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Agreement of label information of cardiovascular drugs in pregnancy among Korea, the USA, the UK, and Japan

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ABSTRACT

Drug label is a common source of information; however, the content varies widely. This study aims to evaluate label information on cardiovascular drugs regarding pregnancy for their similarities in Korea, USA, UK, and Japan. Study drugs were selected as following (1) cardiovascular drugs according to the WHO ATC code (C01–C09) and (2) drugs currently marketed in all four countries were included. Evidence level was classified into five categories ('Definite', 'Probable', 'Possible', 'Unlikely', and 'Unclassified') and recommendation level was classified into four categories ('Contraindicated', 'Cautious', 'Compatible', and 'Unclassified'). Frequency and proportion were presented. Percent agreement and kappa coefficient with 95% confidence interval (CI) were calculated using SAS ver. 9.3. Total of 50 cardiovascular drugs were included. 'Unclassified' was represented the most in Korea, followed by Japan and UK (58%, 54%, and 46%, $p < 0.05$). For recommendation level, the majority of drugs in all four countries were classified as 'contraindicated' or 'cautious'. Japanese labels had the largest proportion of 'contraindicated' level (62%), and Korea and UK followed (58%, 44%, $p < 0.05$). Only in the USA, 10.0% of the drugs were 'compatible' whereas, there were none in Korea, UK, and Japan ($p < 0.01$). Korea and Japan showed a substantial agreement in evidence and recommendation level (kappa = 0.69, 0.67). Labels of cardiovascular drugs in pregnancy differed widely. Reliable safety information in pregnancy should be provided through regular updates.

1. Background

Safety regarding the use of prescription drugs during pregnancy became a major concern since the thalidomide tragedy resulting in birth defects in 1960s (Lagoy et al., 2005; Rajkumar, 2004). Because it is considered unethical to conduct clinical trials in pregnant women, well-controlled human studies are lacking. Therefore, little is known about new drugs regarding their congenital anomalies and other birth outcomes (Johnson et al., 2013). According to Andrade et al. (2004), 64% of pregnant women were using one or more medications at the time of delivery. Such prevalent use of drugs during pregnancy requires careful review of benefit and risk prior to the treatment initiation.

Hypertensive disorders are the most common complications during pregnancy and are crucial factors in maternal and perinatal morbidity and mortality (Gifford et al., 2000). Hypertension complicates 5–7% of all pregnancies (Lindheimer et al., 2009) and it is increasing due to the delay of childbearing as well as the increase of obesity, which is a major risk factor for hypertension. Unlike hypertension in non-pregnant individuals, hypertension in pregnancy should be treated differently considering both benefit and risk (Sibai, 2001). Despite the degree of substantial utilization and experience with antihypertensives, there is still uncertainty with regard to the safety of antihypertensives. Once patients with these conditions get pregnant, the safety of the drugs in pregnancy – both for mother and fetus – becomes important.

Nowadays, with convenient access to large amount of information on healthcare including medicines, patients may easily search online for their drugs of interest. Label information is one of the handy sources for safety profile on drugs utilized by healthcare professionals and patients. It is developed and structured in various ways in different countries; therefore, the content also varies widely (FDA; Lindheimer et al., 2009; Sibai, 2001). A previous study conducted by (Reggi et al., 2003), showed that the label information differed considerably among 26 countries in terms of indication, side effects, and precautions. Another comparative study

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also demonstrated differences of safety information in drug label among the USA, the UK, and Japan. The discrepancies between the information provided by each country may cause confusion among healthcare professionals and patients; thus, evaluation of the consistency of various information sources is essential. Therefore, we aimed to evaluate the agreement of label information of cardiovascular drugs in pregnancy among Korea, the USA, the UK, and Japan.

2. Data and methods

2.1. Data sources

For Korean label information, EZDrug (http://ezdrug.mfds.go.kr/index.jsp/) by Korea Ministry of Food and Drug Safety (MFDS) was searched. The sections called 'Contraindications' and 'Pregnancy and Lactation' were reviewed, and then other relevant information was also referred. Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm) and DailyMed (http://dailymed.nlm.nih.gov/dailymed/about.cfm) were searched for the USA labels. The sections called 'Contraindications' and 'Pregnancy' under 'Use in specific population' were reviewed. For the UK, EMC (http://www.medicines.org.uk/emc/) was searched and 'Pregnancy and Lactation' in Summary of Product Characteristics (SPC) was reviewed. For Japan, English drug name was first translated using weblio (http://ejje.weblio.jp), and then the Japanese term was used for the search in PMDA (http://www.info.pmda.go.jp/). The section called 'Pregnant and Lactating women' was reviewed.

2.2. Selection of study drugs

Drugs were selected based on the WHO ATC code and their market availabilities in four countries. Among 350 single agents with ATC code C01–C09, drugs that had approved products in all four countries were identified ($N = 52$). Betaxolol was excluded because it was only available as ophthalmic solution which is indicated for glaucoma. Indomethacin, which is an NSAID used for anti-inflammatory action, was also excluded. Total of 50 drugs was included in the analysis. Safety information regarding pregnancy is searched in product labels. Selected drug classes include cardiac therapy, antihypertensives, diuretics, peripheral vasodilators, vasoprotectives, beta blocking agents, calcium channel blockers, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), and renin inhibitors (Table 1).

2.3. Definition of evidence and recommendation categories

The definitions of evidence and recommendation level are developed based on levels of evidence (Sackett et al., 2000). For example, pre-clinical data such as animal studies are considered to be at the bottom the ranking pyramid. Evidence level was divided into five categories, 'Definite', 'Probable', 'Possible', 'Unlikely', and 'Unclassified'. 'Definite' indicates that systematic reviews, well-controlled clinical studies, or pharmacoepidemiologic studies clearly demonstrated the evidence of fetal risk. 'Probable' means risk has been reported by adverse event reports, spontaneous adverse event reporting system, and case reports; however, it has not been confirmed with clinical studies. For example, cases of fetal harms such as anomaly or extrapyramidal side effects are reported, but due to small number of the cases, it is difficult to conclude the causality with statistical certainty. Evidence level of 'possible' is when human studies have failed to demonstrate a risk; yet, animal reproduction studies have shown an adverse effect on the fetus. 'Unlikely' indicates that both human and animal studies failed to demonstrate a risk to the fetus. Drugs with lack of information regarding pregnancy and fetal risk were categorized into 'unclassified' group.

Recommendation level is divided into four categories, 'Contraindicated', 'Cautious', 'Compatible', and 'Unclassified'. Drugs that should not be used in pregnancy are defined as 'contraindicated' drugs. 'Cautious' is for drugs with potential fetal risk, but the potential benefit may outweigh the risk. For 'compatible' drugs, which are relatively safe in pregnancy, guidelines on recommended doses are also provided. If label has no information on pregnancy or includes general phrases such as "Consult your doctor or pharmacist before using..." it is categorized into 'unclassified' group.

2.4. Categorization of grade by two independent reviewers

Each reference was reviewed by two different reviewers independently using defined evidence and recommendation level. The evidence was evaluated according to the defined criteria and was assigned to one of the five categories. The recommendation was also evaluated and assigned to one of the four categories. Any disagreement was resolved by a third party.

2.5. Statistical analysis

We calculated the frequency and percentage for each category of evidence level and recommendation level. Statistical significance was assessed using the Chi-square test or Fisher's exact test with Bonferroni correction. We also calculated the percent agreement and kappa coefficient with 95% confidence interval (CI). According to Landis and Koch (1977), kappa coefficient was interpreted as one of the following six degrees of agreement; poor, slight, fair, moderate, substantial, and almost perfect. For all statistical analysis SAS ver. 9.3 was used and p-value < 0.05 was regarded as statistically significant.

3. Results

Among total of 50 study drugs, none of the drugs had evidence level of 'definite' in all four countries, indicating the lack of well-controlled human studies and systematic review demonstrating a risk to the fetus in pregnancy. Out of the five categories of evidence level, 'unclassified' was represented the most in Korea, the UK, and Japan (58%, 46%, and 54%, $p < 0.05$). For the USA, evidence level of 'possible' comprised 54% which is followed by 'unclassified' (26%) (Table 2).

Distribution of recommendation level showed similar pattern to that of evidence level. Japan and Korea had majority of the drugs categorized as 'contraindicated' (62% and 58%, $p < 0.05$). This corresponds with the distribution of evidence level indicating that drugs with insufficient evidence tend to be classified in 'contraindicated' group. Recommendation level of 'cautious' represented 78% and 52% of all 50 drugs in the USA and the UK respectively. With an exception of the USA where 10% was classified as 'compatible', none of the analyzed drugs were 'compatible' with pregnancy in Korea, Japan, and the UK (Table 3).

Percent agreement of evidence level was the highest between Korea and Japan (82%) and kappa coefficient was 0.69 (substantial agreement) (95% CI = 0.51–0.87). Recommendation level of Korea–UK showed percent agreement of 68% with kappa coefficient 0.50 (moderate agreement) (95% CI = 0.32–0.69) and UK–Japan showed percent agreement of 64% with kappa coefficient 0.45 (moderate agreement) (95% CI = 0.26–0.64). The other three pairs of countries, Korea–USA, USA–UK, and USA–Japan had similar percent agreements and kappa coefficients (54%, 0.33-fair; 58%, 0.42-moderate; 52%, 0.29-fair). Also, for recommendation level, Korea and Japan had the highest percent agreement and kappa coefficient