I.6 A computer system for diagnosis of causative drugs and poisons developed by the Japan Poison Information Center (Tokyo)

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Introduction

In addition to the well known Tokyo Sarin Incident in 1995, the arsenic-adulteration incident in Wakayama and the cyanide-adulteration incident in Nagano both in 1998 seem to have triggered several ten poisoning cases, which took place in 1998–1999. An explosion incident of a chemical factory, a turnover incident of a chemical tank truck and a poisoning murder incident for insurance have also occurred recently. Such poisoning-related incidents are becoming more serious social problems also in Japan.

In the arsenic-adulteration incident of Wakayama, the identification of the causative poison was delayed for some time; the serious incident itself together with the criticism upon the delay made the Japanese Government reconsider the crisis-management system of Japan. Since the incident, the Japan Poison Information Center has also studied how to narrow toxin candidates to a single causative one, by methods other than actual analysis of toxins.

As a result of such efforts, the author et al. [1] have constructed a database for estimation of a causative toxin (assisting system for diagnosis of a causative toxin) according to clinical symptoms and a computer system for searching a toxin, which had been used previously, on the basis of poisoning situations. In additions, by registering experts for each toxin, which was targeted in the above systems, information exchange between a clinical doctor treating a poisoned patient and the expert of a poison has become possible [2].

The setting up of a detailed procedure of pretreatments and of conditions for instrumental analysis is usually difficult without any estimation of a target compound. It seems very important for clinical doctors and analysts to narrow causative toxins by means other than instrumental analysis.

Database according to poisoning symptoms (assisting system for diagnosis of a causative toxin)

Drugs and poisons to be targeted

To enhance the probability for estimation of a causative toxin, all of the numerous existing compounds should not be dealt with, but a limited number of toxic compounds should be picked up. Thus, compounds with high general toxicity, which had been used in the previous incidents, were chosen. Specific antidotes are available for some toxins; they were added to the toxins list. However, volatile poisons and corrosive compounds, which can be easily diagnosed by clinical doctors from the circumstances and symptoms, were excluded from the list. As a result, 488 compounds in 75 groups were chosen as shown in *Table 6.1*.

Table 6.1.

Target compounds for the database according to poisoning symptoms (the final poison groups classified)

	Industrial item		Agricultural item
1	Cyanide and its derivatives	1	Organophosphorus pesticides
2	Toluene/xylene	2	Carbamate pesticides
3	Ethylene glycol	3	Organochlorine insecticides
4	Methanol	4	Cartap
5	Carbon tetrachloride	5	Blasticidin S
6	Sulfur-containing compounds	6	Nicotine products
7	Hydrogen sulfide	7	Paraquat/diquat
8	Arsenic and its derivatives	8	Glyphosate
9	Cadmium and its derivatives	9	Glufosinate
10	Mercuric compounds/mercuric chloride	10	Urea herbicides
	–		–
	–		–
	–		–
			75 toxin groups

Listing of keywords for searching and their weighting

In poisoning cases, nausea and vomiting are usually observed in common; contradictory symptoms, such as respiratory acceleration and suppression, sometimes appear in poisoning by the same compound according to its severity. These complicated problems embarrassed us much. Much time and efforts were required for classifying clinical symptoms as keywords and for their weighting. More than 500 words describing poisoning symptoms were carefully checked in view of each pathology and grouped using our massive data being filed according to the kinds of causative toxins. As many as 120 words of clinical symptoms were finally chosen as keywords for computer research; abnormal values of clinical tests were also classified into 50 through the similar examinations and efforts. The weighting using scores of 0–9 was given to each word according to its rapid appearance of a characteristic symptom, but it seems somewhat dogmatic and groundless. For example, the severe diarrhea characteristically appearing in arsenic poisoning was scored 9; while the diarrhea due to cyanide poisoning 3. Conversely, the acidosis caused by arsenic poisoning is scored 1; while that by cyanide poisoning 9.

Construction of the system

After inputting the basic data of the names of toxic compounds and the scored keywords of symptoms into a computer, a system for estimating a causative toxin from a total score of symptoms appearing was constructed. In this system, Visual Basic 6.0 of Microsoft is being used, and it works well by installing it in a computer not powerless than the Windows 98.

In an upper part of the screen of CRT, the names of organs, such as digestive, respiratory and circulatory ones, are shown; when a responsible organ is clicked, the keywords (poisoning symptoms) for the organ appear. When each button on the left side of each keyword is clicked, “Not clear” is changed to “Observable”. After answering to all items of symptoms, the next organ should be clicked to undergo the same procedure; after completion for all organs, toxic compounds together with each total score appear being lined up according to the score number. The order of the candidate compounds is not important, but the difference in the score between the top and the second compounds is useful for the final judgment of a causative toxin.

Another characteristic of this system is the addition of a repeated questionnaire for some clinical symptoms, which is useful for evaluation (weighting) of candidate compounds listed in a high rank. The operator of the computer confirms the presence of symptoms by communicating with the responsible clinical doctor according to the questionnaire; this process can further enhance the probability of a causative toxin. To monitor if a bias in items to be input is present, the numbers of input for each organ and clinical test are shown on the screen at real-time as “item navigator”. When one of the causative toxin candidate is double-clicked, a detailed data file for the toxin can be opened. The 500 keywords of clinical (poisoning) symptoms, which had been chosen at the initial step of this study, are always stored in the computer, and any of the symptoms can be automatically added to the 120 keywords by clicking according to the need.

Although it is a quite different from the above system, the author et al. are developing a new system for estimating a causative compounds by using complex research of up to 14 keywords. In this system, the symptoms observable in common to various poisonings, such as vomiting, diarrhea, convulsion and tachycardia, are not useful for narrow down causative toxins; the symptoms with relatively high selectivity, such as miosis, hyperventilation and hypotension, and also the informations about a toxin, such as the color of solution or powder, smell, the form of a tablet or a capsule, the kind of a container, purpose, the name of manufacturer, solubility and melting point, are used as keywords for narrowing down toxins.

A computer system for estimating a causative toxin, which had been used previously, using the outline of an incident (retrospective diagnostic system)

A place of incident, a matrix of poison, severity of poisoning, the number of victims, described in news reports, were chosen and patterned, using poisoning incidents in which causative toxins had been specified, by searching newspaper database of the past 15 years. The above items chosen were grouped as follows, respectively; nine groups of places, *viz*. store, vending machin, station/underground passage, toilet, nursery school/kindergarten, elementary school/junior high school/senior high school, hospital/laboratory, other indoor or outdoor place, and place not clarified; eleven groups of the matrices in which poisons were mixed, *viz*, drink in a glass bottle, drink in a can, drink in a paper package, drink in a plastic bottle, drink in an unknown container, tea in a pot, tea in a water supply device, seasonings, foods, confectionaries, and others; four groups of severity of poisoning, *viz*. strange smell only, digestive symptom only, hospitalization, and very severe or fatal case; four groups of the number of victims, *viz*. only one, a few, more than ten, and more than several ten.

If a case, in which one person falls into a severe state after taking a drink in a bottle found near a vending machine, is assumed, paraquat and cyanide are shown as causative candidate toxins together with their probability data; when either of the toxins is double-clicked, the details of incidents which took place in the past appear; by this method, detailed informations about a causative toxin can be also obtained.

This kind of research system should have been fundamentally constructed by the police, because the informations obtainable only from the database of newspaper by the author et al. are limited. There were many incidents in which causative poisons could not be identified only from the database; these cases had to be deleted. Veterans of forensic science laboratory of the police might have been able to get more informations about a causative poison or estimate it with high accuracy using so-called "the sixth sense" in the above cases. These informations and estimation by the police on causative toxins and details of incidents seem very useful to construct a more powerful research system.

Database of experts for each causative toxin

The information exchange between an expert of a toxin and a clinical doctor treating a patient can, of course, enhance the probability of identification of a toxin. Therefore, the author et al. decided to register experts for causative toxins in the 75 groups, which had been stored in the present assisting system for diagnosis.

The selection of the registrants was made by literature research using each toxin as keyword and by recommendation by scientists belonging to toxicology-related societies. For complete inclusion of experts, the letters for requesting the recommendation were sent to chairpersons of toxicology laboratories of universities.

Table 6.2 shows the contents of registration for the database of experts for each toxin. Fifty nine experts from the basic science fields, and 22 clinical doctors have been registered. A majority of them belongs to medical schools/medical colleges and pharmaceutical schools/pharmaceutical colleges; others to national institutes of hygiene and health science, laboratories for food and drug safety and agricultural/fishery schools. *Table 6.3* shows examples

Table 6.2

Contents for registration of experts for each causative toxin

1	Causative compound
2	Name and affiliation
3	Special field of study/research subject
4	Communication methods
5	Representative publication of the registrant

Table 6.3

Research subjects of the experts registered in basic sciences

➢	Molecular toxicology of arsenic, heavy metals and semiconductor materials
➢	Studies on the Minamata disease
➢	Effects of silicon compounds on immune cells
➢	Biomedical influence of trace element
➢	Biochemical studies on mechanisms of poisoning by drugs and poisons at cellular levels
➢	Studies on metabolic disorders of lipids induced by drugs
➢	Studies on anticoagulant and antithrombotic effects of annexin (Ca^{++}-dependent and membrane-bound protein)
➢	On the metabolism and toxicity of fluorine compounds (especially hydrogen fluoride)
➢	Mechanisms of induction of cytochrome p-450 caused by drugs and poisons
➢	Studies on neurotoxicity of chemicals
➢	Mechanisms of induction of behavioral abnormality caused by nitrile compounds
➢	Mechanisms of acute poisoning by paraquat; cellular toxicity of furanonaphthoquinone; medicine of active oxygen
➢	Delayed neurotoxicity of organophosphorus compounds
➢	Biomedical influence of organic solvents and their metabolites
➢	Studies on detection methods for volatile compounds and their pharmacodynamics
➢	Studies on quality control and authentication of natural remedies and on the origin of the traditional folk medicine
➢	Analysis of marine toxins and toxicogenic mechanisms in fish and shellfish
➢	Basic studies on signal transduction and gene expression for environmental chemicals
➢	Chemical and toxicological changes of organic compouns by chlorine treatments, and production mechanisms of dioxins
➢	Sensitive analysis of trace drugs and poisons by LC/MS and GC/MS
➢	Immunoassay methods
➢	Studies on analysis on drugs and poisons by mass spectrometry
➢	Hair analysis / mechanisms of transportation of drugs to hair
➢	Natural toxins (especially on the analytical methods of plant toxins)
➢	Detection of poisoning by hydrogen sulfide, hydrogen cyanide, carbon monoxide and other gases

of subjects of studies being conducted by the experts registered in basic sciences. Among the 488 compounds in 75 groups, there are 15 compounds for which no experts were found, but 47 toxic compounds were newly added by suggestion of the experts.

Conclusion

When a patient is brought to an emergency room, the medical and co-medical staffs should doubt poisoning first. When the possibility of poisoning is high, they should communicate with the Japan Poison Information Center on the clinical symptoms and on the results of clinical tests [3]. When estimation of a poison is made only by clinical symptoms and abnormal data, the reliability of such informations is most important. The information exchange should be made between a doctor directly treating the patient and a staff of the Japan Poison Information Center being well aware of the structure of the database according to poisoning symptoms. In their conversation, both of them should clarify clinical symptoms as many as possible; according to a case, additional clinical tests may be necessary. When a causative poison is estimated, the talks are extended to an expert of the poison using the expert database. Using our computer systems, the fairly exact narrowing down of poisons can be achieved.

The database according to poisoning symptoms presented in this chapter was targeted only at compounds, which caused severe damages or even death; such poisoning cases may be not many. For the volatile poisons and corrosive compounds, which had been excluded, a similar diagnostic system should be also constructed. There are many compounds to be added as causative toxins. Efforts should be made for the enhancement of completeness of the diagnostic system; the upgrade of each system is necessary.

References

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