I.7 Practical use of the poison-net developed by the Japan Information Network (Hiroshima)

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Introduction

Forensic autopsy is an important task for proving crimes medically; unfortunately, every department of legal medicine of Japanese universities is suffering from insufficient staffs and budget. About 30 years ago, one of the authors started the analysis of drugs and poisons at the Department of Legal Medicine, Hiroshima University School of Medicine. At that time, the author did not have much knowledge about poison analysis; but it is a good memory that many good friends of toxicological societies gave the author many useful suggestions on analytical methods. Therefore, the author felt that nationwide non-governmental activities for communication about poisoning informations were essential among forensic (analytical) chemists, clinical doctors and other people being involved in poisoning. The authors started creating a communication network first with letters, followed by telephone calls, facsimile, personal computer communication and the mailing list using the Internet; according to the current of times, the communication methods have changed and the number of registrants has increased in our network. At the Department of Legal Medicine, Hiroshima University, a home page (HP) was set up to enable the members to take a look into it subject to passwords. The HP includes the contents of talks, which had been made for information exchange in the network, and many other informations related to poisoning. In this chapter, the authors briefly present the practical use of the network.

What is "poison-net"?

The authors designated the activities of the Japan Poison Information Network as "poison-net", comprehensively. It includes "poisoning mailing list", "analysis mailing list", supply of informations of poisoning on Web, requests for analysis of a causative toxin, trials of toxin analysis and hosting a short course of training for preliminary spot tests of drugs and poisons.

Poisoning mailing list (ml-poison)

The ml-poison (ml-poison@hiroshima-u.ac.jp) was started in about 1994, when the Internet was introduced into Hiroshima University School of Medicine. The members of the poison-net were composed of clinical doctors of emergency rooms, clinical technologists and experts of

toxicology; to protect human rights of patients, the press men and the general public were not allowed to join the ml-poison. The good communication quality is being maintained to be able to cope with the sudden outburst of a poisoning incident or accident; the complementary talks are being refrained as possible. The mailing list is convenient for rapid response to an incident or accident and for getting the newest informations, but caution should be taken against informations obtained through the mailing list, because they are occasionally not reliable. The number of the registrants counted about 700 at the time point of August, 2001. A password is given to each registrant to enable looking into the poisoning information part of HP of the poison-net.

Analysis mailing list (ml-anal)

In 1998, the Ministry of Health and Welfare of Japan distributed analytical instruments for toxins to the 8 advanced critical care medical centers and the 65 critical care medical centers. Each of the latter centers was equipped with an HPLC instrument and an X-ray fluorescence spectrometer, which costed twenty million yen; and the advanced critical care medical centers were equipped with an HPLC, an X-ray fluorescence spectrometer, GC/MS and other instruments with the cost of eighty million yen. However, only with the introduction of such expensive analytical instruments, they do not work in the absence of a sufficient number of experts, who can operate them. Many correspondences and questions about the instrumental analysis were sent to our laboratory through the ml-poison. Therefore, in 1999, the authors decided to separately create ml-anal (ml-anal@hiroshima-u.ac.jp) to support toxin analysis in such critical care medical centers and other hospitals. The registrants of the ml-anal were composed of the members of ml-poison who were interested in the analysis, engineers of manufacturers of analytical instruments and attendees of the short course of the preliminary color tests; the number of the registrants counted more than 300 in August, 2001. At the beginning, both analysts and engineers of manufactures got embarrassed saying, “Which kind of drugs or poisons can be analyzed by HPLC?” and, “Which kind of drugs or poisons do the analysts want to analyze?”, respectively. Later, after the instruments have become to work well, the qualities of the questions became much higher.

Supply of information by the web

The URL of HP of the poison-net is http://maple-www2.med.hiroshima-u.ac.jp; this is expected to be changed in the near future according to servers to be used.

Storage of contents of talks made in the mailing lists (ml-poison plus ml-anal)

The contents of talks made in both ml-poison and ml-anal were rearranged according to causative toxins, and shown in the “poisoning-talking salon” of HP of the poison-net (subject to a password given to each registrant). The causative toxins are composed of daily necessaries, drugs (including over- the-counter drugs), pesticides, natural toxins, industrial materials and others.

Many cases of poisoning and informations on analysis are shown in the HP. If talk contents are opened to the public, the permission by each talker becomes necessary; the authors thus refrain from introducing the contents in this chapter. However, the headlines of the "poisoning-talking salon" are being demonstrated in the top page of HP, which can be accessed without any password.

Databases (DBs) in wide areas of poisoning

Various kinds of DBs related to poisoning are available in HP of the poison-net as shown below.

i. DB for analytical methods

The papers describing analytical methods for drugs and poisons in human specimens were searched by the Medline. The papers were selected by the eleven scientists, who were the members of a joint study project supported by a Grant-in-Aid for Scientific Research (B) from the Ministry of Education, Science and Culture of Japan. Chemical compounds listed were: natural toxins, organic solvent/toxic gases, anaesthetics (local anaesthetics, inhalation anaesthetics, intravenous-injection anaesthetics and muscle relaxants), neuroleptics/antidepressants (psychopharmaceuticals, antiepileptics and antiparkinsonian drugs), amphetamines/narcotics, hypnotics/tranquilizers, pesticide and others. On the basis of extensive informations collected from 900 papers, the most suitable analytical method can be rapidly found by searching with a combination of a specimen name, an analytical method and a chemical name (target) to be analyzed. Each specimen (urine, blood, authentics, serum/plasma, tissues or others) and each method (TLC, HPLC, UV-VIS, GC/MS, GC, immunoassay, MS, LC/MS or others) are chosen using the pulldown menu, and a chemical name (subject) is input. When the search is made with a dubious name of a chemical, there is a possibility not to be able to reach a corresponding analytical method; in this case, the chemical name can be reexamined with a list of "chemical names stored in the DB of analytical methods". The analytical methods included in the DB are reliable, because the scientists who selected them are experts of forensic toxicology. When any question on an analytical method is sent to our Network by the ml-anal, a good answer will be returned by the responsible scientist.

ii. DB for blood concentrations of causative toxins

In forensic cases in which drugs are involved, the assessment of blood drug concentration is necessary. Also in clinical cases, the blood drug levels obtained by analysis should be rapidly classified into therapeutic, toxic and fatal ones to serve for deciding the policy of treatment. The blood levels and symptoms, reported by Mayer and by Winek both in 1994, and other data in actual cases were input into the DB. The items for our input into the DB were: a name of a drug, a name(s) of coexisting drug(s) (single, multiple and not clear), blood levels in the literature, institution number (forensic or analysis numbers), dead or alive, age, sex, interval after ingestion, outline of an incident, clinical or autopsy findings, analytical method, levels of the target drug obtained from blood and other specimens by analysis, unit of the values, the presence of other drugs in blood, cause of death/diagnosis, comments and address for correspondence of a user. Care was taken for enabling an expert to directly correspond to the user about

more details of an actual case. By comparing the analytical results with the data in the DB, it is possible to estimate the antemortem conditions of a deceased and the symptom levels of a living patient.

iii. DB for poisoning-related journals and toxicology society journals

The DB was mainly created by Prof. Shirakawa of Ehime University Hospital, Emergency Units, and covers the contents of domestic journals and abstracts related to poisoning, which are not included in international literature DB. When a user inputs a chemical for research together with "OR" or "AND", a list of journal name, society name, year, volume, page and title appears. By clicking the title, the details of contents (abstract, authors and affiliation) can be obtained. Even in poisoning cases which had been only presented at a meeting and not been submitted to a journal, good ideas for medical treatments may be included. When a poisoning incident takes place with a chemical which is included in the DB, it may give useful informations on treatments and analysis in the poisoning.

iv. DB for contents of talks in the ml-poison

The contents of talks in the ml-poison can be obtained by the method as described in section 1; they are stored in a DB to make keyword research possible.

Other articles about poisoning appearing in HP of the poison-net

i. Simple color test methods for drugs and poisons (ver 2)

Screening or preliminary tests for drugs and poisons are essential before their instrumental analysis to narrow probable compounds for poisoning. The article was abstracted from the book [Department of Legal Medicine, Hiroshima University School of Medicine (ed) (2001) Simple Detection Methods for Drugs and Poisons: The Color Tests. Jiho Inc., Tokyo]. It includes cyanide compounds, carbon monoxide, organophosphorus pesticides, paraquat, bromisovalum, acetaminophen, barbiturates, tricyclic antidepressants, boric acid, amphetamines, screening methods using spot tests and some comments on analytical instruments.

ii. Manual for analysis of drugs and poisons (the first draft)

A manual for analysis of drugs and poisons was first created on our Web site. "Manual for Forensic Toxicology Analysis" was then published by the Forensic Toxicology Working Group of the Japanese Society of Legal Medicine in a printed form, on the basis of this article (the first draft) on the Web. The original draft on the Web contains more detailed description on toxin analysis. It seems desirable to use both printed and Web ones for getting more detailed informations on analysis.

iii. Cautions in analysis of human specimens

In this article, pitfalls in analysis are being discussed. The contents are: the procedure of biomedical analysis, human specimens (sampling methods and cautions upon sampling and storage), preliminary tests (cyanide compounds, arsenic compounds, azide, organophosphorus pesticides, paraquat, glufosinate, controlled drugs, bromisovalum and acetaminophen), pretreatments of specimens (the methods and cautions), confirmatory analysis (analytical instruments, methods and cautions), substantiation of drug standard collection and critical assess-

ment of analytical results. In every item, only basic problems are being discussed; but it is emphasized that the carelessness causes serious mistake.

Mediating service for the request of analysis of causative toxins using the network

It is essential to analyze a causative toxin for making an effective treatment. It is preferable to analyze it at a local laboratory; however, unfortunately, institutions undertaking such analysis are not many in Japan. Private clinical laboratory companies undertake analysis of the limited number of toxic compounds. Therefore, the authors established a system for receiving a request of toxin analysis in the HP of the poison-net to respond to it at any time. When the request form revealed in the HP is filled, it is automatically mailed to a manager who checks the contents of the form; after removal of undesirable parts of the contents, which may violate human rights, it is mailed through the ml-poison to the members. When an analyst is found, direct communication is made between the requester and the analyst. The analytical results are reported to the ml-poison. If the requested analysis is regarded as a joint study between them, the analysis is made free of charge for the requester; in principle, it should be presented at a meeting or published in a journal. When no analyst is found, it is requested to a private clinical laboratory company with a charge. In Japan, many experts are available for analysis of toxic compounds; their results of analysis and maintenance of their analytical instruments are reliable. The above requesting system using the ml-poison can be regarded as a "virtual poison control center" for analysis. In USA and Europe, many poison control centers dealing with toxin analysis are present and well utilized; while, in Japan, the situation is much delayed and no official institutions for toxin analysis are available at the present time. However, thanks to the spread of activities of private express transportation companies, the cooled or frozen specimens can reach any part of Japan within two days. With the intellectual and substantial cooperation of the experts of toxin analysis distributed throughout Japan, similar activities to those of poison control centers can be realized without an enormous cost using the Internet and the above express transportation services. Until now, the authors experienced many cases of analysis requests through the system. For example, in the cresol-poisoning incident which took place in Aomori, cresols in plasma and urine (free and conjugated forms with glucuronide and sulfate) were repeatedly analyzed in Okinawa for specimens sampled from patients at various intervals after ingestion; the results were reported to the ml-poison one week later. A part of list of the analysis requests is shown on the Web (http://maple-www2.med.hiroshima-u.ac.jp/analysis_2.html). As explained above, the mediating service through ml-poison is useful for settlement of a poisoning incident. However, some problems should be mentioned; it sometimes takes a long time for analysis, resulting in no contribution to clinical treatments; when neither presentation at a meeting nor publication in a journal is realized after laborious analysis, the principle of being a joint study collapses, causing a trouble between the analyst and requester on the cost. The authors feel that, even in a joint project, the cost for analysis should be paid by a requester for continuation of the mediating service system for a long time.

Trial for quality of analysis of drugs and poisons

Actual training of analysis is essential rather than collecting informations on analytical methods to make accurate identification and quantitation of a causative toxin. Even with an identical specimen, the discrepancies of analytical results can appear in different institutions, probably due to different levels of skillfulness of analysts or different capability of instruments being used; such discrepancies should be avoided by quality control. For this purpose, the authors are hosting the trial for quality of analysis every year.

In the first trial, a poisoning case was assumed in which a guest staying at a hotel did not come out of his room for checkout; a bellboy discovered the guest collapsing and sent him to a hospital. Together with paper describing fictitious situations and comments by a clinical doctor, each serum specimen, to which a fixed amount of pentobarbital had been added, was sent to 42 analysts who had wished the trial. The second trial (66 participants) was held on pecticide poisoning with addition of an emulsion product of DCPA and NAC. For both trials, answers were collected from the participants after a while; about a half of them could achieve both qualitative and quantitative analyses successfully, and a few could neither make qualitative nor quantitative analysis for both trial. After the collection, the model answers and the summaries of the results given by all participants were returned to them. By examining the report, the self-assessment of each participant could be made; it seemed useful for intensifying a sense of quality self-control. For correspondence and questions to the participants, the trial ML (ml-trial) was used. In U.S.A. and Europe, such trials for analysis in poisoning are very common; while no trials have been made in Japan except ours. Since the trials were made being supported by a Grant-in-Aid from the Ministry of Health and Welfare of Japan, the participants were free of charge. The authors are continuing the trials for improvement of analytical techniques of participants. At the present time, however, they are being made without any financial support; the authors do hope that the national organization or official societies will undertake the quality assurance of analysis of drugs and poisons.

Short course of training for simple preliminary tests of drugs and poisons

As stated before, upon occurrence of a poisoning incident, preliminary tests are required to narrow causative toxin candidates before accurate analysis by instruments of high performance. Although the number of chemicals being analyzable by kits commercially available is limited, it is very easy to handle them. Because of such easiness and simplicity, the authors hosted a short course, in which clinical doctors were trained for simple poison analysis with the kits; they will be able to analyze poisons at bedside by themselves before sending the specimens to analytical experts. The short training course is being held under the auspices of the Committee on Analysis of Japanese Society for Clinical Toxicology on the day before the Annual Meeting of the Society. In the first course, the participants were trained for tests of glufosinate in urine (Basta qualitative kit), TLC for drugs (Toxi-Lab®), organophosphorus pesticides in urine, controlled drugs by an immunoassay (Triage®), acetaminophen in serum and cyanide ion in blood; the number of participants of this course held at Hiroshima University was 80. In the second course held at Azabu University in the next year, the participants were trained for some of the same tests as described above, but two tests were newly added, *viz*. tests for toxic gases and

boric acid in serum; but the participants counted 38 only. The cause of the decrease of participants might be due to that the tests were almost the same as those of the previous year and that some participants wished instrumental analysis. In the next course, the authors are planning to use some instruments.

Perspectives

The poison-net has been supporting people in the field of clinical toxicology, especially in the analysis of drugs and poisons using various methods described above. The authors do hope that more lives suffering from poisoning will be saved with the assistance of the informations obtained from the poison-net. The maintenance of this kind of system by a single institution is too hard; it should be changed to be supported by a governmental organization or scientific societies. The network is based on the mutual trusting relationship of members; it does not exist only for receiving informations, but does exist to supply reliable informations to members positively. The latter will make the network more developed and upgraded.

It seems convenient for readers to take a look into HP and URL describing informations on poisoning. However, the contents and URL will be changed during a long period of time. If the readers can not access our network, please communicate to Hiroshima University Graduate School of Medicine by other means.