Original Article

Intentional or unintentional drug poisoning in elderly people: retrospective observational study in a tertiary care hospital in Japan

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Aim: Intentional or unintentional acute drug poisoning occurs even in elderly people, but little is known about the factors influencing the intention to poisoning. A retrospective study was undertaken to describe the characteristics of acute drug poisoning in elderly people according to whether the poisoning was intentional or unintentional and the responsible agents.

Methods: The study was carried out in a single tertiary hospital in Japan. A total of 145 patients aged ≥65 years who were transferred by an ambulance service and were diagnosed with acute drug poisoning were included. Medical records were used to collect information on the intention behind poisoning and the responsible agents. Patients were divided into two groups according to whether they experienced intentional or unintentional poisoning and were further classified according to the responsible agent. Multivariable logistic regression models were used to estimate the association between hospitalization for acute drug poisoning and the use of benzodiazepine receptor agonists (BzRAs).

Results: Poisoning was unintentional in 102 (70.3%) patients and intentional in 43 (29.7%) patients. In total, 65 (44.8%) patients required hospitalization. Among patients in the unintentional poisoning group, those using non-BzRAs were more likely to be hospitalized than those using BzRAs (odds ratio, 6.64; 95% confidence interval, 2.56–17.22). The length of hospital stay was significantly longer in the unintentional poisoning group than in the intentional poisoning group (13.9 vs. 6.2 days; *P* = 0.013).

Conclusions: The proportion of unintentional poisoning in the elderly is high, and particularly with respect to poisoning with non-BzRAs, the hospitalization rates are high.

Key words: Benzodiazepine receptor agonist, drug poisoning, geriatric, hospitalization, intention

INTRODUCTION

DRUG POISONING OR overdosing, whether accidental or intentional, is a major cause of comorbidity and mortality worldwide. In Japan, it is reported that >20,000 people are admitted to hospitals because of drug poisoning annually.[1,2] It is reportedly the major cause of emergency admissions in Japan, the USA, and other countries.[3]

Drug poisoning can be either intentional or unintentional and occurs in both young adults and elderly people. In elderly people, unintentional drug poisoning occurs more often than intentional drug poisoning, whereas in young adults, the majority of drug poisoning cases is intentional.[4–6] Japan has long had a high suicide rate; it is reported that approximately 40% of people who commit suicide in Japan are aged ≥60 years.[7] Little is known regarding differences between intentional and unintentional poisoning in elderly people.

Previous studies have reported the characteristics of acute benzodiazepine intoxication and intentional poisoning in elderly people.[8–11] However, to the best of our knowledge, studies on the role of non-benzodiazepines in geriatric acute drug poisoning, as well as a better description of their characteristics based on whether the poisoning was intentional or unintentional, are lacking.[5] Therefore, this study aimed to describe the characteristics of acute drug poisoning in

elderly patients by emphasizing clinical courses related to the presence or absence of intention behind the poisoning and the types of responsible drugs.

METHODS

Study design

THIS WAS A retrospective study at a single tertiary care hospital in Sapporo, the prefectural capital of Japan's north island, Hokkaido. Our department observes and examines all emergency patients. Patients can be transferred to our department by ambulance, regardless of the level of triage. Our hospital's electronic database and medical records were used. Because this was a retrospective study based on only medical records and all data were analyzed in our hospital, patient consent was waived. The study was approved by the ethics committee of the hospital.

Selection of participants

Patients who had been transferred to the emergency room by ambulance between May 2007 and March 2016 were identified, and patients aged ≥65 years and diagnosed with acute medical drug poisoning in the emergency room were included in the study. Patients were included regardless of the type of formulation of the responsible drug and whether it was an oral, injection, or inhalation compound.

Because medical drug poisoning was included, non-medical substance poisoning, such as pesticide, household article, or alcohol poisoning, was excluded. Patients who were in a hypoglycemic state and hemorrhagic shock aggravated by medications such as hypoglycemic agents, antiplatelet agents, and anticoagulant agents following a previous study design were excluded;[5] these patients were diagnosed with hypoglycemia, bleeding, hematoma, or hemorrhagic shock rather than drug poisoning. Furthermore, patients for whom the responsible agent could not be determined and for whom the diagnosis of acute drug poisoning was uncertain based on medical records were excluded.

Data collection

Information was collected from medical records of patients who met our inclusion criteria. This information included whether poisoning was intentional or unintentional, age, sex, need for inpatient care, length of hospital stay, level of consciousness at the time of visit, results of blood tests at the time of visit, previous diagnosis of dementia, living arrangements before visit, and responsible agents. For calculation of the length of hospital stay, the day of admission was defined as day 1.

Intentional poisoning was defined as overdosing for the clear purpose of intentionally causing adverse events by patients to themselves. Unintentional poisoning was defined as overdosing without such purpose. Overdosing for which patients took medications with more than the prescribed amount only to seek further medicinal effect without knowing that it might cause any adverse event was also classified as "unintentional poisoning." When the intention behind the poisoning was unclear in the medical records, the patient was included in the unintentional poisoning group. There were no established criteria for admission at the time of the study; therefore, each physician judged the need for inpatient care on an individual case basis.

The level of consciousness was evaluated in four grades according to the eye subscale of the Glasgow Coma Scale (GCS). Because renal and hepatic functions influence drug metabolism, data on estimated glomerular filtration rate, aspartate aminotransferase, and alanine aminotransferase were collected. In addition, creatine phosphokinase was recorded because it is a marker of complications such as rhabdomyolysis and neuroleptic malignant syndrome, which might affect the length of hospital stay. When more than one type of drug was considered the culprit for poisoning, all drugs were regarded as responsible agents. All agents that had benzodiazepine receptor agonistic activity and those that responded to flumazenil were defined as benzodiazepine receptor agonists (BzRAs); these included agents such as zolpidem and zopiclone, which are typically called "non-benzodiazepines."

Outcome measures and primary data analysis

The outcomes of interest were the presence or absence of intention in the acute drug poisoning, need for hospitalization, and length of hospital stay.

Patients were divided into intentional and unintentional poisoning groups and further classified according to the responsible agent (BzRAs versus non-BzRAs) and the need for hospitalization. Multivariable logistic regression models were used to examine the association between hospitalization for acute drug poisoning and use of BzRAs, adjusting for age and level of consciousness at the time of presentation. Variables included in the models were selected based on previous studies, which showed that age[12] and the level of consciousness[13] were factors influencing the need for hospitalization. For patients admitted to the hospital, the length of hospital stay was compared between patients in the intentional and unintentional poisoning groups and between users

and non-users of BzRAs. The length of hospital stay was compared between groups using the Wilcoxon rank sum test.

P values <0.05 were considered to indicate statistical significance. All statistical analyses were carried out with Stata version 14 (Chiyoda-ku, Japan). Results are reported as mean ± standard deviation, unless indicated otherwise.

RESULTS

Patient characteristics

THE CHARACTERISTICS OF patients in the intentional and non-intentional poisoning groups are listed in Table 1. During the survey period, 161 patients met the inclusion criteria. None of the patients suffered cardiopulmonary arrest before or after arriving at the hospital. Six patients for whom the responsible agent could not be identified and 10 for whom the diagnosis of acute drug poisoning was uncertain were excluded. Thus, 145 patients were included in the final analysis.

The unintentional poisoning group comprised 102 (70.3%) patients, and the intentional poisoning group comprised 43 (29.7%) patients. The overall average age was 78.7 ± 8.2 years (range, 65–96 years). Forty-one (40.2%) patients in the unintentional poisoning group spontaneously opened their eyes (GCS E4) at the time of the visit. In contrast, only eight patients (18.6%) in the intentional poisoning group were classified as GCS E4. Patients who were previously diagnosed with dementia comprised 23 (22.5%) of the unintentional poisoning group patients and two (4.7%) of the intentional poisoning group patients. The prevalence of dementia was higher in the unintentional poisoning group than in the intentional poisoning group (*P* = 0.009). In the unintentional poisoning group, 17 (16.7%) patients lived in long-term facilities and three (2.9%) were referred from other hospitals. There were no patients from long-term care facilities or other hospitals in the intentional poisoning group.

Responsible agents

The top 20 most frequent responsible agents are listed in Table 2. The most frequent agent was zolpidem, which affected 31 patients. Table 3 shows the major classes of responsible agents listed in the intentional group. In the unintentional poisoning group, the most frequent agents were the BzRAs, which were solely or partly responsible for poisoning in 59 (57.8%) of 102 patients. Other frequent classes were antihypertensive agents (12.4%), antipsychotics (11.7%), antiarrhythmics (9.7%), and theophylline (5.5%) in

that order. In the intentional poisoning group, BzRAs were identified as the responsible agents in 40 (93.0%) of 43 patients. In three (7.0%) of 43 patients in the intentional poisoning group, the responsible agent was an antihypertensive agent, an antiarrhythmic agent, or an antihistamine. All three patients were hospitalized.

Admission rate

Of the 145 patients, 80 were discharged from the emergency department and 65 were admitted to the hospital. There were 40 (39.2%) admitted patients in the unintentional poisoning group and 25 (58.1%) in the intentional poisoning group (*P* = 0.036). In the unintentional poisoning group, 14 (23.7%) of the 59 BzRA patients and 26 (60.5%) of the 43 non-BzRA patients required hospitalization. Patients in the unintentional poisoning group poisoned by non-BzRAs were more likely to be hospitalized than those poisoned by BzRAs (odds ratio, 6.64; 95% confidence interval, 2.56–17.22) after adjustment for age and level of consciousness at the time of visit (Table 4).

Length of hospital stay

All 65 patients who required hospitalization were discharged alive. The length of hospital stay was 13.9 ± 18.9 days (range, 1–91 days) in the unintentional poisoning group (*n* = 40) and 6.2 ± 9.1 days (range, 1–37 days) in the intentional poisoning group (*n* = 25). The length of hospital stay was significantly longer in the unintentional poisoning group than in the intentional poisoning group (*P* = 0.013). Among hospitalized patients in the unintentional poisoning group, those who were poisoned by BzRAs (*n* = 14) stayed in the hospital for 14.2 ± 25.0 days and those who were poisoned by non-BzRAs (*n* = 26) stayed in the hospital for 13.6 ± 15.2 days (*P* = 0.138) (Table 5). Of the 25 patients in the intentional poisoning group who required hospitalization, 24 were poisoned by BzRAs, and the only patient poisoned by a non-BzRA stayed in the hospital for 37 days.

Major findings

The study revealed the following three remarkable findings: (i) unintentional poisoning occurred more frequently than intentional poisoning, (ii) among patients who experienced unintentional poisoning, those who did not use BzRAs were more likely to require hospitalization than those who used BzRAs, (iii) patients who experienced unintentional poisoning had longer hospital stays than those who experienced intentional poisoning.

Table 1. Characteristics of the study participants

Characteristic	Unintentional poisoning (n = 102)		Intentional poisoning (n = 43)		P-value
	n	%	n	%	
Age (years)					
65–74	26	25.5	21	48.8	0.007
75–84	44	43.1	17	39.5	
>85	32	31.4	5	11.6	
Sex					
Female	61	59.8	30	69.8	0.257
Male	41	40.2	13	30.2	
Admission					
Ambulatory care only	62	60.8	18	41.9	0.036
Inpatient care	40	39.2	25	58.1	
Consciousness					
Glasgow Coma Scale					
E4	41	40.2	8	18.6	0.013
E3	36	35.3	14	32.6	
E2	9	8.8	5	11.6	
E1	16	15.7	16	37.2	
Blood test					
eGFR (mL/min/1.73 m^2)†					
>60	62	60.8	28	65.1	0.503
30–60	30	29.4	9	20.9	
<30	10	9.8	6	14.0	
AST, ALT (IU/L)					
Both ≤40	80	78.4	35	81.4	0.868
Either >40	7	6.9	2	4.7	
Both >40	15	14.7	6	14.0	
CPK (IU/L) (n = 138)					
>230	14	13.7	8	18.6	0.526
≤230	81	79.4	34	79.1	
Dementia					
With	23	22.5	2	4.7	0.009
Without	79	77.5	41	95.3	
Living arrangement					
Living alone	10	9.8	5	11.6	0.020
With family	72	70.6	38	88.4	
Long-term care facility	17	16.7	0	0.0	
Hospital	3	2.9	0	0.0	

†Estimated glomerular filtration rate (eGFR) was calculated by the Modification of Diet in Renal Disease (MDRD) equation for Japanese, $186.3 \times (creatinine)^{-1.154} \times (age)^{-0.203} \times (0.742$ if female$) \times 0.881$.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase.

DISCUSSION

THE PRESENT STUDY described the characteristics of drug poisoning in a Japanese elderly population.

Our findings are consistent with those of a previous Japanese study.[5] Our study showed that a high percentage of patients who experienced unintentional poisoning were older than 75 years. This is probably because the distribution and excretion of drugs and sensitivity to drugs change with age and also because elderly people are more likely to use multiple drugs.[14] According to a previous study,[15] the frequency of accidental drug adverse events among elderly people increases with age.[4]

Table 2. Top 20 agents responsible for acute drug poisoning in 145 Japanese patients aged ≥65 years

	Substance	Total (n = 145)		Inpatient care (n = 65)	
		n	%†	n	%‡
1	Zolpidem	31	21.4	9	29.0
2	Flunitrazepam	22	15.2	10	45.5
3	Brotizolam	22	15.2	8	36.4
4	Etizolam	13	9.0	9	69.2
5	Triazolam	11	7.6	3	27.3
6	Estazolam	9	6.2	7	77.8
7	Quetiapine	9	6.2	4	44.4
8	Theophylline	8	5.5	7	87.5
9	Clotiazepam	8	5.5	5	62.5
10	Risperidone	8	5.5	4	50.0
11	Verapamil	6	4.1	6	100.0
12	Zopiclone	6	4.1	4	66.7
13	Levomepromazine	6	4.1	3	50.0
14	Carvedilol	5	3.4	5	100.0
15	Cibenzoline	5	3.4	4	80.0
16	Diazepam	5	3.4	2	40.0
17	CP/PMZ/PB	4	2.8	2	50.0
18	Alprazolam	4	2.8	1	25.0
19	Nitrazepam	4	2.8	1	25.0
20	Bisoprolol	4	2.8	0	0.0

When more than one drug were considered as a responsible agent, the patient was counted as one patient for each drug.
†Calculated by: the number of patients who were affected by a certain drug divided by the total number of patients in this study.
‡Calculated by: the number of patients who were affected by a certain drug and required hospitalization divided by the number of patients affected by the drug.
CP/PMZ/PB, chlorpromazine/promethazine/phenobarbital.

The tendency of elderly patients to misuse medications might also be related to the age demographics of the unintentional poisoning group. In Japan, the prevalence of dementia among people aged ≥65 years is 15%.[16] In this study, patients in the unintentional poisoning group were more likely to be previously diagnosed with dementia. This finding suggests that patients with dementia could have a higher risk of unintentional poisoning and a lower risk of intentional poisoning. Therefore, when physicians prescribe medications for elderly patients, they should keep dosages to the minimum effective, provide adequate guidance on drug usage to patients and their families, and closely monitor the effects of medication to prevent unintentional poisoning.

Our study found that antihypertensive agents, antiarrhythmic agents, and theophylline played a role as responsible agents, often among the unintentional poisoning group. Poisoning with these agents usually manifests with unstable hemodynamics and/or seizures, and, therefore, these patients are likely to require intensive medical treatment and close monitoring in a hospital. As unintentional poisoning in general occurs from usual doses,[5] the altered level of consciousness in unintentional poisoning with BzRAs is likely to be mild enough for patients to be discharged from the emergency department without hospitalization. This could be the reason that patients in the unintentional poisoning group for whom the responsible agents were identified as BzRAs were less likely to be admitted to the hospital than those poisoned by non-BzRAs.

Although the admission rate was significantly higher in patients in the intentional poisoning group than in those in the unintentional poisoning group, patients in the intentional poisoning group stayed in the hospital for a significantly shorter period than those in the unintentional poisoning group and were also supposed to be likely to have an active psychiatric problem. Therefore, even if patients in the intentional poisoning group were not so physically sick, it could be likely that a physician tended to hospitalize them to keep them waiting for an evaluation by a psychiatrist, which resulted in their high admission rates and short hospital stay.

Among patients poisoned by BzRAs, the average length of hospital stay was significantly longer in the unintentional poisoning group than in the intentional poisoning group, which is evidenced by two of 14 patients poisoned by BzRAs in the unintentional group who stayed in hospital for an exceedingly long time, 45 and 91 days, respectively. One of these developed severe pneumonia and the other developed severe heart failure after they were admitted to the hospital. The occurrence of severe complications was considered a factor that increased the length of hospital stay in the unintentional group poisoned by BzRAs. The average length of hospital stay was increased by these two patients. However, the relationship between the incidence rate of severe complication and intention of overdosing could not be revealed in this study.

Among patients in the unintentional poisoning group, the length of hospital stay did not significantly differ between those using BzRAs and those using non-BzRAs. In the intentional poisoning group, only one inpatient was poisoned by a non-BzRA, and his length of hospital stay was 37 days. It would be inaccurate to conclude that the length of hospital stay of intentional poisoning among patients using non-BzRAs is prolonged based only on this patient. Our results could establish a relationship between the length of hospital stay and intention but not between the length of hospital stay and responsible agent.

Table 3. Major classes of agents responsible for acute drug poisoning in 145 Japanese patients aged ≥65 years

Class	Unintentional poisoning				Intentional poisoning			
	Total (n = 102)		Inpatient care (n = 40)		Total (n = 43)		Inpatient care (n = 25)	
	n	%†	n	%‡	n	%†	n	%‡
Benzodiazepine receptor agonists	59	57.8	14	23.7	40	93.0	24	60.0
Antihypertensive agents	18	17.6	9	50.0	1	2.3	1	100.0
Antipsychotics	17	16.7	7	41.2	6	14.0	4	66.7
Antiarrhythmics	14	13.7	10	71.4	1	2.3	1	100.0
Theophylline	8	7.8	7	87.5	0	0.0	0	0.0
Antidepressants	7	6.9	4	57.1	2	4.7	2	100.0
Antihistamines	3	2.9	0	0.0	1	2.3	1	100.0
Other hypnotics	3	2.9	0	0.0	0	0.0	0	0.0
Opioid	2	2.0	2	100.0	0	0.0	0	0.0

When more than one drug was considered responsible, the patient was counted as one patient for each drug.
†Calculated by: the number of patients who were affected by a certain drug for each intention group divided by the total number of each group patients.
‡Calculated by: the number of patients who were affected by a certain drug and required hospitalization divided by the number of patients by the drug.

Table 4. Admission rate among 145 Japanese patients aged ≥65 years poisoned by benzodiazepine receptor agonist (BzRA) and non-BzRA agents

	Total	Inpatient care		Odds ratio†	95% CI	P-value
		n	%			
Unintentional poisoning						
BzRA	59	14	23.7			
Non-BzRA	43	26	60.5	6.64	(2.56, 17.22)	<0.001
Intentional poisoning						
BzRA	40	24	60.0			
Non-BzRA	3	1	33.3	0.57	(0.04, 8.36)	0.68

†Odds ratio of inpatient care in non-BzRA patients against BzRA patients adjusted by age and consciousness on admission using logistic regression.
CI, confidence interval.

Table 5. Length of hospital stay (LOS) in 65 Japanese patients aged ≥65 years admitted to hospital for benzodiazepine receptor agonist (BzRA) and non-BzRA poisoning

Intention	BzRA			Non-BzRA			P-value†
	n	LOS	SD	n	LOS	SD	
Unintentional	14	14.2	25.0	26	13.6	15.2	0.138
Intentional	24	4.9	6.6	1	37.0	–	–

†Wilcoxon rank sum test for LOS between BzRA and non-BzRA poisoning patients.
SD, standard deviation.

There are two points that should be noted about responsible agents in our study. First, in this study, opioids were the responsible agents in only two (1.4%) patients, whereas a previous study in the USA and Europe found that opioids were one of the most common causes of death due to poisoning.[11] This difference was expected because, in Japan, opioids are under very strict control and are prescribed much less frequently than in the USA and Europe.[17] Second, although theophylline was identified as the responsible agent once or twice every year, it was never identified as the responsible agent during the last 2 year and 10 months of this study, which could be because the guidelines of asthma in Japan recommend inhaled corticosteroids as the first line of therapy instead of theophylline,[18] and the prescription of theophylline might be decreasing in Japan. There was no change in the other responsible agents in the 10 years of the study period.

Our study had several limitations. First, we did not measure blood concentrations of suspected agents in all cases.

Therefore, patients who were diagnosed with drug poisoning by a medical interview alone might have also been poisoned by other drugs or affected with other diseases. Second, the study was undertaken in a single tertiary care hospital in the prefectural capital of Japan's north island, which necessarily limited any claim of external validity or generalizability. Finally, because of limited information in our electronic database, only patients transferred to the hospital by ambulance were included; thus, patients with acute drug poisoning who came to the hospital by other means of transportation were not identified, which could have led to selection bias.

CONCLUSION

THIS STUDY SHOWED that unintentional poisoning was more common than intentional poisoning among elderly patients. In addition, the study revealed that unintentionally poisoned patients affected by non-BzRAs were more likely to be hospitalized than those affected by BzRAs. Our study concluded that when physicians prescribe medications, particularly antiarrhythmic and antihypertensive drugs, to elderly patients, they should keep in mind that these medications frequently cause adverse events and that they should closely monitor the effects.

DISCLOSURE

ACKNOWLEDGEMENTS

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