# The Stability of Atropine Sulfate Solutions Stored in Plastic Syringes in the Operating Room

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nesthetic induction drugs, neuromuscular blockers, and resuscitative drugs are often prepared and stored in syringes in emergency surgical locations. Operating rooms (ORs) that commonly maintain this level of preparedness include sites for cardiac, trauma, and obstetric surgery. The practice of storing drugs in syringes raises questions of drug efficacy and safety. Specific concerns include the possible propagation of microorganisms in drug solutions and the loss of drug potency through chemical decay or chemical interaction with components of the syringe (1-3). Because of these concerns, the Center for Disease Control and the Anesthesia Patient Safety Foundation suggest limiting the storage of drugs in syringes to 24 h, unless otherwise specified by the drug manufacturer (4,5). This standard exists despite compelling evidence that some drugs, especially thiopental, are both exceedingly chemically stable and bacteriocidal (6,7).

Atropine sulfate is frequently prepared in syringes in OR locations where emergency surgery is likely. In independent investigations, Schubert et al. (8) and Lehmann (9) have shown minimal propensity for atropine sulfate in multi-dose vials to support bacterial growth, and, more recently, we demonstrated a low risk of bacterial contamination with atropine stored in polypropylene syringes stored in an obstetric OR (10). However, there is conflicting evidence regarding the chemical stability of atropine sulfate when stored in plastic syringes. Lewis et al. (11) detected a 44% decrease in atropine sulfate concentration in plastic syringes stored for 24 h. A further decrease in concentration occurred over the next 4 days with a maximal decrease of approximately 50% on the third day. No evidence of atropine degradation products was detected by their analysis, and the authors concluded that atropine sulfate is bound by plastic components within the syringe (11). In support of this conclusion,

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a previous report of interaction and binding of nitroglycerin by plastic containers was described (1). However, two studies have demonstrated that atropine sulfate concentrations are not decreased after storage in plastic syringes when atropine is stored as an admixture with other compounds (12,13). Rhodes et al. (12) were unable to detect a decrease in atropine concentration in plastic syringes when stored more than 24 h as an admixture with promethazine and meperidine. Stanaszek et al. (13), in a similar experiment, demonstrated no decrease in atropine concentration in admixtures containing hydroxyzine and meperidine for up to 10 days. It remains unclear whether the differences in atropine concentrations between the admixture studies and the study investigating atropine storage in syringes as the sole agent is the result of the techniques used in quantifying atropine concentrations or the result of a stabilizing effect of other drugs or preservatives present in the solution of the studies done by Rhodes et al. (12) and Stanaszek et al. (13). The purpose of this study was to determine the stability of atropine sulfate in the OR when stored in plastic syringes as a sole drug under normal clinical conditions.

## **Methods**

The chemical stability of atropine sulfate stored in the OR in standard polypropylene syringes was determined at five separate time points: 18 h, 24 h, 2 days, 4 days, and 8 days. Two milliliters of atropine sulfate solution (American Reagent Laboratories, Inc., Shirley, NY; 0.4mg/mL single dose vial, preservative free) was drawn into each of three, 3-mL polypropylene syringes for each time point. The atropine sulfate syringes were stored at ambient temperature in the OR, adjacent to the anesthesia machine and covered by a clean towel, mimicking our usual clinical practice. Beginning at Time 0 and repeated at each time point, three syringes were randomly selected, wrapped in a clean towel, and transported directly to the laboratory for assay for atropine sulfate concentration. Syringes we used were composed of polypropylene with a latex rubber plunger and were

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manufactured by Sherwood Medical, St. Louis, MO (Monoject<sup>®</sup> 3-mL syringes with attached needle).

Atropine sulfate concentration was measured using liquid chromatography as described in the United States Pharmacopeia/National Formulary, First Supplement (14). All concentration determinations were performed by an independent, outside laboratory (Mylan<sup>®</sup> Pharmaceuticals, Inc., Morgantown, WV). The chemists involved were blinded to the storage duration of the syringes. The United States Pharmacopeia/National Formulary technique is summarized below. A solution of atropine sulfate United States Pharmacopeia (USP) reference standard was prepared by dilution with a mobile phase containing a 78:18:4 (vol/vol/vol) ratio solution of triethylamine phosphate buffer (pH 2.7), methanol, and acetonitrile. Weighed aliquots from the syringes were diluted in an identical fashion. To enhance accuracy, estimated sample volumes were calculated from sample weights based on a density of the sample solution of 1.00 g/dL. Final concentrations for both the standard and the syringe samples were nominally 5  $\mu$ g/mL.

The chromatographic system consisted of a 4.6-mm X 15-cm L7 column (octylsilane bonded to porous silica) and a mobile phase as described above. Injection volumes were 100  $\mu$ L, with a flow rate of 1 mL/min. Peak areas were determined by measuring the UV absorbance at 206 nm and integrating the response using an electronic integrator.

The concentrations of atropine ( $\mu g/mL$ ) in the sample solutions were determined by the formula:

$$C_{\rm s} \times (R_{\rm u}/R_{\rm s}),$$

where  $C_s$  is the concentration of the standard in  $\mu g/mL$ ,  $R_s$  is the average peak area of response at 206 nm for the standard, and  $R_u$  is the average peak area of response for each sample preparation.

The data were analyzed by one-way analysis of variance and Fisher's least significant difference test. A linear contrast was used to compare groups of samples stored for <24 h with later groups.

### **Results**

The data are summarized in Table 1. Stock vials and all syringes assayed contained greater concentrations of atropine sulfate than stated on the label, but all were within 5% of the nominally stated concentration, consistent with USP standards. A 1%–2% decrease in atropine sulfate concentration was noted after 24 h of storage. The decreased concentration of atropine sulfate noted at 24 h differed significantly from the standard (Time 0) atropine sulfate concentrations (P < 0.05). No further decrease in atropine sulfate concentrations sulfate concentration was detected beyond 24 h.

Table	1. Concentrations	of Atropine Sulfate in
Stored	Syringes	•

Duration of storage	Concentration
(days)	(mg/mL)
0 0.75 1 2 4 8	$\begin{array}{c} 0.416 \pm 0.006 \\ 0.416 \pm 0.003 \\ 0.410 \pm 0.003^* \\ 0.408 \pm 0.002^* \\ 0.407 \pm 0.001^* \\ 0.410 \pm 0.003^* \end{array}$

Values are mean  $\pm$  sp.

\* Statistically significant from initial (Day 0) concentration (P < 0.05).

## Discussion

We demonstrated no clinically important decrease in atropine sulfate concentration when atropine is stored in plastic syringes for up to eight days. A 1%-2% decrease in concentration (0.006 mg/mL) was noted after 24 hours of storage. Although this decrease was statistically significant, no atropine sample fell below the nominally stated concentration of 0.4 mg/mL, or fell outside of 5% of the labeled concentration as required by the USP. These findings are similar to studies of atropine stability in stored syringes with admixtures of other drugs, including meperidine hydrochloride, hydroxyzine hydrochloride, and promethazine hydrochloride (12,13). However, our results differ from those of Lewis et al. (11), who suggested a 48% decrease in atropine sulfate concentration after 24 hours when stored in polypropylene syringes as the sole drug. The time course of the concentration decreases was similar in this study and in that of Lewis et al. (11), but differed 25–50 fold in magnitude.

The mechanism of the disparity in the concentrations of atropine observed in our and Lewis et al.'s (11) studies and in similar studies by Rhodes et al. (12) and Stanaszek et al. (13) is not clear. Both our study and the study by Lewis et al. (11) used polypropylene syringes with rubber plungers as the storage vehicle, and the differing results cannot be explained by possible differential absorption of syringe components. However, there are several differences between the studies. Lewis et al.'s (11) sample aliquots were dispensed by volume rather than by weight as in our study. By using density values, sample weights can be used to determine volume with much greater accuracy than can volume delivery systems. There were several differences in the methodology of the high-performance liquid chromatography column and assays between our study and Lewis et al.'s (11) that may have affected column mobility and drug detection. These differences included (this study versus Lewis et al. (11), respectively): mobile phase pH of 2.7 vs 5.7, column composition triethylamine phosphate:methanon:acetonitile 78:18:4 versus acetonitrile:methanol:ammonium acetate 85:10:5, and UV wave length for detection of drug 206 vs 257 nm. The magnitude of the possible

effects of these differences on sample concentration cannot be readily determined. Studies by Rhodes et al. (12) and Stanaszek et al. (13) both used gas chromatography rather than high-performance liquid chromatography. Absorbance wavelength was unspecified in the study by Rhodes et al. (12), but Stanaszek et al. (13) used a wavelength of 257 nm. Despite the differences in technique in these studies (12,13) and this study, none of the three investigations detected a decrease in atropine sulfate concentrations during storage in plastic syringes. If these differences in technique resulted in small variations in concentration determinations among the studies, it is unlikely that the magnitude of the variance approaches the differences seen between this study and Lewis et al.'s (11). Our study confirms that atropine sulfate is stable when stored in plastic syringes and that this stability is not dependent on other drugs or preservatives present in an admixture of drugs.

The sterility of atropine sulfate solutions stored in plastic syringes in the OR has been studied with no evidence of bacterial or fungal contamination for as long as eight days (10). Because atropine sulfate remains chemically stabile and sterile when stored in plastic syringes for periods exceeding one week, suggestions made by the Center for Disease Control and Anesthesia Patient Safety Foundation to limit drug storage in syringes to 24 hours appear overly stringent in the case of atropine sulfate.

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