20th EAHP Congress
CP-069

QUALITY OF ANTIBIOTIC TREATMENT IN PRETERM NEONATES: A READY-TO-USE FORMULATION OF GENTAMICIN SULPHATE

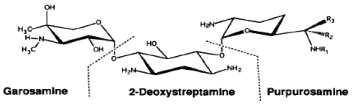
M.S. De Meo (1), C. Polidori (1), A. Pompilio (2), V. Carnielli (3), S. Savini (4), F. Ciuccarelli (2), E. Andresciani (2), A. Garzone (2), L. Carloni (2), V. Moretti (2)

(1) Università degli Studi di Camerino, SSFO, Camerino, Italy; (2) Azienda Ospedali Riuniti di Ancona, SOD Farmacia, Ancona, Italy;
(3) Azienda Ospedali Riuniti di Ancona, SOD Neonatologia, Ancona, Italy; (4) Azienda Ospedali Riuniti di Ancona, SOD Igiene Ospedaliera, Ancona, Italy.

BACKGROUND

Intravenous (IV) drug therapy of preterm neonate is affected by: clinical status (i.e. sepsis/infections, immature physiology, pharmacokinetic/pharmacodynamic variation), shortage of ready-to-use formulations, small doses of drug required and IV route dangerousness.

Fig. 1 Gentamicin



Gentamicin	R_1	R_2	R_3	MW
C1	Me	H	Me	477.60
C2	H	H	Me	463.57
C1a	H	H	H	449.55
C2a	H	Me	H	463.57
C2b	Me	H	H	463.57

Graham et al. Analysis of gentamicin sulfate and a study of its degradation in dextrose solutions. Journal of Pharmaceutical and Biomedical Analysis 1997; 15: 537-543

PURPOSE

"G. Salesi" Children's Hospital-Ancona-Italy is the regional center specialized in pediatric diseases.
This study aimed to support the clinical practice of Neonatology, the ward with the weakest patients. We identified the most prescribed IV antibiotics for compounding ready-to-use formulations with standard concentration (SC) in order to avoid drug handling (reconstitution/dilution) in ward.

MATERIAL AND METHODS

Hospital Pharmacy, Neonatology and Hygiene Department of "Azienda Ospedali Riuniti-Ancona" realized this multiphase study. Phase I: a review of IV antibiotics prescribed to preterm (24^{+0}-31^{+6}weeks) inpatients of Neonatology from 2004-2013. Phase II: study of pharmaceutical quality and stability of SC (2mg/ml) Gentamicin sulphate (the gold standard in sepsis/infections) Aqueous Solution prepared by pharmacists in two different ways: with and without filtration. Both batches were stored in polyethylene syringes for 90 days at 2-8°C and 25°C and were examined for: endotoxin absence with ALL test (Amebocyte Lysate Lymulus, Endosafe®-Portable Test System) according to Italian Pharmacopoeia 12th edition (kinetic-chromogenic technique); sterility test (BacT/ALERT®FA, six days of incubation at 36°C) for aerobic bacteria/fungi; quantification with HPLC-MS/MS technique of major gentamicin components (C1,C1a,C2) (fig. 1) at 0-3-7-14-21-28-60-90 days. Limits of detection (LOD) and quantitation (LOQ) were 0.25ng. SC comes from usual dosage (2.5mg/kg/12hrs) for a patient of 1000g.

RESULTS

Phase I studies certified: 1011 preterm inpatients (521 males, 490 females) (fig. 2), 222 cases of sepsis (52 early, 170 late) and 102 infections (fig. 3). Gentamicin was the most used antibiotic with 1126 doses for 88 patients per year (fig. 4).
Phase II studies certified: sterility (no microbiological growth), endotoxin absence and stability of Gentamicin Sulphate 2mg/ml stored 90 days at 2-8°C and 25°C (fig. 5a, 5b). No significant concentration changes of gentamicin components: P not significant, t-test>0.05 (fig. 6,7,8,9).

Fig. 2 Neonatology inpatients per year

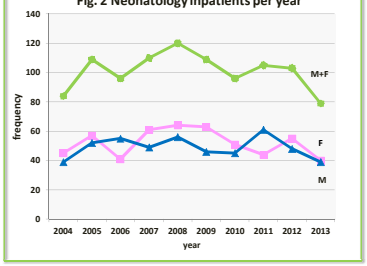


Fig. 3 Distribution of infectious diseases from 2004 to 2013

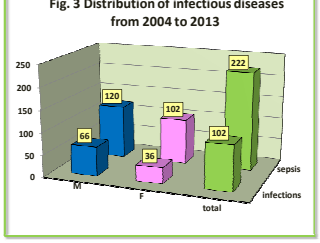


Fig. 4 Gentamicin doses set up for patients and per year

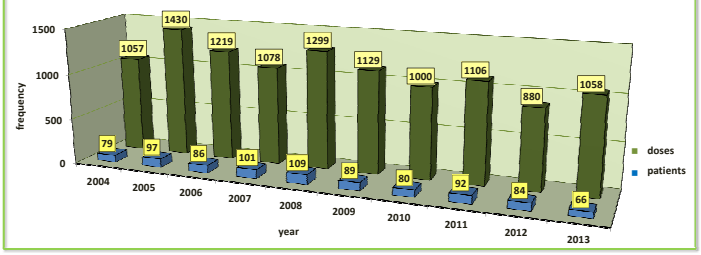


Fig. 6 Residual % of gentamicin in 2 mg/ml solution stored at 25 °C

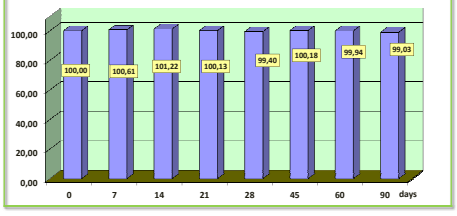


Fig. 7 Residual % of gentamicin in 2 mg/ml solution stored at 2-8 °C

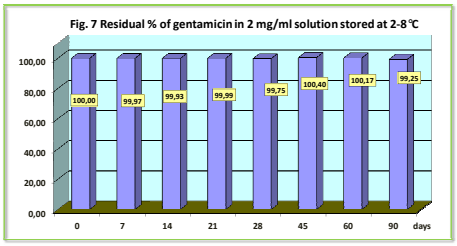


Fig. 5a ALL test at 25°C

```
********* ENDOSAFE Test Record *********
V7.12C 8/25/2011

Device: ..... 5264
OperatorID: ..... FC
Cartridge: ..... Endotoxin
Temperature: .. Start: 37.0C  End: 37.0C
Method: ..... KX-122
Cartridge Lot#: ..... 2250175
Cartridge Cal Code: ..... 117157745529
Range: ..... 1-0.01
Range Time: ..... Sec: 171-977
Onset Times: ..... >977 378 >977 364
Slope: -0.378 ..... Intercept: +2.233
Dilution: ..... 15
Sample Lot: ..... 474-TA
Sample ID: ..... GENTAMICINA
Sample Rxn Time CV: ..... 0.0% Pass
Spike Value: ..... 0.119 EU/mL
Spike Rxn Time CV: ..... 2.7% Pass
Spike Recovery: ..... 79% Pass
Test Suitability: ..... Pass
Sample Value: ..... <0.150 EU/mL
```

Fig. 5b ALL test at 2-8°C

```
********* ENDOSAFE Test Record *********
V7.12C 8/25/2011

Device: ..... 5264
OperatorID: ..... FC
Cartridge: ..... Endotoxin
Temperature: .. Start: 37.0C  End: 37.0C
Method: ..... KX-122
Cartridge Lot#: ..... 2250175
Cartridge Cal Code: ..... 117157745529
Range: ..... 1-0.01
Range Time: ..... Sec: 171-977
Onset Times: ..... >977 400 >977 388
Slope: -0.378 ..... Intercept: +2.233
Dilution: ..... 15
Sample Lot: ..... 474
Sample ID: ..... GENTAMICINA
Sample Rxn Time CV: ..... 0.0% Pass
Spike Value: ..... 0.100 EU/mL
Spike Rxn Time CV: ..... 2.2% Pass
Spike Recovery: ..... 67% Pass
Test Suitability: ..... Pass
Sample Value: ..... <0.150 EU/mL
```

Fig. 8 Gentamicin components (C1,C1a,C2) in 2 mg/ml solution stored at 25 °C

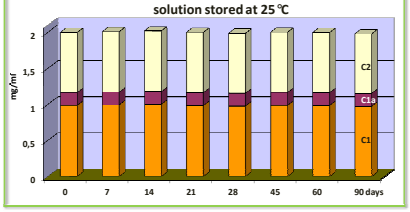
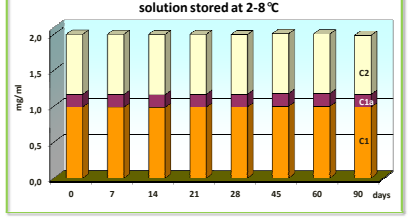


Fig. 9 Gentamicin components (C1,C1a,C2) in 2 mg/ml solution stored at 2-8 °C



CONCLUSION

After this "pilot study" next target could be a compounding center of unit dose therapies right to pediatric patients.