Review

Toxicological analysis on forensic investigation in drug related cases; pharmacological information on 88 psychoactive substances in "Narcotics and Psychotropics Control Act" in Japan

Koutaro Hasegawa*, Osamu Suzuki

Department of Legal Medicine, Hamamatsu University School of Medicine,
1−20−1 Handayama, Higashi-ku, Hamamatsu, Shizuoka 431−3192, Japan

Abstract Forensic toxicology is a field dealing with applications of accepted scientific methods in investigating drug related cases, analytical results of which can be issued and used in court. As unique aspects of forensic medicine/toxicology, various specimens ranging from blood, urine, body fluids to solid tissues can be dealt with in analysis. In addition, target substances to be subjected can also be varied from medicines, abused drugs, chemicals, to daily used substances. In analysis, various high-sensitive instruments such as gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) are being employed throughout the world.

Thus, it should be taken into consideration that various phenomenon including postmortem distribution/redistribution of drugs in the body and matrix effects on analysis can influence results of analysis, making the interpretation of analytical results very complex and difficult in forensic investigations. In this review, we have presented comprehensive perspectives on toxicological analysis and pharmacological information on 88 psychoactive substances in "Narcotics and Psychotropics Control Act" in Japan, which should be of use in drug related cases. It is desirable for examiners to investigate and consider the cause of death based on comprehensive medical perspective, keeping in mind that the results of toxicological analysis are only one of factors in determining the cause of death. In addition, it is also quite important to record details of the samples and analytical procedures employed, so that the previous results can be verified later. These details on toxicological analysis can provide "chain of custody" of the investigation.

Key words: Forensic Toxicology, LC-MS/MS, GC-MS(/MS), postmortem distribution/redistribution, chain-of-custody

Introduction

In the field of forensic medicine, autopsies are performed to investigate and determine the causes, or manners of death in concerned cases. In addition to findings of autopsy, various additional tests such as drug screening and microscopic investigations on pathological findings are also performed to clarify the cause of death itself, and the comprehensive understanding of each case. Regarding drug related cases including drug facilitated crimes (DFC), abuse, misuse of drugs, homicide and even suicide using poisonous substances and/or various kinds of drugs, toxicological analysis shall be performed to investigate the cases; the presence or absence of the targets, the degree of contribution of involved substances in manner of death and also its pharmacological potencies/effects on the cases become focuses of interest in the toxicological approach.

Forensic toxicology is a field where dealis with applications of accepted scientific methods in investigating drug related cases, analytical results of which can be issued and used in court[1,2]. In addition to analyzing samples collected, seized or obtained by the police through their investigations, various complex samples including body fluid sam-

* **Corresponding author**
Koutaro Hasegawa
Department of Legal Medicine, Hamamatsu University School of Medicine, 1−20−1 Handayama, Higashi-ku, Hamamatsu, Shizuoka 431−3192, Japan
Tel: +81−53−435−2239, Fax: +81−53−435−2858
E-mail: 07484771@hama-med.ac.jp
Received: January 31, 2022. Accepted: May 10, 2022.
Epub June 21, 2022.
DOI: 10.24508/mms.2022.06.007

ples such as blood[3], urine [4], bile[5–7], vitreous humor[8,9], even putrefactive effusions[10] and solid organs[11–13] and/or tissues samples[14–18] collected at autopsies can also be subjected to the toxicological analysis depending on each case if necessary[19,20]. Therefore, it is of course very important in investigations of the drug related cases to evaluate the contributions of drugs and/or poisonous substances to each manner of death through analysis, which is based on forensic toxicological perspectives and findings[20].

In particular, the analysis for involved substances in various samples obtained from forensic autopsies should require comprehensive understandings for them based on forensic toxicology[19] and/or forensic medicine to evaluate the analytical results correctly, because of unique characteristics and perspectives of forensic medicine and toxicology, such as diversity of the target samples described above and postmortem changes of the samples[20], which can give various influences over the whole process of analysis. In addition, there are still vast number of drugs and substances, the pharmacological effects on the human body and the evaluation of toxicity and potency of which are unclear, making evaluation of the analytical results of human samples, especially in intoxication cases, quite complex and difficult[21–25].

In this review, we would like to discuss forensic toxicological approaches in investigating causes of death based on results of analysis along with other findings such as those of autopsies, describing on postmortem distribution/redistribution of substances in the human body as a unique phenomenon that should be taken into considerations especially in forensic toxicological area. In addition, as frequently encountered drugs in field of forensic toxicological investigation in Japan, 88 psychoactive substances in "Narcotics and Psychotropics Control Act" with their pharmacological information, which should be of practical use, were dealt with in this paper.

Samples in Forensic Toxicological Investigation

Various kind of human body specimens, or practically almost all kind of specimens, can be subject to analysis in forensic toxicological analysis[19]. As one of unique aspects of forensic medicine/toxicology, which deals with various cases ranging from unnatural death, suicide to crime case, target substances to be analyzed can also be varied from medicines, abused drugs, chemicals, to daily used substances, etc[2]. Table 1 shows the target compounds likely to be encountered in investigations and the samples to be collected at autopsy for them[19]. Also, Table 2 shows the preferable amount of each sample to be collected at autopsy for toxicological investigations.

In general, the distribution of substances in the human body can be greatly affected by various factors such as chemical characters of the substance (polarity, volume of distribution, etc.)[26], manner/route of administration, gradient of concentration in the body, metabolism and of course anatomical positions of organs[27]. Thus, the above table only show a kind of example in sample collection in forensic autopsy; any kind of samples can be the subjects for investigations, in any volumes, regardless of the type of

Table 1. Kinds of target compound, and biological specimens often used in forensic toxicological investigations

	Whole blood/ plasma/serum	Urine	Gastric contents	Liver	Brain	Kidney	Lung
Organic solvent（inhalation）	++			+	+		++
Alcohols	++	++					
Cyanide			++				
Carbon-monoxide	++						
Hydrogen-sulfide							++
Anesthetics	++				++		++
Heavy metals			++	++			
Organic substances（oral）	++	++	++	+	+	+	
Organic substances（injection）	++	++		++		++	
Basic substances（injection）	++	++	+				
Organic phosphorus agents	++		++				
Parent drug	++	+/−	++	+	++	+/−	+
Metabolite(s)	+/−	++		+～++		+	+/−

++: very suitable, +: suitable, +/−: possible/spare

Table 2. Suitable amounts of matrices for forensic toxicological investigation at autopsy

Matrices/Volume		Matrices/Volume (area)	
Gastric tissue	Suitably	Dermal tissue	100 cm^2
Gastric contents	20 mL*2	Adipose tissue	10−20 g*2
Duodenum/intestinal contents	20 mL*2	Bone (including mallow)	10−20 g*2
Brain	10−20 g*2	Hair	50 mg
Lung	10−20 g*2	Injection scar	Around scar
Liver	10−20 g*2	Whole blood/plasma/serum	20 mL*2
Kidney	10−20 g*2	Urine	20 mL*2
Skeletal muscle	10−20 g*2	Nail	Suitably
Gastric lavage residue	20 mL*2	Solid tissue specimens	10−20 g*2
Residue of vomit	As much as possible	Fluidal specimens	10−20 mL*2

* In living human cases, 10 mL of whole blood/plasma/serum and urine, 50 mL of gastric lavage residue should be collected.

drug or toxic substance involved.

In addition to simple judgement on presence or absence of target substance and its concentration in each sample, additional various information on the target compound can also be obtained depending on kinds of tested sample. For example, adipose tissue can store non-polar substances for a long period and in relatively large amounts, so it may be possible to detect substances from adipose tissue that could not be detected in urine or blood samples [28, 29]. With regard to details of this case, we experienced a fatal multiple drug abuse case where synthetic cannabinoids AB-CHMINACA, 5-fluoro-AMB and diphenidine were involved. Although AB-CHMINACA and 5-fluoro-AMB could neither be detected from any body fluids including blood samples even nor urine obtained at autopsy, they could be detected and quantificated at 24.8±2.5 and 18.7±1.1 ng/g in the adipose tissue, respectively, which could provide informative clues to the investigation, showing evident results of ingestions of drugs prior to the death[28].

In the analytical case of hair samples, it is possible to estimate the timing and even interval of ingestion of the target substances by detailed analysis of hair segments[30−33]; Kuwayama *et al.* could successfully detect midazolam, which had been administrated in single dose (3 mg) intravenously 2 months before sample collecting, from well segmented (0.4 mm) hair samples using high-resolution quadrupole-Orbitrap liquid chromatography−tandem mass spectrometry[33]. Thus, as described before, it is possible for examiners to obtain/provide useful clues and information on target compound(s) by analyzing various samples in forensic toxicological investigations.

Detailed analytical procedures for each substance and sample, however, should be referred to in other studies and literatures; it is impossible to present comprehensive analytical procedures for vast kinds of target substances in this review because not only quite various substances but also samples can be involved in forensic investigations. Regarding forensic toxicological examination, analytical results on authentic human abuse cases will not only contribute to the investigation on cause of death in corresponding cases, but also be able to provide reliable and of high reference value data to other drug related cases.

Instrumental Analysis in Forensic Toxicological Investigations

Especially in the field of forensic toxicology, high sensitivity and high specificity of instruments play an important role in the identification and quantitative analysis of target xenobiotics and/or even their metabolites. In this field, gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) are usually/typically employed[34−37] throughout the world. Recently, in addition to them, gas chromatography tandem mass spectrometry (GC-MS/MS) has also been used in the field of forensic toxicology[38].

In mass spectrometry, the molecule of target compound is fragmented into its constituent parts by each collision energy for them, and these fragment ions are separated in a quadrupole mass spectrometer according to their mass weights (m/z)[39], giving product ion mass spectrum obtained from each compound. The qualitative identification analysis of each substance is carried out by comparing the mass spectrum of the target substance with reference libraries and database, which are consisting of known com-

pounds[40]. Quantitative analysis, on the other hand, is usually carried out by examining the area of chromatogram of a specific *m/z* ion selected by selective ion monitoring (SIM) or multiple reaction monitoring (MRM) modes, optimized for respective targets; these SIM and MRM can also be used for high-sensitive qualitative analysis[41]. Using these technique, reliable qualitative and quantitative analysis can be examined[42, 43].

A lot of scientific literatures using LC-MS/MS and GC-MS in forensic toxicological area have been reported so far[34−37,44]; these systems are now being widely employed throughout the world for investigations[45−47]. Their one of advantages is that multiple ionization techniques including electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI) are available in analysis[48−51], according to kinds of target compounds.

In GC systems, they could separate from gaseous mixture into individual substances by passing gas flow through a silica capitally column. Thus, the system is generally robust and have high specificity for analysis of various substances; GC system is thought to be, so to speak, "Gold standard" for either screening or determinating in investigation[36,37]. On the other hand, in GC techniques, target should be thermally stable and volatile substances, which brings limited utility for GC in forensic toxicological investigations; laborious sample preparations such as derivatizations can be required in case of analyzing such not-suitable substances for GC technique in analysis [34,35].

In LC systems, separation of target compounds from liquid mixture can be carried out by passing the liquid through a column filled with various component particles (e.g. C18 and anion/cation exchange resins) and diameter size, as stationary phase [34,35]. They can be of wide utility for remarkable vast range of analytes. Unlike GC, they can separate well even thermally unstable and not-volatile substances[39] through the separation; relatively simpler sample preparation than that in GC is required for LC analysis. However, matrix effects in instrumental analysis derived from target sample matrices should be considered in LC analysis[18,21−24,52], which are not remarkable in GC analysis in many cases.

Ultimately, both LC and GC system should be employed for sensitive and reliable analysis in forensic toxicological area; it is also necessary for reliable identification of target substance(s) in qualitative analysis to be determined by multiple different instrumental techniques, more than one method.

Nowadays, GC−MS/MS systems can be comparable to those of LC−MS/MS in selectivity, sensitivity and easiness of handling them. In spite of such high analytical performance of instruments, the costs of GC−MS/MS are usually lower than those of LC−MS/MS[38]. In research laboratories dealing with biomedical matrices, LC−MS/MS and/or GC−MS systems are now being widely employed. In addition to them, when both LC−MS/MS and GC−MS/MS are available as standard analytical instruments in the future, it is expected that analytical possibilities in toxicological investigations shall be better than as is of nowadays.

Postmortem Distribution/Redistribution of Xenobiotic Substances in Forensic Investigation

It has been described above that distribution of substances in the human body can be greatly affected by various factors such as chemical characters of the substance [26], manner/route of administration (oral intake, inhalation via the respiratory tract, intravenous injection, etc.), gradient of concentration in the body, metabolism and the course of excretion in human body. Furthermore, anatomical position and structure of organs can also contribute to distribution/redistribution of drugs among samples, bringing about various concentration values of corresponding substances though the samples being collected from the same body. With regard to such example, we experienced an intoxication autopsy case due to ingestion of methamphetamine in our department. In the case, it was demonstrated that blood samples obtained from various sites, including aortic arch, right heart ventricle, left heart ventricle, right pulmonary artery, right pulmonary vein, superior vena cava, inferior vena cava, right iliac vein and right femoral vein, showed quite different concentrations of methamphetamine and amphetamine among them; the highest and lowest values of methamphetamine were 911 and 268 ng/mL, in left heart and right femoral vein blood samples, respectively[3].

In addition, such distribution of substances in a human body can occur not only prior to death, but also even in postmortem period[6,53−60]. Regarding post-mortem distribution/redistribution of substances, in addition to the above factors, the period between the death and analysis for them, natural diffusion of the substance according to their concentration[61], environment around the body, postmortem changes such as drying and decomposition of the body, and

even metabolism by microorganisms[62], can be involved and taken into consideration. These factors can make the interpretation of analytical results very complex and difficult in forensic investigations on postmortem distribution/redistribution of drugs in the body[21−24]; above methamphetamine case was autopsied about a week later his death, thus, of course post mortem time interval could also influence distribution of targets and its analytical results in samples examined.

In other words, there is a possibility that the concentrations of target substances in samples collected at autopsy do not always correctly reflect those at the time of poisoning or death[22,61,63−65], which should be essential and important in toxicological investigations. The circumstances in which concerned substances were exposed/involved and the conditions until analysis for them are quite different in each case; no one drug-involved case has the same conditions and background with those of another case in toxicological analysis. Thus, the difficulty in evaluating the results of such analysis has been described as a toxicological nightmare[61].

Blood-plasma Concentrations and Pharmacological Information of 88 Psychoactive Substances in Narcotics and Psychotropics Control Act

In Japan, 88 psychoactive substances including stimulants, analgesics and sedatives are now being regulated and controlled strictly on their distributions among market, hospitals and laboratories, under "Narcotics and Psychotropics Control Act" law[66].

Blood-plasma concentration in therapeutic, toxic and fatal level reported, half-life time, their supplemental information and references on the 88 psychoactive substances are listed in Table 3, which were found and collected from previous published literatures[67−69], drug label inserts and available related data in our efforts. Because xenobiotic substances which can be involved in toxicological investigations are of the quite vast number, thus comprehensive reviewing on them does not seem to be possible in this literature. Practically, it is appropriate and reasonable to refer to related published data according to each concerned drug(s) involved, when toxicological investigation would be carried out in corresponding drug-related cases.

At least, in drug-related cases on above 88 psychoactive substances, listed data on them in the table 3 can be of help for interpretations for concerned cases. A number of related cases of them may be encountered very frequently in toxicological investigations especially in Japan, because all psychoactive substances still being prescribed as medicine for medical treatments nowadays in Japan are contained in the table; practically, the table 3 can be of use in, and deal with every prescribed-psychoactive drugs related/concerned cases in Japan.

Postmortem distribution/redistribution of substances, however, could be concerned in investigations, as described before. Therefore, it must be taken into consideration that these data should be used with caution and sufficient knowledge about them according to each drug-related case[61].

The listed 88 psychoactive substances are categorized into 3 groups in Japan, according to pharmacological efficacy and potency of each substance.

Upon some substances listed in the table, it should be taken into mind that not only psychoactive substances itself as, so to speak, prodrugs and also its active metabolites are contained as regulated substances. For example, clorazepate, diazepam, ketazolam, medazepam, oxazolam and pinazepam are all precursors (prodrugs) of nordazepam (desmethyldiazepam), followed by producing oxazepam as metabolite of nordazepam; oxazepam is also metabolite of temazepam, which can be derived from diazepam[113]. These successive metabolic series are of qualitative and analytical importance in determinations, especially from forensic toxicological perspective on the listed drugs; clorazepate, diazepam, oxazolam, pinazepam, nordazepam, temazepam and oxazepam are all listed in the table and thus regulated by Narcotics and Psychotropics Control Act [66]. Therefore, in drug related case where such drug(s) being suspected to be involved, both targeted substance and its probable precursor should be considered to be analyzed for appropriate determination of involved drug(s) by analytical investigation.

Recent years, abuse of new psychoactive substance (NPS) such as cathinone derivatives and synthetic cannabinoids, so to speak "designer drugs" and "bath salt," are also being a critical social problem in Japan. In addition to Narcotics and Psychotropics Control Act, blanket or generic scheduling system against them have also been implemented containing more than 2000 substances, even increasing the number of regulated substances, by ministry of health, labour and walfare owing to wide distributions of such substances, nowadays.

Table 3. Blood-plasma concentrations, and supplemental information of 88 psychoactive substances in Narcotics and Psychotropics Control Act in Japan

Category-No.	Name (synonym)	Type of efficacy	Therapeutic levels	Toxic levels	Fatal levels	Available in Japan	Supplemental information	Ref.
1-1	Fenethylline	Stimulant	0.04 (C_{max} at therapeutic dose)	n/a	n/a		$T_{1/2}$: 1.3 h ・Fenethylline is amphetamine analog, which consist of amphetamine structure linked to theophylline. Thus, as metabolite of fenethylline, amphetamine can be produced in urine and blood. ・In therapeutic use, adult oral doses are 25−100 mg per day for narcolepsy and depression. ・A 50 mg oral administration gave peak plasma concentration averaging 0.04 μg/mL after 1 h, in adults.	[67]
1-2	Mecloqualone	Sedative	n/a	n/a	n/a		$T_{1/2}$: n/a ・Mecloqualone is methaqualone analog, also having activity to GABA receptors. ・Mecloqualone is first synthesized in 1960, and no longer prescribed globally.	[67, 68] [70]
1-3	Methaqualone	Sedative	1−3	3−5	5−10		$T_{1/2}$: 10−40 h, 20−60 h ・Methaqualone is quinazoline derivatives, having activity to GABA receptors. ・In therapeutic use, adult oral doses are 75−300 mg as free base, and 200−400 mg as hydrochloride salt, in 1 portion. ・A 250 mg oral administration gave peak plasma concentration averaging 2.2 (1.0−4.0) μg/mL after 2 h, in 7 adults.	[67, 68]
1-4	Methylphenidate	Stimulant	0.01−0.06	0.1−0.5, 1	2.3	○	$T_{1/2}$: 1.4−6.2 h, 2−7 h ・Methylphenidate is phenethylamine derivative, which is used as medicine for depression and narcolepsy. ・In therapeutic use, child oral doses are 8.6−40 mg, and 20−100 mg for adult a day. ・Repeated oral administrations of 18 mg gave peak plasma concentration averaging 0.015 μg/mL after 4.5 h, in 48 adults.	[67, 68] [71]
1-5	Modafinil	Stimulant	1−1.7(3)	2.1−3.8, 13−18	n/a	○	$T_{1/2}$: 10−15 h, 9−16 h ・Modafinil is psychostimulant agent, used for sleep disorders and narcolepsy. ・In therapeutic use, adult oral doses are 200−400 mg in 1 portion. ・A 100 mg administration gave peak plasma concentration averaging 2.2 μg/mL after 2.1 h, in 12 adults.	[67, 68] [72]
1-6	Phenmetrazine	Stimulant	0.02−0.25	0.5	4, 1.1 (0.1−4.9)		$T_{1/2}$: 8 h ・Phenmetrazine is used as appetite suppressant, which could be metabolized from its analog phendimetrazine. ・In therapeutic use, adult oral dose is 25 mg at once, up to 3 times per day. ・A 75 mg administration gave peak plasma concentration averaging 0.14 (0.5−0.24) μg/mL after 2 h, in 5 adults.	[67, 68]

Table 3. Continued

Category-No.	Name (synonym)	Type of efficacy	Therapeutic levels	Toxic levels	Fatal levels	Available in Japan	Supplemental information	Ref.
1-7	Secobarbital	Sedative	1.5−5	7−10	10−15, 21(5−52)	○	$T_{1/2}$: 22−29 h, 15−30 h ・Secobarbital belongs to a barbiturate group as sedative drugs, which have binding affinity to GABA receptors. ・In therapeutic use, adult doses are 8−250 mg in oral and rectal administration; intravenous and intramuscular injection are also available. ・A 100 mg oral administration gave peak plasma concentration averaging 1.5 μg/mL after 1 h, in 15 adults.	[67, 68] [73]
1-8	Zipeprol	Antitussive	0.1−0.7	0.3−1.0	5.8, 10.6, 31		$T_{1/2}$: 1.2 h ・Zipeprol is antitussive agent, abuse of which can bring symptoms such as euphoria and hallucinations. ・In therapeutic use, adult oral doses are 150−350 mg per day. ・A 175 mg oral administration gave peak plasma concentration ranging 0.02−0.08 μg/mL after 1 h, in 2 adults.	[67, 68] [74]
2-1	Amobarbital	Sedative	1−5	5−6, 10−30	13−96, 29−163	○	$T_{1/2}$: 8−40 h, 15−40 h ・Amobarbital belongs to a barbiturate group as sedative drugs, which have binding affinity to GABA receptors. ・In therapeutic use, adult oral doses are 100−300 mg once before bedtime, for insomnia. ・A 120 mg oral administration gave peak plasma concentration at 1.8 μg/mL after 2 h, in an adult.	[67, 68] [75]
2-2	Buprenorphine	Analgesic	0.0005−0.01	0.03−0.1	0.008−0.029 0.0011−0.029	○	$T_{1/2}$: 3−5 h (i.v.), 18−49 h (sublingual or transdermal) ・Buprenorphine has affinity to opioid receptors (μ), and act as antagonist for them. ・For injection, 0.2−0.3 mg doses are used at once; transdermal patches contain 5−20 mg of them. ・In use of transdermal patch, plasma level of buprenorphine can be increased until 72 hours after administration.	[67, 68] [76]
2-3	Butalbital	Sedative	1−5	10−15	15−30		$T_{1/2}$: 30−40 h, 35−88 h ・Butalbital belongs to a barbiturate group, which have binding affinity to GABA receptors. ・In therapeutic use, adult oral doses are 30−100 mg at once, not to exceed 300 mg a day. Butalbital is often used as combination with analgesic agents such as acetaminophen and aspirin. ・A 50 mg oral administration gave peak plasma concentration averaging 1.3 μg/mL after 0.9 h, in 15 adults.	[67, 68] [77]
2-4	Cathine (*d*-norpseudoephedrine)	Stimulant	around 0.07	n/a	n/a		$T_{1/2}$: 3−8 h ・Cathine is one of metabolites of pseudoephedrine, and natural stimulant agent contained in Khat leaves. ・As appetite suppressant agent, adult oral doses are 20−60 mg per day. ・1 h chewing of Khat leaves containing 32 mg of cathine gave peak plasma concentration after 2.6 h, averaged 0.071 μg/mL, in 4 adults.	[67, 68]

Table 3. Continued

Category-No.	Name (synonym)	Type of efficacy	Therapeutic levels	Toxic levels	Fatal levels	Available in Japan	Supplemental information	Ref.
2-5	Cyclobarbital	Sedative	2−6	10	20		$T_{1/2}$: 8−17 h ・Cyclobarbital belongs to a barbiturate group, which have binding affinity to GABA receptors. ・In Russia, cyclobarbital was distributed as combination with other drugs (10 mg diazepam and 100 mg cyclobarbital); now, not available. ・Cyclobarbital was frequently used in suicidal cases, and thus withdrawn at 1973 in Japan.	[68]
2-6	Flunitrazepam	Sedative	0.005−0.015	0.05	30, 63, 84	○	$T_{1/2}$: 10−20 h, 9−25 h ・Flunitrazepam is one of aminobenzodiazepine derivatives, which is used for treatment of insomnia and anesthesia. ・In therapeutic use, adult oral or injection doses are 1−2 mg at once, for insomnia or pretreatment of anesthesia. ・A 2 mg oral administration gave peak plasma concentration averaging 0.008 μg/mL after 2 h, in 7 adults. ・In investigations, metabolite 7-aminoflunitrazepam can be detected as predominant target, as substitute of flunitrazepam.	[67, 68] [78]
2-7	Glutethimide	Sedative	0.2−5, 2−12	10−30	20−50, 10−80		$T_{1/2}$: 5−22 h ・Glutethimide is piperidinedione derivative used as sedative, pharmacological actions of which are similar to barbiturate group. ・In therapeutic use, adult oral doses are 250−500 mg at once. ・A 500 mg oral administration gave mean peak plasma concentration at 4.3 μg/mL after 2.2, in 6 adults.	[67−69]
2-8	Pentazocine	Analgesic	0.01−0.2, 0.03−1	1−2, 2−5	3	○	$T_{1/2}$: 2 h, 1−3 h, 5h ・Pentazocine is benzomorphan derivative used as analgesic agent and is also a weak narcotic antagonist. ・30 mg of pentazocine is used at once every 3−4 h for subcutaneous, intramuscular and intravenous injection in adults. ・A 45 mg intramuscular administration gave peak plasma concentration averaging 0.14 μg/mL after 15−60 mins, in 8 post-operative adults.	[67−69] [79]
2-9	Pentobarbital	Sedative	1−10	10−19, 5−	15−25	○	$T_{1/2}$: 20−40 h, 15−48 h ・Pentobarbital is a short to middle acting barbiturate derivative, which used as sedative-hypnotic agent. ・In therapeutic use, adult oral doses are 15−200 mg at once. ・A 100 mg oral administration gave peak serum concentration 1.2−3.1 μg/mL after 0.5−2 hours, in adults.	[67−69] [80]
3-1	Allobarbital	Sedative	2−5	10	20−30	○	$T_{1/2}$: 40−48 h, ・Allobarbital is an intermediate acting barbiturate derivative, which act and used as sedative-hypnotic agent. ・Allobarbital have not been used widely as other barbiturate derivatives so far, without some European countries.	[68] [81]

Table 3. Continued

Category-No.	Name (synonym)	Type of efficacy	Therapeutic levels	Toxic levels	Fatal levels	Available in Japan	Supplemental information	Ref.
3-2	Alprazolam	Sedative	0.005−0.05, 0.025−0.1	0.1−0.4	0.1−2.1	○	$T_{1/2}$: 6−27h ・Alprazolam is triazolobenzodiazepine derivatives, which is used as short acting antidepressant and anxiolytic agent. ・In therapeutic use, adult oral doses are 0.25−2 mg at once, not exceeding to 6 mg, a day. ・A 1 mg oral administration gave peak plasma concentration averaging 0.019 μg/mL after 1.3 hours, in 6 adults.	[67−69] [81] [82]
3-3	Amfepramone (diethylpropion)	Stimulant	0.007−0.02	2	5.4		$T_{1/2}$: 2 h ・Amfepramone is phenethylamine derivative used as appetite suppressant agent. It is widely known as “diethylpropion” than as amfepramone. ・As appetite suppressant, adult oral doses are 75 mg per day. ・A 25 mg oral administration gave peak plasma concentration averaging 0.01 μg/mL after 2 h in 6 adults.	[67, 68] [83]
3-4	Aminorex (aminoxaphen)	Stimulant	n/a	n/a	n/a (at least 34 fatalities reported)		$T_{1/2}$: 1−3 h (intravenous in animal) ・Aminorex is an oxazoline derivative used as appetite suppressant agent, firstly used at 1965. ・After used as appetite suppressant, it was withdrawn in 1972 because primary pulmonary hypertension and cardiovascular disorder were observed in users. However, it could be contained in illegal products.	[67] [84]
3-5	Barbital	Sedative	2−20	20−50, 60−80	50, 90	○	$T_{1/2}$: 2 days ・Barbital is long used sedative-hypnotic agent. It was withdrawn in United States, but is still available in Japan. ・In treatment for insomnia, adult oral doses are 30−200 mg at once before bedtime. ・A 1500 mg oral administration gave peak serum concentration averaging 26 μg/mL after 12 h, in 4 adults.	[67, 68]
3-6	Benzphetamine (benzfetamine)	Stimulant	0.025−0.5	0.5	14		$T_{1/2}$: n/a ・Benzphetamine is used as appetite suppressant agent. Methamphetamine is one of metabolites of benzphetamine. ・In treatment for obesity, adult oral doses are 25−50 mg, in 1−3 portions a day.	[67, 68] [85]
3-7	Bromazepam	Sedative	0.05−0.2	0.3−0.4	1−2, 0.8−5.0	○	$T_{1/2}$: 20 h ・Bromazepam is benzodiazepine derivative having binding affinity to GABA receptors, and acts as agonist. ・In therapeutic use, adult oral doses are 6−30 mg in 2 portions a day. ・A 6 mg oral administration gave peak plasma concentration averaging 0.088 μg/mL after 1.5 h, in adults.	[67, 68] [86]

Table 3. Continued

Category-No.	Name (synonym)	Type of efficacy	Therapeutic levels	Toxic levels	Fatal levels	Available in Japan	Supplemental information	Ref.
3-8	Brotizolam	Sedative	0.001−0.02	0.02	0.01−0.03	○	$T_{1/2}$: 7 h, 3.6−7.9 h ・Brotizolam is triazolobenzodiazepine derivative having binding affinity to GABA receptors, and acts as agonist. ・In therapeutic use, adult oral doses are 0.25−0.5 mg at once before bed time. ・A 0.25 mg oral administration gave peak plasma concentration averaging 0.0049 μg/mL after 0.9 h, in 8 adults.	[67, 68] [87]
3-9	Butobarbital (butethal)	Sedative	2.9−4.1	118	166		$T_{1/2}$: 34−42 h ・Butobarbital (butethal) is barbiturate derivative used as sedative-hypnotic agent. It was withdrawn in United States, but is still available in Europe. ・In therapeutic use, adult oral doses are 50−200 mg at once for insomnia. ・A 200 mg oral administration gave peak serum concentration 2.9−4.1 μg/mL after 0.6−2 h, in 5 adults.	[67]
3-10	Camazepam	Sedative	0.1−0.6	2	n/a		$T_{1/2}$: 20−24 h, 6−10 h (i.v. in animal) ・Camazepam is benzodiazepine derivative, and is metabolized to temazepam as its prodrug *in vivo*. ・In therapeutic use, adult oral doses are 15−30 mg at once a day. ・A 20 mg oral administration gave peak plasma concentration 0.06 μg/mL after 7 h, in adult.	[67, 68]
3-11	Chlordiazepoxide	Sedative	0.4−3	3.5−15, 20	20, 26	○	$T_{1/2}$: 6−27 h ・Chlordiazepoxide can produce other benzodiazepines, as their prodrug. As metabolites, nordiazepam and oxazepam would be produced *in vivo*. ・In therapeutic use, adult oral or intermuscular doses are 5−100 mg, not to exceed 300 mg a day. ・A 30 mg oral administration gave peak plasma concentration averaging 1.6 μg/mL after 4 h, in 2 adults.	[67−69] [88]
3-12	Clobazam	Sedative, Anticonvulsant	0.03−0.3	0.5	1.5 (with diazepam 1.1), 3.9	○	$T_{1/2}$: 10−50 h ・Clobazam belongs to benzodiazepine derivatives, thus act as agonist for GABA receptors. ・In therapeutic use, adult oral doses are 10 mg at once, up to 30 mg a day. ・A 10 mg oral administration gave peak plasma concentration averaging 0.173 μg/mL after 1.4 h, in 14 adults.	[67, 68] [89]
3-13	Clonazepam	Sedative, Anticonvulsant	0.02−0.07	0.1	median 0.3 (with multiple drug overdoses, in 51 persons)	○	$T_{1/2}$: 19−60 h ・Clonazepam is one of benzodiazepine derivatives. As other benzodiazepines, it is used as sedative and anti-convulsant agent. ・In therapeutic use, adult oral doses are 2−6 mg, in 1−3 portions a day. ・A 2 mg oral administration gave peak plasma concentration averaging 0.011 μg/mL after 3.1 h, in 12 adults.	[67, 68] [81] [90]
3-14	Clonazolam	Sedative	n/a	n/a	n/a		$T_{1/2}$: n/a ・Clonazolam is triazolo benzodiazepine analog, which was detected as designer benzodiazepine, and being sold through internet. ・Clonazolam was first reported in 1971 to be highly potent as sedative agent, which can lead to abuse easily.	[91]

Table 3. Continued

Category-No.	Name (synonym)	Type of efficacy	Therapeutic levels	Toxic levels	Fatal levels	Available in Japan	Supplemental information	Ref.
3-15	Clorazepate (Clorazepric acid)	Sedative	0.02−0.8 (as nordiazepam)	1.5−2 (as nordiazepam)	5.5−15 (as nordiazepam)	○	$T_{1/2}$: 1−2 h ・Clorazepate is prodrug for nordiazepam and oxazepam. ・In therapeutic use, adult oral doses are 9−30 mg, in 2−4 portions a day. ・A 15 mg oral administration gave peak plasma concentration averaging 0.16 μg/mL after 2 h, in 2 adults.	[67, 68] [92]
3-16	Clotiazepam	Sedative	0.1−0.7	n/a	n/a	○	$T_{1/2}$: 3−12 h ・Clotiazepam is benzodiazepine derivative, which used as sedative-hypnotic agent. ・In therapeutic use, adult oral doses are 15−30 mg, in 1−3 portions a day. ・A 5 mg oral administration gave peak plasma concentration averaging 0.179 μg/mL after 0.5 h, in 6 adults.	[67, 68] [93]
3-17	Cloxazolam	Sedative	0.016 (4 mg for 24 persons)	n/a	n/a	○	$T_{1/2}$: 50−200 h (as delorazepam), 2−4 h (animal) ・Cloxazolam is prodrug for delorazepam; they have affinity to GABA receptors, which used as sedative-hypnotic agent. ・In therapeutic use, adult oral doses are 3−12 mg, in 3 portions a day. ・A 2 mg oral administration gave peak plasma concentration averaging 0.0074 μg/mL after 2.8 h, in 7 adults.	[67] [94]
3-18	Delorazepam	Sedative	see cloxazolam	see cloxazolam	see cloxazolam		Delorazepam is predominant metabolite of cloxazolam.	[67]
3-19	Diazepam	Sedative, anti-convulsant	0.1−2.5	3−5	4.8−30	○	$T_{1/2}$: 21−37 h, 24−48 h ・Diazepam is benzodiazepine derivative, which used as sedative-hypnotic and anticonvulsant agent by oral, intramuscular and intravenous administration. ・In therapeutic use, adult oral doses are 2−5 mg at once, in 2−4 times. For intravenous or intramuscular injection, 10 mg would be administrated at once. ・A 5 mg oral administration gave peak plasma concentration averaging 0.179 μg/mL after 0.5 h, in 6 adults.	[67, 68] [95]
3-20	Diclazepam (Chlorodiazepam)	Sedative	n/a	n/a	n/a		$T_{1/2}$: 42 h ・Diclazepam is benzodiazepine derivative, which has not been used as prescription medicine. In animal models, pharmacological effect like other benzodiazepines were observed. ・Self-administration study of 1 mg diclazepam gave peak plasma concentration averaging 0.0034 μg/mL after 3 hours in an adult.	[96]
3-21	Estazolam	Sedative	0.055−0.2	1, 1.25	0.48	○	$T_{1/2}$: 10−24 h, 10−30 h ・Estazolam is benzodiazepine derivative, which have affinity to GABA receptor as its agonist. ・In therapeutic use, adult oral doses are 1−4 mg at once before bedtime. ・A 1 mg oral administration gave peak plasma concentration averaging 0.055 μg/mL within 2 h, in 17 adults.	[67, 68] [97]

Table 3. Continued

Category-No.	Name (synonym)	Type of efficacy	Therapeutic levels	Toxic levels	Fatal levels	Available in Japan	Supplemental information	Ref.
3-22	Ethchlorvynol	Sedative	0.5−8	20	50		$T_{1/2}$: 10−25 h, 19−32 h ・Ethchlorvynol have affinity to GABA receptors, acting as its agonist. It is used as sedative and hypnotic agent. ・In therapeutic use, adult oral doses are 100−500 mg at once, up to 1000 mg. ・A 200 mg oral administration gave peak plasma concentration averaging 1.2 μg/mL after 1 h, in 6 adults.	[67, 68]
3-23	Ethinamate	Sedative	1.5−10	50−100	200		$T_{1/2}$: 2 h, 1−3 h ・Ethinamate is carbamate derivative. It is used for treatment of insomnia. ・In therapeutic use, adult oral doses are 500−1000 mg before bedtime. ・A 1000 mg oral administration gave peak plasma concentration averaging 5.9 μg/mL after 1 h, in 8 adults.	[67, 68]
3-24	Ethyl loflazepate	Sedative	n/a	n/a	n/a	○	$T_{1/2}$: 51−103 h (loflazepate) ・Ethyl loflazepate is benzodiazepine derivative. They have affinity to GABA receptors as its agonist, showing anxiolytic, sedative and muscle relaxant properties. ・In therapeutic use, adult oral dose is 2 mg, in 1−2 portions a day. ・A 2 mg oral administration gave peak plasma concentration averaging 0.034 μg/mL after 2.1 h, in 4 adults.	[67] [98]
3-25	Ethyl amphetamine (Etilamfetamine)	Stimulant	n/a	0.5 (with 0.221 amphetamine)	n/a		$T_{1/2}$: n/a ・Ethyl amphetamine is an amphetamine analog, used as appetite suppressant. ・In therapeutic use, adult oral doses are 10−30 mg a day.	[67]
3-26	Etizolam	Sedative	0.008−0.02	0.03		○	$T_{1/2}$: 7−15 h ・Etizolam is benzodiazepine derivative, having affinity to GABA receptor. Its prolonged use can lead to dependency easily. ・In therapeutic use, adult oral dose is 3 mg, in 3 portions a day. ・A 0.5 mg oral administration gave peak plasma concentration averaging 0.008 μg/mL after 0.9 h, in 6 adults.	[67, 68] [99]
3-27	Fencamfamine	Stimulant	0.03 (probably therapeutic level, found in fatal multiple overdose case)	n/a	n/a		$T_{1/2}$: 12−16 h ・Fencamfamine is an amphetamine analog, used as appetite suppressant and psychostimulant. ・In therapeutic use, adult oral doses are 10−60 mg a day.	[67]
3-28	Fenproporex	Stimulant	n/a	n/a	0.9 (in a suicide case by gamma-hydroxybutyrate)		$T_{1/2}$: 2 h ・Fenproporex is a phenethylamine analog, used as appetite suppressant in some countries. ・In therapeutic use, adult oral doses are 10−20 mg a day.	[67]

Table 3. Continued

Category-No.	Name (synonym)	Type of efficacy	Therapeutic levels	Toxic levels	Fatal levels	Available in Japan	Supplemental information	Ref.
3-29	Flualprazolam	Sedative	n/a	n/a	n/a		$T_{1/2}$: n/a ・Flualprazolam is one of benzodiazepine derivative which was synthesized as late as 1970s, although was never marketed throughout the world. In 2018, however, flualprazolam was found in drug abuse case in Sweden.	[100]
3-30	Flubromazolam	Sedative	n/a	n/a	n/a		$T_{1/2}$: n/a ・Flubromazolam is triazolo benzodiazepine analog, which was detected as designer benzodiazepine, and being sold through internet. ・Flubromazolam was estimated to have higher potency than that of its analog flubromazepam, although no detailed data on flubromazolam is available.	[91]
3-31	Fludiazepam	Sedative	n/a	n/a	n/a	○	$T_{1/2}$: 23 h ・Fludiazepam is benzodiazepine derivative, having affinity to GABA receptor and acting as agonist. Its use can lead to dependency. ・In therapeutic use, adult oral dose is 0.75 mg, in 3 portion a day. ・A 0.25 mg oral administration gave peak plasma concentration averaging 0.0058 μg/mL after 1 h, in adults.	[101]
3-32	Flurazepam	Sedative	0.02−01	0.2−0.5	0.5−5.5, 0.8−24	○	$T_{1/2}$: 1−3 h, 2.3−12 h ・Flurazepam is benzodiazepine derivative, used for preoperative sedation and treatment of insomnia. ・In therapeutic use, adult oral doses are 10−30 mg, in 1−2 portions prior to bedtime. ・A 30 mg oral administration gave peak plasma concentration averaging 0.002 μg/mL after 1 h, in 9 adults. After administration, flurazepam is metabolized to active metabolite desalkylflurazepam in short interval.	[67] [102]
3-33	Halazepam	Sedative	0.03−0.1	see nordazepam	see nordazepam		$T_{1/2}$: 30−40 h ・Halazepam is benzodiazepine derivative. After administration, they are metabolized to active metabolite, nordazepam.	[68]
3-34	Haloxazolam	Sedative	n/a	n/a	n/a	○	$T_{1/2}$: n/a ・Haloxazolam is benzodiazepine derivative, having affinity to GABA receptor; its pharmacological potency is similar to nitrazepam. They are used for treatment of insomnia. ・In therapeutic use, adult oral dose is 5−10 mg at once, before bedtime. ・In oral administration for animals, peak organ concentrations were observed after 1 hour. Almost no haloxazolam could not be detected 24−72 h after administration.	[103]

Table 3. Continued

Category-No.	Name (synonym)	Type of efficacy	Therapeutic levels	Toxic levels	Fatal levels	Available in Japan	Supplemental information	Ref.
3-35	Ketazolam	Sedative	0.001−0.02	n/a	n/a		$T_{1/2}$: 1−3 h ・Ketazolam is benzodiazepine derivative, having affinity to GABA receptor. As metabolite, diazepam can be produced from ketazolam *in vivo*.	[68]
3-36	Lefetamine (Lephetamine)	Analgesic	n/a	n/a	n/a		$T_{1/2}$: n/a ・Lefetamine is opioid analgesic and antitussive agent, being developed by Santen pharmaceuticals in Japan in 1940s, as "Santenol". They were abused in Japan in 1950s.	[104]
3-37	Loprazolam	Sedative	0.003−0.01	n/a	n/a		$T_{1/2}$: 5 h ・Loprazolam is benzodiazepine derivative, having affinity to GABA receptor. ・In therapeutic use, adult oral dose is 1−2 mg for insomnia. ・A 1 mg oral administration gave peak plasma concentration averaging 0.004 μg/mL after 2 h, in elderly.	[68] [105]
3-38	Lorazepam	Sedative	0.02−0.25	0.3−0.5	0.52, 2.8	○	$T_{1/2}$: 9−16 h, 10−40 h ・Lorazepam is benzodiazepine derivative, having affinity to GABA receptor. Lorazepam is used for treatment of depression and anxiety. ・In therapeutic use, adult oral dose is 1−3 mg, in 2−3 portions a day. ・A 2 mg oral administration gave peak plasma concentration averaging 0.018 μg/mL after 2 h, in 8 adults.	[67, 68] [106]
3-39	Lormetazepam	Sedative	0.002−0.025	0.1	n/a	○	$T_{1/2}$: 7−17 h, 10−45 h ・Lormetazepam is benzodiazepine derivative, having affinity to GABA receptor. Lormetazepam is used for treatment of insomnia. ・In therapeutic use, adult oral dose is 1−2 mg at once before bedtime. Potency of lormetazepam was stronger than that of diazepam in animals. ・A 1 mg oral administration gave peak plasma concentration averaging 0.0056−0.0070 μg/mL after 2−2.2 h, in 6 adults.	[67, 68] [107]
3-40	Mazindol	Stimulant, Appetite-suppressant	n/a	n/a	n/a	○	$T_{1/2}$: 6−16 h ・Mazindol is amphetamine analog. As monoamine retake inhibitors, it is used for treatment of obesity as appetite suppressant. ・In therapeutic use, adult oral doses are 0.5 mg in 1 portion a day. ・A 2 mg oral administration gave peak plasma concentration averaging 0.0025 μg/mL after 2 h, in 2 adults.	[67] [108]
3-41	Medazepam	Sedative	0.1−1	0.6	n/a	○	$T_{1/2}$: 1−2 h, 2−5 h ・Medazepam is benzodiazepine derivative. Diazepam, temazepam and oxazepam are produced in metabolism of medazepam. ・In therapeutic use, adult oral doses are 10−30 mg a day. ・A 20 mg oral administration gave peak plasma concentration averaging 0.52 μg/mL after 1 h, in 9 adults.	[67] [109]

Table 3. Continued

Category-No.	Name (synonym)	Type of efficacy	Therapeutic levels	Toxic levels	Fatal levels	Available in Japan	Supplemental information	Ref.
3-42	Mefenorex	Stimulant, Appetite-suppressant	n/a	n/a	n/a		$T_{1/2}$: 2.5−4 h (excretion in urine) ・Mefenorex is amphetamine analog; amphetamine is produced as metabolite of mefenorex. ・It is used as appetite suppressant. ・In therapeutic use, adult oral doses are 40−80 mg in 1 portion a day.	[67]
3-43	Meprobamate	Sedative	5−10	10−25	30		$T_{1/2}$: 6−17 h ・Meprobamate is carbamate derivative, intended to be used as tranquilizer. Meprobamate is produced as metabolite of carisoprodol (muscle relaxant); meprobamate can be biomarker of exposure to carisoprodol. ・In therapeutic use, adult oral doses are 200−600 mg at once, for 3−4 times a day. ・A 800 mg oral administration gave peak plasma concentration averaging 12−19 μg/mL after 2 h, in 6 adults.	[67, 68]
3-44	Mesocarb	Stimulant	n/a	n/a	n/a		$T_{1/2}$: 2−4 h ・Mesocarb is phenethylamine analog. It is used for treatment of attention-deficit/hyperactivity disorder (ADHD) as stimulant. ・In therapeutic use, adult oral doses are 5−10 mg once a day. ・A 10 mg oral administration gave peak plasma concentration averaging 0.065 μg/mL after 1.6 h, in 4 adults.	[67] [110]
3-45	Methylphenobarbital (mephobarbital)	Sedative	0.5−1.5	40−			$T_{1/2}$: 48−52 h ・Methylphenobarbital, also known as mephobarbital, belongs to a barbiturate group. Phenobarbital is produced as metabolite of methylphenobarbital. ・In therapeutic use, adult oral maintenance doses are 200−600 mg a day. ・A 800 mg oral administration gave peak plasma concentration averaging 2.5−3.5 μg/mL after 2−8 h, in 2 adults.	[67, 68]
3-46	Methyprylon(e)	Sedative	10−20	25−75	50−100		$T_{1/2}$: 3−6 h, 9−11 h ・Methyprylon is piperidinedione derivatives, used for treatment of insomnia. Its use can lead to dependency. ・After being withdrawn from major markets, methyprylon is not used commonly nowadays.	[68]
3-47	Midazolam	Sedative	0.04−0.25	1−1.5	0.05−2.4	○	$T_{1/2}$: 1.5−6.4 h ・Midazolam is benzodiazepine derivative used for pre-operative sedation by intravenous or intramuscular administration. As GABA agonist, they produce muscle relaxant, sedative and hypnotic effects. ・In preanesthetic use, 0.03 mg/kg dose is administrated intravenously over 1 minute, not exceeding to 0.3 mg/kg. ・A 7.5 mg intramuscular administration gave peak plasma concentration averaging 0.09 μg/mL after 0.5 h, in adults.	[67, 68] [111]

Table 3. Continued

Category-No.	Name (synonym)	Type of efficacy	Therapeutic levels	Toxic levels	Fatal levels	Available in Japan	Supplemental information	Ref.
3-48	Nimetazepam	Sedative	n/a	n/a	n/a		$T_{1/2}$: 10−30 h ・Nimetazepam is benzodiazepine derivative. It is potent muscle relaxant, sedative and hypnotic agent, and can lead to dependency easily. Although nimetazepam was manufactured only in Japan until 2015, it is withdrawn from the market nowadays. ・In therapeutic use, adult oral doses are 3−5 mg once before bedtime. ・A 5 mg oral administration gave peak plasma concentration averaging 0.013 μg/mL after 2−4 h, in adults.	[67]
3-49	Nitrazepam	Sedative	0.03−0.1	0.2−3	5, 1.2−9	○	$T_{1/2}$: 20−30 h, 17−48 h ・Nitrazepam is benzodiazepine derivative. It is use as anticonvulsant agent, and for treatment of insomnia. ・In therapeutic use for insomnia, adult oral doses are 5−10 mg once before bedtime. ・A 10 mg oral administration gave peak plasma concentration averaging 0.084 μg/mL after 2 h, in adults.	[68] [112]
3-50	Nordazepam (nordiazepam, desmethyldiazepam)	Sedative	0.02−0.8	1.5−2	5.5−15		$T_{1/2}$: 40−80 h, 31−97 h ・Nordazepam is one of major metabolites of clorazepate, oxazolam, pinazepam and of diazepam; ketazolam and medazepam can also produce nordazepam. Oxazepam is produced as an active metabolite of nordazepam. ・In therapeutic use, adult oral doses are 7.5−15 mg in one or more portions a day. ・A 5−10 mg oral administration gave peak plasma concentration ranging 0.118−0.228 μg/mL after 2 h, in 8 adults.	[67, 68] [113]
3-51	Oxazepam	Sedative	0.2−1.5	2	3−5, 4.4−6.1		$T_{1/2}$: 4−16 h, 6−20 h ・Oxazepam is benzodiazepine derivative as an active metabolite of clorazepate and nordazepam; temazepam and diazepam are also prodrug of oxazepam. ・In therapeutic use, adult oral doses are 30−60 mg in 3−4 portions a day. ・A 15 mg oral administration gave peak serum concentration averaging 0.31 μg/mL after 1.5 h, in 7 adults.	[67]
3-52	Oxazolam	Sedative	see nordazepam	see nordazepam	see nordazepam	○	・Oxazolam is one of prodrugs of nordazepam, which is active metabolite of oxazolam.	[114]
3-53	Pemoline	Stimulant	1−7	n/a	5	○	$T_{1/2}$: 7−13 h ・Pemoline is used for treatment of depression and sleep disorder, as dopamine retake inhibitor. ・In therapeutic use, adult oral doses are 10−30 mg once a day for depression, 20−200 mg in 2 portions a day for sleep disorder. ・A 37.5−50 mg oral administration gave peak plasma concentration averaging 0.98 μg/mL after 2.7 h, in 4 adults.	[67, 68] [115]
3-54	Phenazepam	Sedative	0.02−0.04	0.208−0.632 (average), 0.04−3.2 (range)	0.386 (with morphine and codeine), 0.97−1.64		$T_{1/2}$: 60 h, 40−300 h ・Phenazepam is benzodiazepine derivative, developed in Russia. It is use for treatment of anxiety. ・In therapeutic use, adult oral dose is 0.5 mg for 2−3 times a day. ・A 3−5 mg oral administration gave peak plasma concentration 0.024−0.038 μg/mL after 4 h, in 2 adults.	[67, 68]

Table 3. Continued

Category-No.	Name (synonym)	Type of efficacy	Therapeutic levels	Toxic levels	Fatal levels	Available in Japan	Supplemental information	Ref.
3-55	Phendimetrazine	Stimulant	0.02−0.1	n/a	0.3−0.7		$T_{1/2}$: 2−4 h, 16−31 h ・Phendimetrazine is phenethylamine analog. It is used as appetite suppressant. ・In therapeutic use, adult oral doses are 70−210 mg a day. ・A 35 mg oral administration gave peak serum concentration averaging 0.09 μg/mL after 1 h, in 5 adults.	[67] [69]
3-56	Phenobarbital	Sedative	10−30	30−40	50−60	○	$T_{1/2}$: 48−144 h ・Phenobarbital is a barbiturate derivative, which is used as sedative and anticonvulsant agent by oral or intramuscular/subcutaneous administration. ・In therapeutic use, adult oral doses are 30−200 mg in 1−4 portions a day as anticonvulsant. For intramuscular or subcutaneous injection, 50−200 mg of doses are administrated in 1−2 portions a day. ・A 120 mg (powder) oral administration gave peak blood concentration averaging 4.6 μg/mL after 2.4 h, in 5 adults.	[67, 68] [116]
3-57	Phentermine	Stimulant, Appetite suppressant	0.03−0.1	0.9	1		$T_{1/2}$: 19−24h ・Phentermine is amphetamine analog. It is used as appetite suppressant for treatment of obesity. ・In therapeutic use, adult oral doses are 15−30 mg a day. ・A 0.375 mg/kg oral administration gave peak blood concentration averaging 0.09 μg/mL after 4 h, in 6 adults.	[67, 68]
3-58	Pinazepam	Sedative	see nordazepam	see nordazepam	see nordazepam		$T_{1/2}$: 12−20 h ・Pinazepam is metabolized to nordazepam (desmethyldiazepam), as its prodrugs.	[67]
3-59	Pipradrol	Stimulant, Appetite suppressant	n/a	n/a	n/a		$T_{1/2}$: n/a ・Pipradrol is piperidine analog stimulant which used for treatment of attention-deficit/hyperactivity disorder (ADHD), and obesity. Pipradrol was withdrawn in Japan, but is still used in some countries nowadays.	
3-60	Prazepam	Sedative	0.2−0.7	1	0.8−5		$T_{1/2}$: 1−3 h ・Prazepam is benzodiazepine derivative; nordazepam is its predominant active metabolite. Prazepam has been withdrawn in Japan. ・In therapeutic use, adult oral dose is 20−60 mg a day. ・After administration, almost all prazepam is estimated to be metabolized to nordazepam.	[67, 68]
3-61	Propylhexedrine	Stimulant	0.01	0.5	2−3		$T_{1/2}$: n/a ・Propylhexedrine is methamphetamine analog. It is used as appetite suppressant, and nasal decongestant agent for rhinitis. ・In therapeutic use, adult inhalation dose is 0.25 mg/inhalation.	[67, 68]

Table 3. Continued

Category-No.	Name (synonym)	Type of efficacy	Therapeutic levels	Toxic levels	Fatal levels	Available in Japan	Supplemental information	Ref.
3-62	Pyrovalerone	Stimulant			0.042 and 0.059 (femoral vein and heart blood)		$T_{1/2}$: 1.5 h (rat) ・Pyrovalerone is synthetic cathinone, used as appetite suppressant. In 2010s, its various analogs have been abused as "bath salt". ・In therapeutic use, adult oral doses are 20−40 mg once. ・Pharmacodynamic data of pyrovalerone in human has not been reported,	[67]
3-63	Quazepam	Sedative	0.01−0.15			○	$T_{1/2}$: 39−53 h ・Quazepam is benzodiazepine derivative, having affinity to GABA receptors. It is used for treatment of insomnia and for preoperative sedation. ・In therapeutic use, adult oral dose is 20 mg before bed time, not exceeding to 30 mg. ・A 25 mg oral administration gave peak plasma concentration 0.148 μg/mL after 1.5 h, in 6 adults.	[67] [81] [117]
3-64	Remimazolam	Sedative	n/a	n/a	n/a		$T_{1/2}$: 0.6−0.9 h ・Remimazolam is very-short acting benzodiazepine derivative, which can lead to dependency easily. Remimazolam was approved as medicine around 2020, and being used for introducing anesthesia and preoperative sedation. ・For introducing anesthesia, 12 mg/kg/h dose is used by intravenous administration; for maintaing anesthesia 1 mg/kg/h dose should be used. ・A 0.5 mg/kg/1 min intravenous administration gave peak plasma concentration 7.0 μg/mL just after administration, in 5 adults.	[118]
3-65	Secbutabarbital (butabarbital)	Sedative	5−15	20	30		$T_{1/2}$: 34−42h ・Secbutabarbital is a barbiturate derivative, which is used as sedative and hypnotic agent. ・In therapeutic use, adult oral doses are 15−30 mg for 3−4 times a day for sedation. ・A 600 mg (unusual large amount) oral administration gave peak blood concentration averaging 12 μg/mL after 0.5 h, in 5 adults.	[67, 68]
3-66	Temazepam	Sedative	0.02−0.9	1	8.2, 14		$T_{1/2}$: 3−13 h, 6−25 h ・Temazepam is active metabolite of diazepam, and temazepam also produce oxazepam as metabolite. ・In therapeutic use, adult oral doses are 15−30 mg before bedtime. ・A 20 mg oral administration gave peak blood concentration averaging 0.363−0.856 μg/mL after 0.25−1.25 h, in 6 adults.	[68] [113]
3-67	Tetrazepam	Sedative, muscle relaxant	0.05−1				$T_{1/2}$: 16−44 h ・Tetrazepam is benzodiazepine derivative, used for muscle relaxant, anxiolytic and anticonvulsant agent. ・In therapeutic use, adult oral doses are 50 mg for 1−2 times a day. ・A 50 mg oral administration gave peak serum concentration averaging 0.512−0.558 μg/mL after 2 h, in 12 adults.	[67, 68]

Table 3. Continued

Category-No.	Name (synonym)	Type of efficacy	Therapeutic levels	Toxic levels	Fatal levels	Available in Japan	Supplemental information	Ref.
3-68	Triazolam	Sedative	0.002−0.02	0.04	0.022−0.078	○	$T_{1/2}$: 1.8−3.9 h, 2−5 h ・Triazolam is wide used benzodiazepine derivative tranquilizer, being well known as "halcion". Triazolam is frequently abused in drug facilitated crimes ・In therapeutic use, adult oral doses are 0.125−0.25 mg a day. ・A 0.25 mg oral administration gave peak serum concentration averaging 0.003 μg/mL after 0.75−1.5 h, in 6 adults.	[67, 68] [119] [120]
3-69	Vinylbital	Sedative	1−3	5	8		$T_{1/2}$: 18−33 h ・Vinylbital is a barbiturate derivative, which is used as sedative and hypnotic agent. Its pharmacological profile is said to be similar to pentobarbital.	[68]
3-70	Zolpidem	Sedative	0.08−0.2	0.5	2−4, 9.6 (intravenous injection case)	○	$T_{1/2}$: 2−3 h ・Zolpidem is imidazopyridine derivative, have different structure from that of benzodiazepine derivatives. Zolpidem is used as short-time acting hypnotic agent. ・In therapeutic use, adult oral doses are 5−10 mg before bed time. ・A 3.5 mg oral administration gave peak serum concentration averaging 0.032 μg/mL after 3 h, in 33 adults.	[67, 68] [121]
3-71	Zopiclone	Sedative	0.01−0.05	0.15	0.6−1.8	○	$T_{1/2}$: 3.5−8 h ・Zopiclone is cyclopyrrolone derivative, used as short-time acting hypnotic agent. Zopiclone is known as one of "Z-drugs" with zolpidem; their pharmacological properties are similar to that of benzodiazepines, though structures are quite different. ・In therapeutic use, adult oral doses are 7.5−10 mg before bed time. ・A 5 mg oral administration gave peak blood concentration averaging 0.029 μg/mL after 1−2 h, in 8 adults.	[67, 68] [122]

C_{max}: maximum serum/plasma concentration, $T_{1/2}$: biological half life time, GABA: γ- Aminobutyric acid, n/a: not available

Toxicological Analysis on Forensic Investigations in Determining Cause of Death

As mentioned before, the distribution/concentration of substances may be changed dynamically due to condition of forensic samples, where various factors can vary widely[6,65,123,124]. Therefore, in drug related cases, it can be often difficult for examiners to determine the degree of contribution of concerned substances to the manner of death, by comparing the lethal and poisoning levels of the drugs in samples with those reported in previous literature or databases, and the administrated amount of the compounds prior to the death[61]; regarding some drugs, there may be no data to refer to. In such cases, it is necessary to evaluate the pharmacological effects of drugs and the cause of death, along with considering autopsy findings and other test results, which are also quite important information in forensic examinations and judgement of cause of the death. When investigating the cause of death in drug related cases, the medical examiner must organically link the autopsy findings with results on forensic toxicological analysis for drugs, considering whether the autopsy findings can be consistent with those of other similar cases and the pharmacological effects of the drugs involved, and also whether other causes of death can be ruled out.

Conclusion

In this review, we have presented and outlined comprehensive perspectives on toxicological analysis and its unique aspects in forensic investigations. On analysis for drugs and toxic substances in investigations, the results of measurements are provided in simple and clear numbers, as their concentrations. For this reason, there should be a possibility (risk) that the concentrations itself may sometimes be taken as, so to speak, a kind of definitive threshold and/or factor determining the cause of death, although they are just one of a lot of evidences/findings in each investigation. Thus, it is desirable for examiner to investigate and evaluate the cause of death based on comprehensive medical/forensic perspective, keeping in mind that the results of toxicological analysis are only one of factors in determining the cause/manner of death, as described before. In addition to each analytical result on target substances, it is also quite desirable to record details of the samples collected including (estimated) time interval until analysis since death, analytical instruments, techniques and procedures used for the analysis, so that the previous results can be verified, compared and, if needed, investigated again later. These details on toxicological analysis can bring about "chain of custody" of the whole investigations.

Acknowledgments

This work was supported by research grant from Japan Society for the Promotion of Science KAKENHI Grant-in-Aid for Scientific Research(C), Grant Number 21K10519.

Conflict of Interest

There are no financial or other relations that could lead to a conflict of interest.

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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