Laboratory Study

Microbiological and Physicochemical Stability of Fentanyl, Oxycodone, Hydromorphone, Ketorolac, Ramosetron, and Ondansetron for Intravenous Patient-controlled Analgesia: An In Vitro Study

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Background: Postoperative patient-controlled analgesia provides pain relief, encourages early mobilization, and results in a shortened hospital stay. Patient-controlled analgesia involves the mixing of different types of drugs. When using patient-controlled analgesia, it is important to confirm the microbiological and physicochemical stability of each drug in a mixture to guarantee that the drug is delivered to the patient in an unaltered form.

Objectives: To confirm the microbiological and physicochemical stability of various drug mixtures for intravenous patient-controlled analgesia.

Study Design: An in vitro protocol to examine the microbiological and physicochemical stability of the most commonly used postoperative intravenous patient-controlled analgesia mixtures at our institution.

Setting: In vitro laboratory study.

Methods: Each mixture contained a total of 4 drugs: fentanyl 400 µg, ketorolac 30 mg, either hydromorphone 4 mg or oxycodone 10 mg, and either ramosetron 0.3 mg or ondansetron 10 mg. Each mixture was placed in a portable patient-controlled analgesia system containing 0.9% saline and stored at a constant temperature of 24°C for 96 hours. Physical properties (color, transparency, and sedimentation) were observed with the naked eye and optical microscopy. Sterility testing was performed to assess microbiological contamination in the drug mixture during the 96-hour study period. The pH of each mixture was evaluated for up to 96 hours after mixing. The concentration of each drug was evaluated by high-performance liquid chromatography every 24 hours until 96 hours after mixing.

Results: All mixtures appeared visibly transparent, and no sediments were visible under the microscope. Bacterial or fungal growth was not observed in any of the samples after 14 days of incubation. The pH variations in all mixtures were maintained within 0.25 over the 96-hour study period. The concentration of drugs, except ketorolac, ranged from 90–110% of the initial concentration up to 96 hours after mixing. In the mixtures with a pH of 4.21–4.39, the concentration of ketorolac significantly decreased at 24 hours and 48 hours.

Limitations: Confirmation of the stability of drugs in vitro does not automatically ensure that the pharmacokinetics and pharmacodynamics of the drugs are not altered in vivo.

Conclusion: With the exception of ketorolac, the drugs used in the intravenous patient-controlled analgesia drug mixtures in this study were physicochemically stable up to 96 hours after mixing. The concentration of ketorolac decreased in more acidic mixtures.

Key words: Patient-controlled analgesia, multimodal analgesia, stability, fentanyl, oxycodone, hydromorphone, ketorolac, ondansetron, ramosetron

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Patient-controlled analgesia (PCA) enables patients to control the administration of analgesics for the management of acute and chronic pain (1). Drug administration via PCA is used to manage postoperative and cancer pain (2,3). The use of PCA in postoperative patients results in early mobilization, reduced hospital stay, and increased patient satisfaction (2,3). Multimodal analgesia is recommended when using PCA (4-6). Multimodal analgesia reduces individual drug dosage, opioid-associated complications, and hospital stay (7-10).

Our institution uses postoperative intravenous (IV) PCA, which includes fentanyl, oxycodone or hydro-morphone, and ketorolac. Fentanyl has a rapid onset time and short duration of action. Oxycodone and hydromorphone have a relatively long onset time and duration of action. The addition of ketorolac, a nonsteroidal anti-inflammatory drug (11-13), reduces the use and side effects of opioids. Antiemetic agents, such as ondansetron or ramosetron, can be added to IV PCA to reduce postoperative nausea and vomiting (14-16). For effective treatment, the drug mixture for PCA may contain 4 different medications.

When drugs are mixed and injected through the PCA catheter, it is assumed that the mixture maintains microbiological and physicochemical stability, that the drugs do not interact, and the original drug concentration is maintained. However, when different drugs are mixed, physicochemical changes may occur, resulting in altered therapeutic properties and unexpected side effects (17,18). In particular, when drugs with different acidities are mixed, crystallization can occur (19,20). Moreover, crystals may block the PCA catheter, and there is a risk of crystals being injected into the patient.

We conducted an in vitro study of IV PCA cocktails containing drugs commonly used at our institution to determine whether the mixtures were microbiologically and physicochemically stable. In addition, we evaluated the stability and shelf life of the mixtures for up to 96 hours.

Methods

Drugs used in PCA

Fentanyl (fentanyl citrate injection, 50 μg/mL, 2 mL; Hana Pharm Co., Ltd., Seoul, South Korea), hydromorphone hydrochloride (Dilid injection, 1 mg/mL, 1 mL; Hana Pharm Co., Ltd., Seoul, South Korea), oxycodone hydrochloride (OxyNorm® injection, 10 mg/mL, 1 mL; Mundipharma Korea, Ltd., Seoul, South Korea),

ketorolac tromethamine (Kerola injection, 30 mg/mL, 1 mL; Dong Kwang Pharm Co., Seoul, South Korea), ra-mosetron hydrochloride (Nasea injection, 0.15 mg/mL, 2 mL; Astellas Pharma, Inc., Seoul, South Korea), and ondansetron hydrochloride (Ondansetron injection, 2.5 mg/mL, 4 mL; Hana Pharm Co., Ltd., Seoul, Seoul Korea) were obtained from commercial suppliers (Table 1).

Preparation of Drug Mixtures

All mixtures for IV PCA contained 400 μg of fentanyl and 30 mg of ketorolac. Either 10 mg of oxycodone or 4 mg of hydromorphone was added as an additional analgesic, and either 10 mg of ondansetron or 0.3 mg of ramosetron was added as an antiemetic agent. These combinations resulted in 4 different mixtures of PCA drugs (Table 2).

For each drug mixture, 0.9% normal saline was added to make up a total volume of 25 mL. For all mixtures, the ratio of each drug was the same as that used clinically; however, the total volume was half of that used clinically. Each mixture was stored in a portable PCA system (AutoFuser pump; ACE Medical Co., Ltd., Seoul, South Korea) that could administer the mixture at a rate of 0.5 mL/h and 2 mL per bolus (lockout time: 10 minutes). Each infusion device was stored in the laboratory under dark conditions at a temperature of 24°C. The concentration of each drug in the mixtures was as follows: fentanyl 0.016 mg/mL, hydromorphone 0.08 mg/mL, oxycodone 0.4 mg/mL, ketorolac 1.2 mg/mL, ramosetron 0.012 mg/mL, and ondansetron 0.32 mg/mL.

To ensure the accuracy of the analysis, each mixture (mixtures 1-4) was prepared 5 times. All mixtures in the PCA delivery system were prepared under sterile conditions.

Evaluation of the Stability of the Mixtures

For each mixture, samples were obtained from the PCA tube immediately after mixing and at 24, 48, 72, and 96 hours after mixing. Both the chemical and physical properties of the mixtures were evaluated. To evaluate the microbiological properties of the drug mixtures, samples were obtained 96 hours after mixing.

Physical Study

Appearance, Clarity, and Color

Aliquots (3 mL) were withdrawn from each mixture at each time interval. To evaluate physical properties, each sample was placed in a colorless silicate

glass test tube, and color, transparency, and crystal formation were visually assessed using white and black backgrounds. Precipitation was evaluated using an optical microscope (Olympus BX51 microscope; Olympus, Germany). Physical stability was originally defined as the maintenance of a visibly transparent solution with no sediments (21).

Microbiological Study

Sterility Test

Four samples (2 mL each) from each mixture were obtained. To determine the presence of aerobic bacteria and Candida albicans, 2 samples from each mixture were seeded in Petri dishes containing trypticase soy broth (TSB). To determine the presence of anaerobic bacteria, 2 samples from each mixture were seeded into Petri dishes containing thioglycolate broth (TGB). To determine if the mixtures maintained sterility, one TSB sample and one TGB sample from each mixture were maintained at a constant temperature (24°C) for 14 days, and one TSB sample and one TGB sample from each mixture were placed in an incubator at 36°C for 14 days. In addition, 2 mL of sterilized distilled water was added to fresh TSB and TGB media and used as a negative control. The samples were incubated for 14 days at 20-36°C, as recommended for bacterial and fungal growth studies (22).

Chemical Study

Measurement of pH

The pH of each aliquot was measured using a digital phs-3c pH meter (Orion Star A212; Thermo Scientific, Melbourne, Australia). Using 5 replicates of each mixture, the average and standard deviation were calculated at each time point. The pH was evaluated to determine whether the chemical properties of each mixture changed over time.

Determination of Drug Concentration

The concentration of individual drugs in each mixture was determined using high-performance liquid chromatography (HPLC). Before analyzing the mixtures, the peaks of the 6 drugs were confirmed using HPLC. For oxycodone, ketorolac, and ondansetron, the HPLC peak was saturated, making it impossible to accurately calculate the concentration area. Thus, to accurately calculate the concentration area, mixtures 1-4 were prepared using the maximum unsaturated

Table 1. *Drug properties*.

Drug	Concentration before mixing (mg/mL)	Chemical formula	Molecular weight	pH
Fentanyl citrate	0.05	$C_{28}H_{36}N_2O_8$	336	5.61
Oxycodone hydrochloride	10	$C_{18}H_{22}C_1NO_4$	315	5.05
Hydromorphone hydrochloride	2	$C_{17}H_{20}C_1NO_3$	285	3.94
Ketorolac tromethamine	30	$C_{19}H_{24}N_2O_6$	254	7.43
Ondansetron hydrochloride	2	$C_{18}H_{20}C_1N_3O$	294	3.14
Ramosetron hydrochloride	0.15	$C_{17}H_{17}N_3O$	279	4.33

Table 2. *Drug combinations evaluated in this study*.

	Opioid (mg)	Additional opioid (mg)	Nonopioid analgesic (mg)	Antiemetic (mg)
Mixture 1	Fentanyl 0.4	Oxycodone 10	Ketorolac 30	Ondansetron 10
Mixture 2	Fentanyl 0.4	Oxycodone 10	Ketorolac 30	Ramosetron 0.3
Mixture 3	Fentanyl 0.4	Hydromorphone 4	Ketorolac 30	Ondansetron 10
Mixture 4	Fentanyl 0.4	Hydromorphone 4	Ketorolac 30	Ramosetron 0.3

concentrations of oxycodone, ketorolac, and ondansetron. To differentiate mixtures with unsaturated concentrations of oxycodone, ketorolac, and ondansetron from mixtures 1-4 (Table 2), the mixtures were labeled as H1–H4. A total of 20 drug mixtures were prepared, 5 each for mixtures H1-H4. The concentrations of the drugs in the H mixtures were as follows: fentanyl 0.016 mg/mL, hydromorphone 0.08 mg/mL, oxycodone 0.1 mg/mL, ketorolac 0.24 mg/mL, ramosetron 0.012 mg/mL, and ondansetron 0.04 mg/mL. The H mixtures were prepared under sterile conditions; they were stored in a portable PCA system and protected from light at a temperature of 24°C in the laboratory.

To determine whether the drug concentrations in the H mixtures were stable over time, 100 μL aliquots were obtained at each time interval. Drug concentrations were measured using HPLC. In addition, using the chromatogram from the sample obtained immediately after mixing, we evaluated whether peaks of decomposition products, which interfered with the quantification of the concentration of each drug,

were generated from 24 hours to 96 hours after mixing. For the 4 drug combinations in the H mixtures, 5 replicates were used to measure drug concentrations at each time point.

For each H mixture, immediately after mixing, the concentration of each drug was set to 100, and the ratio of the change in the concentration of each drug over time was calculated. Using 5 replicates of each H mixture, the mean and standard deviation of the rate of change in concentration over time was calculated. According to the United States Pharmacopeial Convention, drug stability is defined as the maintenance of 90–110% of the initial drug concentration (23).

HPLC Equipment and Chromatography Conditions

A YL9100 HPLC system (YoungLin Clarity, South Korea) was used to analyze the drug concentrations. This instrument consists of a quaternary pump, vacuum degasser, and a UV/Vis detector driven by Clarity software. For solute separation, a Vydac C18 column with a diameter of 250 × 7.6 mm was used. The eluent consisted of 0.05% trifluoroacetic acid-H_2O (A buffer) and 0.05% trifluoroacetic acid-acetonitrile (B buffer). The flow conditions were as follows: the concentration of the B buffer increased from 10% to 70% over 50 minutes. The column temperature was maintained at 24°C with a mobile phase flow rate of 1.5 mL/min, and the injection volume was 100 μL. Detection was performed using a UV-vis detector at wavelengths of 214 and 254 nm.

Analytical Validation

For the validation of analytical techniques, the guidelines published at the International Conference on Harmonization were referenced (24).

Calibration

Linear regression was used to determine the relationship between the peak area for each drug and the amount of added drug. For the 4 drug concentrations of each drug, calibration curves were verified 4 times.

Accuracy

The accuracy of the method for providing information on the recovery of analytes from the sample was assessed in terms of the relative standard deviation (RSD) or the coefficient of variation of accuracy (CVa = RSD × 100). The RSD or CVa for the 4 H mixtures was calculated using the means and standard deviations of the theoretical and experimental concentrations measured using the calibration curve.

Repeatability

Confirmation of crystal formation with the naked eye and microscopy, sterility testing, pH measurement, and HPLC analysis were performed by the same researcher in the same laboratory with the same equipment according to the same analysis procedure. Repeatability was expressed in terms of RSD or the coefficient of variation of repeatability (CVr). The RSD or CVr of the 4 H mixtures was calculated using the mean and standard deviation of the values obtained from the 5 replicates.

RESULTS

Physical Stability

Appearance, Clarity, and Color

Up to 96 hours after mixing, all mixtures were visibly transparent, and no particles or deposits were observed during visual or microscopic examination. All mixtures were physically compatible, without evidence of incompatibility (turbidity, color change, or sedimentation).

Microbiological Stability

None of the 80 samples or negative controls showed bacterial or fungal growth.

Chemical Stability

During the study period, the pH of the mixtures did not change considerably. At every time point, the pH of all mixtures varied within 0.25 (4.44 ± 0.04%) compared with the pH measured immediately after mixing (Table 3).

Concentration

Drug concentrations in each H mixture were measured by determining the area under the appropriate chromatographic peak through integration. The retention times were as follows: fentanyl, 29.8 minutes; oxycodone, 15.5 minutes; hydromorphone, 11.8 minutes; ketorolac, 33.0 minutes; ramosetron, 24.7 minutes; and ondansetron, 23.7 minutes (Fig. 1).

The concentrations of all drugs in the H mixtures, except ketorolac, ranged from 92.2% to 104.8% of the initial concentration (Fig. 2). In mixture H3, the concentration of ketorolac decreased to 86.2 ± 0.01% after 24 hours and to 82.5 ± 0.01% after 96 hours. In mixture H4, the concentration of ketorolac decreased to 87.4 ± 0.01% after 24 hours and to 83.8 ± 0.01% after 96

hours. No decomposition peaks were detected in any H mixture. Linear regression analysis of the concentration–time data revealed that all drugs, except ketorolac, maintained at least 92.2% of the initial concentration for up to 96 hours.
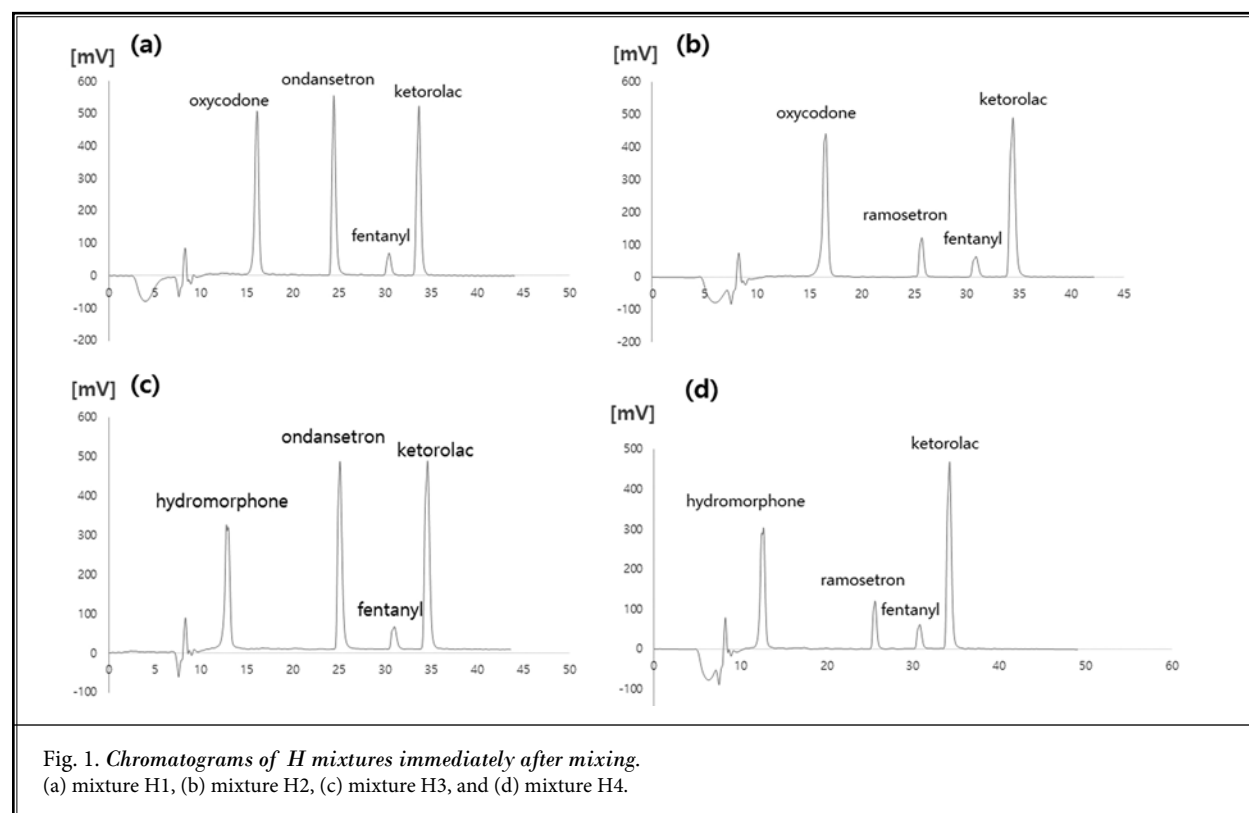
Analytical Validation

Calibration

The linear regression equations were as follows: fentanyl, y = 114004 (x) + 142, mean R^2 = 0.9999; oxycodone, y = 175523 (x) - 807, mean R^2 = 0.9982; hydromorphone, y = 182664 (x) - 1113, mean R^2 = 0.9991; ketorolac, y = 85377 (x) - 1066, mean R^2 = 0.9987; ramosetron, y = 419025 (x) - 1528, mean R^2 = 0.9962; and ondansetron, y = 417090 (x) - 66, mean R^2 = 0.9990. For all drugs, the relationship between the peak area and concentration was linear, with high correlation coefficients (R^2).
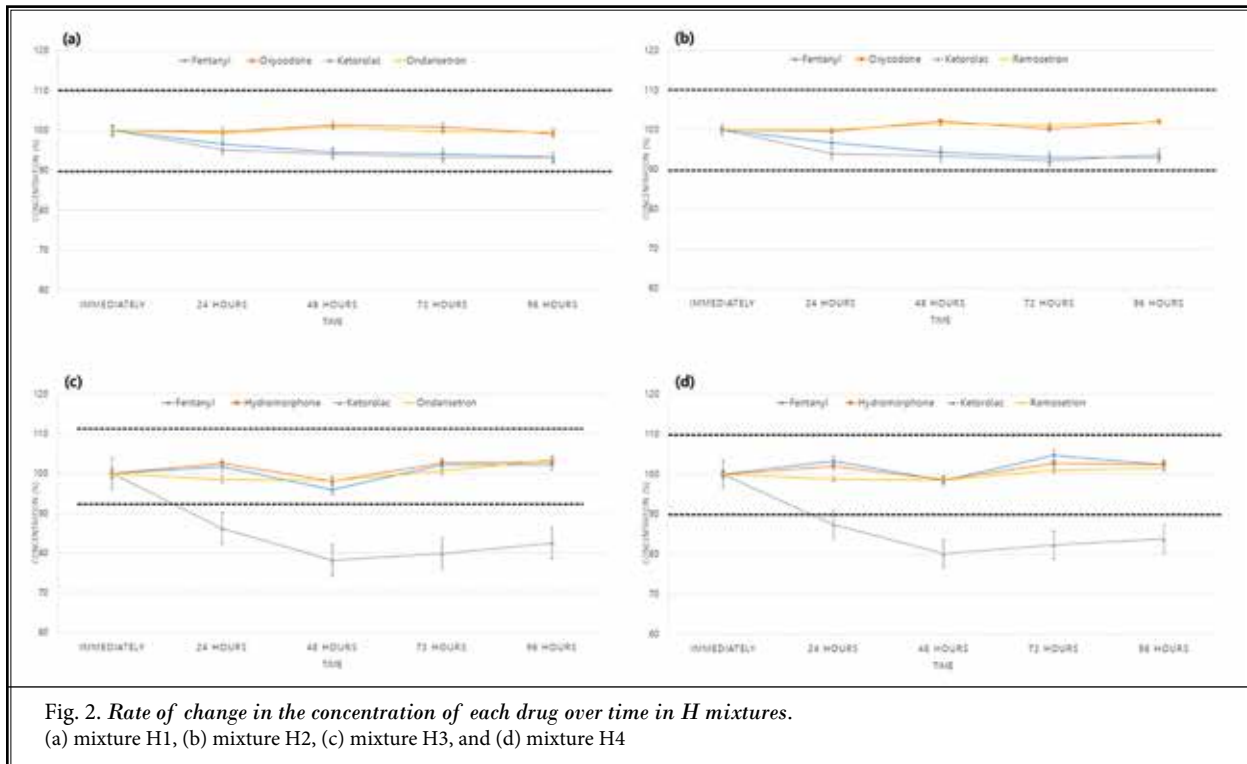
The values for the CVa between the estimated theoretical concentration and observed experimental concentration for each drug were as follows: fentanyl, 2–4% (accuracy ≥ 96.0%); hydromorphone, 2.4-4.3%

Table 3. *Measured pH for each mixture at all time points.*

Time after mixing	Mixture 1	Mixture 2	Mixture 3	Mixture 4
Immediate	5.62 ± 0.04 (100)	5.63 ± 0.10 (100)	4.21 ± 0.03 (100)	4.23 ± 0.03 (100)
24 h	5.78 ± 0.07 (102.85 ± 0.04)	5.79 ± 0.10 (102.84 ± 0.04)	4.31 ± 0.01 (102.38 ± 0.04)	4.31 ± 0.03 (101.89 ± 0.04)
48 h	5.81 ± 0.02 (103.38 ± 0.04)	5.79 ± 0.08 (102.84 ± 0.04)	4.30 ± 0.03 (102.14 ± 0.04)	4.28 ± 0.06 (101.18 ± 0.04)
72 h	5.81 ± 0.09 (103.38 ± 0.04)	5.88 ± 0.11 (104.44 ± 0.04)	4.31 ± 0.05 (102.38 ± 0.04)	4.35 ± 0.03 (102.84 ± 0.04)
96 h	5.82 ± 0.04 (103.56 ± 0.04)	5.83 ± 0.04 (103.55 ± 0.04)	4.36 ± 0.03 (103.56 ± 0.04)	4.39 ± 0.04 (103.78 ± 0.04)

Measured pH and percent (%) change in the pH value versus the pH immediately after mixing. Mixture 1: fentanyl, oxycodone, ketorolac, and ondansetron; mixture 2: fentanyl, oxycodone, ketorolac, and ramosetron; mixture 3: fentanyl, hydromorphone, ketorolac, and ondansetron; mixture 4: fentanyl, hydromorphone, ketorolac, and ramosetron. Data are presented as the mean ± standard deviation.

Fig. 1. *Chromatograms of H mixtures immediately after mixing.*
(a) mixture H1, (b) mixture H2, (c) mixture H3, and (d) mixture H4.

Fig. 2. *Rate of change in the concentration of each drug over time in H mixtures.*
(a) mixture H1, (b) mixture H2, (c) mixture H3, and (d) mixture H4

(accuracy ≥ 95.7%); oxycodone, 1.3-1.5% (accuracy ≥ 98.5%); ketorolac, 4.1-4.8% (accuracy ≥ 95.2%); ramosetron, 4.4-4.9% (accuracy ≥ 95.1%); and ondansetron, 0.4-0.6% (accuracy ≥ 99.4%). The CVa for all 6 drugs in all combinations in the H mixtures was < 4.9%.

Repeatability

The CVr for each drug was estimated using the results obtained from the 5 replicates of each H mixture. The CVr values were as follows: fentanyl, 0.9-1.7% (accuracy ≥ 98.3%); hydromorphone, 1.6-2% (accuracy ≥ 98.0%); oxycodone, 1.1-1.2% (accuracy ≥ 98.8%); ketorolac, 0.8-2.8% (accuracy ≥ 97.2%); ramosetron, 0.4-1.1% (accuracy ≥ 98.9%); and ondansetron, 0.7-3.0% (accuracy ≥ 97.0%). The CVr for all 6 drugs in all combinations in the H mixtures was < 3.0%.

DISCUSSION

In this study, we evaluated the stability of IV PCA mixtures of opioid analgesics (fentanyl, oxycodone, or hydromorphone) with ketorolac and an antiemetic (ramosetron or ondansetron). Except for ketorolac, all drugs were physically, chemically, and microbiologically stable for up to 96 hours. Ketorolac was physicochemically and microbiologically stable in mixtures with a pH of 5.62–5.88, but its concentration significantly decreased in mixtures with a pH of 4.2-4.39.

Intravenous PCA, which contains opioid analgesics, is widely used for controlling postoperative pain (2,5,9). However, the use of postoperative opioids has been associated with delayed postoperative recovery due to nausea, vomiting, dizziness, pruritus, and respiratory depression (25-27). In particular, opioid-induced respiratory depression is a major factor limiting the use of opioids for pain management (28). Combining 2 opioids in IV PCA takes advantage of the different pharmacokinetic activities of each opioid. On combining fentanyl, which has a rapid onset time and short duration of action, with oxycodone or hydromorphone—opioids with a slower onset time but a longer duration of action—we can provide analgesia with a rapid onset time and long duration of action. In addition, to reduce the possibility of respiratory depression owing to the use of 2 opioids, we used a lower hourly dose than that commonly used during PCA (hourly dose of opioids in PCA in our hospital and this study: fentanyl, 0.008 mg/h; hydromorphone, 0.04 mg/h; and oxycodone, 0.2 mg/h vs commonly used opioid doses per hour during PCA: fentanyl, 0.015-0.060 mg/h (29-31); hydromorphone, 0.24-0.26 mg/h (32,33); and oxycodone, 0.3-1.2 mg/h (34)).

In addition, the occurrence of opioid-related side

effects is reduced and the analgesic effect is increased when nonsteroidal anti-inflammatory drugs are used for multimodal PCA (11,13,35).

Incorporating antiemetics into IV PCA is a common approach (14-16). However, the PCA drug mixture is usually prepared using a syringe and injected into the infusion device by a clinician during surgery. The safety of these combinations has been assumed based on extensive drug response reports by the US Food and Drug Administration and years of anecdotal clinical experience. Information on the compatibility of these agents is important for anesthesia providers and patients undergoing anesthesia who rely on the IV route for drug delivery.

Stability studies have been conducted for various drug mixtures (14,36-47); however, no data were available for the drugs used for IV PCA in our hospital. Hwang et al (19) reported that precipitation in drug mixtures occurs primarily due to the interaction between acidic and basic drugs. Except for ketorolac (pH: 7.43), all drugs used in our study were acidic, and the pH of the drug mixtures was acidic. The pH of mixtures 1 and 2 containing fentanyl, oxycodone, ondansetron or ramosetron, and ketorolac was 5.62-5.83. In mixtures 1 and 2, ketorolac was chemically stable without a significant change in concentration over time. However, in mixtures 3 and 4, oxycodone was replaced with a more acidic drug, hydromorphone, and the pH of mixtures 3 and 4 (pH: 4.21-4.39) was lower than that of mixtures 1 and 2. In the more acidic mixtures 3 and 4, the concentration of ketorolac was significantly reduced, suggesting that ketorolac is unstable in a more acidic environment.

Devarajan et al (48) reported that when ketorolac was mixed with hydrochloric acid, an acid degradation product was formed. However, in our study, degradation products were not detected by HPLC analysis, possibly because degradation products were present only in small amounts owing to dilution or because the degradation products permeated through the filter of the portable balloon infusion device.

Helin-Tanninen et al reported that when drug mixtures are stored at room temperature without a rigid secondary package, evaporation of the solution through the polyester infusion bag significantly increases the drug concentrations (49). In the present study, there was no consistent change in the concentra-

tion of drugs over time, except for the concentration of ketorolac in mixtures 3 and 4. This may be attributed to the portable balloon infusion devices, which helped maintain a stable drug concentration without evaporation of the solution.

Limitations

There are limitations to consider when interpreting the results of this study. First, the drugs in all mixtures used in this in vitro study, except ketorolac, were physicochemically and microbiologically stable for up to 96 hours after mixing. However, in vitro stability does not guarantee that the pharmacokinetics and pharmacodynamics are not altered in vivo, and it may be necessary to conduct clinical trials to ensure the pharmacokinetics and pharmacodynamics of these drugs in vivo. Second, the use of clinical concentrations of oxycodone, ketorolac, and ondansetron in the original drug mixture resulted in saturation under HPLC analysis conditions. Therefore, for accurate analysis, HPLC was performed by reducing the concentrations of oxycodone, ketorolac, and ondansetron. This may have resulted in bias when evaluating drug–drug interactions.

CONCLUSIONS

All drugs in the IV PCA mixtures used in this study, except ketorolac, were physicochemically stable for up to 96 hours after mixing. The concentration of ketorolac decreased in more acidic mixtures, suggesting that mixtures 1 and 2 (fentanyl, oxycodone, ketorolac, and ondansetron or ramosetron) are stable and can be used in patients after surgery. Mixtures 3 and 4 (fentanyl, hydromorphone, ketorolac, and ondansetron or ramosetron) may be less clinically useful owing to the reduced ketorolac concentration. Based on the results of this study, evaluation of these mixtures and the mixing conditions in a clinical setting will be useful for confirming the microbiological and physicochemical stability of the mixtures in vivo.

Availability of Data and Materials:

The datasets generated and analyzed in this study are available in the OSF repository, (https://osf.io/rcp8m/ or DOI 10.17605/OSF.IO/RCP8M). Datasets are also submitted with the manuscript files as additional supporting information files.

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