# REPLACEMENT OF SOLID DOSES BY ORAL LIQUID PREPARATIONS FOR PEDIATRICS: A COLLABORATIVE APPROACH BETWEEN 2 SWISS UNIVERSITY HOSPITAL CENTRES

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## INTRODUCTION

The pharmaceutical industry supplies oral solid dosage forms which are generally inadequate for pediatric needs.

This obliges pharmacies, in hospitals that have a pediatric unit, to prepare capsules having doses that correspond to age and weight of the children. Thus a multitude of doses are necessary, which leads to individualized preparations. These solid forms are not only time consuming to make but also sub-optimal in their utilization. In effect, capsules for pediatric use have many disadvantages:

a) There is a risk of confusion which is not negligible
b) The bioavailability can vary with the granulometry of the powders used
c) These capsules in fact only represent a form of transport because they have to be opened when they are administered to small children.

## OBJECTIVES

The two university hospitals of french speaking Switzerland receive the majority of acute pediatric patients. For this reason they have very similar needs in drug doses. Consequently they decided to collaborate with the following objectives:

a) Replacement of the capsules by oral liquid preparations supplying various doses.
b) Development of new formulations and stability tests.
c) Supplying a data base of formulas, excipients, stability, packaging and administration.

## MATERIALS AND METHODS

An inventory of capsules manufactured in the two hospitals in 1998 was realized.

| DRUGS | Total caps. CHUV | Total caps. HUG | TOTAL | No. Of diff. doses CHUV | No. Of diff. doses HUG | Dose limits (low-high) CHUV | Dose limits (low-high) HUG |
|---|---|---|---|---|---|---|---|
| ACENOCOUMAROL (sintrom) | 0 | 2'920 | 2'920 | 0 | 2 | — | 0.25 - 0.5 mg |
| ACETAZOLAMIDE (diamox, glaupax) | 340 | 240 | 580 | 5 | 5 | 5.0 mg - 50.0 mg | 5.0 - 100.0 mg |
| AMILORIDE (moduretic) | 40 | 0 | 40 | 1 | 0 | 10.0 mg | — |
| AZATHIOPRINE (imurek) | 0 | 190 | 190 | 0 | 4 | — | 7.0 - 30.0 mg |
| *CAPTOPRIL (lopirin)* | *3'160* | *60* | *3'220* | *12* | *1* | *0.1 mg - 10.0 mg* | *3.125 mg* |
| CIPROFLOXACIN (ciproxine) | 220 | 0 | 220 | 4 | 0 | 25.0 mg - 75.0 mg | — |
| CLONIDINE (catapressan) | 0 | 300 | 300 | 0 | 1 | — | 0.05 mg |
| COLISTIN (colimycine) | 1'620 | 0 | 1'620 | 3 | 0 | 100'000 UI - 500'000 UI | — |
| DIAZEPAM (valium) | 420 | 0 | 420 | 2 | 0 | 0.5 mg - 1.0 mg | — |
| DIHYDRALAZINE (nepresol) | 40 | 0 | 40 | 2 | 0 | 0.5 mg - 1.0 mg | — |
| ENALAPRIL (reniten) | 0 | 4'330 | 4'330 | 0 | 9 | — | 0.1 - 2.0 mg |
| FOLINIC ACID (leucovorin) | 420 | 195 | 615 | 4 | 1 | 0.5 mg - 5.0 mg | 1.0 mg |
| **FUROSEMIDE (lasix)** | **960** | **3'900** | **4'860** | **9** | **5** | **0.5 mg - 10.0 mg** | **1.0 mg - 20.0 mg** |
| **HYDROCHLORTHIAZIDE (esidrex)** | **2'960** | **1'135** | **4'095** | **10** | **9** | **0.5 mg - 10.0 mg** | **1.0 - 30.0 mg** |
| MEXILETINE (mexitil) | 320 | 80 | 400 | 1 | 3 | — | 5.0 mg - 100.0 mg |
| OMEPRAZOLE (antra) | 0 | 240 | 240 | 0 | 5 | — | 1.0 mg - 5.0 mg |
| OXYBUTYNIN (ditropan) | 20 | 0 | 20 | 1 | 0 | 0.5 mg | — |
| *PHENOBARBITONE (phenobarbital)* | *0* | *1'765* | *1'765* | *0* | *10* | — | *1.0 - 80.0 mg* |
| PHENOXYBENZAMINE (dibenzyran) | 2'440 | 60 | 2'500 | 11 | 1 | 0.5 mg - 8.0 mg | 3.0 mg |
| PHENYTOIN (phenhydan) | 960 | 0 | 960 | 7 | 0 | 1.0 mg - 20.0 mg | — |
| **PROPRANOLOL (inderal)** | **620** | **1'505** | **2'125** | **5** | **9** | **0.5 mg - 6.0 mg** | **0.5 mg - 10.0 mg** |
| **RANITIDINE (zantic)** | **3'460** | **1'470** | **4'930** | **10** | **12** | **0.5 mg - 30.0 mg** | **1.0 mg - 75.0 mg** |
| **SPIRONOLACTONE (aldactone)** | **2'840** | **2'645** | **5'485** | **13** | **6** | **0.5 mg - 20.0 mg** | **1.0 mg - 100.0 mg** |
| TACROLIMUS (prograf) | 0 | 535 | 535 | 0 | 5 | — | 0.1 - 2.5 mg |
| URSODEOXYCHOLIC ACID (ursofalk) | 100 | 730 | 830 | 2 | 11 | 12.0 mg - 80.0 mg | 12.0 mg - 75.0 mg |
| VERAPAMIL (isoptin) | 160 | 0 | 160 | 3 | 0 | 1.0 mg - 10.0 mg | — |
| VIGABATRIN (sabril) | 0 | 295 | 295 | 0 | 4 | — | 150.0 - 340.0 mg |
| VITAMIN B6 (benadon) | 0 | 380 | 380 | 0 | 1 | — | 10.0 mg |
| **TOTAL** | **21'100** | **22'975** | **44'075** | | | | |

As a result of this inventory, the priorities were as follows:

**For the both hospitals:** furosemide, hydrochlorthiazide, propranolol, ranitidine, spiranolactone.

**For the CHUV:** captopril, phenoxybenzamine, phenytoin.

**For the HUG:** enalapril, phenobarbitone, ursodeoxycholic acid.

### MARKET SURVEY

A search was carried out to find suppliers for these drugs.

On the international market, many pharmaceutical companies have liquid oral preparations under their own brand name. These preparations are often made for, or can be adapted for children.

Other companies, such as Rosemont (UK), manufacture drugs which are out of patent. Some are supplied under Rosemont brand names, others have a «specials» licence with a short expiry date (6 to 12 months).

The HUG are now testing the following Rosemont products for patient compliance, with the eventual possibility of purchasing for the two hospitals:

FUROSEMIDE, PROPRANOLOL, SPIRONOLACTONE.

As this poster was being written a liquid form of URSODEOXYCHOLIC ACID arrived on the market in Switzerland.

## DEVELOPMENT AND RESULTS

### FORMULATION AND ANALYTICAL DATA

In 1998 the CHUV developed a hydrochlorthiazide suspension (see formula below) which will be shortly introduced in the HUG. The formula, manufacturing method, analytical conditions and stability data are shown below.

| | | | | | |
|---|---|---|---|---|---|
| INSTITUTION | CHUV - SERVICE DE PHARMACIE - FABRICATION | | | | |
| FORME GALENIQUE | Suspension | CODE | OFF | CL. HL | |
| DENOMINATION | Esidrex pediatric suspension 5 mg / ml | | | | |
| RÉDIGÉ PAR | S. Gloor | DATE RED | 2.12.1998 | | |
| MODIFIÉ PAR | | DATE MOD | | | |
| FORMULE | For 16 Verral bottles (50 ml) | | | | |
| PRODUITS | | QTE | % m/m m/v | STOCKAGE | FRN |
| Esidrex tabs (160 X 25mg ) | | 4000 mg | 5 mg / ml | Ord. | Novartis |
| Ora-Plus | | 400 ml | 50% | 518 / 522 | Paddock |
| Ora-Sweet | | 400 ml | 50% | 518 / 522 | Paddock |

MODE OPERATOIRE

Add 2 more tablets of Esidrex 25 mg to allow for eventual losses.
Crush the Esidrex tablets using a Primax grinder.
Sift the powder through a 500 sieve and place it in a mortar.
Pour 400 ml of Ora-Plus into a graduated cylinder.
Add a series of equal portions to the powder, and then homogenize.
Transfer quantitatively into a previously calibrated 1000 ml beaker.
Top with the Ora-Sweet, mix well (Magnetic agitator).
Fill 16 bottles of 60 ml (each with 50 ml).

**ESIDREX SUSPENSION 5 MG/ML ETUDE DE STABILITE HYDROCHLOROTHIAZIDE**

**METHODE ETALON EXTERNE** NOM Esidrex_SStd.mth

CONDITIONS CHROMATOGRAPHIQUES:
COLONNE RP-SELECT B, LICHROSPHER (25 cm x 4 mm I.D.), MERCK
PRECOLONNE RP-SELECT B, LICHROSPHER 4-4, POMPE Varian Prostar 230 Ser. No: 00196
PHASE MOBILE 30/70 V/V CH3CN/H2O
DETECTEUR λ: 269 nm
ATTENUATION Automatique DEBIT 1.3 ml/min PRESSION P env. 205 INJECTEUR WATERS 717
VOLUME D'INJECTION 20 µl No D'INJECTIONS STDS 2
No D'INJECTIONS ECHANTILLON 3 No D'INJECTIONS TEMOIN CONTROLE 0
TEMPS DE RETENTION rt Hydrochlorothiazide=3.15 min

*PREPARATION DES SOLUTIONS:*

STANDARDS DE CALIBRATION

Solution mère: Dissoudre 71.0 mg d'hydrochlorothiazide (Sigma art.H-4759) dans 40 ml de phase mobile (30/70 V/V CH3CN/H2O) et compléter à 100.0 ml avec le même solvant.

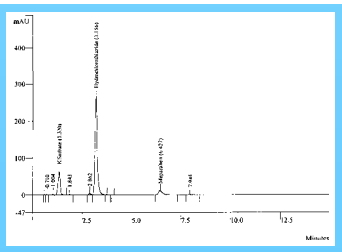
Procéder ensuite aux dilutions suivantes en utilisant pour les prélèvements des seringues SGE

Std1: 500 µl de Solution mère ad 10.0 ml avec la phase mobile (30/70 V/V CH3CN/H2O): 0.0284 mg/ml
Std2: 500 µl de Solution mère ad 10.0 ml avec la phase mobile (30/70 V/V CH3CN/H2O): 0.0355 mg/ml
Std3: 700 µl de Solution mère ad 10.0 ml avec la phase mobile (30/70 V/V CH3CN/H2O): 0.0497 mg/ml
Std4: 900 µl de Solution mère ad 10.0 ml avec la phase mobile (30/70 V/V CH3CN/H2O): 0.0550 mg/ml
Std5: 1000 µl de Solution mère ad 10.0 ml avec la phase mobile (30/70 V/V CH3CN/H2O): 0.0710 mg/ml

Phase mobile: Préparer 400 ml de phase mobile dans un cylindre de 500 ml en prenant 120 ml d'acétonitrile (HPLC qualité gradient Baker Art.8143) et 280 ml de H2O déminéralisée, mélanger et laisser se réchauffer à température ambiante.

Témoin de contrôle: Dissoudre 50.0 mg d'hydrochlorothiazide (Sigma art.H-4759) dans 80 ml de phase mobile (30/70 V/V CH3CN/H2O) et compléter à 100.0 ml avec le même solvant. Prélever 1.0 ml (pipette jaugée) et compléter à 10.0 ml avec la phase mobile.

Echantillon: Passer l'échantillon 15 min aux ultrasons, laisser refroidir à température ambiante, agiter énergiquement, et prélever 1.0 ml avec la seringue Hamilton, ajouter 80 ml de la phase mobile (30/70 V/V CH3CN/H2O) passer aux ultrasons pendant 15 min, laisser refroidir à température ambiante et compléter à 100.0 ml avec le même solvant. Filtrer sur millex-SR et injecter.




Under the conditions described above, an expiry date of eighteen months has been given.

A formula for ranitidine is also in development in the CHUV. In the meantime, Zantic has been imported from the UK with a special licence.

The following products are, at this moment, in the stage of development: at the CHUV, captopril and at the HUG, enalapril and phenobarbitone. For the last product, liquid forms are available on the market but the compliance for children is very poor.

For all these products, data will be published later.

### ADMINISTRATION SYSTEMS

Tests were carried out on branded products supplied in dropper bottles after complaints from the pediatric wards. Up to 60 % error was found, depending on the position of the bottle, whether it was full or not, the density of the liquid and the prevailing temperature.

The administration system BAXA (see website) was chosen for the patient compliance tests. BAXA has a full range of oral syringes (0.5 ml to 60 ml) and a panoply of accessories such as syringe stoppers and adapters for naso-gastric feeding lines.

The important advantages of this system are that the syringes do not accept needles (no risks of injection), and a better measuring accuracy is obtained.

## DISCUSSION

In practice, from the first results of the introduction of oral liquid solutions and of the new system of administration, the following advantages appear :

a) Possibility to dispense different dosages from a single preparation.
b) Reducing the time lag between the medical order and administration to the patient.
c) Cost saving by fewer on-call interventions by the pharmacy, reduction of stock wastage and less production time. For the hydrochlorthiazide, the manufacturing time saving is estimated to 8.5 hours (3'000 capsules).
d) Better administration accuracy.

## CONCLUSION

The use of liquid forms in pediatric wards facilitates the drug administration and improves the patients' security.

Inter-hospital collaboration increases efficacy by sharing out the development of new formulas.

The first results of our experience should incite every pharmacy working for pediatric units to replace capsules by liquid preparations.

## BIBLIOGRAPHY

| | |
|---|---|
| www.baxa.com | Baxa: syringes for oral use |
| www.dial.org.uk | Pediatric Drug Information Advisory Line |
| www.ijpc.com | International Journal of Pharmaceutical Compounding |
| www.iacprx.org | International Academy of Compounding Pharmacists |
| www.civas.co.uk | National Civas Group UK |
| www.wpqa.co.uk | St Mary's Pharmaceutical Unit Cardiff |
| www.wmhp.org.uk | West Midlands Regional Hospital UK |
| www.pharmweb.net | |
| www.paddocklabs.com | Ora-plus, Ora Sweet |
| www.pharmacytimes.com | Pharmacy Times Compounding |
| www.compounder.com | Compounding Hotline |

Trissel's Stability of Compounded Formulations. L.A. Trissel; American Pharmaceutical Association, 1996.
Pediatric Drug Formulations, 3rd ed. M.C. Nahata, T.H. Hipple; Harwey Whitney Books Company.
UK Formulary of Extemporaneous Preparations; Ed. Paul F Grassby, 1995. Secundem Artem on www.paddocklabs.com.
Alder Hey Book of Childrens Doses ABCD. Tony Nunn; Royal Liverpool Childrens Hospital, 1996.
Medecines for Children. Royal College of Pediatrics and Child Health, RCPCH Direct Books, 1999; on www.bmbc.com/rcpch.