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IDIS/Web Search Strategies for Drug Toxicology and Adverse Drug Reactions

United States poison control center data identified more than 2 million human poison exposure cases in 2008.¹ Children less than six years of age accounted for 50 percent of these cases, but only 2 percent of the fatalities. Therefore, children less than six years of age represent the patient population most frequently affected by poison exposures. Because their ingestions are most commonly accidental, they rarely ingest enough poison to cause death. In contrast, patients older than 19 years of age are less frequently exposed to poisons, but because their exposure is more commonly intentional they represent over 98 percent of drug-related fatalities. Generally, it is difficult to distinguish between different types of poisoning based on symptoms alone because the symptoms of a wide array of toxic substances are very similar. There are several key things to remember when handling a poison case. First is to stabilize your patient. Second, obtain an accurate history and physical assessment to evaluate the extent of poisoning and to identify the presence of concurrent conditions that can affect recovery. Third, decontaminate the site of poison administration and then provide poison-specific treatment with administration of antidotes when indicated. These are all essential for successful management.

Poison cases should all be referred to a poison control center that will in turn assist local hospitals in managing these patients. In addition to intentional or accidental poisoning, there are many instances where patients develop serious adverse reactions to normal, or sometimes errant, doses of a medication. During your management of these cases you may be faced with different questions in relation to patient management, such as: How long should I monitor my patient? What is the toxic level? What is the suitable antidote?

The pharmacists working in the Division of Drug Information Service at the University of Iowa have gathered and indexed information for *IDIS*/Web from several types of sources that are useful in answering these kinds of questions. With *IDIS*/Web you can quickly access information from the biomedical literature as well as the U.S. Food and Drug Administration (FDA), the Agency for Healthcare Research and Quality (AHRQ), the United Kingdom National Institute for Health and Clinical Excellence (NICE), and clinical practice guidelines.

Not pictured: Nada Al-Agil, a Clinical Pharmacist and Director of the Drug Information Center at King Fahad Medical City in Riyadh, Saudi Arabia received her pharmacy degree in 2003 from King Saud University and continued to complete her 2 year clinical pharmacy residency in 2006. She recently completed an 8 week specialized drug information training program at the Iowa Drug Information Network (IDIN) and two weeks at the Iowa Statewide Poison Control Center in Sioux City, Iowa.

About the Authors:



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Dr. Ronald A. Herman graduated from the University of Iowa College of Pharmacy in 1976 (B.Sc.), 1978 (M.Sc. Clinical/Hospital Pharmacy) and 1992 (Ph.D. Pharmacokinetics). He is on the faculty of the College of Pharmacy and is Director of the Iowa Drug Information Network. He is involved with didactic and clerkship teaching in the Clinical and Administrative Pharmacy Division. His research interests revolve around the use of technology to improve clinical pharmacy activities.

Tips on how you can best use *IDIS/Web* to answer these types of toxicology questions are presented here. The citations mentioned are representative selections from the articles retrieved and are not intended as the only relevant articles necessary to answer questions on these topics, nor can they answer all of your specific questions. Four examples are chosen to demonstrate some of these search concepts.

What is the role of insulin with dextrose and potassium in the management of calcium channel blocker poisoning?

A search can be conducted combining the drug term of "68200801 INSULIN", in the drug field. The term "TX/POIS-DRUG NEC 977." can be selected in the disease field using either the thesaurus or the disease lookup. Several articles that appeared relevant were retrieved.¹⁻⁵

- Nickson CP, Little M. Early use of high-dose insulin euglycaemic therapy for verapamil toxicity. *Med J Aust* 2009;191(6):350-2. (*IDIS* Article 625641)
- Clark EG, Nykamp DL, Nguyen V, V. High-dose insulin in the treatment of antihypertensive overdose. *Hosp Pharm* 2008;43(3):206-9. (*IDIS* Article 592997)
- Greene SL, Gawarammana I, Wood DM, Jones AL, Dargan P, I. Relative safety of hyperinsulinaemia/euglycaemia therapy in the management of calcium channel blocker overdose: a prospective observational study. *Intensive Care Med* 2007;33(11):2019-24. (*IDIS* Article 587015)
- Shepherd G. Treatment of poisoning caused by beta-adrenergic and calcium-channel blockers. *Am J Health-Syst Pharm* 2006;63(19):1828-1835. (*IDIS* Article 561929)
- Dewitt CR, Waksman JC. Pharmacology, pathophysiology and management of calcium channel blocker and beta-blocker toxicity. *Toxicol Rev* 2004;23(4):223-38. (*IDIS* Article 535361)
- Megarbane B, Karyo S, Baud FJ. The role of insulin and glucose (hyperinsulinaemia/ euglycaemia) therapy in acute calcium channel antagonist and beta-blocker poisoning. *Toxicol Rev* 2004;23(4):215-22. (*IDIS* Article 535360)

Tips for locating articles in *IDIS/Web* relating to the role of an antidote in managing a specific overdose:

Drug field Enter the drug that is being used to treat the overdose, not the drug that caused the overdose.

Disease field Enter the term "TX/POIS-DRUG NEC 977."

Descriptor field Generally will not use a toxicology descriptor.

Is an acetaminophen level obtained prior to 4 hours post overdose ingestion useful, and for how long should we continue monitoring?

Answering this question using *IDIS/Web* involves the following terms and descriptors; "ACETAMINOPHEN 28081221" in the drug name, "SUICIDE/OVERDOSE/POISONING E950." in the disease field, and "PKIN BLOOD CONCENTRATION 63" and "PKIN PHARMACOKINETICS 74" in descriptor. These terms can be selected either by using the thesaurus link on the left of the screen or the lookup button in each of the three respective fields; drug, disease or descriptor. A screenshot of the search window is provided.

The screenshot shows the IDIS search interface. The search criteria are as follows:

- Drug field:** "ACETAMINOPHEN 28081221" (with a "Look Up" button)
- Disease field:** "SUICIDE/OVERDOSE/POISONING E950" (with a "Look Up" button)
- Descriptor field:** "63" and "PKIN PHARMACOKINETICS 74" (with a "Look Up" button)

Other search options include "and" dropdowns, "search" and "clear" buttons, and a "Log off" button in the top left corner.

The following are three of the relevant articles retrieved with this search strategy:

- James LP, Capparelli EV, Simpson PM, Letzig L, et al. Acetaminophen-associated hepatic injury: Evaluation of acetaminophen protein adducts in children and adolescents with acetaminophen overdose. *Clin Pharmacol Ther* 2008;84(6):684-90. (*IDIS* Article 615549)
- Daly FF, Fountain JS, Murray L, Graudins A, Buckley NA. Guidelines for the management of paracetamol poisoning in Australia and New Zealand--explanation and elaboration. A consensus statement from clinical toxicologists consulting to the Australasian Poisons Information Centres. *Med J Aust* 2008;188(5):296-301. (*IDIS* Article 594573)
- Dawson AH, Whyte IM. Therapeutic drug monitoring in drug overdose. *Br J Clin Pharmacol* 2001;52(S1):97S-102S. (*IDIS* Article 469273)

How do you manage a suspected beta-blocker overdose?

There is a class term for beta-adrenergic blockers, but indexers only assign that term when an article discusses beta-blockers in general. It is not assigned to each article that has a beta-blocker as a main part of the study. Nonetheless, it is possible to search for any beta-blocker by using the numerical code for beta-blockers and truncating the last two digits and replacing with an asterisk, the wild card. This term can be identified using the thesaurus, a drug look up, or using the link on the left of the search screen, Drug Hierarchy. With the latter, when you put in any beta-blocker, propranolol or atenolol, for example, you will see all the drugs in that class. You can select one and insert into the drug field. Now edit the drug field to include only the truncated number: beta-blocker (BB) truncated class code, 121601*. In the disease field select

"SUICIDE/OVERDOSE/POISONING E950." This will result with 120 articles if the search is conducted at this stage. If you are interested in a review on the topic, then you might limit your search further to guidelines or systematic reviews. This can be accomplished by adding "PRACTICE GUIDELINE 156" or "SYSTEMATIC REVIEW 161" or "PRIORITY CLIN PRACT GUIDE 168" to the descriptor field. Note when you use the look-up button to select several descriptors, if you wish to find articles with any one of the descriptors, click the button to change the default setting from AND to OR at the top of that screen before you click submit. The search now reveals five articles with the following one that is of particular interest.

Critchley JAJ, Ungar A. The management of acute poisoning due to beta-adrenoceptor antagonists. *Med Tox Adverse Drug Exp* 1989;4(1):32-45. (IDIS Article 251636)

Here is a screenshot of this particular search:

Please identify studies or review articles (not letters to the editor or editorials) that address the use of monitoring drug levels of citalopram in the case of poisoning or overdose.

The drug field should use the term "CITALOPRAM 28160705" obtained from the thesaurus or the drug lookup, and in the disease field use "SUICIDE/OVERDOSE/POISONING E950.", again from either the thesaurus or the disease lookup. In the descriptor field use "PKIN BLOOD CONCENTRATION 63".

The screenshot shows a search form with the following fields and values:

Field	Value	Operator	Action
All Fields		and	
Drug	121601*	and	Look Up
Disease	"SUICIDE/OVERDOSE/POISONING E950."	and	Look Up
Descriptor	"PRACTICE GUIDELINE 156" or "SYSTEM...	and	Look Up
Title		and	
Author		and	Look Up
Abstract		and	
Journal		and	Look Up
Volume			

Lastly to exclude letters to the editor and editorials it is important to remember that the first author for all letters to the editor has the name "Letter to ed" and all editorials use the author name "(Editorial)". Select the author lookup then type "letter to ed", and then select this result. Use the author lookup again and type "(editorial)" - making sure to use the parenthesis, then select this. Notice the two terms are connected with an **AND**; change this to **OR**. Now go up to the descriptor line and change the drop down box at the end of the field from **AND** to **NOT** then conduct the search. A screenshot of the search window is provided. The results now contain 9 articles and the 8 letters to the editor and editorials have now been excluded from the results.

The screenshot shows the IDIS search interface with the following search criteria:

Field	Value	Operator	Action
All Fields		and	
Drug	"CITALOPRAM 28160705"	and	Look Up
Disease	"SUICIDE/OVERDOSE/POISONING E950."	and	Look Up
Descriptor	"PKIN BLOOD CONCENTRATION 63"	not	Look Up
Title		and	
Author	"LETTER TO ED" or "(EDITORIAL)"	and	Look Up
Abstract		and	
Journal		and	Look Up
Volume			

Additional options shown include: starting: [], From: [] To: 2010, Only search records with abstracts, Article Number: [], Sequence Number: [].

Tips for locating therapeutic level monitoring using <i>IDIS/Web</i>	
Drug field	Enter the drug that caused the overdose
Disease field	"SUICIDE/OVERDOSE/POISONING E950."
Descriptor field	"PKIN BLOOD CONCENTRATION 63"

Conclusion

Drug therapy and toxicology information that is needed in the clinical setting can often easily be found in *IDIS/Web*. The searches presented here are just a small sample of the range of valuable information that can be accessed by quick and easy searching. In addition to these resources, the staff at *IDIS* may be contacted by email or by phone to offer assistance in formulating a search.

Reference List

1. Bronstein AC, Spyker DA, Cantilena LR, Green JL, Rumack BH, Giffin SL. 2008 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 26th Annual Report. *Clin Toxicol* 2009;47(10):911-1084.

Drug Information and Poison Center Training – Nada Al-Agil

Nada Al-Agil, a Clinical Pharmacist and Director of the Drug Information Center at King Fahad Medical City in Riyadh, Saudi Arabia received her pharmacy degree in 2003 from King Saud University and continued to complete her 2 year clinical pharmacy residency in 2006. She recently completed an 8 week specialized drug information training program at the Iowa Drug Information Network (IDIN). She spent 6 weeks at IDIN getting both didactic and hands on training in processing drug information requests and in evaluating and interpreting the medical literature. She spent an additional two weeks at the Iowa Statewide Poison Control Center with the directors Linda Kalin, RN and Ed Bottei, MD. She observed how trained poison specialists process requests and manage patients in a call center that handles over 30,000 calls per year from residents and professionals around the state of Iowa. She hopes to use these basic principles as they expand the services of the drug information center back in her 1100-bed hospital.

Nada's training was tailored to meet her specific goals. Part of the time focused on reviewing the administrative aspects of operating an information center, including how to document and record center activities. Time was spent examining how to use a systematic approach to respond to information requests. Database design and use of document templates were addressed to demonstrate how they facilitate an efficient standard approach to service provision and documentation. Essential resources that should be in the center were discussed and then reviewed by Nada to ensure that she was proficient in using each resource. Time was also devoted to reviewing some of the key principles for how to evaluate primary and tertiary drug literature.

Part of the training also was designed to develop writing skills. Nada took the lead role in developing the article in this issue that focuses on how *IDIS* can be a beneficial tool to facilitate the care of patients that may have been exposed to accidental or excessive doses of medications.

Readers interested in more information about the specialized training programs provided by the Division of Drug Information Services at the University of Iowa College of Pharmacy should visit the following link: <http://www.uiowa.edu/~idis/education.htm> Training may be conducted at the University of Iowa or at the requestor's site.

Ron Herman, PhD
Director, Iowa Drug Information Network

New Molecular Entities & Biologicals

FDA Approvals
June 2010 – November 2010

An *IDIS* search retrieved articles relevant to the new drugs and their approved uses. These articles provide a selection of key critical studies and reviews. Additional information on these newly approved drugs will be available in the FDA Approval Package (an official United States Food and Drug Administration [FDA] document) that is compiled for new drugs following approval. The FDA Approval Package includes reviews of the pivotal and supportive clinical studies conducted during the approval process. These studies are often not published elsewhere. FDA Approval Packages are selectively indexed and included as part of the *IDIS* database as they become available. Use the descriptor 155 FDA APPROVAL PACKAGE in combination with the valid drug term to retrieve these documents from the *IDIS* database.

For some newly approved drugs the FDA Approval Package may not yet be available. If the medication has been reviewed by one of the FDA Advisory Committees, you may still access data from pivotal studies, even those that have not been published in peer reviewed literature. These Committee reports are indexed in the *IDIS* database using the descriptor “FDA ADVISORY COMMITTEE 164”. In addition to access to data from pivotal studies, these reports provide critical commentary from the Advisory Committee members, and specific, important questions related to the use and safety of the medication.

Generic Name Trade Name (FDA Review Classification)	Sponsor (Approval Date)	Valid <i>IDIS</i> Drug Term Drug Number (<i>IDIS</i> Citations)	Indication/Use Dosage Form	Valid <i>IDIS</i> Disease Term Modified ICD-9-CM Number
Ceftaroline Fosamil <i>Teflaro</i> (S)	Cerexa (Oct. 29, 2010)	CEFTAROLINE 8120618 FDA Approved indication (5 citations) Total (5 citations)	Bacterial infections. Intravenous infusion	Infection, Bacterial NEC 041.
Dabigatran Etexilate <i>Mesylate</i> (P)	Pradaxa (Oct. 19, 2010)	DABIGATRAN ETEXILATE 20120449 FDA Approved indication (39 citations) Total (120 citations)	Prevent stroke in patients with atrial fibrillation. Oral Capsule	Fibrillation, Atrial 427.3 Disease, Cerebrovascular NEC 436.
Denosumab <i>Prolia</i> (BIOL)	Amgen (June 1, 2010)	DENOSUMAB 10120243 FDA Approved indication (25 citations) Total (71 citations)	Treatment of postmenopausal women with osteoporosis at high risk for fracture. Subcutaneous inject	Osteoporosis 733.0 Disorder, Menopause/Post NEC 627.
Eribulin Mesylate <i>Halaven</i> (P)	Eisai Inc. (Nov. 15, 2010)	ERIBULIN 10120910 FDA Approved indication (3 citations) Total (5 citations)	Breast cancer. Injection	NEOP, MGN-Female Breast 174.
Fingolimod <i>Gilenya</i> (P)	Novartis (Sept. 21, 2010)	FINGOLIMOD 92000013 FDA Approved indication (31 citations) Total (81 citations)	Multiple Sclerosis Oral Capsule	Sclerosis, Multiple 340.
Lurasidone Hydrochloride <i>Latuda</i> (S)	Sunovion Pharma, Inc. (Oct. 28, 2010)	LURASIDONE 28160883 FDA Approved indication (1 citation) Total (1 citation)	Schizophrenia Oral Tablet	Schizophrenia NEC 295.

Generic Name Trade Name (FDA Review Classification)	Sponsor (Approval Date)	Valid IDIS Drug Term Drug Number (IDIS Citations)	Indication/Use Dosage Form	Valid IDIS Disease Term Modified ICD-9-CM Number
Pegloticase <i>Krystelxa</i> (BIOL)	Savient Pharms (Sept. 14, 2010)	PEGLOTICASE 2000208 FDA Approval indication (11 citations) Total (11 citations)	Gout Injection	Gout 274.
Tesamorelin <i>Egrifta</i> (S)	Theratechnologies, Inc. (Nov. 10, 2010)	TESAMORELIN 68280030 FDA Approval indication (12 citations) Total (12 citations)	Lipodystrophy in HIV patients. Injection	Lipodystrophy 272.6

Review Classification:

S=Standard Review, the drug appears to have therapeutic qualities similar to those of one or more already marketed drugs

AA=Accelerated Approval

FT=Fast Track

P=Priority Review, significant improvement compared to marketed products, in the treatment, diagnosis, or prevention of a disease

BIOL=Biological

O=Orphan

2011 Iowa Drug Information Service Exhibit Schedule

Please join us:

American Association of Colleges
of Pharmacy (AACP)

July 9 — July 12, 2011

San Antonio, Texas

USA

71st World Congress of
Pharmacy & Pharmaceutical
Sciences 2011 (FIP)

September 2 — September 8, 2011

Hyderabad

India

Selected Bibliography

Denosumab

Cummings SR, San Martin J, McClung MR, et al. Denosumab for the prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med.* 2009; 361:756-765. (IDIS Article Number 622262)

A total of 7868 postmenopausal women ages 60-90 years with osteoporosis were randomized to receive subcutaneous denosumab 60 mg or placebo every 6 months for 36 months. The primary end point was new vertebral fracture, and secondary end points were nonvertebral and hip fractures. Results showed that, compared with placebo, denosumab reduced the risk of new vertebral fracture with a cumulative incidence of 2.3% in the denosumab group and 7.2% in the placebo group (95% CI, 0.26-0.41; $p < 0.001$), with a relative decrease of 68%. Denosumab reduced the risk of nonvertebral fracture with a cumulative incidence of 6.5% compared with 8.0% in the placebo group (95% CI, 0.67-0.95; $p = 0.01$), and reduced hip fractures with a cumulative incidence of 0.7% compared with 1.2% in the placebo group (95% CI, 0.37-0.97; $p = 0.04$). Side effects of denosumab were reported as similar to placebo.

Fingolimod

Cohen JA, Barkhoff F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med.* 2010; 362:402-415. (IDIS Article Number 631675)

In this double-blind, controlled trial, 1292 patients (aged 18-55 years) with multiple sclerosis were randomly assigned to receive 12 months of oral fingolimod either 1.25 or 0.5 mg daily, or intramuscular interferon beta-1a at 30 mcg weekly. Results showed the annualized relapse rate was lower in both fingolimod groups, 0.20 (95% CI, 0.16-0.26) in the 1.25 mg group, and 0.16, (95% CI, 0.12-0.21) in the 0.5 mg group, compared with the interferon group, 0.33 (95% CI, 0.26-0.42; $p < 0.001$ for both comparisons). There were 2 fatal infections in the 1.25 mg fingolimod group: disseminated primary varicella zoster and herpes simplex encephalitis. Other adverse events in the fingolimod group included herpesvirus infections, bradycardia and atrioventricular block, hypertension, macular edema, skin cancer and elevated liver enzyme levels.

Pegloticase

Sundy JS, Becker MA, Baraf HS, et al. Reduction of plasma urate levels following treatment with multiple doses of pegloticase (polyethylene glycol-conjugated uricase) in patients with treatment-failure gout: results of Phase II randomized study. *Arthritis Rheum.* 2008;2882-2891. (IDIS Article Number 603985)

In this Phase II study, 41 patients with treatment-failure gout were randomly assigned to 1 of 4 treatment regimens of intravenous pegloticase: 4 mg or 8 mg every 2 weeks for a total of 6 doses, or 8 mg or 12 mg every 4 weeks for a total of 3 doses. Investigators found that the mean plasma urate level was reduced ≤ 6 mg/dl within 6 hours in all dosage groups, and the reduction was maintained throughout the treatment period in the 8 mg and 12 mg dosage groups. Twenty-six patients received all protocol doses, and the primary end point (plasma urate < 6 mg/dl for 80% of the study period) was met in 50-88% of patients, with 8 mg every 2 weeks shown to be the most effective dose. Five serious adverse events were attributed to the study drug: one each of anemia, hypersensitivity, infected tophus, and 2 gout flares.



Dr. Nicola Sarrazin is a 1984 graduate of the University of Iowa (B.A. in Anthropology and Asian Studies) and a 1997 graduate of the University of Iowa College of Pharmacy (Pharm.D.). Since that time she has been a pharmacist in the College of Pharmacy's Division of Drug Information Service. Nickie's responsibilities include indexing articles for the IDIS database, overseeing the Drug vocabulary and contributing articles for the *World of Drug Information* newsletter.

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