Regulatory Toxicology and Pharmacology 71 (2015) 478–483

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Increased use in propofol and reported patterns of adverse events among anesthetics in Korea

Hyo-Ju Park [a,1], Ju-Young Shin [a,1], Mi-Hee Kim [a], Byung-Joo Park [a,b,*]

[a] Korea Institute of Drug Safety and Risk Management, Seoul 110-750, South Korea
[b] Department of Preventive Medicine, Seoul National University College of Medicine, Seoul 110-744, South Korea

ARTICLE INFO

Article history:
Received 15 September 2014
Available online 7 February 2015

Keywords:
Propofol
Anesthetic
Consumption
Adverse drug reactions (ADRs)

ABSTRACT

Background: Propofol is an addictive drug, and the problem of its abuse and dependence has occurred. To compare the safety profiles of propofol and other similar anesthetics such as diazepam, lorazepam, and midazolam, we evaluated their uses and related adverse drug reactions (ADRs) using Korean Adverse Event Reporting System (KAERS) data.
Methods: The domestic consumption data and the ADR reports of four anesthetics from 2008 to 2012 were retrieved. ADR proportions were calculated using defined daily dose/1000 inhabitants/day (DID) for the denominator. The patient's characteristics were compared among the four drugs statistically, and the types of ADRs were analyzed.
Results: The consumption and ADR reports increased during the study period, particularly in the cases of propofol and midazolam. Lorazepam showed the highest overall and serious ADR proportions (220.81 reports/DID, 58.47 reports/DID, respectively); however, with respect to death proportion, propofol was the first (19.21 reports/DID). Also, ADRs related to drug addiction were mainly observed in the propofol group.
Conclusions: Four anesthetics were different with regard to the consumption and proportion or the type of ADRs. The use of propofol increased more than 2 times, and propofol showed the highest ADR proportions in death and drug addiction cases among the four anesthetics.

1. Introduction

Propofol is an intravenous sedative–hypnotic agent mainly used for the induction and maintenance of anesthesia or sedation since 1986 (Monroe et al., 2011). Propofol was originally developed as an induction agent, and became a frequently used anesthetic because it had rapid onset and elimination and hence, was relatively safe. Previous researches conducted in the US and Europe have described propofol as a safe anesthetic (Roussin et al., 2007; Eger, 2004). For these reasons, propofol has quickly replaced thiopental (Earley and Finver, 2013) and its use has expanded over time. Nowadays, propofol is widely used both in the operating rooms and in ambulatory care clinics. It is often used outside the operating room for pain relief in spinal disk disorder or for sedation in diagnostic procedures such as endoscopy and simple plastic surgeries.

However, with these advantages and its sedative and relaxing effect, propofol is an addictive substance, and therefore, the problem of its recreational abuse and dependence has arisen. Propofol's abuse potential and real cases related to propofol abuse have been suggested since 1997 (Soyka, 1997). In the US, Michael Jackson died of propofol-related abuse, and thereafter, the Alabama State Board of Health included propofol in Schedule IV of the Controlled Substances Act in 2012. Further, the Drug Enforcement Administration (DEA) has proposed a rule for the listing of propofol in the Control Substances Act (Stocks, 2011). In Korea, the abuse and misuse of propofol has recently become a social problem. Famous entertainers and health providers have been accused of abuse or illegal use of propofol, and some deaths related to propofol abuse have been reported. Accordingly, it was designated as a controlled substance in 2011. Despite regulatory management, propofol-related safety issues such as death, serious adverse drug events, and addiction have constantly been reported.

The Korean Adverse Event Reporting System (KAERS) is a spontaneous reporting system (SRS); thus, a general overview of all

* Corresponding author at: Korea Institute of Drug Safety and Risk Management, 136 Changgyeonggung-ro, Jongno-gu, Seoul 110-750, South Korea. Fax: +82 2 2172 6701.
E-mail address: bjpark@drugsafe.or.kr (B.-J. Park).
[1] Hyo-Ju Park and Ju-Young Shin contributed equally to this work.

http://dx.doi.org/10.1016/j.yrtph.2015.02.001
0273-2300/

types of adverse drug reactions (ADRs) is possible. However, the estimate of the ADR proportion may be incorrect because the patients' exposure to drugs is unknown. The ADR proportion is calculated by dividing the number of cases of ADR caused by each drug during a specific period by the number of patients exposed to the drugs causing ADR during the same period (Kokki and Närhi, 2003). In this context, evaluation of the safety aspects of the addictive anesthetics propofol and comparable agents, including midazolam, lorazepam, and diazepam, was conducted using the KAERS and domestic supply data of each drug.

2. Materials and methods

2.1. Study drugs

The study drugs selected were propofol, midazolam, diazepam, and lorazepam. Although propofol is the only non-benzodiazepine drug among the four drugs, they all have similar properties, which allow the comparison. All four drugs are administered by injection and have sedative effects, so they are used as anesthetics. Also, the four drugs are designated narcotics in many countries as well as in Korea due to their addictiveness and numerous ADRs related to drug addiction despite the national regulation. Based on these common characters and safety issues, the four drugs were chosen for this study.

The defined daily doses (DDDs) of diazepam, lorazepam, and midazolam are based on the anatomical therapeutic chemical/defined daily doses (ATC/DDD) Index 2013 from the world health organization (WHO, 2013). In the case of propofol, not listed in the WHO index, the DDD was calculated on the basis of the "dosages and administrations" of the Korean regulatory authority (Korean Ministry of Food and Drug Safety, MFDS, 2013) and a Finnish reference (Kokki and Närhi, 2003). Consequently, the DDDs of four anesthetics, propofol, midazolam, diazepam and lorazepam were determined as 700, 15, 10 and 2.5 respectively.

2.2. Drug consumption data

2.2.1. Korea Pharmaceutical Information Service (KPIS)

In order to estimate the consumption data of each drug, domestic supply data from Korea Pharmaceutical Information Service (KPIS) were used. KPIS was founded in 2007 with the purpose of managing current information on medicine, from pharmaceutical production to consumption. KPIS collects data by observing domestic and foreign business affairs and analyzes the annual medicine distribution information. KPIS provides data about pharmaceutical production, supply, and registration to the national health insurance every month (Korea Pharmaceutical Information Service, 2013). The data is de-identified and is available to the public upon written request. From KPIS, the domestic supply data of four anesthetics for the period from January 1, 2008 to December 31, 2012 were received. The patients' exposure to the drug represented in DID/1000 inhabitants/day (DID) is calculated by using the DDD of each drug and the consumption data. DID is a rough indicator of proportion of the population treated with certain drugs daily. For example, DID of ten means that 1% of the average population gets a certain drug daily (WHO, 2014).

2.3. ADR data

2.3.1. Korean Adverse Event Reporting System (KAERS)

KAERS is a system for the spontaneous reporting of ADRs that was developed in Korea in 1988 (Choi and Park, 2007), which has been managed by the Korea Institute of Drug Safety and Risk Management (KIDS) since 2012. Regional pharmacovigilance centers including general hospitals and associations of pharmacists, pharmaceutical companies, health providers, and even patients can submit ADR reports to KAERS via paper forms, telephone, or the KIDS website. Currently, most of the reports (99.6%) are from pharmaceutical companies or health providers, whereas, only 0.4% of the reports are from patients (Korea Institute of Drug Safety and Risk Management, 2014).

The ADR reports are submitted to the Regional Pharmacovigilance Centers (RPVCs) designated by KIDS and reviewed by the healthcare professionals at RPVCs. The healthcare professionals double check the completeness of ADR reports and evaluate the causality between drug and ADR. These thoroughly examined reports are submitted to KAERS database. The preferred terms (PTs) of WHO-ART named 'drug abuse' or 'drug dependence' are designated to certain ADRs when the healthcare professionals judge that the ADRs are caused by drug abuse or drug dependence. We analyzed these ADRs labeled with drug abuse or drug dependence to identify ADRs related to anesthetic misuse.

Each report contains information about patient demographics, concomitant drugs, ADRs, patient outcome, reaction severity, reporting centers, and the results of causality assessments. However, identifiable information such as patient name and registration number are completely removed from the record at the time of KAERS submission. The institutional review board (IRB) of KIDS approved the analysis with KAERS data. Currently, access of the KAERS data is limited to researchers at KIDS; however, it will be made available for the public starting in 2015.

Total ADRs and serious ADRs belonging to total ADRs of KAERS are defined by either the terminology of the International Conference on Harmonisation (ICH, 2013) or the WHO-ART critical term (Uppsala Monitoring Centre, 2013). Drug names are drawn from the ATC classification, and the terminology of ADRs is in accordance with WHO-ART. All ADRs caused by propofol, midazolam, diazepam, and lorazepam reported to the KAERS database from January 1, 2008 to December 31, 2012 were retrieved.

2.4. Calculation of ADR proportion

As mentioned above, the ADR proportion was calculated using the patient's exposure and the number of ADRs. The patients' exposure to a drug was expressed in DID, and the DID was calculated using the DDD and the consumption data of each anesthetic. The consumption data were the domestic supply data of KPIS from January 1, 2008 to December 31, 2012.

All system organ class (SOC) and preferred term (PT) of ADR reports were assigned by healthcare professionals, and the safety profile of anesthetics was analyzed using SOC and PT. The frequently reported ADRs were analyzed in terms of SOC and PT of WHO-ART by calculating the percentage of the numbers of drug-SOC or drug-PT pairs to the total pairs. In the case of SOC, the denominator was the total drug-SOC pairs of each anesthetic, and in the case of PT, denominator was total drug-PT pairs of the four anesthetics.

To identify ADRs by drug addiction for each anesthetic, we selected the PTs meaning drug addiction, and calculated the number of drug-corresponding PT pairs. The selected PTs were "drug abuse" and "drug dependence". The percentage of each drug–drug abuse or drug dependence pairs to total drug-PT pairs of total ADRs, serious ADRs and death cases was calculated.

2.5. Statistical analysis

The monthly DIDs of four drugs were calculated using KPIS consumption data and the annual numbers of ADR reports for study drugs were obtained from KAERS data during study period. To understand patient characteristics including gender, age, and the