J. Med. Toxicol. (2011) 7:259–265
DOI 10.1007/s13181-011-0177-z

TOXICOLOGY INVESTIGATION

The Toxicology Investigators Consortium (ToxIC) Registry

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Published online: 29 September 2011

Abstract Many medical toxicologists are interested in participating in a practice-based, multicenter research and toxicosurveillance network. In 2009, the American College of Medical Toxicology established the Toxicology Investigators Consortium (ToxIC). One facet of ToxIC is a registry that can be used for surveillance of new or old agents, assessment of treatment decisions, and the creation of new research questions. This paper describes the development of and the initial experiences with this registry of toxicology patients. In November 2009, ACMT invited members to participate in a new registry of cases evaluated and cared for by practicing medical toxicologists who provide direct hands-on clinical care. A password-protected, encrypted, online registry data site was created to upload a newly developed electronic case report form (CRF) on registry patients. The CRF includes demographics; encounter circumstances; agent; syndrome, symptoms, and signs; and treatment. A test version at four sites began in January 2010, seven additional sites were added in March 2010 for the beta phase, and the registry was opened to all interested US medical toxicology practices in April 2010. The CRF underwent continuous modifications based upon frequent feedback from and discussion among the participants. Thirty-three toxicology practice sites, encompassing 56 hospitals and clinics, have entered data into the ToxIC Registry. During the first 14 months of data collection, 5,412 patients were entered. The experience thus far demonstrates that the creation of this registry is feasible and constitutes a potentially powerful toxicosurveillance and robust research tool.

Keywords Medical toxicology · Registry · Poisoning database

Previous Presentations The preliminary data were presented at NACCT 2010, Denver, CO.

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Introduction

Medical toxicology is an American Board of Medical Specialties recognized specialty that addresses the diagnosis and management of adverse effects of exposure to chemical substances. In the USA, medical advice on how to manage exposures has traditionally been provided by poison centers. These centers utilize specialists in poison information, usually nurses or pharmacists, to offer advice to callers via the telephone. For patients who are ill and in the hospital, telephone consultations by board-certified medical toxicologists are also sometimes available through poison centers. Thus, in the past, the provision of most medical toxicology consultative services has primarily occurred over the telephone. However, as training programs have proliferated, an increasing number of medical toxicologists have established traditional medical practices caring for patients at the bedside in hospitals or in outpatient clinics. This shift in practice to the bedside or clinic consultation model is comparable to the standard practice pattern of most medical specialties and recognizes the importance of direct clinical care by specialists in the field.

In 2008, we first investigated the current prevalence of direct, bedside toxicology practice in the USA. An

electronic survey was sent to all 350 American College of Medical Toxicology (ACMT) members who were board-certified in medical toxicology to determine their toxicology practice patterns and their interest in participating in a clinical practice-based national research network and toxicosurveillance system [1]. In that survey, a medical toxicology practice was defined as providing direct care to inpatients or outpatients, either as a consultant or as the primary attending physician. Forty-five distinct sites practicing medical toxicology in the USA were identified with annual site census varying from ten to more than 1,000 patients per year. Most respondents also expressed an interest in participating in a practice-based national research and toxicosurveillance network.

Based on this preliminary information, in 2009 we established ACMT's Toxicology Investigators Consortium (ToxIC). One goal of ToxIC was to establish the infrastructure for a multicenter research network. Another goal of this consortium was the creation of a database, or registry, of all patients directly cared for by practicing medical toxicologists. The latter was established because in recent years there have been calls for the development of high-quality clinical databases and registries to improve clinical research issues that cannot be addressed through traditional approaches such as randomized clinical trials [2–4]. At the 2009 North American Congress of Clinical Toxicology, potential ToxIC investigators met and expressed a strong sentiment for the establishment of such a registry. In January 2010, ACMT's ToxIC Registry was initiated. This paper describes the development and initial experience with the registry.

Methods

In November 2009, via an e-mail announcement, all ACMT members were invited to participate in the new registry. Patients would be included in the registry as long as they were evaluated or treated at the bedside or in a clinic by the medical toxicologist. Patients seen by a medical toxicologist while working in other capacities such as functioning as an emergency physician were excluded. This policy preserves a fundamental and unique component of the registry concept—that all patients have full medical toxicology evaluations as part of their medical records.

To build the registry, a case report form (CRF) was developed to capture key elements of the medical toxicology evaluation for each patient. The creation of the case report form had to balance the collection of too little versus too much data. Adequate data are needed in order to do toxicosurveillance or generate hypotheses that could be tested through the ToxIC Multicenter Research Network or through registry-based research projects. Conversely, too many data fields render the data entry process too time consuming, potentially limiting the number of medical toxicologists who might participate. Moreover, it was believed that many studies that would originate with the ToxIC Registry would still require going back to the actual patient medical record, including the medical toxicology notes, in order to collect further information for institutional review board (IRB) approved research studies.

An encrypted, online registry data website was created to upload the completed CRFs. The CRF is divided into five sections: demographics; encounter circumstances; agent; syndrome, symptoms, and signs; and treatment (Table 1).

Table 1 Key data elements collected as part of ACMT's ToxIC Registry

A. Identifier information
1. Institution
2. Patient code
3. Unusual or novel case
4. Age range
5. Sex
6. Pregnancy status
B. Encounter information
1. Location and nature of initial encounter
2. Source of referral
3. Type of encounter
C. Agents
1. Agent class
2. Specific agents
D. Syndromes, symptoms, and signs
1. Toxidrome
2. Notable vital sign abnormities
3. Cardiovascular
4. Pulmonary
5. Nervous system
6. Metabolic
7. GI/hepatic
8. Heme
9. Renal
10. Muscle
11. Derm
12. Psych
E. Treatment information
1. Antidotes
2. Antivenom
3. Chelators
4. Pharmacologic support
5. Decontamination
6. Elimination
7. Nonpharmacologic support

The complete set of fields can be seen at http://acmt.net/_Library/Registry/data_sheet_toxic.pdf

Each section has multiple data fields. The CRF was designed so that data could be easily and quickly entered by simply checking off relevant information and entering a small amount of free text for each patient.

During the first year of the registry, the data fields were modified several times. These decisions were based upon the consensus of focus groups with participating sites that communicated routinely via conference calls.

A critical component of the registry was maintenance of patient confidentiality. In compliance with the Health Insurance Portability and Accountability Act (HIPAA), the central, electronic CRF was designed so that it would be impossible to identify specific patients. The demographic data are fully "de-identified" and contain only institution and patient's age range and sex. None of the potential identifiers specified by HIPAA, such as patient name, medical record number, or dates of birth or service, are included. Each patient is identified by a ToxIC code number assigned by the treating medical toxicologist who uploaded the case to the registry. The patient's identity and any other potential identifiers are only known, therefore, to the treating physician(s). The medical toxicologist participants maintain their own personal database at their site enabling the identification of the patient from the ToxIC code. A participating toxicologist would only access a patient's actual medical record if required/allowed by law, for example if the FDA requested additional information about an adverse drug reaction reported to the registry or if done in the context of an IRB-approved research project.

Patient data are generally uploaded immediately after the initial encounter. However, the electronic CRF may be updated by the treating medical toxicologist with data reflecting an evolving clinical course, an unexpected diagnosis or outcome such as death, or new treatments such as hemodialysis or organ transplantation.

Participating sites may access most of the registry data, perform queries, and export the data to an excel spreadsheet for further analysis. This access enables registry participants to determine the number of patients that meet their search criteria in the entire registry. However, they are blinded to the code numbers, institutions, or medical toxicologists providing these cases. If investigators desire to do studies that necessitate review of actual medical records, they must first submit a formal request to the ToxIC Research Committee. If approved, and the investigator has appropriate IRB approval, the investigator is then provided the contact information for the medical toxicologists whose cases are of interest. Participants can also search all of the ToxIC data entered at their site.

During the fall of 2009, a test version of the electronic ToxIC registry site CRF was developed. Starting on January 10, 2010, four medical toxicology sites began to jointly pilot test the initial CRF: Bellevue Medical Center, New York, NY; Porter and Littleton Adventist Hospitals, and Swedish Medical Center in the Denver, CO area; University of Massachusetts Medical Center, Worcester, MA; and University of Texas Southwestern Medical Center, Dallas, TX. This initial 6-week pilot test collected more than 150 cases. Based on this pilot test, the CRF was modified and, on March 1, 2010, the collaboration was expanded to seven additional sites to form the beta test phase of the registry. These additional sites were at the Children's Hospital, Boston, MA; Harrisburg Hospital, Harrisburg, PA; Hartford Hospital, Harford, CT; Robert Wood Johnson Medical Center, New Brunswick, NJ; St Mary's Hospital, Duluth, MN; University of Illinois Hospital, Chicago, IL; and the University of Utah Hospital, Salt Lake City, UT [5].

Following this beta test phase, the CRF was further modified and, on April 15, 2010, the registry project was opened to all interested US medical toxicology practices. Sites were invited to participate regardless of the volume of their service. In order to promote maximal participation in the registry, a threshold minimum number of cases for any one site were not established. However, in order to adequately reflect the actual patients seen in the toxicology practices, each site was asked to enter every clinical case, both in the inpatient and outpatient setting, to assure representativeness of the patients entered.

All participating sites were asked to seek IRB approval in order to contribute to the registry. Responses from the IRBs varied. Because there are no patient identifiers and there is no patient intervention associated with entering data in the registry, some IRBs determined that entering patients in the registry did not meet the definition of human subject research and therefore did not require IRB approval or oversight for participation in the registry. IRBs at other sites took a different approach and decided that registry participation required IRB oversight but granted an IRB exemption.

One of the fundamental aims of the registry is to provide real-time toxicosurveillance for a number of activities such as new and emerging adverse drug reactions, syndromic surveillance for new diseases or biological or chemical terrorism, or new drugs of abuse. Therefore, a mechanism was recently established whereby all unusual or suspicious cases are identified by means of a check off field to denote an unusual or novel case and assessed in terms of other cases reported to the registry. This mechanism enables appropriate actions to be quickly effectuated.

The registry is managed under the leadership of a steering committee that oversees several core working groups. These cores include (1) data form update and development, (2) quality assurance, (3) database management, (4) education and training, (5) toxicosurveillance, and (6) research.

Table 2 Locations of ToxIC Registry sites (N=33) and institutions (N=56)

State/country	City	Institutions
Arizona	Phoenix	Banner Good Samaritan Medical Center
		Phoenix Children's Hospital
California	Loma Linda	Loma Linda University Medical Center
	San Francisco	San Francisco General Hospital
Colorado	Denver	Denver Health and Hospital
		Porter Adventist Hospital
		Littleton Adventist Hospital
		Swedish Medical Center
		University of Colorado Hospital
Connecticut	Hartford	Connecticut Children's Medical Center
		Hartford Hospital
		John Dempsey Hospital
		University of Connecticut Health Center
Illinois	Chicago	UIC-Rush-Cook
	Evanston	Evanston North Shore University HealthSystem
Indiana	Indianapolis	Indiana University Hospital
		Methodist Hospital
		Riley Hospital for Children
		Wishard Memorial Hospital
Maine	Portland	Maine Medical Center
Massachusetts	Boston (1)	Children's Hospital Boston
	Boston (2)	Beth Israel Deaconess Medical Center
	Worcester	UMass Memorial Medical Center
Michigan	Grand Rapids	Spectrum Health Hospitals
Minnesota	Duluth	SMDC Medical Center
		St Luke's Hospital
		St Mary's Medical Center
	St Paul	Regions Hospital
Missouri	Kansas City	Children's Mercy Hospital & Clinics
Nebraska	Omaha	University of Nebraska Medical Center
New Jersey	New Brunswick	Robert Wood Johnson University Hospital
	Newark	Newark Beth Israel Medical Center
		New Jersey Medical School University Hospital
New York	Manhasset,	North Shore University Hospital
	New York City (1)	Bellevue Medical Center
		NYU Langone Medical Center
	New York City (2)	Elmhurst Hospital Center
		Mount Sinai Hospital
	Rochester	Strong Memorial Hospital
North Carolina	Charlotte	Carolinas Medical Center
Oregon	Portland	Oregon Health and Science University Hospital
Pennsylvania	Harrisburg	Harrisburg Hospital
	Pittsburgh	Children's Hospital of Pittsburgh of UPMC
		Magee-Women's Hospital of UPMC
		UPMC Presbyterian/Shadyside
Texas	Dallas	University of Texas Southwestern Aston Clinic
		Children's Medical Center of Dallas
		Parkland Memorial Hospital
		UT Southwestern University Hospital—St. Paul

Table 2 (continued)

State/country	City	Institutions
Utah	Salt Lake City	Primary Children's Medical Center
		University of Utah University Hospital
Virginia	Richmond	VCU Medical Center
Wisconsin	Milwaukee	Children's Hospital of Wisconsin
		Froedtert Memorial Lutheran Hospital
Canada	Toronto	Hospital for Sick Children
Israel	Haifa	Rambam Health Care Campus

Results

Between January 2010 and March 2011, 33 bedside toxicology practice sites started to enter data into the ToxIC Registry (Table 2). Thirty-one sites are in the USA, and two international sites joined in January 2011. These 33 medical toxicology practices care for toxicology patients at 56 hospitals and clinics. Staffing at each site varied from one to ten medical toxicologists. The 31 US sites are well represented geographically across the country. Sixteen of the 24 medical toxicology fellowship programs that have fellows at the time of this writing are enrolling patients into the registry.

During the first 14 months of data collection (as of March 22, 2011), 5,412 patients were entered into the registry. The nature of these encounters varies widely (Table 3). For example, even in this first year, when most participating sites were only entering cases for a fraction of the year, we have collected over 200 adverse drug reactions, over 60 adverse drug events involving medication errors, over 750 cases of prescription drug abuse, and over 900 cases of analgesic toxicity.

Table 3 Types of encounters (based on first 5,415 cases entered)

ADE (medication error resulting in harm)	53 (1%)
ADR (undesirable effect of a medication used in a normal dose)	210 (4%)
Agricultural injury	0 (0%)
Envenomation	143 (3%)
Environmental evaluation	137 (3%)
Interpretation of lab data	111 (2%)
Non-prescription drug abuse	637 (12%)
Non-pharmaceutical toxicant—intentional	376 (7%)
Non-pharmaceutical toxicant—Unintentional	271 (5%)
Occupational evaluation	150 (3%)
Occupational injury	23 (<1%)
Organ system dysfunction (e.g., liver failure)	139 (3%)
Pharmaceutical overdose—intentional	2396 (44%)
Pharmaceutical overdose—unintentional	739 (14%)
Prescription drug abuse	753 (14%)
Withdrawal	385 (7%)

The median number of patients entered into the registry at each site was 84, and the range was from 1 to 847. Eight additional medical toxicology practices are currently awaiting IRB approval and are expected to soon start entering cases. The time required to enter the data into the registry is 1–2 min per patient.

As of the time of this writing, nine abstracts based on data collected from the registry have been accepted to scientific meetings.

Discussion

This is the first multicenter registry of patients directly cared for by medical toxicologists at the bedside or in the outpatient setting. The experience thus far demonstrates that the creation of this registry is feasible and constitutes a potentially powerful toxicosurveillance and research tool. The fact that the majority of medical toxicology practices in the USA committed to participating in the registry within the first 14 months and started to enter patient data demonstrates that a robust case registry enjoys broad support by the medical toxicology community.

Other databases such as the National Poison Data System (NPDS) also collect information on poisoned patients [6]. The NPDS is a very large database that collected information on 4,280,391 contacts to poison centers in the USA in 2009. To its credit, the NPDS has been the source of data for much research in clinical toxicology. However, like all databases, the NPDS has limitations. It collects information over the telephone and the vast majority of its data are on patients who remained at home and were never seen in a health care facility, let alone by a medical toxicologist. Moreover, the data that the NPDS collects on the patients seen in health care facilities are not collected from any specific source, rather they are obtained from various health care providers available on the telephone and who usually have not even seen the patients. Even if a poison center-based medical toxicologist provides

telephone consultation on a case, that physician will still rarely actually go to the patient's bedside. The indirect collection of the data, the lack of a toxicologist's bedside evaluation, and the fact that the poison center record is assembled from telephone conversations limit the quality of the NPDS data.

In contrast to the NPDS, the ToxIC Registry is far smaller. However, the strength of this registry is that all case data are collected directly by medical toxicologists who have personally assessed and treated the patients. The toxicologic data in the registry do not have the same limitations of the NPDS data, and their quality is quite high. In 2002, Whyte and his medical toxicology colleagues developed a database of patients that presented to their toxicology service in the Newcastle area of New South Wales, Australia [7]. While this Australian database is limited in its geographic scope, much useful research has been published utilizing this approach [8, 9].

In the USA, toxicosurveillance and research in medical toxicology have been mostly limited to NPDS information collected through poison centers and cases seen by medical toxicologists at their local institutions. Given the relative rarity of many types of poisoning, important observations are often limited to the very lowest forms of empirical evidence such as case reports or the occasional small case series. The registry should provide ample opportunities for multicenter toxicological studies on a much larger number of patients than the small case series of the past. In addition, the registry provides for a unique opportunity to study medical toxicology practice patterns both in the inpatient and outpatient environments. The potential of the registry can be seen in the large number of abstracts that have been produced from it in just the short period since its inception. These studies, however, are based on superficial information entered on the CRFs. It is expected, however, given the potential to abstract very detailed information about patients in the registry, that it will be used for more sophisticated studies as it continues to grow.

Registries function in concert with clinical studies. First, they provide timely data. Second, registries enroll all patients, not just those that meet study criteria, thus providing a more real world dataset. Also, unlike many studies, they are not time limited and therefore can collect a large number of cases. Registry data can be used for surveillance of new or old agents, assessment of treatment decisions, and the creation of new research questions. For example, the assessment of outcomes of real world patients who have received an antidote could suggest a change in management that could be further studied.

The ToxIC Registry has greatly amplified the ability to collect cases by recently beginning to add international sites. Importantly, the cases in the registry tend to involve serious toxicity. With the exception of a small number of outpatients that were seen at clinics not requiring a referral, all of the cases in the registry were deemed to be of sufficient concern by another service or physician that a consultation by a medical toxicologist was specifically requested.

Now that the number of cases in the registry has exceeded 5,000 and 100–200 new cases are being added per week, it has evolved into a viable, growing, and high-quality toxicosurveillance and research tool. The "unusual or novel case" field allows for real-time identification of sentinel cases and sentinel series of cases that have important public health significance such as cases involving emerging drugs of abuse, new adverse drug reactions, and overdoses of newly marketed drugs. Future plans for ToxIC are to implement a toxicosurveillance system that will make available this important information to partner agencies including the Food and Drug Administration, the Centers for Disease Control and Prevention, the National Institutes of Drug Abuse, and the Department of Justice.

Evaluation of the registry data can be used to generate study hypotheses prompting further research. More definitive registry-based studies such as those using controlled cohort or case-control designs can be done. With appropriate IRB approvals for specific studies, if needed, data can be abstracted from individual patient medical records.

Continuous practice monitoring and improvement is becoming a component of Maintenance of Certification requirements for physicians in the USA. The registry database can be used to describe and track medical toxicology practice patterns that may be useful for practice quality improvements and the design of curricula for training programs and continuing education activities.

In conclusion, the ToxIC Registry is feasible and constitutes a potentially powerful toxicosurveillance and research tool. It contains data about toxic exposures, adverse drug reactions, and poisonings that are more sophisticated than those found in previous databases. In another publication, we will report an overview of the data collected over the registry's first year of operation.

Sources of Funding None.

Conflict of Interest None.

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