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BRIEF REPORT

Stability and compatibility of the mixture of tramadol, ketorolac, metoclopramide and ranitidine in a solution for intravenous perfusion

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KEYWORDS
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Abstract
Objective: To determine whether a mixture for intravenous perfusion containing tramadol (5 mg/ml), ranitidine (1.5 mg/ml), ketorolac (1.5 mg/ml) and metoclopramide (0.5 mg/ml) in a 0.9%sodium chlorides solution is compatible and stable at room temperature during a 48-hour period.
Methods: We tested the mixture for stability using the HPLC technique (high performance liquid chromatography), with parallel visual assessments of any changes in colour, appearance of precipitate or phase separation indicating incompatibilities between the components.
Results: At the end of the trial, chromatography data showed a mean metoclopramide concentration between 100%and 105%of the initial level, while concentrations of tramadol, ketorolac and ranitidine were between 99%and 102%of initial levels. There was no evidence of incompatibility between the drugs at any time during the study period.
Conclusions: The combination is stable as a solution and its components are physically and chemically compatible in the concentrations used in the study, during at least 48 hours at room temperature.

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PALABRAS CLAVE
Tramadol;
Ketorolaco;
Metoclopramida;
Ranitidina;
Analgesia multimodal

Estabilidad y compatibilidad de la mezcla de tramadol, ketorolaco, metoclopramida y ranitidina en una solución para perfusión intravenosa

Resumen
Objetivo: Establecer si una mezcla para perfusión intravenosa que contiene tramadol (5 mg/ml), ranitidina (1,5 mg/ml), ketorolaco (1,5 mg/ml) y metoclopramida (0,5 mg/ml) en cloruro sódico al 0,9%es compatible y estable a temperatura ambiente durante un periodo de 48 h.
Métodos: Se realizó un estudio de estabilidad de la mezcla mediante la técnica de cromatografía líquida de alta presión, comprobando visualmente, de forma paralela, los posibles cambios de color, la aparición de precipitado o la separación de fases indicativos de incompatibilidad entre los componentes.
Resultados: Los datos de la cromatografía mostraron al final del ensayo una concentración media para la metoclopramida comprendida entre el 100-105%de la inicial, mientras que para el tramadol, el ketorolaco y la ranitidina, las concentraciones obtenidas se encontraron entre el 99 y el 102%de las de partida. No hubo evidencia de incompatibilidad entre los fármacos a lo largo del tiempo de estudio.
Conclusiones: La combinación es estable en solución y sus componentes son física y químicamente compatibles en las concentraciones utilizadas en el estudio durante al menos 48 h a temperatura ambiente.

Introduction

In clinical practice we often turn to the combination of different drugs that complement their mechanisms of action, counteract their side effects or enhance their action. Within these combinations is multimodal analgesia,[1-4] consisting of the choice of two or more compounds that improve the quality of analgesia and minimise side effects when compared to the use of each of them separately.

Opioids and nonsteroidal anti-inflammatory drugs (NSAID) are important drugs for pain control. Opioids, although highly effective with analgesics,[5,6] have numerous side effects such as respiratory depression, sedation, nausea and vomiting, which limit their use. Administration of NSAID enhances the analgesic action of opioids and reduces the appearance of side effects associated with their use. However, the administration of NSAID also entails some risks, and gastroduodenal mucosal lesions are one of the most frequent problems associated with their use. A proposal was made to the anaesthesiology, resuscitation and pain treatment department of the hospital to apply a protocol of multimodal analgesia (continuous IV perfusion/48 h using a pump) in various surgical specialties for severe to moderate pain. This analgesia combined 500 mg of tramadol (a weak opioid causing little respiratory depression and whose main side effects are nausea and vomiting[7,8]), 150 mg of ketorolac (an NSAID with similar effectiveness to the opioids morphine and meperidine in treating post-surgical pain[9,10]), 50 mg of metoclopramide (a common antiemetic, which has also been reported to have an analgesic effect when administered with opioids and NSAID[11,12]) and 150 mg of ranitidine (a potent inhibitor of gastric acid secretion which, when administered prophylactically, reduces the incidence of gastroduodenal ulceration induced by NSAID[13,14]). This mixture was prepared from the proprietary drugs Adolonta® (tramadol 100 mg/2 ml), Toradol® (ketorolac 30 mg/1 ml), Primperan® (metoclopramide 10 mg/2 ml) and Zantac® (ranitidine 50 mg/5 ml). The mixture of these drugs is completed with a saline solution to a final volume of 100 ml and administered to patients using a perfusion pump for 48 hours.

In order to administer a solution of drugs, it is necessary that the drugs be mutually compatible and remain stable at room temperature. The aim of this study was to determine the stability of the above mentioned analgesic mixture through analysis by high-pressure liquid chromatography (HPLC) 48 hours after preparation, and to study the compatibility of its components through observation of its evolution during this period of time.

Methods

The stability of the mixture was evaluated using the HPLC technique. The HPLC grade acetonitrile used in the study was purchased from Scharlau (Barcelona, Spain), analytical grade phosphoric acid was supplied by Merck (Madrid, Spain) and sodium dihydrogen phosphate was purchased in Prolabo (Fontenay sous Bois, France). The pharmaceutical products Adolonta® (Grünenthal, Spain), Toradol® (Roche, Spain), Primperan® (Sanofi Aventis, Spain) Zantac® (Glaxo SmithK, Spain) and 0.9% sodium chloride (Braun, Spain) were provided by the pharmacy department.

All solutions were prepared using demineralised water using a Milli-Q gradient A-10 system (Millipore Iberica®, Spain).

To construct the calibration curve, five dilutions of the mixture were used, which were prepared in quadruplicate from the corresponding proprietary drugs, using 0.9%sodium chloride as a solvent. The compositions of each of the five dilutions were as follows:

Table Concentration of drugs in the mixture obtained by HPLC

Drug	Mean concentration at 48 h (SD), mg/ml (no.=4)	Mean percentage of the baseline concentration at 48 h
Tramadol	4.9867 (0.02309)	99.66
Ranitidine	1.5167 (0.06351)	101.50
Ketorolac	1.5233 (0.05774)	101.55
Metoclopramide	0.5107 (0.01848)	103.26

SD indicates standard deviation.

Dilution 1: 3 mg/ml of tramadol, 1 mg/ml of ketorolac, 0.3 mg/ml of metoclopramide and 1 mg/ml of ranitidine.

Dilution 2: 4 mg/ml of tramadol, 1.2 mg/ml of ketorolac, 0.4 mg/ml of metoclopramide and 1.2 mg/ml of ranitidine.

Dilution 3: 5 mg/ml of tramadol, 1.5 mg/ml of ketorolac, 0.5 mg/ml of metoclopramide and 1.5 mg/ml of ranitidine.

Dilution 4: 6 mg/ml of tramadol, 1.8 mg/ml of ketorolac, 0.6 mg/ml of metoclopramide and 1.8 mg/ml of ranitidine.

Dilution 5: 7 mg/ml of tramadol, 2 mg/ml of ketorolac, 0.7 mg/ml of metoclopramide and 2 mg/ml of ranitidine.

The tested solution was also prepared in 0.9% sodium chloride from the corresponding proprietary drugs in aseptic conditions and in quadruplicate. The final concentration of the drugs was as follows: 5 mg/ml of tramadol, 1.5 mg/ml of ranitidine, 1.5 mg/ml of ketorolac and 0.5 mg/ml of metoclopramide, concentrations corresponding to the analgesic compound used in clinical practice. This solution was tested 48 hours after its preparation, a period of time during which it was stored at room temperature.

The chromatographic analysis was performed under isocratic conditions, at room temperature. In each case, 20 µl of the mixture was injected into a high-pressure liquid chromatograph (Waters) equipped with a model 1525 binary pump system, a model 717 plus automatic injector and a model 2996 UV-Vis detector.

The column was the Ultrasphere® ODS, 240 mmx4.6 mm (internal diameter) and 5 µ particle size. The mobile phase consisted of a mixture of acetonitrile and phosphate buffer in a 50:50 v/v ratio. The pH was adjusted to 3.3 using phosphoric acid, using a 1 ml/min flow. Chromatographic development time was 30 minutes.

The wavelengths selected in the detector were 220 nm and 322 nm, and the data were processed using Empower software.

The physical compatibility of the sample was determined by visual examination at the time of mixing and 6, 12, 24 and 48 hours later, using change in colour, phase separation and precipitation of the solution as criteria for incompatibility.

Results

The chromatograms showed a satisfactory separation of the compounds and the baseline remained stable under the study conditions. For the four drugs, the calibration curve used showed a linear relationship between peak heights and concentrations. The linear correlation coefficients obtained for tramadol, ranitidine, ketorolac and metoclopramide were 0.980, 0.999, 0.983, and 0.993, respectively.

The retention time for ketorolac was 4 minutes and its maximum absorption was obtained at a wavelength of 312 nm. For tramadol, the retention time was 8 minutes and its maximum absorption occurred at 217 nm. For metoclopramide, the maximum absorption was at 213 nm, with a retention time of 9 minutes. For ranitidine, the retention time was 6 minutes with a maximum absorption at 322 nm.

The analysis of the mixture did not reveal any degradation product in the development of the chromatogram, with the retention times remaining stable for each of the included drugs. The data show that the concentration of metoclopramide in the mixture was between 100% and 105% of its initial value, while the concentrations for tramadol, ketorolac and ranitidine were found to be between 99% and 102% of the baseline concentration (Table).

Visual examination did not detect the presence of any precipitate in the solutions, or change in colour, appearance of precipitate or any other indication of physical incompatibility.

Discussion

Assessing the stability of drugs by HPLC is a reliable method that has been used in previous studies for assessing formulations used in hospitals. This technique has been applied to the assessment of the stability of active ingredients such as captopril,[15] the mixture of tobramycin and vancomycin,[16] and the mixture of etomidate and pentobarbital.[17]

In our study, the results indicated no degradation products, with the concentrations for each of the tested products remaining stable over time, with no significant changes with respect to the initial theoretical concentrations. For all the drugs, these values lay within 99% and 105% of the initial concentration. Similar or even less restrictive values were obtained in previously mentioned studies. For captopril, the concentration values were between 95% and 105%. For the mixture of tobramycin and vancomycin or the mixture of pentobarbital and etomidate, the product was considered stable until its concentration reached 90% of the initial concentration. The concentration values obtained in our study are in line with the recommendations given by the International Conference on Harmonisation, which limits

stability to the range of concentrations that are between 90%and 105%of the baseline concentration.

The data obtained in the visual examination of the solutions was also used as the compatibility and stability index, in the same manner as the previously mentioned stability studies. At the time of preparation of the mixture and over time after observation, this examination did not reveal changes of colour, appearance of precipitates and phase separation, which are indicative of incompatibility between the drugs.

Based on these results and as a conclusion, it can be established that the formula consisting of a combination of tramadol (5 mg/ml), ranitidine (1.5 mg/ml), ketorolac (1.5 mg/ml) and metoclopramide (0.5 mg/ml) is stable and compatible in a 0.9%saline solution for at least 48 hours at room temperature, making it suitable under these conditions for use in clinical practice.

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