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Drug Monitoring and Toxicology

Automated liquid-chromatographic analyzer used for toxicology screening in a general hospital: 12 months' experience

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We evaluated the clinical utility of an automated HPLC system (Remedi, Bio-Rad) for identification of drugs and metabolites in biological fluids. Serum or urine or both from 354 consecutive cases of poisoning were analyzed by the system and by a set of fluorescence polarization immunoassay (FPIA, Abbott) and thin-layer chromatographic (TLC) procedures. Antidepressants and most phenothiazines were recognized by the new system. Comparison of Remedi results with final clinical diagnoses yielded diagnostic specificity and sensitivity of 80% and 90%, respectively. Remedi detected 26 additional compounds that were neither reactive in the immunoassay screening tests nor detected by TLC procedures. Because the Remedi expands the range of drugs covered by the immunoassays and provides a rapid, preliminary report in emergency situations, we conclude that this system can be a useful complementary technique in the clinical toxicology laboratory. Although urine toxicological screening seemed adequate for a good toxicological report, blood analysis allows extra toxicokinetic data such as blood concentrations and half-life estimations.

INDEXING TERMS: drug screening • chromatography, thin-layer • fluorescence polarization immunoassay • urine • gastric lavage

For toxicological screening during acute drug poisoning, laboratories must implement rapid and specific methods. Many laboratories use broad-spectrum screening to determine unknown agents in a patient's sample. Several studies have shown that toxicological screening frequently identifies unsuspected drugs in patients with drug overdoses *[1, 2]*. In a majority of cases, all that is required to guide therapy is qualitative drug screening.

Some authors have developed methods for toxicological screening *[3, 4]* based on thin-layer chromatography (TLC) separation and ultraviolet (UV) spectral detection, respectively.[3] Toxi-Lab (Irvine, CA) has developed a drug-screening procedure based on liquid–liquid extraction, TLC separation, and reagent-spray detection (sulfuric acid, Draggendorf reagent).

Recently, Bio-Rad (Hercules, CA) Labs. developed Remedi, an automated liquid-chromatographic analyzer for detecting drugs in urine, serum, and gastric lavage fluid by on-line sample cleanup and isocratic multicolumn separation with full-scan UV detection. Coupled with a computer memory, Remedi allows identification of 450 drugs in one analysis. Two reports have been published on the analytical evaluation of Remedi *[5, 6]* on urines and stomach contents.

In our study, we screened urine, serum, and gastric contents for drugs. The aim of our work was to assess the clinical utility of Remedi after 1 year of toxicological screening at the hospital of Pontoise. Although Remedi allows the determination of >450 drugs, a few drugs could not be detected, e.g., carbamates and acidic drugs (aspirin, acetaminophen, chloroquine), so two complementary methods were systematically used in conjunction with Remedi: fluorescence polarization immunoassay (FPIA) and TLC.

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[3] Nonstandard abbreviations: TLC, thin-layer chromatography; UV, ultraviolet; and FPIA, fluorescence polarization immunoassay.

Materials and Methods

TLC

All drugs and reagents were analytical grade (Sigma, St. Louis, MO). Barbiturates (phenobarbital, butobarbital, and secobarbital), meprobamate, antidepressant agents (amitriptyline, nortriptyline, imipramine, and clomipramine), phenothiazines (acepromazine, alimemazine, and cyamemazine), and benzodiazepines (diazepam, bromazepam, flunitrazepam, clonazepam, alprazolam, nitrazepam, nordazepam, and prazepam) were extracted from 5 mL of serum, 20 mL of urine, or 20 mL of gastric lavage fluid by Tox-Elut^R from Varian (Harbor City, CA). The extracts were evaporated to dryness at 45 °C. The residues were each dissolved in 500 μL of methylene chloride, of which 10 μL was deposited on 20 × 20 cm TLC plates (F_{256}; Merck Labs., Darmstadt, Germany). TLC was performed with methods commonly used for drug detection *[7]*. In brief, the elution solvents were chloroform:acetone:diethylamine (50:40:10 by vol) for barbiturates and meprobamate; toluene:acetone:250 g/L ammonia solution purchased from Merck (80:20:10 by vol) for phenothiazines and antidepressant agents; and hexane:diethylamine:ethanol (75:8:16 by vol) for benzodiazepines. Detection solvents were 0.5 g of diphenylcarbazone in 1 L of methylene chloride:20 g/L mercuric chloride in ethanol for barbiturates and meprobamate identification; 3.2 g/L ammonium cerium(IV) sulfate in 7 mol/L orthophosphoric acid solution for antidepressant agents and phenothiazine identification; and $PtCl_4$/KI (1 g/25 g in 1 L of distilled water) solution for benzodiazepine identification.

ASSAYS

FPIA. Tricyclic antidepressants, benzodiazepines, and barbiturates were analyzed in urine and serum by FPIA with a TDx analyzer (Abbott, Abbott Park, IL), with scrupulous application of the manufacturer's instructions.

Remedi. The Remedi broad-spectrum drug identification system used a multicolumn approach to extract, purify, and analyze drugs in patients' samples by full-scan UV detection. For sample processing, the samples are diluted with an internal standard mixture and centrifuged. Because amphoteric or weakly basic drugs are eluted from the separation cartridges early, whereas basic drugs are eluted later, two internal standards are used to monitor the chromatographic behavior of the cartridges: *N*-ethyldiazepam and chlorpheniramine. The prepared sample is then combined with a buffer and passed through four cartridges. The purification cartridge extracts and concentrates the drugs while allowing proteins and salt to pass through. Once the drugs are eluted from this cartridge, a mobile phase is introduced that sends the drugs through the extraction cartridge. Here, endogenous organic acids are retained while weakly acidic, neutral, and basic drugs pass through. The third cartridge, Separation I cartridge, is a reversed-phase cartridge that separates weakly basic compounds. The fourth cartridge, Separation II, differentiates basic compounds by cation exchange. All separations are isocratic. A conditioning cartridge is used to saturate the mobile phase with silica, thereby protecting the two separation cartridges from any dissolution.

Drug identification is performed by a full-scan UV detector coupled with a sophisticated computer algorithm. As each drug enters the detector from the last cartridge, a UV scan from 200 nm to 300 nm is made. Sample spectra are then automatically compared with the library of known drug spectra stored in memory. This, combined with the chromatographic data, allows identification of the drug. The procedure is completed in ~20 min. A very thorough analytical study of this technique has been published by Binder et al. *[8]*.

All reagents used with the Remedi were supplied by Bio-Rad; however, the composition of the mobile phase and other reagents and the exact characteristics of the stationary phase of the cartridges were not disclosed. Sample volume was 1 mL for serum, urine, and gastric content.

Other techniques. Alcohol (ethanol) was assayed by an enzyme method (Sigma), acetaminophen (paracetamol) by TDx, and salicylic acid by the Trinder reaction.

SUBJECTS

Patients (n = 354) with symptoms of poisoning (retrospective study) were admitted to the medical emergency unit (Pontoise Hospital) during 1994. The specimens analyzed were 184 paired urine and blood samples, 35 urine only, and 135 blood only; we also analyzed 117 gastric contents (not paired).

STATISTICAL METHOD FOR CLINICAL DIAGNOSIS

The statistical study was based on screening tests described by Laplanche et al. *[9]* for determining the diagnostic power of medical apparatus.

Results

Table 1 summarizes the data for the paired serum and urine specimens. The screening results were positive for 226 drugs in serum and for 242 drugs in urine. In all, 246 drugs were found by one or more techniques used. Thus, the sample of choice is the urine ($[\chi]^2 = 10.26$, $P < 0.01$).

To summarize the clinical assessment of the Remedi data, we used a retrospective statistical study in which the status of patients included in this study had been well established after various investigations (biology, radiology, examination, history). Of 55 cases of poisoning, Remedi identified 36 true positives (TP), 3 false positives, 4 false negatives (FN), and 12 true negatives (TN). The sensitivity or probability that a poisoned patient gave a positive result by Remedi, determined by the formula 100× TP/(TP + FN), was 90%. The specificity, or proba-

Table 1. Simultaneous analysis of paired urine and blood (serum) samples from 184 cases of poisoning.

	Serum			Urine		
	Remedi	FPIA[a]	TLC	Remedi	FPIA	TLC
Benzodiazepines	35	82	23	6	82	69
Tricyclic antidepressants	51	53	28	59	53	40
Amitriptyline	28	36	22	32	36	29
Maprotiline	12	4	–	14	4	–
Clomipramine	8	8	4	8	8	8
Nortriptyline	1	3	2	3	3	3
Doxepin	2	2	–	2	2	–
Other antidepressants						
Fluoxetine	1	–	–	6	–	–
Viloxazine	1	–	–	1	–	–
Fluvoxamine	1	–	–	1	–	–
Phenothiazines[b]	20	–	19	20	–	19
Cyamemazine	11	–	11	11	–	11
Alimemazine	5	–	5	5	–	5
Acepromazine	3	–	3	3	–	3
Thioridazine	1	–	–	1	–	–
Hypnotic drugs						
Zopiclone	2	–	–	2	–	–
Zolpidem	2	–	–	2	–	–
Meprobamate	–	–	22	–	–	19
Other psychotropic drugs						
Hydroxyzine	8	–	–	8	–	–
Trihexyphenidyl	1	–	–	1	–	–
Amfepramone	2	–	–	2	–	–
Tropatepine	1	–	–	1	–	–
Analgesic drugs						
Dextropropoxyphene	7	–	–	7	–	–
Meperidine	1	–	–	1	–	–
Codeine	2	–	–	3	–	–
Chlormezanone	2	–	–	2	–	–
Cardiac agents						
Acebutolol	3	–	–	4	–	–
Diltiazem	1	–	–	1	–	–
Cold–cough remedies						
Ephedrine	3	–	–	5	–	–
Phenylpropanolamine	2	–	–	2	–	–
Fenspiride	1	–	–	0	–	–
Quinine	1	–	–	1	–	–
Antihistaminic drugs						
Ranitidine	5	–	–	5	–	–
Diphenhydramine	1	–	–	2	–	–
Astemizole	0	–	–	1	–	–
Brompheniramine	0	–	–	1	–	–
Other drugs						
Indoramine	1	–	–	1	–	–
Metoclopramide	1	–	–	2	–	–

Serum samples were positive for 226 drugs; urines were positive for 242.

[a] Drugs determined by FPIA were identified by anamnesis, Remedi, or both.

[b] Phenothiazines were not analyzed by antidepressants kit-FPIA, because of cross-reactions.

bility that a nonpoisoned patient gave a negative result by Remedi, determined by the formula 100× TN/(TN + FP), was 80%. The positive predictive value, or probability that a patient with a positive result is poisoned, determined by the formula 100× TP/(TP + FP), was 92%. The negative predictive value, or probability that a patient with a negative result is not poisoned, determined by the formula 100× TN/(TN + FN), was 75%.

Table 2. Drugs detected in 354 consecutive poisoning cases.

Drugs	Frequency	Drugs	Frequency
Benzodiazepines	155	Analgesic drugs	
Tricyclic antidepressants		Dextropropoxyphene	12
Amitriptyline	46	Acetaminophen	4
Maprotiline	14	Acetylsalicylate	3
Clomipramine	12	Meperidine	1
Nortriptyline	7	Codeine	4
Doxepin	3	Chlormezanone	2
Dosulepin	1	β-Adrenergic blocking agents	
Imipramine	1	Acebutolol	5
Amoxapin	1	Propranolol	1
Other antidepressants		Cold–cough remedies	
Fluoxetine	8	Ephedrine	7
Mianserin	4	Phenylpropanolamine	4
Viloxazine	1	Fenspiride	2
Fuvoxamine	3	Quinine	1
Neuroleptic agents		Anti-H_1 and Anti-H_2 drugs	
Cyamemazine	18	Ranitidine	7
Hydroxyzine	16	Diphenhydramine	3
Metoclopramide	11	Astemizole	1
Alimemazine	10	Brompheniramine	1
Acepromazine	5	Other psychotropic drugs	
Thioridazine	1	Trihexyphenidyl	4
Carbamates		Amfepramone	3
Meprobamate[a]	37	Tropatepine	1
Febarbamate	3	Other drugs	
Hypnotic drugs		Indoramine	3
Zopiclone	7	Diltiazem	3
Phenobarbital	5	Raticide agents (identified in another laboratory)[a]	
Zolpidem	4		

Twenty-three substances were detected but not identified.
[a] Not identified by Remedi.

Table 2 summarizes the drugs detected in specimens from all 354 patients admitted with symptoms of poisoning. The screening was done by TLC, FPIA, Remedi, and other techniques (e.g., Trinder reaction for salicylates). As Table 2 shows, a great number of therapeutic drugs were involved in poisoning. The main drugs involved in suicide attempts (benzodiazepines, antidepressant agents, neuroleptic agents) accounted for nearly 59.6% (211 cases) of all drugs detected, and the proportion of drug-positive results in suicide attempts was ~ 93%. In our study, digoxin and theophylline overdoses were found only in therapeutic drug monitoring and not in suicide attempts.

Benzodiazepines were often associated with antidepressants or other psychotropic drugs (phenothiazines, meprobamate, hypnotics) in di- or polypoisoning (Table 3).

Table 3. Evaluation of drug combinations associated with poisoning.

BDZ	BDZ							
TAD	47 (5)[a]	TAD						
Phenothiazines	2 (10)	4 (3)	Phenothiazines					
Carbamates	15 (8)	– (1)	5 (6)	Carbamates				
Hypnotics	5 (2)	2 (–)	2 (1)	–	Hypnotics			
Cardiac agents	–	–	– (1)	–	– (1)	Cardiac agents		
Antihistaminics	1 (2)	–	–	–	1 (–)	–	Antihistaminics	
Analgesics	– (7)	–	– (1)	–	–	– (1)	– (2)	Analgesics
OPD	3 (3)	7 (–)	–	1 (–)	–	–	–	3 (3)

[a] Numbers of poisonings due to a combination of two drugs (28%) or three or more drugs (6.7%) are given in parentheses.
BDZ, benzodiazepines; TAD, tricyclic antidepressants; OPD, other psychotropic drugs.

Discussion

DRUG IDENTIFICATION

Benzodiazepines. Immunoenzymatic techniques identified all benzodiazepines in both urine and serum. Benzodiazepines data from Table 1, used to compare Remedi and FPIA, showed a significant difference between FPIA and Remedi for benzodiazepine screening: Among 82 patients with positive FPIA urine tests, serum FPIA was positive in all 82, whereas Remedi was positive in only 35 and 6 cases in serum and urine, respectively (χ^2 = 65.6 for serum, $P < 0.01$; χ^2 = 140.1 for urine, $P < 0.01$). Benzodiazepines with low therapeutic and nontoxic concentrations (such as clonazepam and alprazolam) were not identified by Remedi. The FPIA technique must be preferred to Remedi in benzodiazepine screening. Benzodiazepine detection limits were 0.02 mg/L for FPIA and 0.2 mg/L for Remedi. Because the upper limit of the therapeutic range for some benzodiazepines is ~0.1 mg/L, Remedi is not useful in the identification of benzodiazepines with low toxic concentrations, e.g., loprazolam, flunitrazepam, clonazepam, alprazolam, triazolam, estazolam, and nitrazepam. In urine, moreover, benzodiazepines excreted in conjugated form were not often recognized by Remedi.

Barbiturates. Of five cases of phenobarbital poisoning, three were identified by Remedi, whereas TLC identified all five. Remedi recognition of phenobarbital was incomplete because the UV spectrum of this drug is not characteristic. The Remedi also had problems identifying other drugs that lack a specific spectrum, e.g., phenytoin, phenobarbital, and primidone. We therefore use our TLC procedure to identify some barbiturates as well as meprobamate.

Tricyclic antidepressants. Some antidepressants such as maprotiline are identified by FPIA only at relatively high concentrations (TDx system operation manual, Abbott). Although the FPIA (because of its good analytical detection limit) is more sensitive than Remedi for some antidepressants such as amitryptiline and nortryptiline, the FPIA antidepressant kit showed interference from phenothiazines. Recent antidepressants such as viloxazine and fluoxetine were not identified by FPIA. The TLC technique we used did not identify the metabolites, whereas Remedi did. For these reasons, Remedi is preferred to FPIA and TLC for screening for antidepressants (see Table 1). Remedi identified more products in urine than in serum (59 in urines vs 51 in serum), again making urine the sample of choice.

Phenothiazines. Phenothiazines are widely metabolized and their identification in urine is not always easy by Remedi. Indeed, their identification by FPIA is not possible. Thus Remedi, as well as TLC, would be suitable for phenothiazine screening (Table 1).

Carbamates. We screened for meprobamate, which in France is still a cause of drug poisonings, by TLC only. No immunological method for meprobamate screening is commercially available. Moreover, meprobamate does not absorb UV energy and thus is not identified by Remedi.

Ethanol. Ethanol-containing drugs were prescribed by physicians to 28% of the patients screened, and all samples from these patients were found to be positive.

Others products. Some cardiac, psychotropic, antihistaminic, and other drugs were identified only by Remedi (see Table 2).

URINE, SERUM, OR GASTRIC WASH

As noted above, we found more substances in urine than in serum. However, identification of drugs is easier in serum than in urine by Remedi, because the unchanged drug is generally excreted in small amounts in urine. The metabolites generally have the same UV spectra as the parent drug and are eluted earlier.

Serum samples allowed semiquantification of the drugs, but assay of urine samples allowed us to find some drugs not identified in the serum. In one case of poisoning by fenspiride, the drug was found in serum and not in urine. Perhaps the fenspiride was not quantitatively eliminated in urine by the time of the sampling. For a good toxicological report, analysis from both urine and blood is needed.

For 169 gastric washes received, 33.7% were positive for drugs. The positivity of gastric content analysis allows physicians (*a*) to determine whether the gastric washing was "productive," and (*b*) to evaluate the duration of poisoning.

CLINICAL ASSESSMENT OF REMEDI

As a clinical tool, Remedi seemed sensitive and specific, and its positive predictive value (92%) and negative predictive value (75%) were suitable. The high detection limit for some poisons by Remedi (in some cases, as great as 0.5 mg/L) explains the low negative predictive value.

The success of a general unknown analysis, i.e., the detection and unequivocal identification of an unknown toxic substance, depends on the quality of the identification system used for the analysis. According to Maier and Bogusz *[10]*, such a system should meet several requirements: It should cover the broadest possible range of relevant substances detectable by means of a given technique; it should be standardized to enable the establishment of an applicable, common, interlaboratory database of identification markers; and the identification markers used should be independent and uncorrelated. Identification systems have found broad application in systematic toxicological screening *[11]*. Bailey *[12]* studied the use of limited toxicological screening vs comprehensive toxico-

logical screening. He found only 71% agreement between the two approaches. Remedi allows comprehensive toxicological screening with rapid turnaround time and can be used 24 h per day, the same as in limited toxicological screening.

INCIDENCE AND PRODUCTS INVOLVED IN POISONING

Nonsteroidal antiinflammatory drugs are not detected by the methods (FPIA, Remedi, TLC) we used. Moreover, we did not use mass spectrometry to detect these drugs and to verify their identification. Although we regularly performed drugs-of-abuse screening with Remedi within the framework of the methadone substitution program, no drug of abuse was observed during the study. Thus, these substances are not listed in Table 2.

In limited toxicological screening, four groups of drugs were usually screened: antidepressants, benzodiazepines, ethanol, and barbiturates. However, as the number of drug overdoses in individuals with suicidal intent has increased, the number of drugs involved in poisoning has also increased, to now include β-adrenergic blocking agents (propranolol and acebutolol), new hypnotic drugs (zolpidem and zopiclone), and new antidepressants (amoxapine, mianserin, and viloxazine).

Overdoses from barbiturates were more frequent before 1980 *[13]*. Phenobarbital was the only barbiturate we found in this study.

For certain compounds such as propoxyphene and its metabolites, diphenhydramine, promethazine, and lidocaine and its major metabolite monoethylglycinexylidide, Remedi scored remarkably high. Other compounds, such as histamine H_2-receptor antagonists cimetidine and ranitidine, and β-adrenergic blocking agents acebutolol and propranolol, were detected exclusively by Remedi. This is in agreement with the data reported by Harris et al. *[14]* and Demedts et al. *[5]*.

In the UK, antidepressants (dothiepin, amitriptyline, and imipramine) accounted for ~15% of all drug overdoses, and older tricyclic antidepressants are reported to have a fatal toxicity index 5 to 8 times higher than that of new antidepressants such as mianserin *[15]*. The following widely prescribed drugs were commonly identified by Remedi: amoxapine, viloxazine, maprotiline, zopiclone, zolpidem, fluoxetine, and cyamemazine.

Lidocaine, an anesthetic agent, is commonly used in overdose patients who require intubation and was often found by Remedi, as was caffeine.

Among drugs involved in suicidal and poisoning cases, analgesic drugs were the first cause of drug poisoning reported in poison control centers *[16]*; they were involved in few poisoning cases in our study. Ethanol is commonly associated with other drugs in suicide attempts *[17]*. Poisoning situations were sometimes caused by associations of different drugs, which aggravated the clinical status of patients. Table 3 shows that main combinations were of ethanol and psychotropic drugs. The 1994 Annual Report of the American Association of Poison Control Centers *[16]* showed that a single substance was implicated in 93.2% of reports, whereas 1.6% of patients were exposed to more than two possibly poisonous drugs or products.

Guitton et al. *[6]* evaluated Remedi and assessed its ability to detect in urine and gastric lavage fluids the main psychotropic drugs ingested with suicidal intent. Our findings agree with theirs. Antidepressants and most phenothiazines were well identified; benzodiazepine identification was less certain. Because of their low sensitivity in Remedi, some benzodiazepines must be screened by an immunoassay such as FPIA or an immunoenzymatic assay (Emit; Behring, Palo Alto, CA). Our results concerning benzodiazepines are in agreement with those of Demedts et al. *[5]*. Compared with Emit, Remedi was less sensitive but allowed precise identification of the offending poison, quantified the amount, and allowed broad toxicological screening of pharmaceutical classes inaccessible to Emit.

Remedi offered another advantage: semiquantification of the main metabolites of the drug involved in poisoning and evaluation of some toxicokinetic characteristics of this drug. The forensic application of Remedi, including analysis of whole blood and tissue and comparisons with traditional laboratory methods, has been recently reported *[18]*.

We have already applied the Remedi system to analyses in different toxicological cases. Even after the injection of >5000 samples (from whole blood, stomach contents, and urine), we observed no drift in retention behavior and no loss of efficiency, demonstrating the robustness of the system. The ability to identify the metabolites of some drugs (generally metabolites show the same spectrum and are eluted earlier than parent drugs) and to analyze urine, serum, and gastric content allowed us to determine the toxicokinetics of some drugs.

In conclusion, by using in combination several analytical techniques (e.g., FPIA for benzodiazepines and narcotics, TLC for carbamate derivatives and chloroquine, colorimetric reactions such as Trinder reaction for salicylates, and Remedi), we obtained positive results for 93% of the drug-containing samples—compared with 65% obtained by Bailey *[19]*, for example—and confirmed some results found by different techniques. We use these techniques routinely and suggest that a combination of different analytical techniques, including a broad-spectrum screening method such as Remedi, is the best strategy for toxicology screening in a hospital laboratory.

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