COMPATIBILITY AND 30-DAY STABILITY OF FOUR INTRAVENOUS MIXTURES FOR MULTIMODAL ANALGESIA

Carmen López-Cabezas[1], Mireia Marcé-Briansó[2], Alba Escolà[1], Susana Ceamanos[1], Marina Bellot[2], Guadalupe Ballesteros[1], Judith Báguena[2], Francesc Broto-Puig[2], Dolors Soy[1]
[1]Pharmacy Service. Division of Medicines. Hospital Clínic de Barcelona - Universitat de Barcelona
[2]Analytical and Applied Chemistry Department, IQS School of Engineering, Universitat Ramon Llull

Background and Importance

Multimodal analgesia is based on the combination of different drugs and analgesic techniques in order to alleviate postoperative pain. One of the limitations of this technique is the lack of evidence about the stability of these mixtures in clinical practice.

Aim and Objectives

To evaluate the 30-day physico-chemical compatibility of four analgesic mixtures of tramadol and ketamine, combined with dexketoprofen or ketorolac, ±methadone, in saline solution bags, for patient-controlled analgesia.

Materials and Methods

Mixtures studied

V1	TRA 7,5MG/ML	KETA 0,2 MG/ML	DKT 2,3 MG/ML	
V2	TRA 7,5 MG/ML	KETA 0,2 MG/ML	DKT 2,3 MG/ML	MET 0,075 MG/ML
V3	TRA 7,9 MG/ML	KETA 0,4 MG/ML	KETOR 0,95 MG/ML	
V4	TRA 7,9 MG/ML	KETA 0,4 MG/ML	KETOR 0,95 MG/ML	MET 0,08 MG/ML

TRAMADOL (TRA)
KETAMINE (KETA)
DEXKETOPROFEN (DKT)
KETOROLACO (KETOR)
METHADONE (MET)

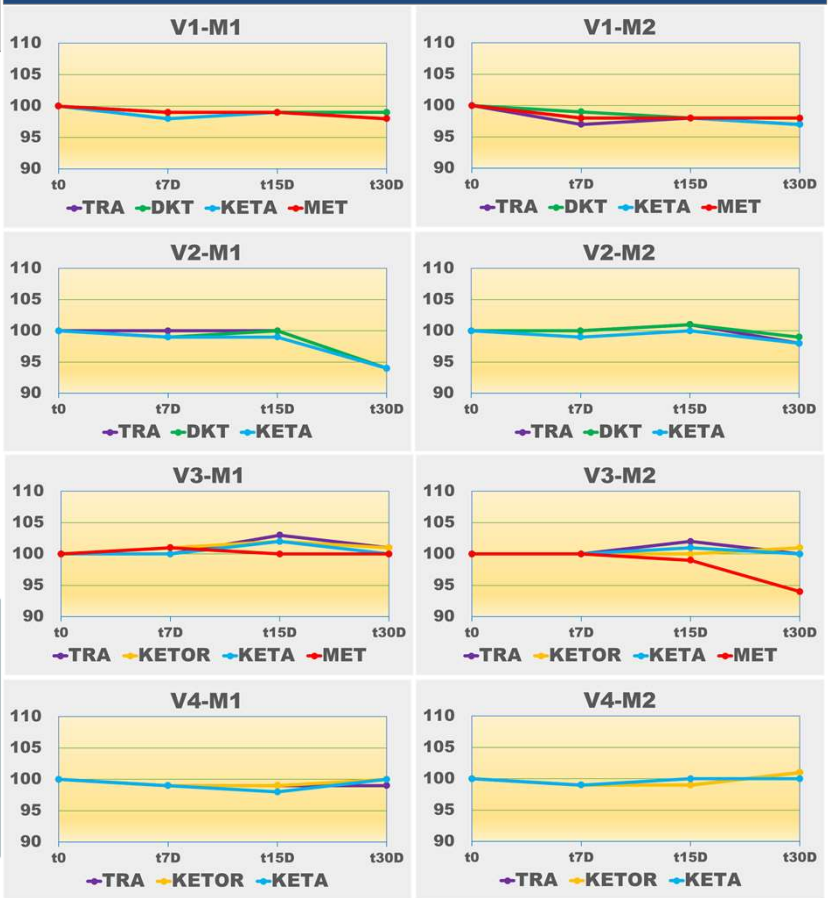
Diluent: 100 mL NS (polypropylene bags)
4 batches of each mixture + 1 batch for microbiological control
Study conditions: bags were protected from light and stored between 2-8 °C
Study points: immediately after preparation (t_0), and 7, 15 and 30 days after (t_{7d}, t_{15d}, t_{30d})
Two **chromatographic methods** developed (**M1, M2**)

Results

HPLC instrumentation and chromatographic conditions (UHPLC-DAD, Acquity UHPLC H-Class®)	
Column	Acquity HSS-C18 (M1) Acquity BEH-C18 (M2)
Mobile phase	Acetonitrile/water Acidic aqueous phase (M1) Acetonitrile/water Basic aqueous phase (M2)
Flow rate	0.025 mL/min
Injection volum	2 microliters
Stability indicating test: accelerated degradation with HCl 1M,80°C, NaOH 1M,80°C and H2O2 15%,TA	
Linearity	0.5-500 mg/L (r^2> 0.999)
Detection limit	0.1-0.3 mg/L (λ=215 nm)
Accuracy	96-102 %
Precision	0.1-3.3 %

Physical parameters and pH remained unchanged during the study; pH range for V1,V2: 7.08-7.28; V3,V4: 6.76-6.91
% of drug recovery remained in the range 90-110% of the initial concentration (t_0); CV(%): 0.1-2.4
All samples preserved their sterility during the study

Percentage of drug recovery with M1 and M2



Conclusion and Relevance

The four analgesic mixtures of **tramadol and ketamine**, combined with **dexketoprofen or ketorolac**, **±methadone**, **were stable for 30 days at 2-8°C** in the conditions described in the study, allowing its centralized preparation at pharmacy service.

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