BMC Pharmacology and Toxicology

RESEARCH Open Access

Appropriate use of triazolam in elderly patients considering a quantitative benefit-risk assessment based on the pharmacokinetic-pharmacodynamic modeling and simulation approach supported by real-world data

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Abstract

Background Triazolam is a typical drug commonly used in the elderly; however, there have been concerns about its adverse events resulting from age-related changes in physiological function and drug interactions with concomitant drugs. Thus, updated information contributing to the appropriate use based on the latest pharmacokinetic and post-marketing surveillance methods is needed. In this study, we evaluated the appropriate use of triazolam in the elderly by integrating real-world data with a modeling and simulation approach.

Methods The occurrence risk of adverse events in the elderly was evaluated using the spontaneous adverse event reporting regulatory databases from Japan and the United States. Information on drug concentrations and reactions was extracted from previous publications to estimate the threshold for plasma triazolam concentrations that cause adverse events. The pharmacokinetic/pharmacodynamic (PK/PD) model was then constructed, and the dose and administration were evaluated in various situations anticipated in medical practice.

Results Among all prescriptions, 25.4% were prescribed to individuals aged 80 years or above, and 51.8% were for those aged 70 years or above. A majority of cases involved CYP3A-metabolized drug combinations, accounting for 85.6%. Elderly individuals were at a higher risk of developing delirium and fall-fracture. Based on the constructed PK/PD model, the risk of adverse events increased when the plasma concentration of triazolam exceeded the calculated threshold of 0.44 ng/mL at approximately 6 h after administration. Administering 0.125 mg of triazolam, is half the approved dose for the elderly in Japan was deemed appropriate. Moreover, there was a substantial risk of adverse events even at a dosage of 0.0625 mg in combination with a moderate or strong inhibitor of cytochrome P450 3 A.

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Conclusion Analyzing large-scale databases and existing research publications on PK/PD can practically contribute to optimizing triazolam drug therapy for the elderly in the daily clinical setting.

Keywords Adverse events, Elderly, Modeling and simulation, Triazolam

Introduction

Population aging has become an issue in many countries, and drug therapy for the elderly is becoming increasingly important. The elderly are prone to potential safety issues resulting from many factors, such as age-related decline in liver and kidney function [1–3] and polypharmacy [4, 5]. To improve drug therapy for the elderly, guidelines on the appropriate use of pharmaceuticals have been issued in Japan [6, 7]; however, generally, the elderly do not participate in clinical studies and there is insufficient data on drug dosing, including dosage and administration adjustments for pharmaceuticals. Therefore, it is necessary to generate new information to improve drug therapy that considers the unique characteristics of the elderly.

Chronic insomnia is common in the elderly [8, 9], and triazolam, a short-acting benzodiazepine receptor agonist, is frequently prescribed [10, 11]. However, triazolam poses the risk of inducing geriatric syndromes, such as amnesia; thus, it is necessary to avoid using it as much as possible [12–14]. In addition, benzodiazepine hypnotics have a prolonged half-life in the elderly [15–17]. Greenblatt et al. observed an increase in plasma triazolam concentration with reduced clearance in the elderly when triazolam was administered to young people (mean, 30 years) and the elderly (mean, 69 years). They also reported that indicators of delirium and cognitive function correlated with changes in plasma concentration [18]. Therefore, when using triazolam in the elderly, there is a higher risk of developing adverse events associated with exposure to high drug concentrations; thus, the practice of more thorough drug treatments is required. However, triazolam has been on the market for a long time and is used based on the experience of healthcare professionals in many cases, so it is a major issue to update information contributing to its proper use.

Epidemiological studies that evaluate the appropriate use of pharmaceuticals and research that reexamine the available data have received a lot of attention recently. In particular, post-marketing pharmacovigilance has become important [19], and the use of large-scale databases is essential for analyzing the safety information of pharmaceuticals. In addition, spontaneous adverse event reporting databases are publicly available in the United States and Japan, which reflect the real-world. They have made it possible to gather data on age groups and lengths of therapy, such as data on elderly patients that is not often available through clinical trials. The pharmaceutical evaluation method of modeling and simulation is also widely used, from pharmaceutical development to actual clinical practice. It contributes significantly to the prediction of the efficacy and adverse events of pharmaceuticals [20]. These methodologies allow for the extraction and evaluation of previously unidentified issues and trends.

This study aimed to provide evidence that contributes to the optimization of triazolam drug therapy in the elderly by integrating spontaneous adverse event reporting databases with existing information on pharmacokinetics and pharmacodynamics.

Methods

Data sources

To analyze triazolam prescriptions and patient age distribution, we extracted claims data from April 2014 to March 2018 from Japan's National Database of Health Insurance Claims and Specific Health Checkups (NDB), published by the Ministry of Health, Labor, and Welfare. To comprehensively assess the appropriate use of triazolam, we first evaluated adverse event spontaneous reporting data that reflected the medical practice in Japan and also considered information on similar databases in the United States. Both the Japanese Adverse Drug Event Report database (JADER) and the FDA Adverse Event Reporting System (FAERS) were utilized to analyze a wide range of adverse event data from both databases, covering the period from April 2004 to March 2019. Adverse event data in patients receiving triazolam were analyzed to evaluate concomitant drug use using information from JADER. For pharmacokinetic interactions, using the University of Washington Drug Interaction Database, drugs with an area under the blood concentration-time curve increase ratio (AUCR) after triazolam dosing of 1.25 times or greater were extracted and are listed in Table 1 [21, 22].

Definitions of adverse events

Fall-fracture, delirium, disturbed consciousness, liver disorders, renal disorders, gastrointestinal disorders, and hypoglycemia were extracted as the seven typical adverse events associated with triazolam in the elderly [23, 24]. Based on the terminology described in the Medical Dictionary for Regulatory Activities Japanese version (MedDRA/J, version 22.0), adverse events were classified using the preferred terms listed below the classification. To determine the occurrence risk of adverse events, the cut-off age was set at 70 and 80 years, and the evaluation was performed with reporting odds ratio (ROR) and 95% confidence interval (95% CI) in the elderly versus

Table 1 Drug-drug interaction for triazolam

Interacting drug	AUCR	Ref.
Antidepressant		
Nefazodone	3.90	[26]
Antibiotics		
Clarithromycin	5.26	[27]
Erythromycin	3.80	[27]
Troleandomycin	3.76	[28]
Isoniazid	1.46	[29]
Antifungals		
Itraconazole	27.1	[30]
Ketoconazole	22.4	[30]
Fluconazole	4.42	[31]
Protease Inhibitor		
Ritonavir	40.7	[32]
H_2 Receptor Antagonists		
Cimetidine	2.20	[33]
Ranitidine	1.31	[34]
Calcium Channel Blockers		
Mibefradil	8.36	[35]
Diltiazem	3.38	[36]
Other drugs		
Grapefruit juice	2.43	[37]
Hormonal contraceptives	1.44	[38]

AUCR ratio of area under the curve (AUC) in the presence of an interacting drug to that in the absent, *AUCR* triazolam AUC with precipitant / triazolam AUC without precipitant

the non-elderly. The signal detection criteria for adverse event occurrence was determined as 95%CI > 1.

Pharmacokinetic-pharmacodynamic modeling

To obtain information on changes in triazolam blood concentration and drug susceptibility (sedation and cognitive function), we extracted the mean value of each from the report by Greenblatt et al. [18] using WebPlot Digitizer version 4.3 (https://automeris.io/WebPlotDigitizer/). Since the original literature used as a reference for the analysis provided only mean values of blood concentration time course obtained from information on young and elderly subjects (30 years old, 72 kg and 69 years old, 69 kg), the effect of age was incorporated in a general power law form in the pharmacokinetic-pharmacodynamic (PK/PD) model based on this literature information [18]:

$$\text{clearance} = \theta_{\text{clearance}} \times \left(\frac{\text{age}}{30}\right)^{\theta\text{cov}} \quad (1)$$

where θ is the estimated value of parameters. The basic pharmacokinetic model used in this study is a one-compartment model; when the dose is constant, the inverse of AUCR was added as a covariate of clearance. We set the threshold for drug susceptibility at the value where the fluctuation was less than 10% compared to the value with the largest fluctuation. This threshold was based on the signal-to-noise ratio of 10, a predominantly used lower limit in quantification, and previous results [18] showing minimal PD fluctuation in placebo and baseline regression post-triazolam administration. We calculated the blood concentration during the development of drug susceptibility using receiver-operating characteristic (ROC) analysis for values below this threshold. A PK/PD model was developed using a nonlinear regression model to estimate changes in drug susceptibility versus blood concentration. Both direct response and effect compartment models were considered for the PD model, with testing conducted for linear and Emax models, respectively. In the setting of the error model, inter-individual variability was not estimated, and the proportional error model (Eq. 2) was used for the PK model. In contrast, the additive error model (Eq. 3) was used for the PD model as residual variability:

$$\text{Obserbation}_j = \text{Prediction}_j \times (1 + \varepsilon) \quad (2)$$

$$\text{Obserbation}_j = \text{Prediction}_j + \varepsilon \quad (3)$$

Obserbation_j and Prediction_j are the j^{th} observation and prediction, respectively, whereas ε denotes a random variable following a normal distribution with a mean of 0 and a variance of σ^2. The validity of the model was determined using a coefficient of variation (CV%) of the estimated values, objective function value (OFV), goodness-of-fit plots and Akaike's information criterion. The NLME software (version 8.1; Certara, St. Louis, MO, USA) was used for model construction, parameter estimation, and simulation.

Simulation

The following estimates in different age groups during the combined use of typical drugs were evaluated by simulation using the constructed final model:

I: Estimation of the time required for blood concentration after 0.25 mg of triazolam dosing to decrease to the threshold in healthy young people.

II: Estimation of acceptable triazolam dose and administration, in which the blood concentration reaches the threshold at the time estimated by I in the elderly.

III: Estimation of changes in blood concentration during the combined use of 0.0625 mg of triazolam and various cytochrome P450 (CYP) 3 A inhibitors and estimation of the acceptable AUCR range, in which the blood concentration reaches the threshold at the time estimated by I in the elderly.

Table 2 Signals of adverse events of triazolam in patients

Averse events	JADER					FAERS				
	Total	Cut-off age		Reporting odds ratio (95% CI)		Total	Cut-off age		Reporting odds ratio (95% CI)	
		≥ 80	≥ 70	80 years	70 years		≥ 80	≥ 70	80 years	70 years
Consciousness disturbed	110	9	24	0.6 (0.3 – 1.2)	0.8 (0.5 – 1.3)	679	119	282	1.7 (1.4 – 2.1)*	1.9 (1.6 – 2.2)*
Liver disorders	61	2	11	0.2 (0.1 – 0.9)	0.6 (0.3 – 1.3)	1363	204	470	1.4 (1.2 – 1.7)*	1.4 (1.2 – 1.5)*
Delirium	33	13	23	5.2 (2.5 – 10.7)*	7.7 (3.6 – 16.5)*	254	50	127	2.0 (1.4 – 2.7)*	2.6 (2.0 – 3.3)*
Gastrointestinal disorders	33	8	13	2.4 (1.0 – 5.4)*	2.0 (0.9 – 4.1)	2310	314	704	1.3 (1.1 – 1.4)*	1.1 (1.0 – 1.3)*
Hypoglycemia	21	3	3	1.2 (0.3 – 4.1)	0.5 (0.2 – 1.7)	115	15	46	1.2 (0.7 – 2.1)	1.7 (1.2 – 2.5)*
Fall-fracture	20	7	10	4.0 (1.6 – 10.4)*	3.1 (1.3 – 7.6)*	522	92	228	1.7 (1.4 – 2.2)*	2.0 (1.7 – 2.4)*
Renal disorders	17	7	9	5.3 (2.0 – 14.2)*	3.5 (1.3 – 9.2)*	705	131	272	1.8 (1.5 – 2.2)*	1.6 (1.4 – 1.9)*
Total	784	97	196			36,770	4094	10,269		

95%CI 95% confidence interval, *JADER* Japanese adverse drug event report, *FAERS* Food and Drug Administration Adverse Event Reporting System. **P*, ≤ 0.05

Statistical analysis

The R Commander Plug-in for the EZR package version 4.0.2 (RcmdrPlugin.EZR) was used for statistical analyses [25].

Results

The quantity of triazolam prescribed in Japan from April 2014 to March 2018 was 181.6 – 275.9 million tablets per year, and no particular trend was observed in the age distribution of patients prescribed with triazolam between the years. Of all prescriptions, 25.4% were for individuals aged 80 years or above, and 51.8% were for those aged 70 years or above. In addition, only 2.3% of all prescriptions were for individuals under 30 years of age. Among all of the JADER data, there were 4116 entries containing triazolam, which was the 97th highest among all drugs registered in JADER, after the hypnotic sedatives brotizolam, zolpidem, etizolam, and flunitrazepam. There were many combinations containing benzodiazepines and cases of drug combinations involving CYP3A in metabolism, accounting for the majority at 3542 cases (85.6%). Fifteen drugs were extracted as drugs with an AUCR of 1.25-fold or greater (Table 1). Of these, there were 354 cases (8.6%) of combinations with triazolam. Among these, there were 78 cases of combinations with clarithromycin, 16 cases with itraconazole, and no case with ritonavir, respectively, which are strong CYP3A inhibitors [21, 22]. There were 78 cases of combination with diltiazem, 14 cases with fluconazole, and 8 cases with erythromycin, respectively, which are moderate CYP3A inhibitors [21, 22].

Table 2 shows the occurrence risk of adverse events in JADER and FAERS, and triazolam was reported as the suspected drug in 784 and 36,770 adverse events, respectively. Occurrence signals were detected in the elderly because of delirium, fall-fracture, and renal disorders. In particular, delirium exhibited a higher ROR for age 70 years or above compared with the other adverse events, which were 7.7 in JADER and 2.6 in FAERS. In addition, although JADER had a smaller number of cases and calculated ROR values tended to be higher compared with FAERS, the two regulatory databases demonstrated similar trends in terms of the categories of adverse events detected.

Table 3 Population pharmacokinetic/pharmacodynamic parameters of triazolam

Parameter (unit)	Estimate	CV%
Pharmacokinetic model		
Population mean		
Ka = θ1		
θ1 (1/hr)	3.16	5.27
Vd = θ2× (age/30)$^{\theta 4}$		
θ2 (L)	119	1.86
θ4	−0.49	6.53
CL = θ3 × (age/30)$^{\theta 5}$ × 1/AUCR		
θ3 (L/hr/kg)	0.47	1.92
θ5	−0.53	4.30
Residual variability		
σ (%)	6.20	10.8
Pharmacodynamic model		
Population mean		
Keo (1/hr)	3.42	12.6
Sedation constant	12.1	1.05
Cognitive function constant	−11.0	3.14
Residual variability		
σ Sedation (mm)	6.81	21.8
σ Cognitive function (%)	3.27	14.5

AUCR area under the blood concentration-time curve increase ratio; *CV* coefficient of variation; *CL* clearance; *Ka* first-order absorption rate constant; *Keo* plasma-effect compartment equilibration rate constant; *Vd* distribution volume; *θ* population mean; *σ* residual variability. Sedation = 12.1 × concentration, Cognitive function = −11.0 × concentration

Table 3 lists the estimated parameters for the resulting PK/PD model. For the PK model, a one-compartment model including a first-order absorption process best representing the changes in blood concentration and age was incorporated into distribution volume and clearance, respectively, as a covariate. For the PD model, an anticlockwise hysteresis loop was observed between blood concentration and drug efficacy; therefore, an effect compartment model was adopted to eliminate the time difference. Furthermore, a drug susceptibility against

concentration in the effect compartment exhibited a positive linear correlation. The OFV values during the model building process were OFV 223.5 for the linear and OFV 225.2 for the Emax in the direct response model. Compared to the direct response model, OFV 193.7 in the effect compartment model showed a significantly lower OFV and, therefore, was determined as the more appropriate model. The parameters and structure of the PK/PD model had a low CV% of 1.05−21.8%, and the goodness-of-fit plots between values estimated from the model and extracted values indicated the appropriate model fitting and valid (Supplemental fig). The threshold for sedation and cognitive function deterioration were 0.44 and 0.58 ng/mL, with the resulting sensitivity values of 0.85 and 1.00 and specificity values of 0.90 and 1.00, respectively.

Based on the results of a simulation, 5.95 h was required for blood concentration after a 0.25 mg dose of triazolam in healthy young people to fall below 0.44 ng/mL (Fig. 1). In contrast, when triazolam was administered to the elderly, 0.15 mg was required for blood concentration to fall below 0.44 ng/mL after 5.95 h. In addition, when 0.0625 mg (half of a 0.125 mg tablet) was administered to the elderly, the blood concentration was 0.44 ng/mL after 5.95 h, and a concomitant AUCR of 2.27 was observed (Fig. 2). The larger the AUCR of the drug, the more delayed the elimination. The half-life of triazolam with an AUCR of 1.0 was 2.9 h, whereas the half-life of itraconazole with an AUCR of 27.1 was 69.8 h.

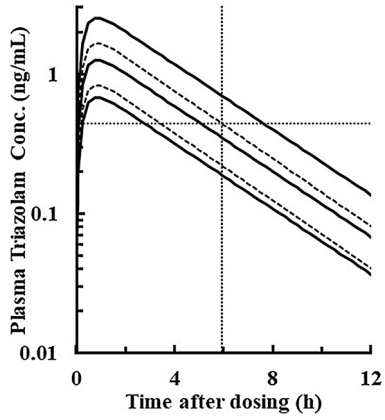

Fig. 1 Simulated Plasma Triazolam Concentration-time Profile in young and elderly patients. Dashed lines: 30 years old (dosage: 0.250 and 0.125 mg/body), solid lines: 69 years old (dosage: 0.250, 0.125, and 0.0625 mg/body). Dotted lines (horizontal axis): cut-off concentration (0.44 μg/mL), dotted lines (vertical axis): time required to reach cut-off concentration in young patients (5.95 h)

Discussion

In this study, the appropriate use of triazolam in the elderly was evaluated using a modeling and simulation approach, supported by real-world data. Triazolam has been on the market for a long time, and more information regarding its efficacy and safety has been collected following its manufacturing and marketing, compared with the approval and application phase. The approach proposed in this study on prescription status, adverse event reporting, and dose adjustment using modeling and simulation proved particularly useful for such drugs.

Fall-related fractures in the elderly greatly impact their quality of life and pose a risk of inducing fatal diseases, such as bedriddenness and aspiration pneumonia; thus, prevention is particularly important [39]. As triazolam has a very short half-life of 2.9 h and the effect of carry-over to the next morning is considered small, it tends to

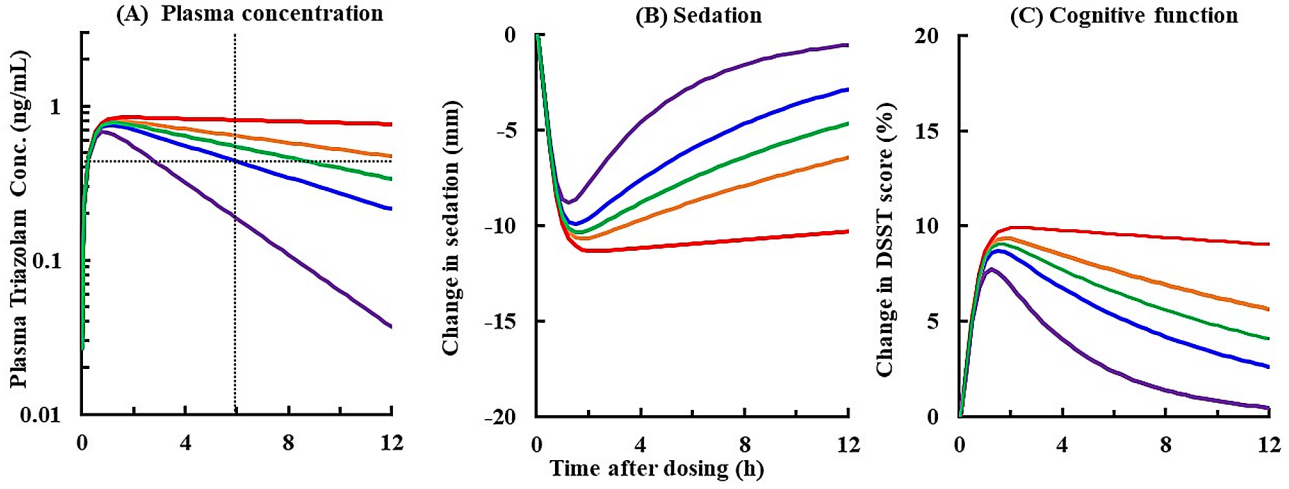

Fig. 2 Plasma triazolam concentration, sedation, and cognitive function versus time profiles in elderly patients, when combined with CYP3A inhibitors. Cut-off concentration: 0.44 μg/mL, time required to reach cut-off concentration in young patients: 5.95 h. Dosage: 0.0625 mg/body (69 years old). Red line, AUCR = 27.1 (itraconazole); orange line, 5.26 (clarithromycin); green line, 3.38 (diltiazem); blue line (0.44 ng/mL after 5.95 h), 2.27; and purple line, 1. AUCR: area under the concentration-time curve ratio

be more commonly used on the elderly compared with long-acting benzodiazepines. However, it has also been reported that the risk of falls is the same regardless of half-life or the presence or absence of a benzodiazepine skeleton [40]. Thus, there is no consensus on the effects of factors such as half-life on falls. In the present study, the occurrence signals of fall-fracture after triazolam dosing were detected in both JADER and FAERS at 70 or 80 years and above. Therefore, the results supported that of previous reports, in which dosing of triazolam in the elderly above 70 years old poses a fall risk and the Guidance of Appropriate Medication for Elderly Patients notified in May 2018 [6] and Jun 2019 [7] in Japan.

We constructed a PK/PD model to determine the relationship between changes in blood concentration after triazolam dosing in the elderly and pharmacodynamic events such as sedation and cognitive function. Blood concentration and pharmacological events are highly correlated [18], and the transfer half-life from the blood to sites of action was also rapid at 6.9 min. Thus, using blood concentration to indicate pharmacological events is considered useful. Interestingly, pharmacological events rarely occur when the blood concentration falls below the threshold. If it falls below the threshold within the period from dosing to waking up, the occurrence risk of fall-fracture may be reduced. In the present study, the threshold was estimated to be 0.44 ng/mL. When 0.25 mg of triazolam was administered to healthy young people (30 years), it took 5.95 h to decrease below the threshold. In other words, the blood triazolam concentration falls below the threshold when an individual wakes up. In contrast, when 0.25 mg of triazolam was administered to the elderly, it took 7.80 h to reach a threshold and blood triazolam concentration was not sufficiently reduced at waking time, suggesting that the risk of adverse events resulting from carry-over is increased. Next, we estimated that a dose of 0.156-mg triazolam was required for the concentration to fall below the threshold in the elderly at the same time as in healthy young people (Fig. 1). In the package insert, a warning is included that states, "in the elderly, dosing should be started from a low dose." However, the specific dose for the elderly is not mentioned. Based on the results of this study, we suggest that dosing at a half-dose (0.125 mg) significantly reduced the risk of carry-over.

Polypharmacy, aimed at treating comorbidities, is common in the elderly [21, 22], and changes in blood concentration tend to be affected by other pharmaceuticals. Itraconazole, a CYP3A inhibitor, and human immunodeficiency virus protease inhibitors are contraindicated for combined use, while diltiazem and clarithromycin are considered medications to be used with caution. [41], it is necessary to pay attention to potential drug-drug interactions when administering triazolam in clinical settings for drug treatment. In the present study, we simulated changes in blood triazolam concentration and pharmacological events in the elderly when used in combination with diltiazem, clarithromycin, and itraconazole, whose combined use was reported in JADER, which is the adverse event report from medical settings in Japan (Fig. 2). In addition, even though the dose was set at 0.0625 mg, which is 1/4 of the usual dose, blood concentration did not decrease sufficiently when combined with pharmaceuticals with an AUCR exceeding 2.27, even when administered at a low dose outside the approved dose range, which suggests the possibility of carry-over. Therefore, it is desirable to avoid using triazolam when administering medications with inhibition activity on CYP3A to the elderly and to consider alternative medications instead.

There were several limitations to our study. Firstly, the published adverse events and judgment on the involvement of pharmaceuticals are at the discretion of the reporters who judge the involvement of pharmaceuticals, and there is also missing information, such as age. Secondly, there were many confounding factors present in this study, such as concomitant drugs and dose and unavoidable selection bias. Thirdly, ROR was exploratorily used as a qualitative signal; thus, quantitative evaluations, such as occurrence frequency, are impossible. Finally, in the PK/PD model, the effect of age was assumed to be linear, and indications for ages other than 30 or 69 years, as described in previous reports, are unknown.

Conclusion

In this study, based on available information from medical settings in Japan, notable adverse events associated with triazolam dosing in the elderly (delirium, fall-fracture) were extracted. Constructing a PK/PD model using age as a covariate allowed for establishing a dosing strategy for elderly patients using concurrent medications. Triazolam is frequently prescribed for elderly patients, and the findings will help with the optimal dose.

Abbreviations

95% CI	95% confidence interval
AUCR	Area under the blood concentration-time curve increase ratio
CV	Coefficient of variation
CYP	Cytochrome P450
FAERS	FDA Adverse Event Reporting System
JADER	Japanese Adverse Drug Event Report database
NDB	National Database of Health Insurance Claims and Specific Health Checkups of Japan
OFV	Objective function value
PK/PD	Pharmacokinetic-pharmacodynamic
ROR	Reporting odds ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40360-024-00777-z.

Supplementary Material 1

Acknowledgements
This study was supported by a Japan Society for the Promotion of Science (JSPS) Grant-in-Aid for Young Scientists, Grant Number 19K20736 (AO). The authors thank Ms. Natsuko Takano from Musashino University for assisting in the collection of some data for this study.

Author contributions
AO and NN contributed equally to the conception, design of the research, and acquisition of the data; AO and SS contributed to the analysis of the data. All the authors critically revised the manuscript, and read and approved the final manuscript, and agree to be fully accountable for ensuring the integrity and accuracy of the work.

Funding
This study was supported by a Japan Society for the Promotion of Science (JSPS) Grant-in-Aid for Young Scientists, Grant Number 19K20736 (AO).

Data availability
JADER, FAERS, NDB open data Japan, and DIDB data files can be downloaded from [https://www.pmda.go.jp/safety/info-services/drugs/adr-info/suspected-adr/0004.html (Accessed 2020-08-20, Japanese)], [https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases (Accessed 2020-08-20)], [https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000177182.html (Accessed 2020-08-20, Japanese)], and [https://www.druginteractionsolutions.org/ (Accessed 2020-08-20)].

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 30 May 2023 / Accepted: 7 August 2024
Published online: 03 September 2024

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