

## BACKGROUND

Admixtures containing local anesthetics and epinephrine are increasingly used in epidural pain management. Published reports on the stability of ropivacaine-epinephrine containing admixtures (with or without opioids) are lacking.

Previous studies have demonstrated the stability of ropivacaine for an extended period of time. However, the stability of epinephrine is reported to be widely variable. Analysis of epinephrine stability studies indicates that protection from light is an important variable. When protected from light, degradation is dramatically reduced and stability of epinephrine has been reported for 30 days at 4°C or 23°C (Carr, Decarie & Ensom), 60 days at 4°C (Helin-Tanninen) or 182 days at 4°C or 23°C (Priston). The latter two studies evaluated the stability of epinephrine with bupivacaine or levobupivacaine.

Therefore, an evaluation of the stability of epinephrine with ropivacaine is warranted. The need for protection from light also requires further study.

## OBJECTIVES

The objective of this study was to evaluate the stability of epinephrine 0.005mg/mL in combination with ropivacaine 0.125%, 0.3% or 0.5% in cassette reservoirs at 23°C or 4°C, with or without protection from light. During the 60-day study period, the drug concentration was determined on 10 study days (days 0, 1, 2, 4, 7, 10, 15, 23, 36, 50 and 60).

## METHODS

### LIQUID CHROMATOGRAPHIC METHOD

A liquid chromatographic stability-indicating method with UV detection developed and validated. Concentrations of ropivacaine and epinephrine were measured accurately (with 3% of known) and reproducibly (CV averaged 2%).

### STABILITY STUDY

On study-day zero, 24 solutions of epinephrine and ropivacaine were prepared in 250 mL medication cassette reservoirs (Smiths Medical, CADD®) and stored at 4°C and 23°C protected from fluorescent room light using amber plastic bags. An additional 8 solutions of 0.005 mg/mL epinephrine with 0.3% ropivacaine, also prepared in 250 mL cassette reservoirs (CADD®), were exposed to normal fluorescent light. Samples were assayed on 10 study days over a 60-day period using a validated, stability-indicating, liquid chromatographic method with ultraviolet detection.

### DATA REDUCTION AND STATISTICAL ANALYSIS

Analysis of variance was used to test differences in observed concentration between the storage temperatures and container combinations. A 95% Confidence Interval was constructed around the degradation rate and the Time to Achieve 90% of the initial concentration (T-90) was calculated. Stability was defined as the time taken for the concentration to decline to 90% of the initial concentration, based on the fastest degradation rate determined from the 95% confidence interval.

## RESULTS

### EPINEPHRINE AND ROPIVACAINE STABILITY

The initial concentration and the percent remaining observed for ropivacaine and epinephrine are listed in Tables 1 and 2, respectively. On all study days the concentrations remained above 95.1%. In both Tables 1 and 2, the 95% confidence interval for the degradation rate for both epinephrine and ropivacaine includes an estimated degradation rate of zero (%/day) and concentrations greater than 90% would be maintained for more than 60 days with 95% confidence.

Mean differences in concentration due to the effect of light, temperature or concentration do not exceed 1% and are not considered practically important.

Table 1. Percent Remaining<sup>1</sup> of Ropivacaine During Storage.

Observed Initial concentration (mg/mL)	2.91±0.04	2.96±0.01	2.93±0.00	2.98±0.01	1.23±0.01	1.23±0.01	4.80±0.08	4.88±0.00
	Protected From Light 4°C	Protected From Light 23°C	No Light Protection 4°C	No Light Protection 23°C	Protected From Light 4°C	Protected From Light 23°C	Protected From Light 4°C	Protected From Light 23°C
2	101.14±0.59	101.03±0.08	102.02±0.49	100.13±0.77	100.63±1.06	101.00±0.52	102.21±1.04	101.01±0.37
4	101.73±0.87	100.97±0.65	102.09±0.53	99.86±0.73	100.30±1.03	100.29±1.55	102.25±1.11	100.88±0.49
7	101.95±1.13	101.16±0.85	101.01±1.26	100.01±1.07	100.52±0.95	102.24±2.06	102.64±0.55	100.96±0.46
15	102.11±0.79	101.00±0.45	101.13±1.39	100.09±0.95	100.67±0.53	102.20±0.88	102.66±0.39	100.79±0.45
23	102.59±1.62	101.26±0.40	101.75±1.12	100.09±0.23	99.79±0.67	102.01±0.66	103.01±0.44	100.79±0.47
36	103.20±1.98	101.24±0.08	101.92±1.32	100.81±0.45	100.13±0.36	101.70±0.82	103.22±0.48	100.97±0.14
50	103.01±1.66	101.28±0.26	101.97±0.87	100.30±0.66	100.14±0.30	101.64±0.72	103.35±0.81	100.92±0.19
60	97.83±1.77	98.44±2.15	100.56±3.70	100.94±0.61	101.59±0.60	102.28±1.57	103.30±0.92	101.38±0.40
Slope <sup>2</sup> [Degradation Rate] (%/day)	-0.0121	-0.0171	0.0013	0.0141	0.0091	0.0219	0.0324	0.0096
Sy.x <sup>3</sup>	1.783	0.916	0.799	0.225	0.525	0.761	0.799	0.318
Confidence Interval for slope <sup>4</sup>	0.0674	0.0347	0.0302	0.0085	0.0198	0.0288	0.0302	0.0120
Lower Limit of 95% Confidence of Slope (%/day) <sup>4</sup>	-0.0795	-0.0517	-0.0289	0.0056	-0.0107	-0.0069	0.0022	-0.0024
Shortest T-90 [95% CI] – (days) <sup>4</sup>	125.8	193.3	317.5	442.9	344.9	197.3	159.7	462.4

- Each value is based on duplicate determination of three samples. Percent Remaining is based on 100% found on Day 0.
- Slope represents the change in concentration as determined by linear regression of percent remaining on each study day. Change in concentration is largely due to water loss.
- Sy.x is the standard deviation of regression. This is equivalent to the inter-day variability of the analytical method.
- Time to achieve 90% of initial concentration (T-90) based on the degradation rate and is generally regarded as the Beyond Use Date.

Table 2. Percent Remaining<sup>1</sup> of Epinephrine During Storage.

Observed Initial Concentration (µg/mL)	4.55±1.69	4.72±1.30	4.72±0.49	4.70±0.57	4.52±0.76	4.55±0.76	4.54±0.94	4.37±0.00
Study Day	Protected From Light 4°C	Protected From Light 23°C	No Light Protection 4°C	No Light Protection 23°C	Protected From Light 4°C	Protected From Light 23°C	Protected From Light 4°C	Protected From Light 23°C
2	99.06±2.57	98.54±1.47	95.72±0.37	96.00±0.46	98.62±0.67	98.44±1.86	100.33±0.48	100.50±1.53
4	99.46±3.59	96.03±1.58	96.26±0.48	97.24±1.13	95.94±0.38	100.33±0.72	100.14±0.95	98.38±0.70
7	100.68±0.98	95.84±0.80	97.71±0.62	98.62±1.66	96.30±0.97	101.36±0.39	100.57±0.80	99.81±0.21
10	98.64±3.72	96.62±1.48	97.47±1.08	97.85±1.23	97.06±2.76	97.32±0.65	97.72±0.67	98.58±0.64
15	99.22±3.75	98.49±2.52	98.34±1.10	98.91±0.88	97.03±1.08	97.75±1.43	99.47±1.79	98.56±1.02
23	100.14±0.68	96.73±1.73	97.27±0.68	95.74±4.41	97.58±4.16	101.32±1.09	100.83±0.60	100.18±0.09
36	98.87±2.21	98.74±1.31	96.74±0.54	97.93±0.95	99.48±0.42	100.78±0.66	101.36±3.16	95.90±0.89
50	97.30±1.84	97.09±1.37	95.99±1.59	97.11±0.30	98.06±1.58	99.21±0.69	99.81±3.16	95.10±0.84
60	101.12±2.44	100.42±1.97	96.66±0.91	96.51±0.51	97.63±0.75	98.10±1.01	98.67±1.01	97.44±1.17
Slope <sup>2</sup> [Degradation Rate] (%/day)	-0.0040	0.0248	-0.0234	-0.0233	0.0073	-0.0090	-0.0059	-0.0652
Sy.x <sup>3</sup>	1.164	1.625	1.241	1.326	1.373	1.580	1.120	1.279
Confidence Interval for slope <sup>4</sup>	0.0423	0.0590	0.0450	0.0481	0.0498	0.0574	0.0406	0.0464
Lower Limit of 95% Confidence of Slope (%/day) <sup>4</sup>	0.0383	0.0838	0.0217	0.0248	0.0571	0.0484	0.0348	-0.0187
Shortest T-90 [95% CI] – (days) <sup>4</sup>	216.4	119.4	146.1	139.9	175.1	150.6	214.9	89.6

- Each value is based on duplicate determination of three samples. Percent Remaining is based on 100% found on Day 0.
- Slope represents the change in concentration as determined by linear regression of percent remaining on each study day. Change in concentration is largely due to water loss.
- Sy.x is the standard deviation of regression. This is equivalent to the inter-day variability of the analytical method.
- Time to achieve 90% of initial concentration (T-90) based on the degradation rate and is generally regarded as the Beyond Use Date.

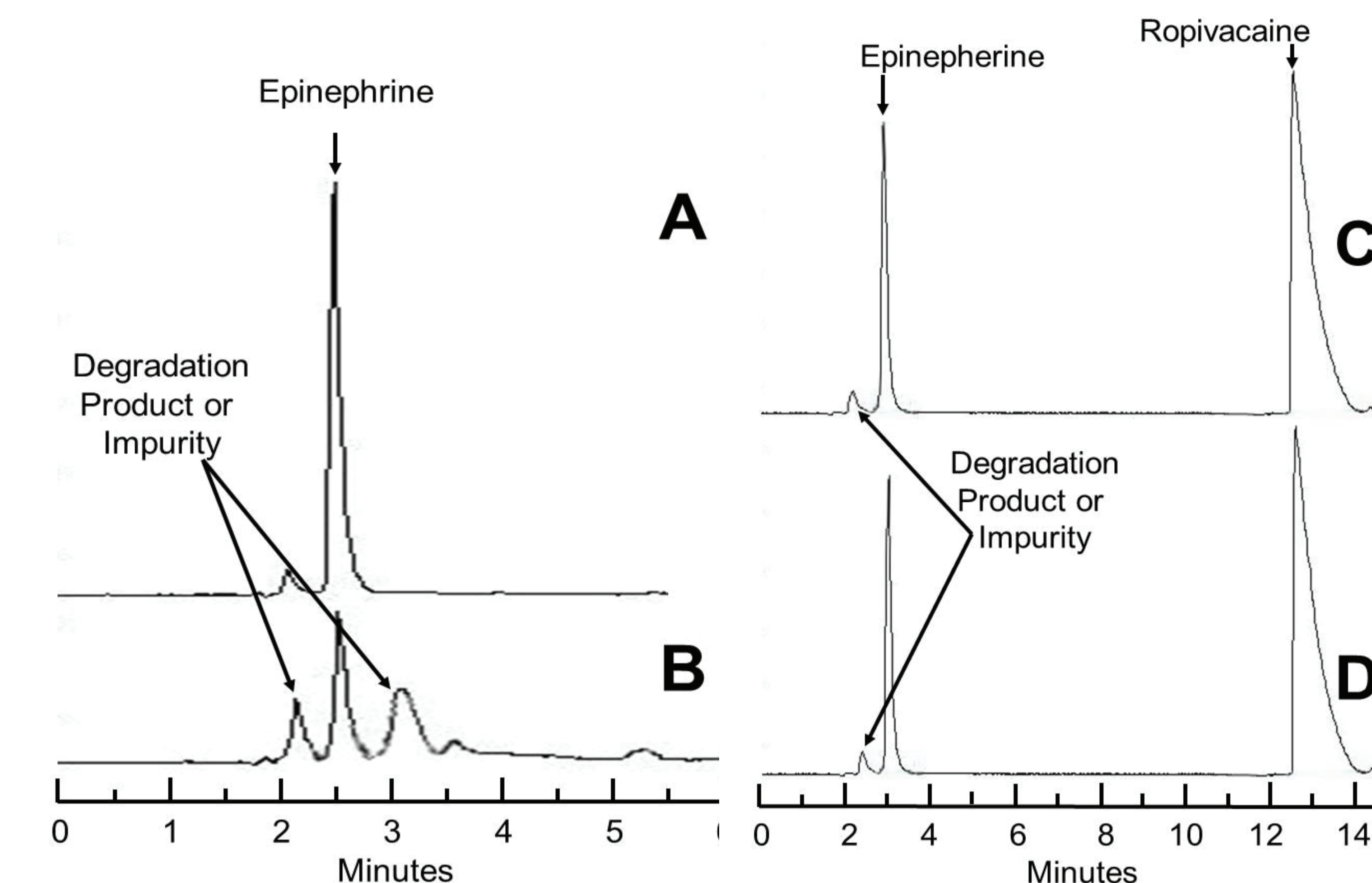


Figure 1. Chromatogram A represents an 10 µg/mL epinephrine solution at time zero prior to incubation in a water bath at 80°C. Chromatogram B shows the same sample after 125 minutes at 80°C, when about 28% of the initial epinephrine concentration remained. Chromatogram C represents a 5 µg/mL solution of epinephrine and 0.3% ropivacaine on day zero. Chromatogram D shows the same sample after storage at RT for 60 days, exposed to light. Concentration is unchanged and degradation products are not observed.

## DISCUSSION & CONCLUSION

The results from this study indicate that the degradation rate of epinephrine in ropivacaine/epinephrine admixtures in CADD® cassette reservoirs was not affected when exposed to fluorescent light.

We conclude that solutions of epinephrine 0.005mg/mL in combination with ropivacaine 0.125%, 0.3% or 0.5% stored in CADD® cassette reservoirs at 23°C or 4°C maintain concentrations greater than 95% for 60 days without protection from fluorescent light. The shortest time to achieve 90% of the initial concentration (T-90) calculated from a 95% confidence interval constructed around the degradation rate, exceeds the study duration of 60 days. These results suggest that the extended stability of these admixtures may allow batch preparation.

When establishing a beyond use date for intravenous admixtures of ropivacaine and epinephrine epidural solutions, consideration should be given to sterility of the admixtures utilizing USP 797 guidelines for compounded sterile products (CSP) based on risk level and storage conditions.

