

# SUBCUTANEOUS INFUSION OF TRAMADOL COMBINED WITH DEXAMETHASONE IN PALLIATIVE CARE

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## Abstract

The delivery of subcutaneous medication by continuous infusion is common in palliative medicine. Many centres combine multiple medications, but the analytical confirmation of the compatibility and stability of these combinations has rarely been performed. This study examined the compatibility and stability of tramadol and dexamethasone using high performance liquid chromatography.

## Resumen

La administración de fármacos mediante infusión subcutánea es hoy en día práctica habitual en Medicina Paliativa. En muchas ocasiones se recurre a la administración de mezclas de fármacos, aunque hay pocos estudios en los que se evalúe la compatibilidad y estabilidad de dichas combinaciones. En este estudio se realiza un estudio de la compatibilidad y estabilidad de tramadol y dexametasona mediante cromatografía líquida de alta resolución.

## Introduction

In Palliative Medicine it is very common to combine two or more drugs in solution for s.c. infusion to terminally ill cancer patients (1-4). The compatibility and efficacy of such combinations in syringe pumps is assumed, but often has not been scientifically validated.

During the advanced stages of cancer, nearly 75% of the patients have pain. Patients presenting moderate to severe pain should be started at the second or third step of the WHO analgesic ladder. Tramadol is a very effective second step analgesic agent which is mainly

used when treating chronic pain conditions, especially bone and visceral pain and including neurophatic pain (5).

Dexamethasone is extensively used in Palliative Medicine to treat numerous symptoms such as pain, nausea and vomiting, weakness, raised intracranial pressure, anorexia/cachexia syndrome, and spinal cord compression. Due to its anti-inflammatory effect it is useful when treating metastatic bone pain, dyspnoea and, inoperable bowel infiltration (6).

Dexamethasone is commonly given by intermittent s.c. injection however, it has been proven to be incompatible when mixed with midazolam lactate, morphine hydrochloride, and haloperidol lactate (1,4,7).

In this study we investigated the compatibility and physical stability of binary admixtures of tramadol hydrochloride and dexamethasone sodium phosphate destined to subcutaneous administration to terminally ill patients followed at home by staff of Palliative Care Units.

## Materials and methods

The following nine binary admixtures were prepared in triplicate using saline to complete a volume of 60 ml (drug infuser) in order to reflect a 5-day treatment. The doses assayed are those more frequently given by palliative care units (Table 1).

All admixtures were prepared in polypropylene syringes and stored at 25°C protected from direct light exposure. At times 0, 5, and 15 days the following parameters were checked: volume, colour changes, turbidity and/or precipitation, and

pH. HPLC was the analytical technique used to quantify both drugs in the admixtures. Simultaneous determination of tramadol hydrochloride and dexamethasone sodium phosphate was performed for quantification. A tracer extrasil ODS 2 column (150x4 mm, 5µm) was used with a mobile phase consisting of acetonitrile:0.01M potassium dihydrogen phosphate buffer (35:65) adjusted to pH 5.9 with triethylamine. The flow rate was 1 ml/min and the detection wavelength was set at 218 nm. Method validation was performed according to the guidelines defined in CDERs reviewer guidance on Validation of Chromatographic Methods (8).

Admixture	Tramadol		Dexamethasone	
	mg/ml	mg/day	mg/ml	mg/day
1	6.66	400	2.08	20
2	3.33	200	2.08	20
3	1.66	100	2.08	20
4	6.66	400	1.66	16
5	3.33	200	1.66	16
6	1.66	100	1.66	16
7	6.66	400	0.416	4
8	3.33	200	0.416	4
9	1.66	100	0.416	4

Table 1.- Drug admixtures assayed

## Results and Discussion

None of the samples showed changes in colour, precipitation or measurable loss of volume. The pH values were basic and remained almost constant over the study period.

Concentrations measured for tramadol hydrochloride and dexamethasone sodium phosphate in syringes at time of preparation was within 4% of the target value.

After 5 days of storage at 25°C the losses of tramadol HCL and dexamethasone sodium phosphate in the drug admixtures tested were lower than 7% and 6%, respectively. In the clinical situation, it is generally accepted that a difference of less than 10% is not significant.

However, after 15 days, even though the solutions remained clear, the losses of tramadol HCL and dexamethasone sodium phosphate ranged from 7-15% and from 11%-20%, respectively. Therefore the clinical implications of these results are that tramadol hydrochloride and dexamethasone sodium phosphate should not be

combined in infusion solutions for more than 5 days.

Admixture	Tramadol			Dexamethasone		
	Time (days)			Time (days)		
	0	5	15	0	5	15
1	97.5	96.7	86.7	98.9	95.8	82.2
2	96.7	95.7	90.6	102.2	96.8	81.9
3	99.9	96.5	85.0	101.2	98.3	81.2
4	98.2	96.4	91.2	97.6	92.2	81.4
5	97.4	90.8	86.3	100.2	98.3	82.6
6	97.2	92.6	88.4	98.7	95.4	81.8
7	99.1	98.4	86.3	99.7	96.8	86.7
8	99.4	96.3	88.7	100.3	97.5	89.2
9	99.9	98.6	87.5	98.7	95.2	81.3

Table 2.- Mean percentages of tramadol HCL and dexamethasone sodium phosphate remaining in the admixtures stored at 25°C.

The drug admixture was given to four patients of mean age 71 years with Karnofsky's index between 10% and 30%: one with colorectal carcinoma, one with hepatic cancer, one with non-Hodking lymphoma and the last one, with breast cancer presenting brain metastases. In two cases, pain improved from moderate to mild and in the other two cases, moderate pain was completely relieved. Two patients exhibited perceptive alterations which improved with the admixture. Local tolerance to the admixture was good.

## Conclusion

Tramadol hydrochloride (dose range 100 mg/day-400 mg/day) and dexamethasone sodium phosphate (dose range 4 mg/day to 20 mg/day) can be combined in saline for subcutaneous administration during a period of time of 5 days when kept at 25°C.

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