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Adverse drug reactions for medicine newly approved in Japan from 1999 to 2013: Syncope/loss of consciousness and seizures/convulsions

Takashi Nagayama *

Non-Clinical Development, Science, Services & Planning, UCB Japan Co., Ltd., Shinjuku Grand Tower, 8-17-1 Nishi-shinjuku, Shinjuku-ku, Tokyo 160-0023 Japan

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ABSTRACT

Many approved medicines are used with their adverse drug reactions (ADRs) appropriately managed in the clinical setting based on their risks and benefits. In this survey, the correlation between human ADR (specifically syncope/loss of consciousness and seizures/convulsions) and safety signals reported in animal studies has been investigated for 393 Japanese medicines which were approved between September 1999 and March 2013. Clinically important drug-induced ADR, syncope/loss of consciousness and seizures/convulsions are reported in this paper. Of 393 medicines, 101 (25.7%) showed syncope/loss of consciousness and 105 (26.7%) showed seizures/convulsions. Syncope/loss of consciousness and seizures/convulsions were reported for many medicines affecting the central nervous system. The animal toxicity concordance ratio with syncope/loss of consciousness and seizures/convulsions was 4.0% (4/101) and 23.8% (25/105), respectively. The underlying cases of syncope/loss of consciousness attributed to hypotension, arrhythmia, hypoglycemia or acute toxic reaction was 16.8%, 5.0%, 4.0% or 4.0%, respectively. Mechanism of seizures/convulsions for the remaining 101 medicines was not identified except for four local anesthetics. This survey suggested that the careful attention to and understanding of medicine profiles is necessary for the appropriate use of recently approved medicines in Japan.

1. Introduction

A safe medicine is ideally exempt from adverse drug reactions (ADRs), but it is often difficult to distinguish ADR from the intended pharmacological action. During the drug developmental to select a candidate compound, every effort is made to provide safe medicines. *In vitro*, *in vivo* and *in silico* pharmacological studies, pharmacokinetics studies and also many animal toxicity studies are conducted before human use. Some compounds which exhibit unacceptable toxicity are discontinued from development prior to clinical studies. Many medicines on the market are used with their ADR appropriately managed in clinical settings based on the risk:benefit ratio. Unfortunately, there is no medicine without ADR. The aim of this survey was to clarify the correlation between ADR in humans and safety signals observed in animal toxicity studies, in order to contribute to constructing safe drug developmental strategies as well as ensuring the appropriate use of marketed medicines in the clinical setting. As it is difficult to analyze all ADRs, we selected two clinically important ADRs. Selected ADR for our survey were syncope and loss of consciousness, seizures and convulsions, hypertension and hypotension, arrhythmia, blood glucose increase and lipid metabolism disorders, changes in the number of leukocytes, dyspnea, hallucination and delusion, vision impairment, hearing impairment, dysgeusia and dysosmia, creatine kinase increase, BUN and creatinine increase, proteinuria and hematuria, dizziness, and vertigo. These parameters are clinically important and significant and some of them showed low translatability from animal toxicity findings. Investigational results for syncope/loss of consciousness and seizures/convulsions have been presented in this paper and investigational results for other ADR will be the subject of a second paper. Due to the difficulty in evaluating the pro-syncope effects in animal models, investigations into the underlying mechanisms such as cerebral circulation insufficiency may be useful. Hypotension, arrhythmia, hypoglycemia and anemia may lead to cerebral circulation insufficiency, finally leading to syncope. On the other hand, pro-seizure effects are frequently evaluated using animal safety pharmacology studies for drug development. Animal models are not perfect; however they can be useful in order to extrapolate pro-seizure effect in humans, especially for CNS targeting drugs. The mechanism of action of a drug is also important; excitatory neuron agonists and inhibitory neuron antagonists may have pro-seizure effects. There is some debate on the necessity and usefulness of animal studies for these kinds of CNS effects. The

* Fax: +81 3 6864 7609.
E-mail address: Takashi.Nagayama@ucb.com

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survey results are expected to contribute toward constructing safe drug developmental strategies as well as ensuring the appropriate use of marketed medicines in the clinical setting.

2. Methods

We reviewed medicines which have been approved in the past 13 years in Japan in terms of (1) what kinds of ADR were observed for each medicine in clinical studies, (2) whether animal toxicity findings that correspond to the concerned ADR were observed or not, (3) how the concerned ADR were predicted before clinical studies or before market distribution in cases where no relevant findings were noted in animal studies, and (4) how the ADR were managed in clinical use.

ADR information for 393 human medicines approved for use in Japan as a new drug substances between September 1999 and March 2013 were used for this survey. The ADR described in each package insert were collected. This survey included many ADRs, but only the following are reported in this paper: syncope/loss of consciousness and seizures/convulsions, specifically syncope, loss of consciousness, depressed level of consciousness, consciousness level depression, depressed consciousness, altered state of consciousness, and disturbance of consciousness for syncope/loss of consciousness category and seizures, convulsions, epilepsy, epileptic seizures, petit mal seizures, grand mal seizures and partial seizures for seizures/convulsions category. Comparable animal toxicity findings with ADR were collected by thorough investigation of the review reports and the summary of new drug applications (common technical documents (CTD) Module 2.4 and 2.6) available on the web site of the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan. Survey data was also analyzed for recent trends of syncope/loss of consciousness and seizures/-convulsions for recently approved Japanese medicines. In addition, we assessed the correlation with ADR and animal toxicity findings for the medicines. These results suggest improvements in animal and clinical studies to provide safer medicines, and to propose suggestions for clinical use of these medicines to contribute to patient safety. A statistical analysis was not performed in this study. Concordance ratio was used to evaluate translatability of ADR in human patients from animal toxicity findings. The concordance ratio was calculated by the following equation, generally named true positive rate or sensitivity:

$$\begin{aligned}\text{Concordance ratio}(\%) &= \text{true positive rate (sensitivity)} \times 100 \\ &= \text{true positive}/(\text{true positive} \\ &\quad + \text{false negative}) \times 100\end{aligned}$$

3. Results

3.1. Syncope/loss of consciousness and seizures/convulsions in recently approved Japanese medicines

The 393 medicines investigated contained a broad category of medicines for example 50 CNS drugs, 26 cardiovascular drugs, 39 antineoplastics, 50 antibacterial and antiviral agents, 22 monoclonal antibodies, 19 vaccines. According to the search of the package inserts, 101 of 393 medicines (25.7%) showed syncope/loss of consciousness and 105 of 393 medicines (26.7%) showed seizures/-convulsions (Fig. 1). A total of 60 medicines (15.3%) have both syncope/loss of consciousness and seizures/convulsions, while 146 medicines (37.2%) showed syncope/loss of consciousness or seizures/convulsions. Our research results showed that more than one third of the recently approved medicines in Japan induce ADR

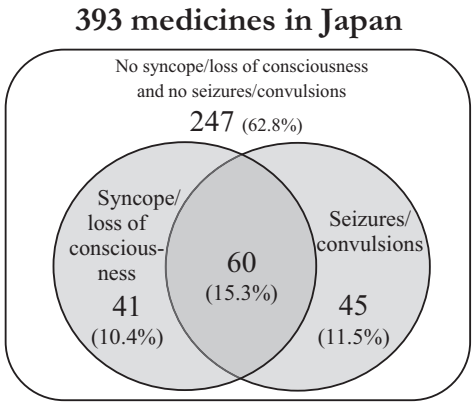

Fig. 1. Adverse drug reactions of syncope/loss of consciousness and seizures/convulsions in recently approved 393 Japanese medicines. Adverse drug reaction information for 393 medicines approved for human use in Japan as a new drug substance from September 1999 to March 2013 were used for this survey. 101 (25.7%) medicines showed syncope/loss of consciousness and 105 (26.7%) medicines showed seizures/convulsions. 247 (62.8%) medicines did not show syncope/loss of consciousness nor seizures/convulsions.

such as syncope/loss of consciousness and/or seizures/convulsions directly or affect the metabolic cascade.

3.2. Syncope/loss of consciousness and seizures/convulsions in each class of medicine

Evaluated medicines in this study were distributed across a wide range of treatments. In terms of the numbers of medicines in each category, there were 39 antineoplastic agents, 29 anti-virus agents, 26 agents using antibody, 19 vaccines, 19 hormones and hormone analogs, as well as many other categories. The categories with the least number of medicines were synthetic narcotics and agents for otic and nasal use, both of which numbered 3.

Syncope/loss of consciousness were reported in many medicines affecting CNS, i.e. all antiparkinsonian agents and 80.0% of psychotropic agents (Fig. 2). Psychotropic agents included 6 antidepressants, 8 antipsychotics and one medicine for attention deficit hyperactivity disorder. Syncope/loss of consciousness was reported in 83.3% of antidepressants and 75.0% of antipsychotics. There are mechanistic associations for syncope/loss of consciousness induction for CNS medicines. Syncope/loss of consciousness was also reported in 80.0% of agents affecting peripheral nervous system (local anesthetics). It was reported in 75.0% of antihypertensives, 62.5% of synthetic antibacterials, and 60.0% of interferons.

Seizures/convulsions were reported in many medicines affecting CNS, i.e. 87.6% of psychotropic agents and 66.7% of antiepileptics (Fig. 3). Psychotropic agents were further classified to antidepressants and antipsychotics, with seizures/convulsions reported in 100.0% of antidepressants and 87.5% of antipsychotics. Seizures/convulsions were also reported in 80.0% of agents affecting the peripheral nervous system (local anesthetics) and in 100.0% of interferons, 80.0% of vasoconstrictors, 75.0% of synthetic antibacterials, and 52.6% of vaccines.

3.3. Concordance of human adverse drug reactions with animal toxicity

Doses and blood concentration in humans and animals were not directly evaluated in this survey. Whenever the finding was observed in animal studies at any dose used by the sponsor, we evaluated that the toxicity finding as positive in animal studies.