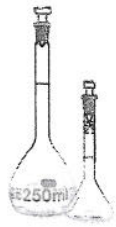
Inaccurate dosage; Results from the FIP-LMCS collaborative study



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Introduction

Despite obvious advantages, the administration of liquid medicines to children or to those patients unable to swallow a solid formulation may have accuracy problems. Several reports have been published, addressing this issue in the administration of liquid preparations. In 1987 Gribetz et al. conducted a study involving 96 young children and it was revealed that sub-dosing of acetaminophen was occurring in nearly 26% of patients. A similar study developed by Hyam et al. concluded that the mean dose administered was only approx. 65 % of the recommended dose. Simon et al. evaluated the caregivers (parent or guardian) role in relation to the dose accuracy for OTC medication and concluded that the accuracy could probably be improved by educating the caregivers.

Litovitz identified three major causes of dosing errors associated to the use of liquid medication. The errors were related with teaspoon/tablespoon confusion, the assumption that the dispensing cup was the unit of measure, and that the full dispensing cup was the actual dose.

It is clear from the above examples that accuracy of dosing of liquid preparations may have a significant impact on the outcomes of therapy and thus also on patient safety. Therefore, we designed a study to assess the dosing accuracy and reproducibility in the administration of amoxicillin/clavulanic acid suspensions, and to identify the main sources of variation in a controlled and uncontrolled laboratory environment.

Other participants in the study:

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- R. Bouwerc, Centre for Quality Assurance of Medicines, South Africa
- J. Petrid, Zentrallaboratorium Deutscher Apotheker, Germany
- P. Trommelmanse, Medicines Control Laboratory, Belgium
- B. Kamelf, Laboratoire National de Controle des Medicaments des Produits Cosmétiques, d'Hygiéne Corporelle et de Despistage du Dopage, Tunisia
- A. Gemalg, Fundação Oswaldo Cruz, Brazil
- H. Wagenaar, Laboratory of the Dutch Pharmacists (LNA), the Netherlands

Materials and methods

Participants

Eight laboratories from different countries participated in the study. Products evaluated were those described in Table 1. A reference product distributed by the study coordinators was included in the study.

Experimental procedure

All laboratories performed four different experiments with all products. For the analysis of amoxicillin, the method included in USP25 monograph "amoxicillin and clavulanate potassium for oral suspension" was used as a reference.

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Table 1: Identification of the participating laboratories, medicines studied and measuring device used

Laboratory	Country	Study products	Measuring device
Central State Lab for Quality of Medicines	Ukraine	Reference Amoxiclav®	Measuring spoon
Centre for Quality Assurance of Medicines	South Africa	Reference Ranclav® Augmaxcil S® Clavumox S® Clamentin S®	Dosing cap Measuring spoon
Zentrallaboratorium Deutscher Apotheker	Germany	Reference Amoclav trockensaft® Amoxi-Clavulan AL® Amoxi-Clavulan Stada TS® Amoxiclav von ct TS® Augmentan trockensaft®	Measuring spoon
Medicines Control Laboratory	Belgium	Reference Amoxiclav BC® Co-Amoxi-Ratiopharm® Merck-Amoxiclav® Augmentin® Co-Amoxilan E.G.®	Measuring spoon
Laboratoire National de Controle des Medicaments des Produits Cosmétiques, d'Hygiéne et de Despistage de Dopage	Tunisia	Reference Augmentin enfant®	Measuring spoon
Fundação Oswaldo Cruz – Instituto Nacional de Controle de Qualidade em Saúde	Brazil	Reference Amoxicilina + clavulanato de potássio Amoxicilina + clavulanato de potássio	Measuring spoon
LEF – laboratório de estudos Farmacêuticos	Portugal	Reference Augmentin® Clavamox 125® Clavepen® Penilan®	Measuring spoon
Laboratory of Dutch Pharmacists LNA	The Netherlands	Reference Amoxicilline / Clavuaanzuur	Measuring spoon

Experiment 1. Content of the suspensions for amoxicillin

Experiment 1 evaluated the amoxicillin content of the different study products

Experiment 2. Dosing accuracy

Agitation of the suspension was to be performed accordingly to the instructions provided by the manufacturer (if any) or for 30 seconds. After 1 minute standing on the bench, the equivalent to one dose (5 ml) was to be measured using a graduated glass pipette. The pipette was rinsed into the same flask. Following filtration, the filtrate was to be used as the assay preparation within one hour. Each laboratory performed 3 tests per product.

Experiment 3. Dosing accuracy by subject A

The equivalent to one dose (5 ml) of each product was measured by a technician, using the device provided with the product and transferred to an appropriate volumetric flask. The device was rinsed into to the same volumetric flask. The filtrate was to be analyzed within one hour. Each laboratory performed 3 tests per product.

Experiment 4. Dosing accuracy by subject B

Experiment 4 was the same as experiment 3, but the sampling was done by a non-laboratory worker.

Results and Discussion

Reference product

Mean essay values as well as the standard deviation obtained are represented in Table 2.

Table 2: Mean values and standard deviation of the reference product

Experiment	N (Total number of assay data)	Mean value (mg/5 ml)	SD (mg/5 ml)
1	16	126.2	7.7
2	24	126.7	8.0
3	24	130.8	16.7
4	24	127.1	32.0

Table 3: ANOVA results reference products

Source of variation	Sum of Squares	Degrees of freedom	Mean square	F value	P value
Experiment	7.1056	3	2.3685	33.15	<0.0001
Laboratory	5.3783	7	0.7683	10.75	<0.0001
Interaction	8.0727	21	0.3844	5.38	<0.0001
Error	4.0016	56	0.0715		
Total	24.5581	87			

Although mean essay values are similar and within the quality specifications (90% to 120% of the declaration on the label), a four fold increase in variance was found from experiment 1 to experiment 4. The CV% in all laboratories for experiment 1 is 6.1%. Once the manipulation of the suspension is introduced as a variable (experiment 2), a negligible increase in the CV% is observed (6.4%). Experiment 3, showed a CV of 12.8%, representing nearly a two-fold increase. In experiment 4, a two-fold increase in variability was found in comparison with experiment 3 and a four-fold increase when compared to experiment 1.

Two-way ANOVA fixed-effects model (on log transformed data) with replication for the absolute percent deviations from the label (table 3) detected significant differences between experiments and between laboratories ($p < 0.05$). Data analysis for multiple comparisons showed significant differences between experiment 1 and experiments 3 and 4. Similar results were found for the comparisons between experiments 2 and experiments 3 and 4.

Since the major differences from experiments 1 and 2 to experiments 3 and 4 are the measuring device and the manipulation of the suspension according to the manufacturers' instructions, it seems that both the measuring device and the person handling the suspension represent major sources of variability.

Local market amoxicillin / clavulanic acid suspensions

Table 4 represents the mean and standard deviation for content, by experiment, for all local market products.

As observed for the reference product there is an increasing variability from experiment 1 to 4, although less pronounced. Several measured doses of amoxicillin are outside the accepted quality specification limits of 90% to 120% of the label value. In experiment 1, one result out of 48 is below 90% of the label (125 mg/5 ml). In experiments two, three and four, 9, 15 and 22 results out of 72 are outside the 90% to 120% of the label.

Two-way ANOVA fixed-effects model (on log-transformed data) with replication for the absolute percent deviations obtained from label, detected significant differences between experiments and between laboratories. Results are included in table 5.

Significant differences between experiments and between laboratories were observed ($p < 0.05$). Multiple comparisons revealed significant differences between experiment 1 and experiments 3 and 4. Similar results were obtained for the comparisons between experiment 2 and experiments 3 and 4.

Conclusions

The mean assay values for the reference product were similar among the four experiments. The increase in variability corresponds to the introduction of the measuring device and the person handling the product. Statistically significant differences (ANOVA) observed between experiments confirm these findings.

The results from the local market products are similar to those obtained with the reference product. In experiment one, 2.1% of the 48 results is outside the 90% to 120% quality specification, while this percentage increases to 12.5% in experiment two, and to 20.8% and 30.6%, in experiments three and four, respectively.

As other studies have already pointed out, the dosing of amoxicillin/clavulanic acid suspensions (and thus other liquid preparations) with dosing devices may not be very accurate. The dosing device and the person handling the product seem to be the major sources of variability. The variability may possibly be reduced by a better design of the measuring devices and through better education/ information of caregivers by pharmacists when dispensing this type of medication.

Bibliography

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Table 4: Mean values and standard deviations (SD) obtained with the local market product

Experiment	N (Number of assay values)	Mean value (mg/5 ml)	SD (mg/5 ml)
1	50	127.14	9.36
2	75	124.80	10.43
3	75	130.29	21.32
4	75	124.59	18.29

Table 5: ANOVA results local market products.

Source of variation	Sum of Squares	Degrees of freedom	Mean square	F value	P value
Experiment	6.9828	3	2.3276	31.96	<0.0001
Laboratory	15.3155	24	0.6381	8.76	<0.0001
Interaction	22.6780	72	0.3150	4.33	<0.0001
Error	12.7436	175	0.0728		
Total	57.7199	274			