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Proficiency Testing on Drugs of Abuse: One Year's Experience in Spain

J. Segura, R. de la Torre, M. Congost, and J. Camí

The need for external quality control for drugs-of-abuse urinalysis has long been recognized. Based on experiences in other countries, a proficiency testing program has been introduced recently in Spain. Sterile urine samples containing different concentrations of drugs and metabolites are analyzed by participating laboratories four times a year. Comprehensive educational reports reviewed by an advisory committee are released after each batch analysis. The first year's results verify (*a*) a beneficial influence of the program in regard to reducing errors when adequate techniques are used, (*b*) the need for using confirmatory techniques, and (*c*) the importance of experience and laboratory resources for optimizing results. The educational aspects of the program for the second year are stressing especially the *in situ* training of analysts and the supply of solutions of drugs and metabolites to be used as reference standards.

A main use of urinalysis in Europe is follow-up of drug addicts who are under clinical care, although screening procedures for certain occupational groups are also beginning to increase in major western European countries (*1*). However, unlike in the United States, not much experience has been obtained in Europe concerning proficiency of laboratories involved in drugs-of-abuse urinalysis. The European toxicological programs (*2, 3*) generally do not involve drugs of abuse in urine but rather serum samples related to therapeutic drug monitoring or emergency toxicology. An Italian program dealing specifically with testing for drugs of abuse in urine was originated in Padova University (*4*) and included 35 participating laboratories from 1980 to 1985. Only minor attempts have been reported in other European countries (*5*).

Urinalysis for drugs of abuse received little attention in Spain until 1983, when the government developed new regulations for methadone maintenance programs (*6*). Because of the strict rules for patient treatment in those programs, there was need for quality assurance of results of tests for drugs of abuse. The practical consequence was the design and implementation of a Proficiency Testing Program for urine drug-testing laboratories in Spain. The program does not now involve "accreditation" of laboratories, although this is being considered for the future. The initial focus has been to ascertain the status of drug analysis in Spain, to detect its main problems, and to improve the education of the analysts involved.

Here we report a summary of the first year (1987) of development of the Spanish Proficiency Testing Program.

Materials and Methods

Design of the Program

The program, sponsored in part by the national Spanish Government ("Plan Nacional Sobre Drogas"), which coordinated the efforts of four different ministries (Health, Army, Labor, and Foreign Affairs), covered the major abused drugs analyzed by those Spanish laboratories performing urinalysis. Each laboratory could choose which groups of drugs it would analyze. Only screening or additional confirmatory analyses were considered. In 1987, the laboratories enrolled in the program received four shipments of six samples each. The samples contained from none to four of the substances included in the menu (Table 1). Twenty working days were allowed for the analysis of the samples. One month after the return of the results to the Coordinating Center (Institut Municipal d'Investigació Mèdica, Barcelona), the laboratories received a comprehensive coded report for that shipment (see below). A unique code number had been assigned to each laboratory, known only to the Coordinating Center. By the end of 1987, the number of laboratories enrolled in the program had increased from the initial 13 to 25; 14 more were added the next year.

Five non-Spanish laboratories (see *Acknowledgments*), acted as reference centers, validating the content of the samples. An advisory committee (see *Acknowledgments*), experts in the analysis and pharmacology of abused drugs, helped the establishment of the testing criteria and performed the follow-up of the program.

The Participating Laboratories

Of the 25 laboratories participating in 1987, 13 were public clinical centers involved in detoxification programs or methadone maintenance treatments, five were laboratories in public hospitals, three were medical school laboratories, two were laboratories involved in research and forensic analysis, and two were private laboratories.

These laboratories were classified into three groups (Table 2), according to (*a*) the number of analytes (groups) tested, (*b*) the techniques used, (*c*) the number of workers performing urinalysis for abused drugs, and (*d*) the number of samples analyzed per year. In each case, a number of points (partial score) was assigned to each laboratory as described in Table 2. The partial scores were used to assign the final classification, based on the following algorithm: $(A + 2B + C + 2D)/4$. This emphasized the importance of techniques used (*b*) and number of samples analyzed (*d*). Laboratories with a final score between 2 and 2.9 points were included in group 1 (n = 13), the ones with 3–3.9 points made up group 2 (n = 9), and those with 4–4.9 points were included in group 3 (n = 3).

Preparation and Control of the Samples

Table 1 lists analytes used in the four shipments during the first year. The matrix used to prepare the drug-containing samples (all but cannabis) was an abused-drug–free urine obtained in-house, which sometimes contained nicotine, caffeine, or both. The urine containing cannabinoid metabolites came from healthy volunteers who agreed to smoke a cigarette containing hashish and to collect their urine during the next 24 h. Several blank urines were pooled, generating lot A. The urines containing cannabinoids were mixed, generating lot B. These two pools of urine

Institut Municipal d'Investigació Mèdica, Departament de Farmacologia i Toxicologia, Passeig Marítim 25–29, 08003 Barcelona, Spain.

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Table 1. Setup of the Spanish Proficiency Testing Program for Drugs of Abuse in Urine

Menu	No. of times included[a]	Drug amounts added, mg/L		Least concn (mg/L) of drug potentially present
		Lowest	Highest	
Amphetamine group	6			
Amphetamine	3	1.3	2.0	1.0
Phenylpropanolamine	3	5.0	6.0	5.0
Barbiturates group	4			
Secobarbital	1	1.5	1.5	1.0
Phenobarbital	3	1.0	1.5	1.0
Pentobarbital	0			1.0
Benzodiazepines group	6			
Oxazepam	2	0.6	0.7	0.5
Nordiazepam	2	0.8	0.8	0.5
Flunitrazepam	2	1.0	1.0	0.5
Opiates group	16			
Morphine	9	0.3	0.7	0.5[b]
Morphine-3-glucuronide	4	0.5	1.0	
Codeine	3	1.3	1.5	1.0
Other opiates group	11			
Methadone	8	1.0	1.5	1.0[c]
Meth. metabolite (EDDP)	1	1.0	1.0	
Dextropropoxyphene	2	1.2	2.0	1.0
Naltrexone	0			1.0
Cocaine and (or) cocaine metabolites group	8			
Cocaine	0			2.0
Benzoylecgonine	8	2.0	3.0	2.0
Cannabinoids group	4			
Cannabinoids	4	>0.1	<0.4	0.1

[a] Included in the sets of samples sent out for testing during 1987.
[b] Concentration for morphine plus morphine-3-glucuronide.
[c] Concentration for methadone plus metabolites.

Table 2. Distribution of the Participating Laboratories into Three Groups[a]

	Partial score	% of total laboratories		
		Group 1 (n = 13)	Group 2 (n = 9)	Group 3 (n = 3)
Groups analyzed (A)				
1–2 groups	*1*	38	0	0
3–4 groups	*2*	15	11	0
5–7 groups	*3*	46	88	100
Techniques used (B)				
EMIT	*1*	38	11	0
EMIT/TLC	*2*	61	56	0
EMIT/instrumental techniques	*3*	0	33	100
Personnel (C)				
1–2 persons	*1*	38	44	0
3–4 persons	*2*	61	33	66
≥5 persons	*3*	0	22	33
Samples per year (D)				
<1000	*1*	77	33	0
1000–10 000	*2*	23	55	33
≥10 000	*3*	0	11	66

[a] Selected according to assigned partial scores for characteristics *A–D*, weighted as $(A + 2B + C + 2D)/4$.

were analyzed to verify that they did not contain any of the substances in question (lot A) or that they contained only cannabinoid metabolites (lot B). We checked lots A and B by enzyme immunoassay, using enzyme immunoassays ("EMIT"; Syva Co., Palo Alto, CA) for amphetamines, barbiturates, benzodiazepines, opiates, methadone, dextropropoxyphene, benzoylecgonine, and cannabinoids. The presence of cannabinoids in lot B was verified by fluorescence polarization immunoassay (FPIA) with a TD_x analyzer (Abbott Laboratories, North Chicago, IL) and gas chromatography–mass spectrometry (GC-MS).[1] If no undesired drugs were detected, the urine was filtered through a 0.45-μm (pore-size) filter, with use of nitrogen pressure. The drugs or metabolites were then added to the filtered urine. The filtration instrument, its filters, the 50-mL glass vials to contain the samples, and the rubber stoppers of the vials were sterilized at 120 °C and 101 kPa for 20 min. After that, the samples were sterilized by filtration through a filter and prefilter (pore sizes 0.22 and 0.45 μm, respectively) in a laminar-flux cupboard. The urine of each batch was filtered directly into 50-mL, labeled, sterile, glass vials, which were immediately stoppered and sealed in the sterile cupboard. An aliquot of the filtered urine was subsequently tested for sterility. The prepared samples were stored at 4 °C.

After preparing the six pools of samples in each shipment as described above, we analyzed three vials of each pool, first of all by performing a general screening with EMIT for all the substances checked previously in the blank urine, then screening with FPIA for benzoylecgonine, opiates, and cannabinoids. Positive results for the added drugs (see groups listed in Table 1) were confirmed as follows:

- Amphetamine and phenylpropanolamine were measured by gas chromatography with nitrogen–phosphorus detection (GC-NPD) and GC-MS (*7*).
- Cocaine and benzoylecgonine were extracted with chloroform:isopropanol (9:1, by vol), after alkalinizing the urine (*8*). The organic layer was evaporated and the residue was trimethylsilylated (*9*) before analysis by GC-MS.
- Benzodiazepines were measured by thin-layer chromatography (TLC) (*7*) and also by GC-MS. The latter was also used for dextropropoxyphene. Samples were extracted as for cocaine, but the residue was not trimethylsilylated before GC-MS.
- Barbiturates were measured by GC-MS after acidifying the urine and extraction with chloroform:isopropanol (9:1, by vol).
- Morphine was measured by GC-MS and TLC (*7*). Morphine was also detected by "high-performance" liquid chromatography (HPLC), as was morphine-3-glucuronide (*10*). Codeine was measured by GC-NPD, GC-MS, TLC (*7*), and HPLC (*10*). Methadone was measured by GC-NPD and GC-MS (*7*). Naltrexone was detected with GC-MS and HPLC (*10*).
- Cannabinoids were measured by GC-MS (*9*) and TLC, with use of the same extraction procedure in both techniques (*9*). For TLC, 0.25-mm-thick silica gel G plates (E. Merck, Darmstadt, F.R.G.) and a mobile phase of heptane:ether:acetic acid (70:20:4, by vol) were used. After the plate was developed, it was sprayed with Fast Blue B, 1 g/L in 0.5 mol/L NaOH solution.

Once the batches were prepared and checked, they were assigned randomly generated numbers. A set of six vials and a results reporting sheet were placed in a plastic box with packing to prevent breakage. The safety of the samples

[1] Nonstandard abbreviations: FPIA, fluorescence polarization immunoassay; GC-MS, gas chromatography–mass spectrometry; GC-NPD, gas chromatography with nitrogen–phosphorus detection; and TLC, thin-layer chromatography.

was guaranteed with a sealing system similar to that used by the International Olympic Committee in the Olympic Games (*11*). The boxes were sent to the laboratories (enrolled and reference) by a courier service that guaranteed delivery of the samples within 48 h. The same courier service collected the results and brought them to the Coordinating Center.

Evaluation of Results

When all the results had been returned, the laboratories received a preliminary notice indicating the drug content of the samples. Shortly afterwards, the Coordinating Center performed a computerized analysis of the results and prepared a comprehensive general report. This general report, which was reviewed by a member of the advisory committee before it was sent to the laboratories, was prepared to emphasize the problems detected in the results and to suggest solutions to the participants.

This report, which might be 8–12 pages long, consisted of three different parts. In the first, the frequency with which the analytical techniques were used by the participant laboratories in the analysis for each group of drugs was listed. In the second, the results for the analysis of each sample were listed, along with comments on the possible causes of the errors detected, considering the analytical technique used in each case. The third summarized the errors (false positives and false negatives) for each group of drugs.

Accompanying this general report were several computer printouts listing the content of the samples; the results of the laboratory and the techniques used; the comparison of the laboratory's results with the content of the samples; and the techniques used by the laboratories for the analysis of each drug in each sample and their relationship with the false-positive and false-negative results reported by all laboratories. When necessary, confidential comments about individual problems detected were sent to some laboratories.

Results

The 25 participating laboratories generated results for 2824 analyses. Taking into account all the errors detected in the different batches of control urines, the mean percentage of errors was 2.8% (Table 3). Twenty-one (84%) of the 25 laboratories made at least one error in some of the controls. The errors generated by all the laboratories when participating for the first time in the program was 3.6% of the total number of analyses (Figure 1). After four consecutive batches, this percentage dropped to 1.3% for the initial 13 laboratories that completed the whole cycle.

Grouping the laboratories according to the criteria described in Table 2 demonstrated that the group 3 laboratories (good instrumentation and a large number of samples to be routinely processed by a large staff) had a low number of false results (Table 4). Laboratories in group 1 (quite small, using only enzyme immunoassay, and analyzing only a few analytes from the program menu) had a relatively low number of errors and improved their performance during the program. Of special note was the large number of errors of laboratories in group 2, which had a lot of false-negative results in all batches despite some improvement in eliminating false positives.

The majority of participating laboratories used EMIT as screening technique, either alone (62%) or associated with a chromatographic technique for confirmation (24%), e.g., GC-NPD, GC-MS, and TLC (either in the form of commercially available methods or developed in the laboratory); the use of the HPLC was less important. Some laboratories used FPIA and commercial TLC methods as screening techniques.

Table 3. Number of False-Positive and False-Negative Results According to Analyte, and Overall Percentage of Errors

Analyte group	No. of analyses[a]	False positive	False negative	Total errors
Amphetamines	357	1	12	13
Amphetamine	78	0	0	0
Phenylpropanolamine	43	0	1	1
Barbiturates	137	0	10	10
Phenobarbital	33	0	1	1
Secobarbital	16	1	0	1
Benzodiazepines	271	1	2	3
Nordiazepam	38	1	1	2
Oxazepam	34	2	1	3
Flunitrazepam	28	0	1	1
Opiates	407	4	8	12
Morphine/glucuronide	90	1	0	1
Codeine	84	0	2	2
Methadone	357	0	2	2
Propoxyphene	112	1	2	3
Benzoylecgonine/cocaine	392	9	3	12
Cannabinoids	353	14	1	15
Total	2824	35	47	82
Percentage of errors		1.2	1.6	2.8

[a] The maximal number of potential analyses for each group of drugs was 408 ($\Sigma_{i=1,4}$ six samples × four batches × n_i laboratories in each batch).

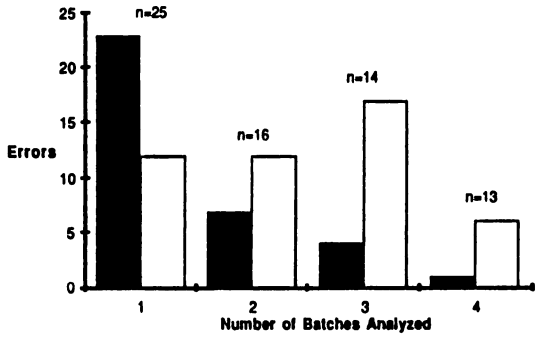

Fig. 1. Evolution of the absolute number of false-negative (*open bars*) and false-positive (*closed bars*) results

n indicates the number of laboratories analyzing one, two, three, or four batches during the first year, depending on when they joined the program

The percentage of errors, especially false-positive results, decreased when results by the EMIT technique were combined with a chromatographic technique (from 1.7% to 0.5% for false positives and from 2.0% to 1.5% for false negatives, see Figure 2). The number of errors decreased to 0.3% for both false-negative and false-positive results (last bar in Figure 2) if confirmation analysis by commercial TLC was omitted.

Complete (100%) success was reached only in the analysis for amphetamine itself (Table 3). There was a large number of false-negative results in the amphetamine group (n = 12), most of them related to the presence of phenylpropanolamine in the samples. According to the rules of the program, the presence of phenylpropanolamine in concentrations >5 mg/L should be reported as positive for the amphetamine group. Most of the laboratories using EMIT for screening were able to detect the presence of an amphetamine-like compound, but with a response lower than 1 mg of amphetamine per liter (the minimum amount potentially present for such compound). When further confirmation was not carried

Table 4. Number of Errors by the Different Groups of Laboratories

Group[a]	Test batch[b] 1	2	3	4	Total no. of errors
Group 1					
FP	9	1	3	0	13
FN	2	1	3	0	6
Group 2					
FP	13	6	1	1	21
FN	9	9	11	4	33
Group 3					
FP	1	0	0	0	1
FN	1	2	3	2	8
Total	35	19	21	7	82

[a] Laboratories grouped according to the criteria described in Table 2; no. per group as in Table 2.

[b] The batch numbers refer to the number of batches analyzed by each laboratory during 1987 (see Figure 2). It depends on the date of initial participation of each laboratory in the Program (see Figure 1).

FP: false positive, FN: false negative.

out to detect the presence of phenylpropanolamine, such urines were sometimes erroneously reported as negative for the amphetamine group.

A similar situation appeared in the barbiturates group, with a high rate of false negatives (n = 10) reported for urines containing phenobarbital, a drug with low cross-reactivity in the EMIT test for barbiturates. These kind of interpretative errors should disappear in the future (see *f* in the *Discussion*).

The situation was different for the false positives (n = 9) for cocaine when only benzoylecgonine was present. Some laboratories faced with a positive result in the test for benzoylecgonine by EMIT reported a positive result for cocaine instead of, or in addition to, benzoylecgonine when according to the program instructions only benzoylecgonine should have been reported.

In the opiates group, most of the false-negative results (n = 8) were related to the presence of codeine and morphine-3-glucuronide in the urines, for which reactivities with the antibody were less than for the free morphine when immunological techniques were used or when chromatographic techniques were used without a hydrolysis step.

Finally, many false-positive results (n = 14) were reported for the cannabinoids group, primarily from a small group of laboratories that used only EMIT as the analytical technique. This was very difficult to explain. Taking into account the successful results reported by the remaining laboratories, the high degree of automation of the technique, and the objectivity in the interpretation of the results, such false positives seemed related to poor implementation of adequate internal quality-control practices and to the absence of confirmatory analysis in these laboratories (see below). This remark can be extended to the false-positive results (n = 4) in the detection of opiates.

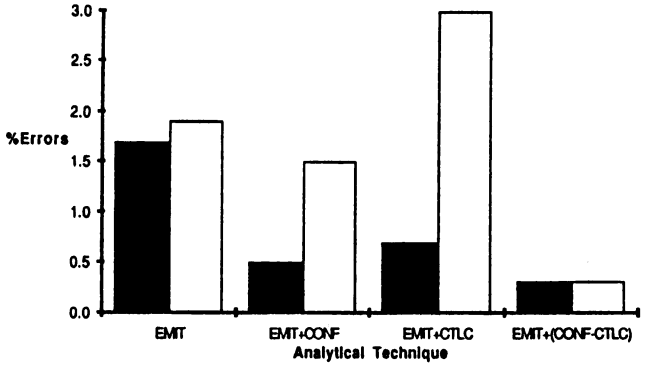

Fig. 2. Percentage of false-negative (*open bars*) and false-positive (*closed bars*) results when the laboratories used EMIT alone, EMIT associated with any confirmatory technique (EMIT + CONF), EMIT associated only with commercially available TLC confirmation methods (EMIT + CTLC) and EMIT associated with any confirmatory technique except commercial TLC [EMIT + (CONF − CTLC)]

Discussion

Emphasis during the first year of implementation of the Proficiency Testing Program has been especially directed towards educational activities. Some of the laboratories involved had been just recently created, and the personnel involved had limited experience and knowledge of specific techniques. Therefore, the minimal concentrations for detection have been maintained relatively high and much attention was paid to interpreting and reporting of results.

The misinterpretation of cross-reactivities is of special concern to us, because some of the laboratories did not use confirmatory techniques. Apparently, some of the laboratories do not pay attention routinely to possible false positives caused by cross-reactions with some medications not considered to be abused drugs. When these drugs (e.g., codeine, phenylpropanolamine) were present in the samples, the report by the Coordinating Center included strong comments stressing the importance of confirmatory techniques.

Enzyme immunoassay is the screening method of choice among laboratories included in our program. Its commercial availability and its simplicity are important factors for its preference to other screening techniques, such as TLC, which requires more experience and more-elaborate quality control (*12*). In fact, a large number of errors in our program are from laboratories using "commercially available thin-layer chromatography for drugs of abuse," either alone (screening) or as a confirmation of a previous false result by enzyme immunoassay. Both the low sensitivity (false negatives) and the subjectivity of interpreting commercial TLC results previously found positive by EMIT (false positives) affect the reliability of this technique among the laboratories participating in our program.

The use of confirmatory techniques other than commercial TLC significantly reduced the number of errors, both false positives and false negatives. However, even those laboratories having a satisfactory confirmatory level should pay special attention to the way they report a result. Only the specific analyte detected (e.g., benzoylecgonine) should be reported, and the statement that "[the specific drug detected] is compatible with the ingestion of the parent drug" (e.g., cocaine) could be added to the report. Every effort to promote correct interpretation and reporting in the drugs-of-abuse field is important, because reports sometimes can be misunderstood by the press and other nonspecialized media.

The improvement in correct results as laboratories participated in the program is highly significant, especially with respect to the decrease in false positives. For instance, the frequency of false-positive results decreased by more than 10-fold for those laboratories that participated in the program for a complete year. Although the advance in decreasing false-negative results is not so evident, the overall improvement of results is encouraging, as has been observed elsewhere (*13*).

The detailed analysis of errors made by laboratories in group 2 (Table 4) points out that their structure and experience seems less than optimal. Despite having more instrumental resources than the group 1 laboratories, their error rate is excessively high. Apparently not enough experienced personnel are present to take advantage of the better instrumental resources, and the instruments are not used regularly. For these centers to perform screening and confirmatory analysis adequately, they should have characteristics closer to those in group 3: a large number of samples, drugs to be analyzed, experimental techniques, and skilled personnel. When these are not obtainable, we recommend that these centers perform only screening analysis and send the samples to well-equipped and experienced laboratories for confirmation. Another approach is to contribute actively to the improvement of experience in confirmatory techniques in all the laboratories by means of training programs (see recommendations below). In any case, the implementation of standard operating procedures and adequate internal quality control in all laboratories before the release of final results is a requirement that must be understood and developed (*14*).

After evaluation of the first year's operation of the Spanish Proficiency Testing Program, several recommendations were made for the second year, including:

(*a*) Laboratories should be provided with methanolic stock solutions of parent drugs and (or) metabolites to be used as standards for confirmatory methods.

(*b*) An on-site two-week practical education program in the Coordinating Center should be implemented, for participating laboratories (one analyst per center) to learn and practice confirmatory techniques.

(*c*) The accreditation of laboratories by the Spanish Administration should be a logical extension of the program in the near future for laboratories involved in nonclinical urinalysis for drugs of abuse.

(*d*) Some drugs should be added to the menu: 6-acetylmorphine as a marker of heroin ingestion; 7-amino-flunitrazepam as the main metabolite of flunitrazepam (a benzodiazepine highly abused in Europe); and ecgonine methyl ester as an important metabolite of cocaine.

(*e*) Removal of some drugs should be considered: pentobarbital, because of its low urinary excretion; naltrexone, which is used only in a few controlled clinical trials; and unmetabolized cocaine, which is present only after "crack" ingestion (currently uncommon in Spain) or after intentional addition to the urine.

(*f*) Minimal drug concentrations added to the urine will be those that yield a response higher than that of the "low" calibrator of the most commonly used screening procedure in our laboratories (enzyme immunoassay).

(*g*) Suspected abuse of buprenorphine (*15*) should be substantiated before this drug is added to the program, e.g., through performing studies to detect its prevalence. The advisory committee expressed concern because of the slow implementation by the manufacturers of potential techniques to detect metabolites of drugs being abused in Europe, even if they are not abused in the United States (e.g., buprenorphine, flunitrazepam).

The development of the Proficiency Testing Program carried out so far is considered encouraging by the parties involved (administration, Coordinating Center, advisory committee, and participating laboratories). The next step seems to be to interact with other international initiatives in this field, if any. The possibility of a European Proficiency Testing Program should be considered.

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