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Compatibility and stability of parenteral analgesic admixtures for multimodal analgesia

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Abstract

Study objective: Moderate post-operative pain is managed well by giving several analgesic drugs, such as paracetamol, ketoprofen, tramadol and/or nefopam, via IV. The admixture of these drugs in the same container would simplify nursing care but is forbidden by the technical summary of product characteristics covering each individual drug. The aim of this study was to validate the admixture of these analgesic drugs.

Methods: Admixture compatibility and stability were monitored over 24 hours at room temperature and in daylight conditions. Stability was compared between admixtures (paracetamol and ketoprofen; paracetamol and tramadol; paracetamol and nefopam; ketoprofen and tramadol; ketoprofen and nefopam; paracetamol, ketoprofen and tramadol; and paracetamol, ketoprofen and nefopam) and solutions of each drug alone. Each analgesic solution was monitored by chromatographic dosage, pH assessment and visual inspection.

Results: No variation in concentrations of the analgesics over 5% was observed according to International Conference on Harmonisation (ICH) guidelines. The pH of each analgesic solution remained unchanged throughout the study and was compatible with human administration. There was no visual alteration of analgesic admixture over the 24 hours of the study.

Conclusion: Based on the presented results, investigated admixtures of analgesics remain stable under the study conditions and can be used to give efficient and safer treatment for moderate post-operative pain.

Keywords

Admixture, ketoprofen, nefopam, paracetamol, stability, tramadol

Introduction

Multimodal analgesia is commonly used in the management of post-operative pain by giving several analgesic drugs intravenously [1]. These combinations of analgesic regimens can improve post-operative analgesia and functional outcome after surgery [1-4]. The drug combinations can make it possible to reduce the amounts of the individual components while achieving the same analgesic effect, with a lower incidence of side effects [1]. However, giving several analgesic drugs increases the workload for nurses because of repeatedly preparing the drugs and the associated drug administration tasks. Such work overload risks nursing error [5]. Hence, the admixture of analgesics in the same container is a potentially promising means of improving the management of pain in post-operative patients. However, the summary of product characteristics provided with these drugs generally emphasises that the mixing of parenteral drugs is forbidden. Furthermore, injectable solutions of paracetamol (Perfalgan, Bristol-Myers Squibb, France) are now commercially available and can replace the previous prodrug, i.e. propacetamol. Perfalgan solutions can be used, together with other analgesic drugs, when paracetamol is required.

The aim of this study was to validate the compatibility and stability of analgesic admixtures for parenteral use.

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Methods

Drugs

The investigated drugs were paracetamol (Perfalgan 1 g/100 mL, Bristol-Myers Squibb, France), ketoprofen

(Profenid 100 mg, sanofi-aventis, France), tramadol (Contramal 100 mg/2 mL, Grünenthal, France) and nefopam (Acupan 20 mg/2 mL, Biocodex, France).

Analyses

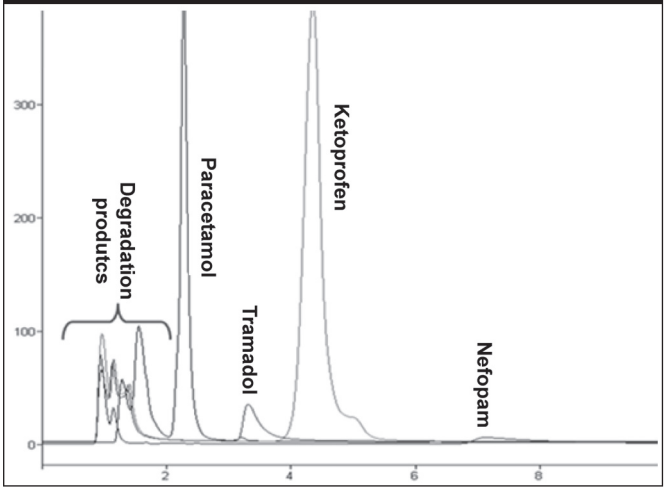
Analgesics were assayed by liquid chromatography using the following instrumentation (Jasco, France): a PU-980 pump, an AS-950 autosampler and a UV-975 detector with Azur v4.5.0.0 integrator software (Datalys, France). The column was type C18 (125/4.6 LiChrospher 100 RP 18 endcapped 5 µm, Macherey-Nagel, France). Detection wavelength was adjusted to 220 nm for each analysis. Injection volume was 5 µL for each analysis. For analysis of paracetamol, ketoprofen and tramadol, the mobile phase was a phosphate buffer (sodium dihydrogenophosphate, 6.89 mg/L adjusted to pH 5 with HCl 1 N) and acetonitrile (70/30, v/v) used at a flow rate of 1 mL per minute (Method 1). The mobile phase used to analyse nefopam was a phosphate buffer (sodium-1-heptanesulfonate 1.10 g/L and potassium dihydrogenophosphate 2.04 g/L adjusted to pH 3.7 with HCl 1 N) and acetonitrile (70/30, v/v) at a flow rate of 1.5 mL per minute (Method 2).

Chromatographic assays were validated for each analgesic with a calibration curve range from 0.1 mg/mL to 1 mg/mL. Intraday and interday assay variability were performed with 10 samples. The validation of the calibration curve was the following: paracetamol ($y = 20499.46x + 20499.46$, $r^2 = 0.999$; 0.1 to 1 mg/mL intraday and interday assay variability <5.05%), ketoprofen ($y = 12522034.26x - 24322.30$, $r^2 = 0.999$; intraday and interday variability <5.04), tramadol ($y = 5381760.37x - 56409.71$, $r^2 = 0.999$; intraday and interday variability <8.50%), nefopam ($y = 6722223.84x - 214490.70$, $r^2 = 0.999$; intraday and interday variability <5.73%).

The chromatographic method used was validated specifically to study the stability of each analgesic according to Trissel's guidelines [6]. The method had to be able to detect and separate each analgesic from any degradation products. We therefore carried out a 10-20% degradation of each molecule in sodium hydroxide 0.5 N for paracetamol and nefopam, 2 N for ketoprofen and tramadol, at 75°C over a period of four hours. The solution obtained was analysed chromatographically to check that there was no interference of degradation products with each analgesic. Figures 1 and 2 show that degradation products did not interfere with the peaks of the analgesics.

The pH measurements were performed using pH-indicator strips (pH 4.0-7.0, Merck, Germany). Test solutions were visually examined under normal laboratory fluorescent light

Figure 1: Chromatogram of degraded analgesics analysed using the method 1 (mobile phase at pH 5)

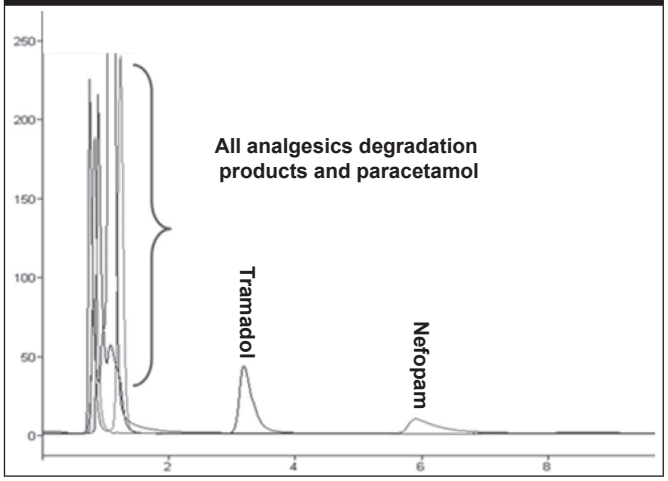


(PW Allen & Co, LV28) for precipitation, colour change or other visually detectable changes. In these visual analyses, Perfalgan and sodium chloride 0.9% (NaCl 0.9% 100 mL, Lavoisier, France) solutions were used as references.

Design of the stability study

Admixture compatibility and stability checks were performed on several drug associations: paracetamol and ketoprofen, paracetamol and tramadol, paracetamol and nefopam, ketoprofen and tramadol, ketoprofen and nefopam, paracetamol, ketoprofen and nefopam, and paracetamol, ketoprofen and tramadol. We chose analgesic doses prepared to treat moderate post-operative pain in adults by IV infusion: paracetamol 1 g, ketoprofen 100 mg, tramadol 100 mg and nefopam 20 mg. The combinations containing ketoprofen, tramadol and nefopam were mixed

Figure 2: Chromatogram of degraded analgesics analysed using the method 2 (mobile phase at pH 3.7)



in 100 mL of paracetamol solution (Perfalgan), and when the combination did not include paracetamol the analgesics were mixed in 100 mL of sodium chloride 0.9% solution for infusion (NaCl 0.9% 100 mL, Lavoisier, France). Each analgesic admixture was prepared in a colourless glass receptacle containing Perfalgan solution or in a colourless glass receptacle containing sodium chloride 0.9% solution according to each admixture. No data are available for the compatibility of these analgesics with various materials used for receptacles. However, all these analgesics are sold in glass containers: paracetamol and ketoprofen in glass vials while tramadol and nefopam are in glass ampoules.

Three batches of each analgesic admixture were prepared and 1 mL was sampled from each solution to perform analyses at each time point.

The criteria of significant change for a drug product are defined by ICH guidelines [7]. These guidelines cite: a 5% change in assay from its initial value; any degradation product exceeding acceptance criteria; failure to meet the acceptance criteria for appearance, physical attributes and functionality test; failure to meet the acceptance criterion for pH. Working to these guidelines, admixture stability was monitored for 24 hours in an experiment conducted at room temperature (22°C ± 2°C) and in daylight conditions. Decomposition of analgesics was considered to have been effected if there was a decrease of at least 5% and/or by the appearance of degradation products [7]. High pH variation could also have led to drug incompatibility [8]. Physical or visual incompatibility was reported when particulate formation, precipitation or colour change was observed [9]. The same analyses were performed on solutions of analgesic alone as a reference.

Results

The stability results of analgesic alone are presented in Table 1. The stability results of an admixture of two analgesics are shown in Table 2: paracetamol and ketoprofen, paracetamol and nefopam, paracetamol and tramadol, ketoprofen and tramadol, ketoprofen and nefopam; admixtures of three analgesics are shown in Table 3: paracetamol, ketoprofen and nefopam, and paracetamol, ketoprofen and tramadol.

Table 1: Concentrations of analgesic solution alone: paracetamol (10 mg/mL), ketoprofen (1 mg/mL), tramadol (0.98 mg/mL) and nefopam (0.196 mg/mL)

Time (hours)	0	1	24
Concentration [m ± sd (n)]	mg/mL	Percentage of initial concentration	
Paracetamol	9.64 ± 0.01 (3)	99.5 ± 1.1% (3)	98.6 ± 0.9% (3)
Ketoprofen	0.96 ± 0.02 (3)	97.3 ± 1.4% (3)	96.9 ± 2.7% (3)
Tramadol	0.89 ± 0.06 (2)	100.3 ± 3.9% (3)	102.1 ± 4.3% (3)
Nefopam	0.19 ± 0.00 (3)	98.8 ± 2.0% (3)	98.2 ± 1.2% (3)

m: mean; sd: standard deviation; n: number of samples analysed

From time zero and throughout the 24 hours of analysis, variations in analgesic alone or in admixture remained under the 5% threshold. No degradation products were detected during the experiment.

The pH of the solution of analgesic alone was within the 4.4 to 5.8 range (paracetamol: 4.4, ketoprofen: 5.8, tramadol: 5.3, nefopam: 5). The pH of the admixtures was slightly higher, within a 4.7 to 5.8 range (paracetamol and ketoprofen: 5, paracetamol and nefopam: 4.7, paracetamol and tramadol: 4.7, ketoprofen and tramadol: 5.5, ketoprofen and nefopam: 5.8, paracetamol, ketoprofen and nefopam: 5, and paracetamol, ketoprofen and tramadol: 5). No variation of pH was reported throughout

Table 2: Concentrations of analgesic admixture in a combination of two analgesics

Time (hours)	0	1	24
Concentration [m ± sd (n)]	mg/mL	Percentage of initial concentration	
Solution 1: Paracetamol	10.63 ± 0.43 (8)	102.4 ± 4.5% (8)	99.8 ± 5.1% (8)
Ketoprofen	1.00 ± 0.03 (8)	98.0 ± 2.9% (8)	97.5 ± 4.9% (8)
Solution 2: Paracetamol	9.99 ± 0.63 (8)	101.4 ± 7.3% (8)	97.8 ± 5.7% (8)
Nefopam	0.20 ± 0.01 (8)	100.0 ± 1.1% (8)	98.9 ± 10.7% (8)
Solution 3: Paracetamol	9.44 ± 0.86 (8)	104.2 ± 11.7% (7)	96.5 ± 13.6% (7)
Tramadol	0.94 ± 0.06 (8)	99.7 ± 13.4% (7)	100.9 ± 13.9% (7)
Solution 4: Ketoprofen	0.95 ± 0.02 (7)	100.5 ± 5.1% (8)	102.9 ± 10.2% (7)
Tramadol	0.97 ± 0.11 (8)	98.9 ± 10.3% (8)	96.1 ± 10.1% (7)
Solution 5: Ketoprofen	0.93 ± 0.03 (8)	99.4 ± 2.5% (8)	97.6 ± 2.5% (8)
Nefopam	0.21 ± 0.01 (8)	100.1 ± 3.6% (8)	98.9 ± 3.2% (8)

Solution 1: paracetamol (10 mg/mL) + ketoprofen (1 mg/mL) in Perfalgan solution; Solution 2: paracetamol (10 mg/mL) + nefopam (0.196 mg/mL) in Perfalgan solution; Solution 3: paracetamol (9.8 mg/mL) + tramadol (0.98 mg/mL) in Perfalgan solution; Solution 4: ketoprofen (0.98 mg/mL) + tramadol (0.98 mg/mL) in NaCl 0.9% solution; Solution 5: ketoprofen (0.98 mg/mL) + nefopam (0.196 mg/mL) in NaCl 0.9% solution.
m: mean; sd: standard deviation; n: number of samples analysed

Table 3: Concentrations of analgesic admixture in a combination of three analgesics

Time (hours)	0	1	24
Concentration [m ± sd (n)]	mg/mL	Percentage of initial concentration	
Solution 1: Paracetamol	9.86 ± 0.14 (8)	98.6 ± 3.1% (8)	101.8 ± 4.2% (7)
Ketoprofen	0.96 ± 0.03 (8)	98.3 ± 2.5% (8)	96.2 ± 2.7% (7)
Nefopam	0.20 ± 0.01 (8)	99.0 ± 6.4% (8)	96.0 ± 4.8% (7)
Solution 2: Paracetamol	10.04 ± 0.36 (7)	101.6 ± 3.7% (6)	98.2 ± 3.5% (7)
Ketoprofen	0.96 ± 0.01 (8)	100.6 ± 1.1% (8)	99.7 ± 2.1% (8)
Tramadol	0.96 ± 0.08 (8)	97.3 ± 7.1% (8)	97.9 ± 6.9% (8)

Solution 1: paracetamol (9.8 mg/mL) + ketoprofen (0.98 mg/mL) + nefopam (0.196 mg/mL) in Perfalgan solution; Solution 2: paracetamol (9.8 mg/mL) + ketoprofen (0.98 mg/mL) + tramadol (0.98 mg/mL) in Perfalgan solution.
m: mean; sd: standard deviation; n: number of samples analysed

the study for each analgesic admixture between times zero hour and up to 24 hours.

The admixtures remained clear and colourless after visual inspection, without formation of any particles. The visual inspections were performed to check that each component of the parenteral solutions, i.e. both drugs and adjuvants, remained soluble during the experiment.

Discussion

The results of the analytical method, the pH assessment and the visual controls strongly suggest that investigated admixtures of analgesics (paracetamol and ketoprofen; paracetamol and tramadol; paracetamol and nefopam; ketoprofen and tramadol; ketoprofen and nefopam; paracetamol, ketoprofen and tramadol; and paracetamol, ketoprofen and nefopam) in the same solution, i.e. Perfalgan or sodium chloride 0.9%, are compatible and stable for at least 24 hours at room temperature and exposed to daylight. It should be underlined that in clinical practice these analgesics are generally used rapidly, i.e. before a maximum of one hour after the preparation is made.

All analgesic concentrations throughout the study remained under the 5% variation compared with their initial value as defined by the quality guidelines of the ICH [7]. Consequently, the presented results suggest that analgesic admixtures can be prepared well in advance.

High pH variations can lead to changes in the solubility of drugs and the formation of precipitates [8]. In the presented study, the analgesic admixtures remained within a relatively tight range of pH, 4.7 to 5.8, which is in accordance with the lack of change in the admixtures. The pH of admixtures remained compatible with IV administration to humans.

Admixtures of ketoprofen lysine salt and tramadol hydrochloride have already been analysed by chromatographic assays, pH measurements and visual inspection [10]. These admixtures have been validated in an elastomeric infusion system, at up to seven days at room temperature and protected from light [10]. Admixtures of paracetamol (Perfalgan) and ketoprofen (Profenid) have been monitored by others in the same conditions as the presented study, and the combination remained stable and compatible for up to 24 and 48 hours at room temperature [11, 12]. Admixtures of paracetamol (Perfalgan) and nefopam, and ketoprofen and nefopam have recently been validated at room temperature and over a 24-hour period [12]. However, no data are available on the following admixtures: paracetamol and tramadol, paracetamol, ketoprofen and tramadol, and paracetamol, ketoprofen and nefopam.

This study demonstrated that in clinical practice, analgesic admixtures would permit economic savings by using fewer medical devices and liquid infusions, and reduce the time spent by the nurses to prepare each analgesic infusion. However, medico-economic studies are necessary to support this hypothesis. Moreover, as the stability of the investigated analgesic admixtures is validated up to a 24-hour period, these admixtures could be prepared in advance benefiting the organisation of work.

Conclusion

Multimodal analgesia is an important therapeutic protocol for the relief of moderate post-operative pain [1]. Many analgesic combinations can be used in order to improve analgesia: pure analgesics (paracetamol), non-steroidal anti-inflammatory drugs (ketoprofen), opioid analogues (tramadol), or centrally-acting drugs (nefopam). These combinations make it possible to cover a large spectrum of pain and of different origins, whether peripheral, central or inflammatory. In order to improve the feasibility of this approach, a confirmation of the compatibility and the stability of these admixtures is necessary. Investigated analgesic admixtures were validated in this study, paving the way towards more efficient and safer treatment of moderate post-operative pain.

Conflict of Interest

The authors declare no conflict of interest.

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