The Art and Science of Infusion Nursing

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# Hydrogen Profiles of Dobutamine Hydrochloride and Fentanyl Citrate Solutions According to Intravenous Administration Systems, Temperature, and Luminosity Conditions

## ABSTRACT

Factors such as temperature, light exposure, drug concentration, ionic strength, time of infusion, and duration of drug association can influence the effectiveness of pharmacological solutions, which can compromise the solutions' quality, resulting in unstable solutions and drug incompatibility. The aim of this study was to determine the pH of solutions of dobutamine hydrochloride, fentanyl citrate, and their combination in 5% dextrose in water (D5W) under various light exposures and temperature conditions over time. The analysis was performed by measuring the pH of the substances in both pharmacological (commercial) preparations and in D5W under dark fluorescent light in the presence or absence of sunlight exposures, intravenous apparatus packaging (clear and amber burettes), and temperature (22°C and 37°C). Samples were collected immediately after preparation and after 0.5, 1, 2, 3, 4, and 24 hours of exposure to the various conditions; data were analyzed using mean standard deviations. Of the 260 pH values obtained, 50 (19.2%) were from commercial preparations and 210 (80.8%) from solutions exposed to various experimental conditions. Significant pH differences were found among the vials of the commercial preparation drugs. The largest pH value difference (0.88) was observed for fentanyl citrate, in which a pH increase of 0.88 (4.23 ± 0.62) was observed. The combination of drugs in D5W resulted in more acidic values than those of fentanyl citrate and of D5W and fentanyl citrate in D5W, but they were closer to what was observed for the solution of dobutamine hydrochloride in D5W. This solution was more acidic than fentanyl citrate diluted in

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DOI: 10.1097/NAN.0000000000000064

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The research reported here was supported by grants 476295/2004-1 from Brazil's National Council for Scientific and Technological Development (CNPq, Brazil).

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D5W. The lower acidity of fentanyl citrate had a minor influence on the final pH of the combined drug solution in D5W. Under most conditions, the drug solutions kept at 22°C had pH values that were more acidic and less variable. Temperature was a major factor controlling the chemical behavior of the solutions analyzed. Analysis of chemical behavior in response to light exposure indicated that the solutions were more stable over time when kept in the dark.
**Key words:** medication error, pediatric critical care units, patient safety

The continuous infusion of medications in children is a common practice in pediatric intensive care units (PICUs), and many times, the drugs are administered in combination. Dobutamine hydrochloride and fentanyl citrate are drugs that are commonly administered, sometimes in combination.[1-4]

Factors such as temperature, light exposure, drug concentration, ionic strength, time of infusion, and duration of drug association can influence the effectiveness of pharmacological solutions, which can compromise the solutions' quality, resulting in unstable solutions and drug incompatibility.[5,6]

The absorption of light energy can, through the activation of photodegradation reactions, cause the decomposition of molecules or their chemical rearrangement. The stronger the light source and/or the closer the light source is to the photosensitive drug, the greater the rate and degree of degradation.[5,7-9]

Temperature is another element capable of influencing drug degradation. When elevated, it can increase the reaction rates of a given substance by increasing the kinetic energy of the molecules.[7-10] Because many drugs are unstable and readily decompose under alkaline or acidic solutions, the pH of each component of a given solution must be examined to avoid therapeutic damage and other complications.[7,11]

In a PICU clinical nursing practice, solutions containing dobutamine hydrochloride, fentanyl citrate, and a combination of these drugs are often administered intravenously. The components are changed every 24 hours, independent of the infusion rate, drug concentration, and light exposure or temperature, according to the manufacturers' recommendations. In a PICU without controlled thermal conditions, drug solutions infused continuously remain exposed to intense light and temperatures above 27°C. This is common in tropical countries.

The aim of this study was to determine the pH of solutions of dobutamine hydrochloride, fentanyl citrate, and their combination in 5% dextrose in water (D5W) under various light exposures and temperatures over time.

## MATERIALS AND METHODS

Experiments were conducted in the research laboratory of a university in São Paulo, Brazil. pH values of the solutions were measured using a waterproof digital pH meter (ExStik PH100, Extech) consisting of a millivoltimeter coupled with an electrode selective for hydrogen ions with a scale that converts the voltage from the electrode to pH units with an accuracy of 0.01.[12] The pH meter was calibrated immediately before the experiment.

Experiments were performed at both 22°C, the temperature generally recommended for hospitals with temperature control capabilities, and 37°C, the temperature possibly reached in hospitals without temperature control in tropical countries. Temperature maintenance at 22°C was achieved through the use of a portable air conditioner unit (Freecom RCS-M2600HTR, Freecom Company). Temperature maintenance at 37°C was achieved through the use of an incubator (FANEM C-186 TS, FANEM). The temperature was monitored by a digital thermometer (TFA Dostmann).

The room where the experiments were performed was illuminated by 2 fluorescent lamps inside 2 ceiling lights with capacities of at least 12 $\mu W/cm^2$ nm. The illumination in the environment from the fluorescent lights was measured with a light meter. All solutions were exposed to fluorescent lighting of at least 12 $\mu W/cm^2$ nm, which frequently is used in PICUs. Ambient light is defined here as exposure to fluorescent light in addition to sunlight from 6 windows, with greater exposure likely to occur in the afternoon, a common occurrence in PICUs in tropical countries.

Drug solutions were placed in graduated acrylonitrile burettes. The apparatus for these devices is made of polyvinyl chloride, with the exception of its middle segment, which is made of silicone to allow the installation of an infusion pump. Clear and amber burettes were used, the latter being used for their photoprotective capabilities and indicated for the administration of photosensitive solutions. Experiments were performed with 4 mg/mL dobutamine hydrochloride and 5 μg/mL fentanyl citrate. Solution volumes were calculated based on a total experimental time of 24 hours and an infusion rate of 0.5 mL/h, conditions that were established by linear volumetric peristaltic infusion pumps to allow for sufficient volume to fill the intravenous system. Ten administration conditions for dobutamine hydrochloride, fentanyl citrate, and combinations of both drugs at 7 time points were analyzed (Figure 1).

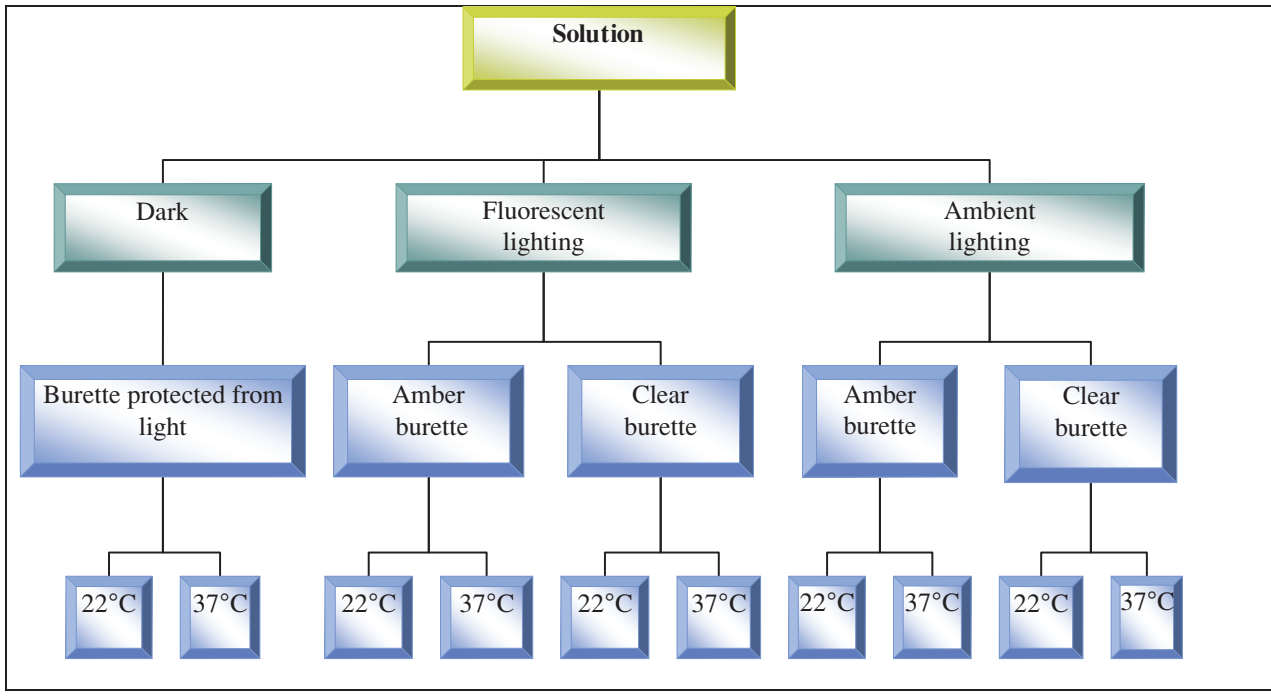


**Figure 1** Schematic representation of the experimental design used in the analysis of pH with various exposure times, luminosities, and temperature conditions.

The pH of commercial drugs was measured immediately after opening the vials. Because 2 vials of each drug were used for each experiment, 2 pH values were obtained for each drug. The control solution for the role of light on the pH was contained in a clear device protected by a black plastic case to prevent light entry; this solution was maintained at 22°C.

The order of the experimental conditions was randomly determined by drawing. For each of the previously described conditions, the pH of the solution was evaluated at 7 time points from the beginning of solution administration: T0 (0), T1 (0.5 hours), T2 (1 hour), T3 (2 hours), T4 (3 hours), T5 (4 hours), and T6 (24 hours). Data were collected after obtaining study approval from the Ethics in Research Committee from the institution (record CEP 0688/08).

To analyze the influence of sunlight on the chemical behavior of the drugs, we chose to start the experiments at approximately 11:00 AM. Solution samples of 1 to 2 mL required for pH measurements were collected in beakers from the end of the apparatus (as that would be the connection point to the patient's intravenous catheter), using sterile techniques at the same temperature as the solution. In addition to pH analysis, the physical conditions of the solutions were inspected during the experiment and at the time of sample collection. Descriptive figures and tables were used to represent the data obtained from analysis of the pH alterations. We used the arithmetic mean and standard deviation (SD) to analyze and represent the data. The results underwent variance analysis using GB-Stat software (The Higher Education Academy, UK), with a significance level (*P* value) less than .05.

## RESULTS

The study analyzed 260 pH values; 20 (7.7%) of dobutamine hydrochloride, 20 (7.7%) of fentanyl citrate, and 10 (3.9%) of D5W were of the commercial preparation of the drugs. The remaining 210 pH measurements were of drugs exposed to the environmental conditions analyzed in the study. These consisted of 70 (26.9%) of dobutamine hydrochloride in D5W, 70 (26.9%) of fentanyl citrate in D5W, and 70 (26.9%) of the combination of dobutamine hydrochloride and fentanyl citrate in D5W.

The mean pH values of the commercial drug preparations were 3.21 ± 0.27 for dobutamine hydrochloride, 4.23 ± 0.62 for fentanyl citrate, and 4.60 ± 0.21 for D5W. These values were within the normal ranges described for the substances.

After dilution in D5W, the solutions showed chemical behavior similar to the drugs in their commercial form. The mean pH values found were as follows: 3.76 ± 0.57 for dobutamine hydrochloride in D5W and 4.54 ± 0.13 for fentanyl citrate in D5W. The combination of the drugs in D5W resulted in a mean pH of 3.86 ± 0.25, similar to the values obtained for dobutamine hydrochloride in D5W.

The mean pH values of solutions submitted to control conditions were observed to be similar to those seen for drugs immediately after dilution in D5W, with the exception of fentanyl citrate in D5W, for which the value was the same, indicating a greater equilibrium of this substance (Figure 2).

  

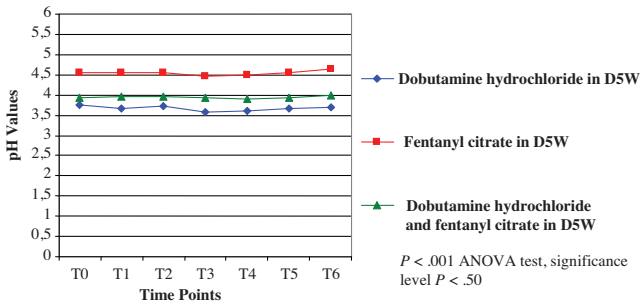


**Figure 2** pH values of solutions at 22°C in the absence of light at different time points. *Abbreviation: ANOVA, analysis of variance between groups.*

Figure 3 shows that the mean pH values of solutions kept in the dark at 37°C were higher than those seen in both the commercial form and under control conditions for all of the drugs analyzed. The mean values under these conditions were as follows: 4.19 ± 0.16 for dobutamine hydrochloride in D5W, 4.80 ± 0.14 for fentanyl citrate in D5W, and 4.31 ± 0.14 for the drug combination in D5W. The SDs for the pH values in all 3 experiments were less than 0.2.

The lowest pH value (2.88) for the dobutamine hydrochloride solution in D5W was found for solutions kept in a clear apparatus for 2 hours at 22°C under fluorescent light, indicating that this compound is more acidic when suspended in D5W and closer to commercial form at 22°C. However, the highest variations for solutions of dobutamine hydrochloride in D5W (3.26 ± 0.21) were observed under the same experimental conditions. The lowest variability was seen when solutions were kept in amber devices at 22°C under either ambient (SD ± 0.02) or fluorescent (SD ± 0.02) light, with mean pH values of 3.60 and 3.64, respectively (Table 1).

Regarding the fentanyl citrate in D5W, the lowest pH value (4.31) was recorded when the solution was kept in a clear apparatus at 22°C and exposed to fluorescent light for 3 hours (Table 1). The maximum pH value was seen when the solution was kept in an amber apparatus at 37°C and exposed to fluorescent light for 24 hours. These conditions were also the conditions in which the greatest pH variation was observed (SD ± 0.26).

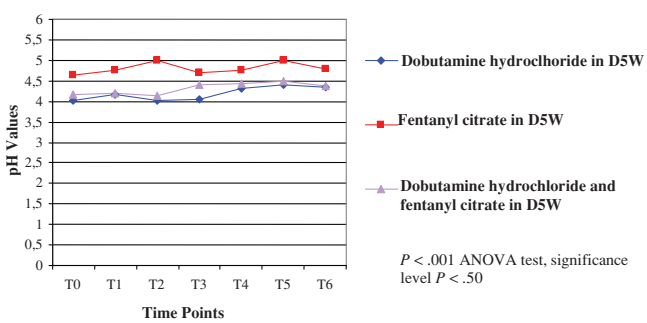


**Figure 3** pH values of solutions at 37°C in the dark at different time points. *Abbreviation: ANOVA, analysis of variance between groups.*

Analysis of the mean pH values from the combination of dobutamine hydrochloride and fentanyl citrate in D5W showed that the solution was more acidic at 22°C. The lowest pH values (3.32) were observed when the solution was in a clear apparatus and kept at 22°C under fluorescent light for 1 hour. The highest pH value (4.19) was observed when the solution was in an amber apparatus and kept under fluorescent light for 24 hours. The highest pH variation (SD ± 0.14) was observed when the solution was in a clear apparatus and kept at 22°C. These were the same conditions under which the most acidic mean pH (3.56) was observed. The lowest pH variation (3.82 ± 0.04) was observed when the solution was in an amber apparatus under fluorescent light at 22°C. These results showed a uniform pattern of variation in the solution of dobutamine hydrochloride and fentanyl citrate in D5W even after 4 hours of exposure, the maximum time recommended in the literature for mixtures of these drugs (Table 1).

## DISCUSSION

In this study, drug solutions were exposed to environmental conditions mimicking those of PICUs in the tropics. The solutions were prepared and packaged in systems frequently used for intravenous drug administration, in which extrinsic and characteristic PICU environmental factors (such as temperature and light exposure) could cause drug degradation and interfere with their chemical behavior.

The study indicated that the maximum variation allowed in the hydrogen potential of solutions is 0.20, values above which are considered a significant indication of incompatibility.[13] According to the literature, the pH of dobutamine hydrochloride can vary between 2.5 and 5.5, while that of fentanyl citrate can vary between 4.0 and 7.[14] This study found that when the vials were opened, the pH levels of both drugs were within normal pH ranges. However, questions emerged concerning the pH variations observed for dobutamine hydrochloride (SD ± 0.27) and fentanyl citrate (SD ± 0.62) because it is expected that a drug from the same manufacturer and same lot submitted to the same storage conditions would have similar chemical behavior and only small variations in pH. It is noteworthy that data were collected in a research laboratory across a 4-month period. The study observed a pH value difference of 0.39 among the vials of dobutamine hydrochloride and as much as 0.88 among the vials of fentanyl citrate.

The most acidic pH values were seen in the pharmaceutical preparation of dobutamine hydrochloride (3.21 ± 0.27). Fentanyl citrate was less acidic, with a mean pH of 4.23 ± 0.62. After dilution in D5W, the solutions presented chemical behaviors similar to the drugs in commercial preparations. The mean pH value observed for the combination of these drugs in D5W solution was

**TABLE 1**

# pH Values of Solutions According to Temperature and Luminosity

| Drug | pH | | | |
|---|---|---|---|---|
| | Minimum | Maximum | Mean | SD |
| Commercial preparation | | | | |
| Dobutamine hydrochloride | 3.02 | 3.41 | 3.21 | 0.27 |
| Fentanyl citrate | 3.79 | 4.67 | 4.23 | 0.62 |
| D5W | 4.45 | 4.75 | 4.60 | 0.21 |
| Dobutamine hydrochloride in D5W | 3.36 | 4.17 | 3.76 | 0.57 |
| Fentanyl citrate in D5W | 4.45 | 4.64 | 4.54 | 0.13 |
| Dobutamine hydrochloride and fentanyl citrate in D5W | 3.68 | 4.04 | 3.86 | 0.25 |
| Control | | | | |
| Dobutamine hydrochloride in D5W | 3.59 | 3.76 | 3.67 | 0.05 |
| Fentanyl citrate in D5W | 4.47 | 4.63 | 4.54 | 0.04 |
| Dobutamine hydrochloride and fentanyl citrate in D5W | 3.90 | 3.98 | 3.94 | 0.02 |
| Absence of light at 37°C | | | | |
| Dobutamine hydrochloride in D5W | 4.02 | 4.40 | 4.19 | 0.16 |
| Fentanyl citrate in D5W | 4.64 | 5.00 | 4.80 | 0.14 |
| Dobutamine hydrochloride and fentanyl citrate in D5W | 4.13 | 4.50 | 4.31 | 0.14 |
| Fluorescent light with clear apparatus at 22°C | | | | |
| Dobutamine hydrochloride in D5W | 2.88 | 3.50 | 3.26 | 0.21 |
| Fentanyl citrate in D5W | 4.31 | 4.58 | 4.47 | 0.09 |
| Dobutamine hydrochloride and fentanyl citrate in D5W | 3.32 | 3.75 | 3.56 | 0.14 |
| Fluorescent light with amber apparatus at 22°C | | | | |
| Dobutamine hydrochloride in D5W | 3.62 | 3.67 | 3.64 | 0.02 |
| Fentanyl citrate in D5W | 4.46 | 4.52 | 4.49 | 0.02 |
| Dobutamine hydrochloride and fentanyl citrate in D5W | 3.76 | 3.87 | 3.82 | 0.04 |
| Ambient light with clear apparatus at 22°C | | | | |
| Dobutamine hydrochloride in D5W | 3.41 | 4.06 | 3.79 | 0.20 |
| Fentanyl citrate in D5W | 4.42 | 4.55 | 4.46 | 0.04 |
| Dobutamine hydrochloride and fentanyl citrate in D5W | 3.72 | 3.87 | 3.79 | 0.05 |
| Ambient light with amber apparatus at 22°C | | | | |
| Dobutamine hydrochloride in D5W | 3.58 | 3.64 | 3.60 | 0.02 |
| Fentanyl citrate in D5W | 4.42 | 4.50 | 4.47 | 0.02 |
| Dobutamine hydrochloride and fentanyl citrate in D5W | 3.86 | 4.04 | 3.92 | 0.06 |
| Fluorescent light with clear apparatus at 37°C | | | | |
| Dobutamine hydrochloride in D5W | 3.66 | 3.80 | 3.72 | 0.05 |
| Fentanyl citrate in D5W | 4.50 | 4.67 | 4.58 | 0.06 |
| Dobutamine hydrochloride and fentanyl citrate in D5W | 3.83 | 3.97 | 3.89 | 0.05 |
| Fluorescent light with amber apparatus at 37°C | | | | |
| Dobutamine hydrochloride in D5W | 3.90 | 4.17 | 4.02 | 0.10 |
| Fentanyl citrate in D5W | 4.40 | 5.23 | 4.70 | 0.26 |
| Dobutamine hydrochloride and fentanyl citrate in D5W | 4.00 | 4.19 | 4.08 | 0.06 |
| Ambient light with clear apparatus at 37°C | | | | |
| Dobutamine hydrochloride in D5W | 3.30 | 3.57 | 3.46 | 0.08 |

(*continues*)

  

**TABLE 1**

## pH Values of Solutions According to Temperature and Luminosity (*Continued*)

| Drug | pH | | | |
|---|---|---|---|---|
| | Minimum | Maximum | Mean | SD |
| Fentanyl citrate in D5W | 4.45 | 4.74 | 4.55 | 0.09 |
| Dobutamine hydrochloride and fentanyl citrate in D5W | 3.56 | 3.91 | 3.74 | 0.10 |
| Ambient light with amber apparatus at 37°C | | | | |
| Dobutamine hydrochloride in D5W | 3.61 | 3.72 | 3.68 | 0.04 |
| Fentanyl citrate in D5W | 4.48 | 4.80 | 4.60 | 0.11 |
| Dobutamine hydrochloride and fentanyl citrate in D5W | 3.97 | 4.14 | 4.06 | 0.05 |

*Abbreviations: SD, standard deviation; D5W, 5% dextrose in water.*

3.86 ± 0.25, which is closer to the value of dobutamine hydrochloride in D5W.

The study concluded that the pH values of dobutamine hydrochloride in D5W are more acidic and closer to the commercial drug preparation at 22°C. The change in color of dobutamine hydrochloride in D5W solution kept in a clear apparatus under ambient light at 37°C for 24 hours could be an indicator of chemical degradation or loss of therapeutic efficacy.

The pH values of solutions kept at 22°C and 37°C were similar, independent of the type of lighting used. The solutions kept at 22°C generally had more acidic pH values and smaller variations.

With regard to light exposure, the solutions kept in the dark were more stable over the experimental period. It was noted that solutions under control conditions had mean pH values similar to those obtained immediately after dilution in D5W. Fentanyl citrate in D5W was an exception; the pH values obtained were the same throughout the experiment, indicating greater stability of the chemical compared with dobutamine hydrochloride.

These results indicate a uniform pattern of variation in solutions of dobutamine hydrochloride and fentanyl citrate in D5W, even after 4 hours of exposure, the maximum time recommended in the literature for mixtures of these drugs. This study underscores the need for studies of the pharmacological quality of these solutions, both qualitatively and quantitatively, to promote practices that meet the needs of pediatric patients in intensive care.

## CONCLUSION

Temperature was a major factor controlling the chemical behavior of the solutions analyzed. Analysis of chemical behavior in response to light exposure indicated that the solutions were more stable over time when kept in the dark.

Amber-colored systems of intravenous administration seem to contribute to maintenance of the pH levels of drug solutions, while ambient temperature does not seem to alter the chemical behavior, measured here by pH changes, of dobutamine hydrochloride and fentanyl citrate solutions.

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