Internet in October 2016 as a simplified comprehensible database for free use by the general public, which motivated us to apply the NDB-ODJ to the estimation of the total prescription weight of APIs in human medicines in Japan as a point of departure for the prediction of the environmental concentration for an ERA. An updated version of the NDB-ODJ is supposed to be published every year since its inception in 2016, and the second version of the NDB-ODJ was used for our estimations in the present study. Japan consists of 47 prefectures, and the NDB-ODJ provides not only the total number of prescriptions in Japan but a separate number for each of the 47 prefectures, which allowed us to investigate the regional diversity in prescription weights along with other basic statistics.

In this study, we attempted to estimate annual distribution of active pharmaceutical ingredients (APIs) in prescription medications for human use in Japan to obtain a point of departure for the prediction of environmental concentrations in an ERA.

2. Material and methods

2.1. NDB-ODJ and National Health Insurance drug price list

The second version of the NDB-ODJ was issued in September 2017, and statistics for the number of prescriptions were provided as fundamental spreadsheets that sum the claim data up to the 100 most-prescribed drugs in each of the 179 therapeutic categories during fiscal year 2015 in Japan, from April 2015 to March 2016, and the specific health checkup data of fiscal year 2014, from April 2014 to March 2015 (MHLW, 2017b). Prescriptions for both outpatients and inpatients were combined in our analysis. While formulations are divided into 3 categories, i.e., oral dose, injection and external use, in the NDB-ODJ, we summed the total weight regardless of the categories when the unit of strength (dosage level) was given as the weight. When the content per formulation was given as the volume, the volume was converted into weight, assuming a specific gravity of 1. When content per formulation was given in units that could not be converted into weight (i.e., %, unit, times or Bq), the formulation was excluded from our analysis. Combination products including multiple APIs in the same formulation were also excluded because only the number of prescriptions for the combination products were provided and no information on the dosage levels of all APIs in the combination products was provided in either the National Health Insurance drug price list or the NDB-ODJ. The drug statistics are listed separately by commercial name, dosage level, formulation, drug prices and status of patent (generic or branded) with the corresponding codes used in the National Health Insurance drug price list (WHO, 2012).

The code in the National Health Insurance drug price list was used to identify the API and dosage level for each commercial formulation listed in the NDB-ODJ, because the NDB-ODJ provides commercial drug names and does not identify APIs. The NDB-ODJ and National Health Insurance drug price list were consolidated into one database by Microsoft Access (2016) using the code in the National Health Insurance drug price list as a linker. In the consolidated table, the content (weight) of a target API in a formulation included in the National Health Insurance drug price list was multiplied by the number of prescriptions of the commercial product including the API with the same code in the NDB-ODJ to determine the total weight of the API in the sum of all prescriptions of a commercial product. Once the annual total weight of the target API in one commercial product at one dosage level in one formulation was determined, we then summed the annual total weight of the target API used for any commercial brand, formulation or dosage level, regardless of patent status or business model such as co-marketing (multiple commercial brands distributed by multiple companies) or co-promotion (single commercial brand promoted by multiple companies).

2.2. Selection of APIs for further analysis

Initially, APIs with an annual prescription weight of 1 metric tonne or more were selected to align with thresholds for submission in the EU's Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) (EC, 2016) and Japan's Chemical Substances Control Law (CSCL) (Ministry of Economy, Trade and Industry (METI), 2016), although neither REACH nor CSCL are really relevant for pharmaceuticals. We then discarded the APIs that are not applicable to ERA based on current ERA directives in the US (FDA, 1998), EU (EMA, 2006) and Japan (MHLW, 2016a). The categories of discarded APIs for ERA included vitamins, electrolytes, amino acids, peptides, proteins, enzymes, hormones, carbohydrates, lipids, alcohols, vaccines, gas/inhalation anesthetics, natural products derived from plants (i.e., herb, seaweed and beans), animals (i.e., blood, serum, tissue and milk), bacteria and minerals, and biotechnology-derived pharmaceuticals defined in ICH S6(R1) (ICH, 2011). Finally, we classified the APIs into 2 categories, i.e., “new API” and others, to investigate the relationship between drug history on the Japanese market and the prescription weight. Drugs were assigned to the new API category in our analysis when the API was commercially available on the Japanese market for the first time in the 21st century (2001 or later) and no generic drugs containing the same API are available. As in the US or EU, branded drugs are exclusively provided by brand-name pharmaceutical companies, and no generic drug can be legally introduced to the market as long as the patent of the branded drug is still effective in Japan. Generic drugs are provided by single or multiple generic manufacturers and can be introduced to the market, with or without branded drugs, after the patent of the branded drug expires; however, generic drugs are not always available even after expiration of the patent of the branded drug due to various business reasons, and in such case, only “old” branded drugs are present in the Japanese market. Our definition of the new API category allowed us to exclude old branded drugs without effective patents.

2.3. Fraction of the population receiving the drug (Fpen)

For the APIs with a prescription weight of 1 tonne or more, the penetration factor (Fpen), defined as the proportion of the population being treated daily with the API, was determined based on the annual number of prescription in the NDB-ODJ divided by 365 days and the total population in Japan of 127 million. Numbers of prescriptions are used for calculation of Fpen assuming the case where an individual receives a single prescription in one day and therefore Fpen will be overestimated in cases of multiple prescriptions/individual/day such as BID (bis in die) or TID (ter in die).

2.4. Statistics other than prescription weight

The prescription weights in each of the 47 prefectures were ranked for the APIs with total prescription weights in Japan of 1 tonne or more, and rankings were also prepared for the prescription weights divided by the population, land area, number of doctors and pharmacists, total per capita income, water supply quantity or precipitation. The population (2016), land area (2015) and annual precipitation (2015) data were based on e-Stat, the portal site of the Official Statistics of Japan promoted by the Statistics Bureau in the Ministry of Internal Affairs and Communications (MIAC) (MIAC, 2018). The amount of rainfall (m^3) was calculated by multiplying the annual precipitation (mm) by the land area (km^2). The number of doctors or pharmacists (2016) was