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Commutability of proficiency testing material containing amitriptyline and nortriptyline: A study within the framework of the Dutch Calibration 2.000 project

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ABSTRACT

Background: External quality assessment schemes (EQAS) can provide important information regarding accuracy and comparability of different measurement methods if the sample matrices are composed of commutable material. The aim of this study was to assess the commutability of different matrices for the material used in an EQAS for amitriptyline and nortriptyline.

Methods: Proficiency testing material (PTM) and patient samples containing amitriptyline and nortriptyline were prepared, collected, pooled, and distributed to participating laboratories for analysis. Low, medium and high concentrations of both drugs in liquid pooled human, lyophilized human and lyophilized bovine serum were tested in this study. The measurement deviation of the PTM results to the patient serum regression line were normalized by dividing through the average within-laboratory SD (SD_{wi}) derived from the results reported in the official EQAS, resulting in a relative residual. The commutability decision limit was set at $3 SD_{wi}$.

Results: With 10 laboratories participating in this study, 45 laboratory couples were formed. All matrix types delivered several relative residuals outside the commutability decision limit. The number and the magnitude of relative residuals for both drugs were lower for liquid human sera as compared to lyophilized human and bovine sera.

Conclusions: The PTM used for amitriptyline and nortriptyline is preferably prepared with human serum, although not all relative residuals are within the commutability decision limit.

1. Introduction

Participation in external quality assessment schemes (EQAS) for periodic review of the quality of analysis is a requirement for medical laboratories accredited according to the International Organization for

Standardization (ISO) standard 15,189 [1]. The EQAS provider is, on his turn, required to act according to the ISO standard 17,043 [2], which states that the EQAS provider uses proficiency testing material (PTM) that “match in terms of matrix, measurands and concentrations, as closely as practicable, the type of items or materials encountered in

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; EQAS, External quality assessment schemes; GC, gas chromatography; HPLC-RP, high performance liquid chromatography reverse phase; HPLC-SP, high performance liquid chromatography straight phase; ISO, International Organization for Standardization; KKG, Association for Quality Assessment in Therapeutic Drug Monitoring and Clinical Toxicology; LC/MS/MS, liquid chromatography coupled with two mass spectrometers; PTM, Proficiency testing material; SD_{wi} , within-laboratory standard deviation; SKML, Dutch Foundation for Quality Assessment in Medical Laboratories

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routine testing or calibration” [2]. This characteristic of PTM is also known as commutability, and is defined by the Clinical and Laboratory Standards Institute (CLSI) as “the ability of a material to yield the same numerical relationships between results of measurements by a given set of measurement procedures, purporting to measure the same quantity, as those between the expectations of the relationships obtained when the same procedures are applied to other relevant types of material” [3].

The use of commutable material is, besides assignment of the target value by a reference measurement procedure or a certified reference material and/or repeated measurement of the same sample, a characteristic that determines the value of evaluation of results obtained in the EQAS [4]. In a category 1 EQAS all these characteristics are present and the value of evaluation is highest, in a category 6 EQAS all characteristics are absent and the value of evaluation is lowest [4]. The results obtained from category 1 EQAS can give a first idea about the need and starting point of harmonization [5], which is of particular importance in this time were patients visit several different hospitals for specialized treatments and/or surgeries [6,7].

This study is part of the Calibration 2.000 study group, a working group initiated by the Dutch national EQAS provider SKML (Foundation for Quality Assessment in Medical Laboratories) [8,9]. Within this group several studies aiming for harmonization were performed [10–14], and a pilot category 1 EQAS scheme was executed in different European countries [15–17].

The section Association for Quality Assessment in Therapeutic Drug Monitoring and Clinical Toxicology (KKG) of SKML provides the interlaboratory comparisons for therapeutic drug monitoring and clinical toxicology. Previous commutability studies in the field of therapeutic drug monitoring for EQAS samples containing anti-epileptic drugs [18] and antibiotic drugs [19] were also part of the Calibration 2.000 philosophy. In this study the sample containing amitriptyline and nortriptyline is evaluated for commutability.

2. Materials and methods

2.1. Study design and data analysis

The study design is in analogy with the designs used for the commutability evaluation of PTM containing carbamazepine and valproic acid [18] and tobramycin [19]. In the psychotherapeutic drugs EQAS of the KKG, five samples containing several psychotherapeutic drugs are sent to the participants. In this study the commutability of a sample containing amitriptyline and nortriptyline was tested.

For the commutability evaluation all participating laboratories were instructed to measure amitriptyline and nortriptyline in pooled patient samples and candidate matrices samples (see below for preparation details). Results were analyzed according to CLSI guideline EP30-A [20], as follows:

Results of the patient samples of each of the laboratories were plotted against the results of each of the other laboratories (X_{lab1} vs. Y_{lab2} , X_{lab1} vs. Y_{lab3} , X_{lab1} vs. Y_{lab4} , X_{lab2} vs. Y_{lab3} , etc.), and Passing and Bablok regression analysis [21,22] was performed for all 45 laboratory couples. Results of the candidate matrices samples were then compared to the patient samples by calculating the orthogonal residuals between the X_{labA} , Y_{labB} coordinates of the candidate matrix samples and the Passing and Bablok regression line of the corresponding laboratories. See Fig. 1 for an example. For comparison, the relative residuals were calculated by dividing the orthogonal residual by the concentration dependent average within-laboratory standard deviation (SD_{wl}). The SD_{wl} 's used in this study are the average SD_{wl} 's from EQAS results for amitriptyline and nortriptyline over a period of 3 years. The commutability decision limit was set at $3 SD_{wl}$, comparable to the decision limits set at the carbamazepine/valproic acid and tobramycin commutability studies [18,19].

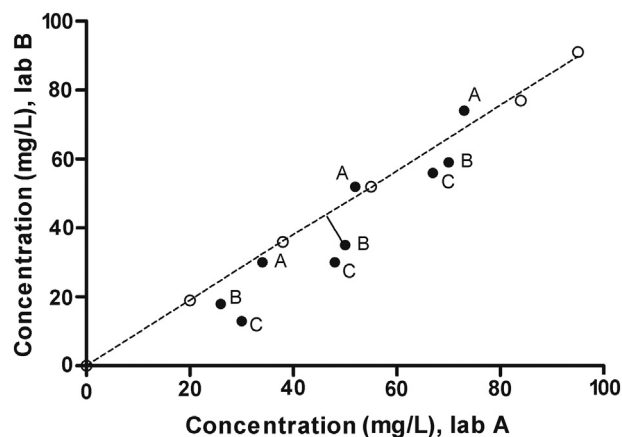


Fig. 1. Example of data analysis of two laboratories. ○, patient samples; ●, candidate matrix samples (A, B, or C); dashed line (---), patient sample regression line; continuous line (—), orthogonal residual.

2.2. Patient material preparation

Left over patient serum samples from routine clinical analyses were collected three months prior to the study and stored at -80°C . Hemolytic and icteric samples were discarded; no criteria for lipemic samples were defined. Pools were prepared aiming at 4 concentration levels for both drugs ranging from slightly below the therapeutic window to slightly above the therapeutic window of both drugs. Prior to pool preparation serum samples were defrosted at room temperature for 1 h. After pooling the serum was divided in aliquots of 2.50 mL and stored at -20°C prior to dispatch.

Four patient pool sera containing amitriptyline, four patient pool sera containing nortriptyline and one blank human serum were sent to the participating laboratories. Patient pool sera containing amitriptyline also contained nortriptyline, and vice versa. Participating laboratories were informed and instructed about which analyte to analyze in which vial/tube. The mean values of the samples measured by the participating laboratories in this commutability study for amitriptyline in the patient pool sera were 27.3 ± 4.1 , 83.9 ± 12.9 , 123.7 ± 21.2 and $214.6 \pm 43.5 \mu\text{g/L}$. Mean nortriptyline concentrations were 35.6 ± 6.8 , 80.5 ± 12.9 , 121.4 ± 18.6 and $180.2 \pm 41.3 \mu\text{g/L}$.

2.3. Candidate matrices

In this commutability study, human and bovine sera were used as candidate matrices. Since lyophilization of the samples is preferred for maintaining stability during storage and distribution, the effect of lyophilization on both human and bovine serum was tested. Three candidate matrices are tested in this commutability study: frozen liquid human serum, lyophilized human serum and lyophilized bovine serum. No liquid bovine serum sample was included in this commutability study because the two previous studies also showed a preference for samples of human serum and we hypothesized that the comparison with lyophilized bovine serum would give sufficient data for the comparison [18,19].

Blank human serum was obtained from the national blood bank and stored according to instructions at -20°C . The blank bovine serum was obtained from Invitrogen (gamma irradiated newborn calf serum, Paisley, Scotland, UK, www.invitrogen.com) and stored at -20°C . Both sera were defrosted overnight at room temperature before pooling and sample preparation.

2.4. Candidate matrices sample preparation

The candidate matrix samples were prepared by adding a volumetric quantity of amitriptyline and nortriptyline stock solutions to

Table 1

Amitriptyline and nortriptyline concentrations (in mg/L) in different stock solutions.

		Concentration
Amitriptyline	ami-st-I	361.3
	ami-st-II	14.5
	ami-st-III	4.3
Nortriptyline	nor-st-I	434.7
	nor-st-II	13.0
	nor-st-III	4.2

blanc matrices. The amitriptyline and nortriptyline stock solutions were prepared by dissolving amitriptyline (Lundbeck, Copenhagen, Denmark) (ami-st-I) and nortriptyline (Lundbeck, Copenhagen, Denmark) (nor-st-I) in a mixture of distilled water, 0.1 M HCl and absolute alcohol in a ratio of 3:3:4. Both stock solutions were diluted twice with distilled water creating ami-st-II, ami-st-III, nor-st-II and nor-st-III stock solutions that were used for spiking the candidate matrices. The final candidate matrices contained less than 0.02% ethanol. See Table 1 for final concentrations of the different stock solutions.

Three concentration levels of amitriptyline and nortriptyline in bovine serum were prepared by spiking 80 mL blank bovine serum with 1.0 mL ami-st-III and 1.0 mL nor-st-III, 2.0 mL ami-st-III and 2.0 mL nor-st-III, and 1.0 mL ami-st-II solution and 1.0 mL nor-st-II solution. The human serum samples were prepared by spiking 130 mL blank human with 1.5 mL ami-st-III and 1.5 mL nor-st-III, 1.0 mL ami-st-II and 1.0 mL nor-st-II, and 1.5 mL ami-st-II and 1.5 mL nor-st-II to obtain low, medium and high concentrations amitriptyline and nortriptyline (see Table 2). Matrices were stirred for 10 min, according to the local preparation protocol for EQAS material. The bovine serum was dispensed in vials in 2.50 mL aliquots and subsequently lyophilized. Half of the human serum was dispensed in laboratory tubes in 2.50 mL aliquots and the other half was dispensed in vials in 2.50 mL aliquots and subsequently lyophilized. All samples were stored at -20°C prior to dispatch.

2.5. Participants and measurement methods

All participants of the psychotherapeutic drugs EQAS were informed about this commutability study and asked for voluntary participation.

Before shipment of the samples laboratories received written instructions about dispatch of the samples, storage condition, reconstitution of lyophilized samples, minimum/maximum time between samples receipt and analysis and contact information details. All samples were sent on dry ice and delivered over night. Laboratories were instructed to analyze all samples in duplicate in one run. Lyophilized samples should be stored in the refrigerator until reconstitution and analysis. The liquid samples should be stored in the freezer and thawed at a laboratory bench at room temperature before analysis. Analysis should be performed within 72 h after receipt of the samples. When the liquid samples were received thawed, it was advised to store the samples in the refrigerator and analyze immediately or within 24 h of

Table 2

Amitriptyline and nortriptyline concentrations (in $\mu\text{g/L}$) in candidate matrices samples.

		Human serum (liquid)	Human serum (lyophilized)	Bovine serum (lyophilized)
Amitriptyline	Low	50.1	47.3	51.4
	Medium	111.3	105.0	103.2
	High	168.0	158.8	171.2
Nortriptyline	Low	48.2	45.5	49.5
	Medium	100.4	94.8	99.4
	High	151.7	143.3	154.5

receipt.

Lyophilized samples should be reconstituted by adding 2.50 mL of distilled water, leaving the vial for 15 min on the laboratory bench, and then carefully mixing without shaking the vial until completely dissolved. Participants were instructed to homogenize thawed liquid samples before analysis by vortex method.

3. Results

Ten laboratories participated in this commutability study that analyzed all samples. Amitriptyline and nortriptyline were analyzed with three different methods of analysis. Five laboratories used high performance liquid chromatography-reverse phase or straight phase (HPLC-RP or HPLC-SP), four laboratories used liquid chromatography coupled with mass spectrometers (LC/MS/MS) and one laboratory used gas chromatography (GC). Ten participating laboratories formed 45 unique laboratory couples in this study.

3.1. Amitriptyline

Fig. 2 depicts the calculated relative residuals for amitriptyline and nortriptyline. For amitriptyline the number of residuals outside 3SD_{wl} is largest in the lyophilized bovine serum samples, see Table 3. All relative residuals outside the cut-off of 3SD_{wl} in liquid and lyophilized human serum were produced by laboratory couples which contain two of the ten participating laboratories. One relative residual derived from a low amitriptyline concentration sample in lyophilized human serum formed an exception and fell within the cut-off range. In lyophilized bovine serum half of the residuals outside 3SD_{wl} were produced by these two laboratories. Of these two laboratories, one laboratory was the only laboratory using a GC method, the other laboratory used a LC/MS/MS method. The laboratory using the GC method shows relatively large duplicate differences, indicating a large within-laboratory variation. No explanation for non-commutability could be found for the laboratory using the LC/MS/MS method.

When discarding these laboratories, only one relative residual outside 3SD_{wl} remains for human serum and multiple residuals remain for bovine serum, see Table 4. Also, the number of relative residuals outside 2SD_{wl} , a more stringent commutability decision limit, shows the same result, the number of relative residuals is the highest in the bovine serum samples.

3.2. Nortriptyline

For nortriptyline the number of relative residuals outside 3SD_{wl} is also largest in the lyophilized bovine serum samples (see Table 3). The difference between relative residuals in liquid and lyophilized human serum samples is smaller compared to the difference seen in the amitriptyline liquid and lyophilized human serum samples, though still lower for liquid sera. No specific laboratories are responsible for the relative residuals outside 3SD_{wl} .

4. Discussion

The results of this commutability study indicate that the samples containing amitriptyline and nortriptyline used in the EQAS for psychotherapeutic drugs are preferably prepared using blanc human serum, even though none of the candidate matrices produced all relative residuals below the commutability cut off limit of 3SD_{wl} .

A frozen liquid human serum sample produced the lowest relative residuals for amitriptyline compared to lyophilized human serum and lyophilized bovine serum. Relative residuals outside the commutability cut off limit are all produced by laboratory couples containing two out of ten participating laboratories. The results of these laboratories were divergent from the results of the other laboratories but because their results were consistent over the different matrices they were not

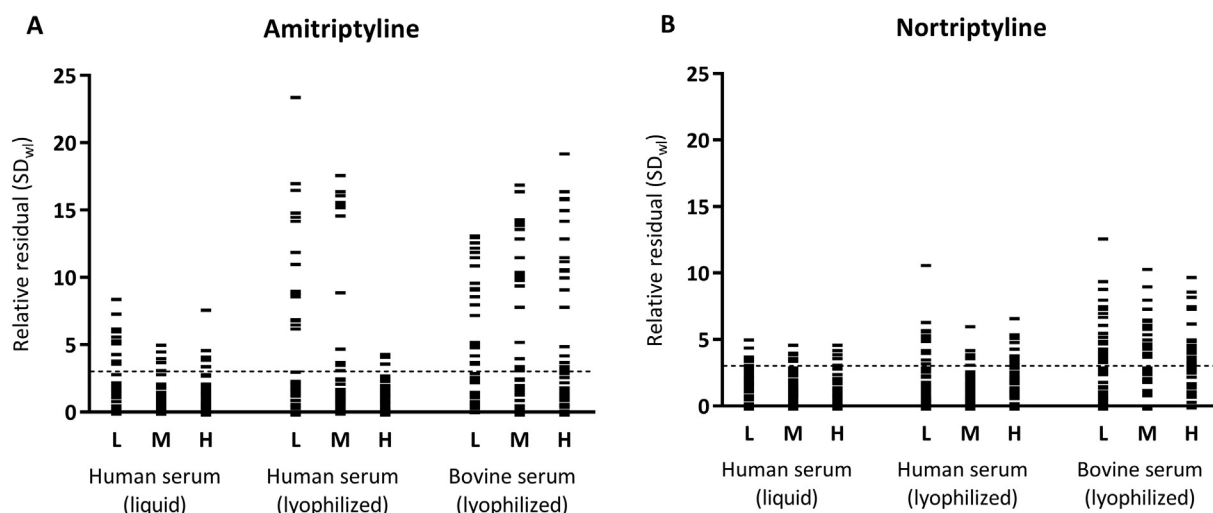


Fig. 2. Relative residuals for low (L), medium (M) and high (H) concentrations of amitriptyline (A) and nortriptyline (B) in liquid human, lyophilized human and lyophilized bovine sera.

Table 3

Number of relative residuals for low, medium and high amitriptyline and nortriptyline concentrations above the commutability decision limit at $3 SD_{wl}$.

		Human serum (liquid)	Human serum (lyophilized)	Bovine serum (lyophilized)
Amitriptyline	Low	13	17	25
	Medium	6	13	22
	High	9	3	24
Nortriptyline	Low	11	14	23
	Medium	7	8	24
	High	8	15	24

Table 4

Number of relative residuals outside $2 SD_{wl}$ and $3 SD_{wl}$ for low, medium and high amitriptyline concentrations produced by laboratory couples when discarding two specific laboratories.

		Human serum (liquid)		Human serum (lyophilized)		Bovine serum (lyophilized)	
		$2 SD_{wl}$	$3 SD_{wl}$	$2 SD_{wl}$	$3 SD_{wl}$	$2 SD_{wl}$	$3 SD_{wl}$
Amitriptyline	Low	2	0	7	1	17	13
	Medium	3	0	3	0	16	12
	High	1	0	3	0	15	13

identified as outliers. When discarding these results, all remaining relative residuals for amitriptyline are below the commutability cut off limit for both liquid and lyophilized human serum, but not for lyophilized bovine serum.

No large differences exist between liquid frozen human serum and lyophilized human serum for nortriptyline, with a slight preference for liquid frozen human serum. In none of the candidate matrices all relative residuals are below $3 SD_{wl}$, and no specific laboratory or method of analysis is accountable for it.

In an earlier commutability assessment of EQAS sample material for drug proficiency testing that assessed carbamazepine, the presence of metabolites in the patient samples and absence of metabolites in the candidate matrices could be an explanation of non-specificity [18]. This is not the expectation for amitriptyline and nortriptyline since the metabolites of these components are the hydroxy-metabolites and the methods of analysis used in this study are able to separate them from their parent compounds.

This study is the first of our commutability studies [18,19] in which

no immunoassay's were used for analysis of the samples. The previous studies also showed a preference for human serum, which could have been attributable to the immunoassays that are more prone to be influenced by the matrix. The results of this study show that also results produced by HPLC, GC and LC/MS/MS can be influenced by the type of matrix.

Because of stability and shipment issues, a lyophilized human serum sample is preferred for both analytes.

The design of this study is comparable to the previous studies and is previously described as an X-ling design [19]. A strength of this methodology is the possibility to compare all methods with each other. In this design the laboratories do not exchange patient serum samples and candidate matrices samples in one pair according to CLSI EP30-A guideline [20], but all laboratories analyze the same sera. When analyzing the same sera, each laboratory is coupled with each of the other laboratories, creating several laboratory couples and therefore several comparisons of analytical methods.

A limitation of this study is pooling of patient sera left over from clinical analysis, which was necessary to obtain sufficient amounts of sera. This pooling can be a disadvantage when one of the patient samples contains a substance that interferes with the analysis since it could affect the entire pool. On the other hand, if an interfering substance is present in one of the samples, it will be diluted and therefore probably will not affect the results of the commutability study. EQAS samples will probably foremost be samples without interfering substances representing the majority of the patient samples in clinical practices. Therefore, samples without interfering substances are preferred in a commutability study with the aim to identify the most suitable matrix for the EQAS program. Another limitation of this study is the uncertainty whether the relative residuals outside the commutability cut off limit are the result of the methods of analysis used by the laboratories and/or the PTM since commutability is a combination of both these factors.

To our knowledge this is the first commutability study for proficiency testing material containing amitriptyline and nortriptyline. Even though not all relative residuals are below the commutability cut off limit, a preference for human serum is manifest. Further research is needed to study whether the two laboratories producing relative residuals outside the cut off limit have inadequate methods of analysis or if the PTM is of insufficient quality.

5. Conclusion

The sample used in the psychotherapeutic drugs EQAS containing

amitriptyline and nortriptyline is preferably prepared in not lyophilized human serum.

Declarations of interest

None.

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