The Stability of a Ketamine-Morphine Solution

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Recent advances in acute pain mechanisms and management have implicated the *N*-methyl d-aspartate receptor-ion channel complex in the development of postoperative hyperalgesia and acute opiod tolerance. *N*-methyl d-aspartate receptor antagonists such as ketamine have been used increasingly in clinical studies in an effort to minimize acute postoperative pain and reduce opiod requirements. A mixture of ketamine and an opiod administered in the same solution and syringe would be a practical and useful technique for postoperative epidural analgesia, continuous IV infusion, or patient-controlled IV analgesia. We investigated the stability of a morphine sulfate and racemic ketamine solution in saline at pH 5.5–7.5 over a period of 4 days. Our study demonstrates that the ketamine morphine mixture at a clinically relevant concentration seems to be stable at room temperature, at a wide range of pH values, for at least 4 days.

Advances in the understanding of acute pain mechanisms have led to a renaissance of the use of ketamine hydrochloride because of its actions as an *N*-methyl d-aspartate receptor antagonist (1). Clinical studies have reported improved pain relief using ketamine as an adjunct to various analgesics in the treatment of acute postoperative pain (2–5) and cancer pain (6).

Of particular interest is the combination of smalldose ketamine with opioids, the most commonly used drugs for postoperative pain relief. In the clinical setting, subanesthetic doses of ketamine administered with opioids reduced opioid requirements and opioidrelated adverse effects (2,7,8) perhaps because of the ability of small-dose *N*-methyl d-aspartate antagonists to interfere with the development of acute opioid tolerance (9) and opioid-induced hyperalgesia (10,11).

A mixture of ketamine and an opioid administered in the same solution and syringe would be a practical and useful technique for postoperative epidural analgesia, continuous IV infusion, or patient-controlled IV analgesia. However, to administer such a mixture of drugs safely to the patient over a period of several days, one must ensure that the mixture demonstrates physical and chemical stability. Because morphine is the most frequently used opioid for the treatment of acute and chronic pain, we investigated the stability of a morphine sulfate and racemic ketamine solution in saline at pH 5.5–7.5 over a period of 4 days.

Materials and Methods

To prepare the stock solutions, the following materials were used: 1 20-mL vial of ketamine hydrochloride (Ketalar®; Parke-Davis, Scarborough, ON, Canada) containing 10 mg/mL ketamine; 2 1-mL vials of morphine sulfate 15 mg/mL (Abbott Laboratories, Ltd., Saint-Laurent, QC, Canada); 2 1-mL vials of morphine sulfate 10 mg/mL (Abbott Laboratories); 1 1-mL vial of morphine sulfate 2 mg/mL (Abbott Laboratories); NaCl, NaOH 10 N, HCl 6 N (Fisher Scientific Ltd., Nepean, ON, Canada).

A stock solution of 0.9% NaCl was prepared in water; 50 mL was aliquoted, and the pH of each aliquot was adjusted to 5.5, 6.0, 6.5, 7.0, and 7.5. The ketamine and morphine were mixed together in the saline at pH 5.5–7.5 at a final concentration of 1.33 mg/mL for ketamine and 2.0 mg/mL for morphine. The total volume of the solution was 25 mL. As soon as the mixtures were ready, 6 1.0-mL aliquots were taken and kept at _20°C in Falcon polystyrene tubes until analysis. The remaining solution was kept at room temperature, also in Falcon polystyrene ubes, for the subsequent 4 days. Each day, the same exercise was repeated: 1.0 mL was aliquoted in 6 small vials. They were placed immediately at _20°C and kept there until analysis. For ketamine analysis, a high-pressure liquid chromatography (HPLC) method (12) was used with some modifications. Briefly, the mobile phase was 0.1 M sodium dihydrogen phosphate buffer pH 2.1 (adjusted with phosphoric acid) containing 1 mM dodecyl sulfate and 22% acetonitrile. The flow rate was 0.8 mL/min and the

Table 1. Mean Ketamine and Morphine Concentrations and CV Across Days 1–4 at pH 5.5–7.5

	pH				
	5.5	6.0	6.5	7.0	7.5
Ketamine					
Mean concentration (mg/mL)	1.521	1.446	1.391	1.345	1.525
CV Days 1–4	2.348	3.874	1.048	3.385	1.614
Overall mean	1.49				
CV pH 5.5–7.5	9.40				
Morphine					
Mean concentration (mg/mL)	2.485	2.336	2.264	2.188	2.317
CV Days 1–4	2.181	4.454	1.226	3.091	1.666
Overall mean	2.362				
CV pH 5.5–7.5	7.905				

CV _ coefficient of variation.

column was Prodigy™ ODS (3) 5 _m, 150 _ 4.6 mm (Phenomenex, Torrance, CA). We used a Shimadzu HPLC system equipped with a spectrophotometric detector set at 215 nm (Mandel Scientific, Guelph, ON, Canada). For quantitation, a standard solution in saline was prepared from the same Ketalar vial that was used for sample preparation. For morphine analysis, the same HPLC method was used. For quantitation, an aliquot from a new vial of morphine sulfate 2 mg/mL was used. In addition, morphine was also measured in each sample by using an enzyme-linked immunosorbent assay method. The StatView® SE program (SAS Institute Inc., Cary, NC) was used for statistical analysis. The mean concentration of ketamine and morphine was calculated each day. Within-the-day and between-the-days coefficient of variation was calculated for each compound.

Results and Discussion

Our study demonstrates that the ketamine-morphine mixture at a clinically relevant concentration seems to be stable at room temperature, at least for four days at a wide range of pH (Table 1). Initially, we examined the stability of the solution at pH 5.5 only; however, although the ketamine seemed to be very stable, the morphine results were more erratic. There was no clear pattern of concentration decrease in time, but the coefficient of variation was rather high. The same pattern was observed using both methods of analysis: HPLC and enzyme-linked immunosorbent assay. In the present stability study, we therefore modified the original HPLC method (12) by adding an ion pairing agent to the mobile phase; the ketamine results were unchanged, but the coefficient of variation for morphine decreased considerably, from 11.04 to 2.18 at this particular pH (Table 1). There is some indication in the literature (13) that, at pH higher than 5.9, the mixture is no longer stable. However, in that study, much larger concentrations (i.e., ketamine 41.2 mg/mL and morphine 17.6 mg/mL) were used and the pH was adjusted with sodium bicarbonate. We conclude that a ketamine-morphine solution can be used at physiologic pH, at the abovementioned concentrations and that it is stable for up to four days at room temperature.

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