RESULTS OF A SYSTEMATIC LONG-TERM STABILITY STUDY FOR READY-TO-USE INJECTABLE DRUGS PRODUCED BY A CENTRALIZED INTRAVENOUS ADMIXTURE SERVICE.

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Background

Other injectable preparations than parenteral nutrition admixture and injectable cytotoxic drugs could be prepared by Centralised IntraVenous Admixture Service (CIVAS) if the long-term stability of the drugs is known. However, this information is not always available.

Purpose

To develop a program of chemical drug stability analysis in collaboration between Hospital Pharmacy, Medical Laboratory and Scientific Support Unit to determine the long-term stability of largely used injectable anti-infectious and non anti-infectious drugs.

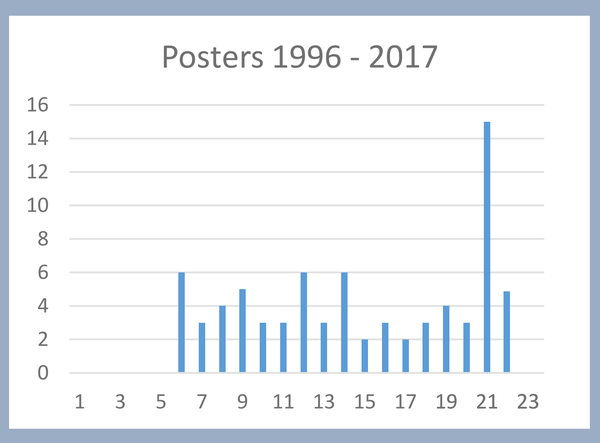
DRUG STABILITY RESEARCH GROUP 1996 - 2017

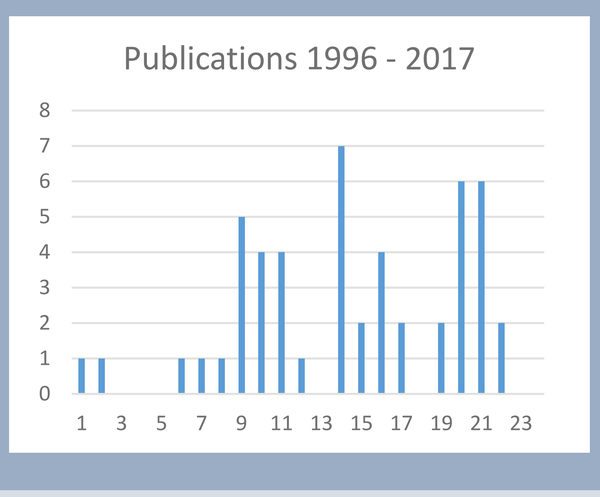
PUBLICATIONS NATIONALES ET INTERNATIONALES : 50

POSTERS : 77

ORAL COMMUNICATIONS : 18

PRIX ET NOMINATIONS : 5





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Material and methods

- After a setup of the High Performance Liquid Chromatography (HPLC) or Ultra Performance Liquid Chromatography(UPLC) method, 29 drugs (11 antiinfectives, 5 anesthetics, 2 propulsives, 2 detoxifying agents for antineoplastic treatment and 9 with other properties) were reconstituted in laminar air flow hood.
- Two of them were stored at 32 °C, 1 at room temperature, 17 at 5 ± 3°C. Twenty drugs were stored in the freezer at – 20°C, thawed by microwave following a standardised procedure and stored at 5 ± 3°C before use.
- Concentration stability was evaluated by regression analysis.
- For ten molecules, a preliminary study of physical stability has been achieved.

Results

- For each drug, long-term stability has varied from 11 days to 180 days.
- The freeze-thaw treatment by microwave may enhance the stability (from 30 to 120 days) and allows batch-scale production of intravenous drugs, less expensive in term of manpower and sterile device than a drug reconstitution at the ward.
- The results were published by 77 posters in international congress and by 50 publications in national and international pharmaceutical journals.
- This collaboration led to the foundation in 2009 of a drug stability research group included in the CHU UCL Namur and already saw itself decreeing 5 prices and nominations.
- Three Symposium were also organised.
- In the ranking carried out by the Stabilis database, the DSRG is the leading research center at the European level in terms of the number of publications

STABILITE CHIMIQUE A 5 ± 3°C

Nom	Concentration (mg/ml)	Solution	Conteneur	Durée
Acyclovir GSK	5.0	s	polyolefine	21 jrs
Acyclovir HOSPIRA	5.0	s	polyolefine	21 jrs
Cefazoline sodique	10.0	d5	pvc	30 jrs
Cefuroxime sodique	15.0	d5	pvc	13 jrs
Cefuroxime	15.0	d5	polyolefine	31 jrs
Cefuroxime	15.0	d5	polyolefine	31 jrs
Dexamethasone + Alizapride	0.10 + 1.0	s	polyolefine	30 jrs
Dexamethasone + Ondansetron	0.10 + 0.080	s	polyolefine	30 jrs
Fluorouracile + Folinate sodique	24.0 3.2	d5	easy pump (32°C)	11 jrs
Fluorouracile + Folinate sodique	24.0 3.2	d5	infusor (32°C)	11 jrs
Folinate sodique	3.2	d5	polyolefine	30 jrs
Ketamine HCl	50.0	-	seringue (25 ??)	180 jrs
Morphine HCl	1.0	s	polyolefine	58 jrs
Morphine HCl	1.0	s	seringue polypropylene	58 jrs
Procaïne HCl	0.20	solution de cardioplégie*	pvc	60 jrs
Sufentanil citrate + Levobupivacaine	0.001 1.250	s	pvc	58 jrs
Teicoplanine	4.0	d5	pvc	6 jrs
Tramadol + Alizapride	1.0 0.5	d5	polyolefine	30 jrs
Tramadol + Dehydrobenzperidol	1.0 0.025	d5	polyolefine	30 jrs
Tramadol + Metoclopramide	1.0 0.10	d5	polyolefine	30 jrs
Vancomycine GSK	5.0	d5	pvc	58 jrs
Vancomycine GSK	10.0	d5	pvc	58 jrs
Vancomycine MYLAN	10.0	d5	polyolefine	57 jrs
Voriconazole	4.0	d5	pvc	15 jrs

* Natrium 6.09 – Natrium lactas 3.19 – Kalium chloride 1.349 – Calcium chloride 2 ag 0.200 q – Magnesium sulfas 7 ag 2.46g aqua ad 1000 ml – Natrium bicarbonate 0.586 g

optimal conditions

minimall conditions

Table 2 : Microwave Freeze Thaw Treatment : Our Results

Drug	Dosis/100 ml	Container	Storage	Conditions	Cycle	Final storage at 5 ± 3°C
Acyclovir GSK	500mg/ 100ml nacl 0,9%	polyolefine	90 days	Optimal	270 W	21 days
Acyclovir HOSPIRA	500mg/100ml nacl 0,9%	polyolefine	90 days	Optimal	270 W	21 days
Cefepime	2 g	pvc	30 days	Optimal	270 W	11 days
Ceftriaxone	2 g	polyolefine	98 days	Optimal	270 W	44 days
Ceftriaxone	2 g	polyolefine	98 days	Optimal	800 W	56 days
Cefuroxime	1.5 g	pvc	90 days	Optimal	270 W	15 days
Cefuroxime	1.5 g	polyolefine	98 days	Optimal	800 W	21 days
Cefuroxime	1.5 g	polyolefine	98 days	Optimal	270 W	23 days
Cefuroxime	1.5 g	polyolefine	98 days	Minimal	270 W	21 days
Cefuroxime	1.5 g	polyolefine	98 day	Minimal	800 W	18 days
Diclofenac	75 mg + 42 mg bica natrium	polyolefine	60 days	Optimal	270 W	60 days
Esomeprazole	40 mg	polyolefine	30 days	Optimal	270 W	20 days
Esomeprazole	80 mg	polyolefine	30 days	Optimal	270 W	29 days
Fluorouracile	800 mg/100 ml NaCl 0,9 %	pvc	79 days	Optimal	270 W	28 days
Folinate Sodique	800 mg/250 ml	polyolefine	90 days	Optimal	270 W	30 days
Ketorolac	10 mg	polyolefine	15 days	Optimal	270 W	35 days
Ketorolac	10 mg	polyolefine	15 days	Optimal	800 W	35 days
Ketorolac	20 mg	polyolefine	90 days	Optimal	270 W	60 days
Ketorolac	30 mg	polyolefine	15 days	Optimal	270 W	30 days
Ketorolac	30 mg	polyolefine	15 days	Optimal	800 W	35 days
Levofolinate Calcique	400 mg/250 ml	polyolefine	95 days	Optimal	270 W	30 days
Morphine HCL STEROP	100mg/100ml nacl 0,9%	polyolefine	90 days	Optimal	270 W	58 days
Morphine HCL STEROP	100mg/100ml nacl 0,9%	Seringue polypropylene	90 days	Optimal	270 W	58 days
Ondansetron + dexamethasone	8 mg + 10 mg	polyolefine	90 days	Optimal	270 W	30 days
Piperacilline + Tazobactam	4 g + 0,5 g	pvc	90 days	Optimal	270 W	35 days
Sufentanil + Levobupivacaine	0.6 mg + 625 mg/500 ml NaCl 0.9 %	pvc	120 days	Optimal	270 W	70 days
Tramadol	100 mg	pvc	120 days	Optimal	270 W	60 days
Vancomycine	500 mg	polyolefine	105 days	Optimal	270 W	56 days

Etudes de stabilité physique

Nom	Firme	Concentration mg/ml	Diluant	Contenant	Firme	Température de stockage	Résultat (heures)
Alizapride + clorazépate	San + San	1,0 + 0,10	G5	polyolefine	BAX	Ambiante	24 hrs
Alizapride + dexamethasone	San + Org	1,0 + 0,10	S	polyolefine	BAX	Ambiante	24 hrs
Amiodarone	Sanofi	25,0	G5	seringue polypropylene	BD	Ambiante	48 hrs
Isosorbide	Takeda	0,60	S	seringue polypropylene	BD	Ambiante	48 hrs
Lorazepam	Pfizer	0,16	S	seringue polypropylene	BD	Ambiante	48 hrs
Noradrenaline	Aguettant	0,12	S	seringue polypropylene	BD	Ambiante	48 hrs
Noradrenaline	Aguettant	0,24	S	seringue polypropylene	BD	Ambiante	48 hrs
Salbutamol	GSK	0,06	S	seringue polypropylene	BD	Ambiante	48 hrs
Valproate	Mylan	12,0	S	seringue polypropylene	BD	Ambiante	48 hrs

Conclusions

Our findings contribute to enhance the knowledge on the chemical stability and the scale of drugs that may be prepared by a CIVAS.

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Possible conflict of interest : nothing to disclose.