The solubility of morphine and the stability of concentrated morphine solutions in glass, polypropylene syringes and PVC containers

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Abstract

Morphine solutions are frequently used in palliative settings for the treatment of severe cancer pain. There is, however, no complete information concerning the solubility, isotonisation and shelf-life of these solutions. The solubility limits of morphine hydrochloride (M) were determined as 50 mg/ml in water and 5% dextrose, and 30 mg/ml in 0.9% NaCl at 22°C, figures which decreased to 30 and 20 mg/ml, respectively at 4°C. Isotonisation of the M solutions with NaCl or dextrose did not cause any solubility problems at room temperature. The stability of isotonic M solutions and M solutions in water was investigated over a concentration range of 10–50 mg/ml. All solutions were stored in borosilicate glass, polypropylene syringes and PVC containers at 4, 22 and 40°C in the absence of light. Samples were taken immediately after preparation and after 1, 3, 7 and 14 days, 1, 2 and 3 months of storage. All samples were evaluated visually (colour and precipitation) and pH and osmolality were measured. Determination of morphine, morphine-N-oxide, pseudomorphine and apomorphine was done with a reversed-phase ion-pair HPLC assay. During storage at 4°C of M solutions at a concentration above 20 mg/ml, a white precipitate was formed that was difficult to redissolve. In all samples the pH and the osmolality remained nearly unchanged over the study period, except when stored in PVC containers at 22 and 40°C where there was a gradual increase of the osmolality during storage. In the solutions stored in PVC containers at 22 and 40°C an increase in M concentration of up to 105% of the theoretical concentration was detected after 1 month and 1 week, respectively. In all samples only two degradation products were found: morphine-N-oxide and pseudomorphine. During storage the concentration of both degradation products gradually increased, but remained below 0.4% for morphine-N-oxide and below 2% for pseudomorphine. The type of reservoir and the composition of the solution had only a minor influence on the degradation of M. This study indicates that concentrated M solutions are stable for 3 months under all conditions tested, but should be stored at 22°C to avoid precipitation. © 1997 Elsevier Science B.V.

Keywords: Morphine hydrochloride; Stability; HPLC analysis; Solubility; Osmolality

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1. Introduction

The use of pre-filled morphine syringes for the treatment of chronic pain in cancer patients has become common practice. Although the stability of morphine solutions for intrathecal or epidural administration has been extensively studied, there are no extensive data concerning the stability of the concentrated morphine solutions used for subcutaneous infusion. Roksvaag et al. (1980); Deeks et al. (1983); Bray et al. (1986); Caute et al. (1988); Hung et al. (1988); Walker et al. (1989); Altman et al. (1990); Duafala et al. (1990); Dolezalova (1992); Roos et al. (1992) and Strong et al. (1994) studied the stability of low concentrations of morphine and/or evaluated the stability by determination of morphine without quantifying the degradation products. The degradation process of morphine to morphine-\textit{N}-oxide and pseudomorphine is well known (Yeh and Lach (1961)). Orr et al. (1982) also identified apomorphine as a degradation product during storage of morphine hydrochloride solutions in plastic syringes. In none of the above mentioned studies was morphine-\textit{N}-oxide determined. Besides stability, there is also the problem of solubility when highly concentrated morphine solutions have to be prepared. In the literature no data were found concerning the solubility of morphine in isotonic solutions. In this study the solubility and the osmolality of the morphine solutions was determined. For the evaluation of the stability of isotonised and non-isotonised morphine hydrochloride solutions the concentration of morphine, morphine-\textit{N}-oxide, pseudomorphine and apomorphine in the solutions was measured.

2. Materials and methods

2.1. Materials

For the preparation of the solutions morphine hydrochloride (M) (Belgopia, Louvain-La-Neuve, Belgium), freshly distilled water, 0.9\% NaCl solution (Baxter, Brussels, Belgium) and 5\% dextrose solution (Baxter, Brussels, Belgium) were used. For the preparation of the solutions for HPLC analysis ammonium acetate (pro analyse, UCB, Leuven, Belgium), sodium dodecyl sulphate (puriss. for ion pair chromatography, Fluka Chemie, Buchs, Switzerland), anhydrous acetic acid (Lab Chemie, Novolab, Belgium), sodium metabisulphite (Aldrich Chemie, Steinheim, Germany) and acetonitrile (Minimal Transmission Level, Analytical Sciences, Labscan, Dublin, Ireland) were used. As reference substances M (Belgopia, Louvain-La-Neuve, Belgium), morphine-\textit{N}-oxide (Macfarlan Smith, Edinburgh, UK), pseudomorphine (Macfarlan Smith, Edinburgh, UK) and apomorphine hydrochloride (Federa, Brussels, Belgium) were used. Codeine (Belgopia, Louvain-La-Neuve, Belgium) was used as the internal standard. The stability of M was investigated in the reservoirs most commonly used for portable infusion pumps in palliative care, i.e. polypropylene syringes (10 ml, Becton Dickinson Benelux, Aalst, Belgium) and PVC containers (50 ml, Pharmacia, Brussels, Belgium), and in borosilicate glass (Corning glass ware, Novolab, Geraardsbergen, Belgium). The borosilicate tubes were closed with polyethylene caps (Böttger, Bodenmais, Germany), the syringes were closed with luer tip caps (Becton Dickinson Benelux, Aalst, Belgium) and the containers were closed with polyethylene caps (Pharmacia, Brussels, Belgium).

2.2. Methods

2.2.1. Solubility

The solubility of M was investigated in freshly distilled water, 0.9\% NaCl and 5\% dextrose solutions at 4, 10, 15, 20, 25, 30, 35 and 40°C, respectively. Temperatures up to 20°C were obtained using a cryostate (Vel, Leuven, Belgium), higher temperatures were obtained using a Termaks (Led Techno, Eksel, Belgium). Supersaturated solutions of M were prepared by weighing 1.00 g of M in a 10-ml volumetric flask. The solution was stirred with a magnetic stirrer for 24 h at the tested temperature. The filter was kept at the same temperature for 24 h. After 24 h the solution was filtered through a cellulose acetate membrane filter in a polycarbonate housing (Minisart NML, Sartorius, Göttingen, Germany). The filtrate was diluted (1/50; v/v) with freshly distilled
water and the absorbance was measured using an UV spectrophotometer (DU-65, Beckmann Instruments, Fullerton, USA) operating at a wavelength of 284 nm. Each test was performed in triplicate. The adsorption of M to the filters was determined for each concentration of the drug in water, 0.9% NaCl and 5% dextrose solutions.

2.2.2. Isotonisation

The osmolality of M solutions in pure water was determined as follows. M solutions were prepared in five different concentrations (10, 20, 30, 40 and 50 mg/ml) in freshly distilled water and the osmolality was measured using an osmometer (Type M, measuring cell 150 μl, Knauer, Berlin, Germany). Each concentration was prepared in triplicate and the average osmolality was used for further calculations. The osmolality was plotted against the M concentration and the curve was analyzed by linear regression. The percentages water and isotonic solution required to prepare an isotonic M solution were calculated from the ratio of the M concentration to be prepared and the isotonic M concentration.

2.2.3. HPLC analysis

For the determination of M and its degradation products an ion-pair reversed phase HPLC method was optimised and validated. The HPLC analysis was carried out using an isocratic pump (L-7100, Lachrom, Merck, Overijse, Belgium) operating at a flow rate of 1 ml/min and a variable wavelength detector (UV 2000, Spectra System, Thermo Separation Products, Wilrijk, Belgium) operating at a wavelength of 254 nm. Samples were diluted and mixed with the internal standard using an autoinjector (Autoinjector 234, Gilson, Analis, Gent, Belgium), and injected through a Rheodyne valve (Type 7010, Analis, Gent, Belgium) fitted with a 20 μl sample loop. Separation of the components was performed on a 250 × 4.6 mm stainless steel column, packed with 5 μm particle size Ultrasphere ODS bonded silica (Beckman Instruments, Fullerton, USA). The chromatograms were processed using the Spectra Physics software package PC 1000 (Thermo Separation Products, Wilrijk, Belgium). The mobile phase consisted of 37.5% (v/v) acetonitrile in water, with 5 mM sodium dodecyl sulphate, 0.08 M ammonium acetate, and the pH was adjusted to
4.93 with anhydrous acetic acid. The internal standard solution consisted of 200 μg/ml codeine and was prepared in eluent. For M a 50 mg/ml stock solution was prepared, for the degradation products 50 μg/ml stock solutions were prepared. All stock solutions and calibration curves were prepared in eluent, except for apomorphine hydrochloride, where 0.5% sodium metabisulphite was added as an antioxidant. For determination of the detection and quantification limits, solutions of the degradation products were prepared from the respective stock solutions and analyzed 10 times. For determination of linearity and reproducibility the following calibration curves were prepared from the respective stock solutions: 1000, 1200, 1400, 1600, 1800 and 2000 μg/ml for M, 1.0, 2.0, 5.0, 10.0 and 20.0 μg/ml for morphine-N-oxide and apomorphine hydrochloride and 0.4, 1.0, 2.0, 5.0, 10.0, 20.0 and 40.0 μg/ml for pseudomorphine. Prior to injection all solutions were diluted 1/1 (v/v) with the internal standard solution. Peak area was used for quantification. The lowest concentration for which a 10-fold analysis resulted in a relative standard deviation (R.S.D.) smaller than 20% (n = 10) was used for the calculation of the detection and quantification limit of the degradation products. The detection limit was calculated as the lowest concentration with a R.S.D. < 20% (n = 10) plus 3 times the R.S.D. The quantification limit was calculated as the lowest concentration with a R.S.D. < 20% (n = 10) plus 10 times the R.S.D. For the determination of linearity and reproducibility all calibration curves were prepared and analyzed in fivefold on one day and on 5 consecutive days. Linearity was calculated using linear regression. The reproducibility of the method was determined by calculation of the within and between day coefficient of variation. As a quality control the calibration curves were analyzed weekly and the R.S.D. of the regression coefficients were calculated. All samples were diluted to a final concentration of approximately 800 μg/ml M in order to obtain peak areas for the degradation products above the quantification limit. All samples were analyzed in duplicate.

2.2.4. Stability study

For the stability study isotonic M solutions and M solutions in water were prepared in concentrations of 10, 20, 30, 40 and 50 mg/ml. Isotonic M
Table 1

<table>
<thead>
<tr>
<th>Compound</th>
<th>DL (µg/ml)</th>
<th>QL (µg/ml)</th>
<th>Range (µg/ml)</th>
<th>R.S.D. (%) within day (n = 5)</th>
<th>R.S.D. (%) between day (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine-N-oxide</td>
<td>0.27</td>
<td>0.44</td>
<td>0.5–10.0</td>
<td>4.19 ± 1.26</td>
<td>5.91 ± 1.86</td>
</tr>
<tr>
<td>MorphineHCl</td>
<td>--</td>
<td>500</td>
<td>1000</td>
<td>1.42 ± 0.37</td>
<td>1.51 ± 0.40</td>
</tr>
<tr>
<td>Codeine</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Pseudomorphine</td>
<td>0.11</td>
<td>0.19</td>
<td>0.2–20.0</td>
<td>3.50 ± 0.83</td>
<td>5.6 ± 2.59</td>
</tr>
<tr>
<td>ApomorphineHCl</td>
<td>0.30</td>
<td>0.50</td>
<td>0.5–10.0</td>
<td>7.17 ± 1.90</td>
<td>15.69 ± 3.20</td>
</tr>
</tbody>
</table>

DL, detection limit; QL, quantification limit; R.S.D., relative standard deviation (mean ± S.D.).

Solutions were prepared using either 0.9% NaCl or 5% dextrose solutions as isotonising agent. The solutions were stored in borosilicate glass tubes, polypropylene syringes and PVC containers. To avoid the presence of air in the solutions the borosilicate tubes were gassed for 15 s with N₂ before closing; from the syringes and the containers all air bubbles were removed. All solutions were stored for 3 months at 4, 22 and 40°C in the absence of light. Samples were taken immediately after preparation and after 1, 3, 7 and 14 days, and 1, 2 and 3 months. Immediately after sampling the solutions were inspected visually for discoloration and precipitate. Measurement of pH and osmolality was done immediately after preparation and after 3 months of storage. For the determination of M and its degradation products the samples were stored at −20°C. In this study quantitative measurement of the decomposition products, rather than that of the parent drug, was used to evaluate the stability of a drug. The percentage of each degradation product was calculated using equation 1.

% degradation product = (concentration degradation product / total morphine concentration) × 100

3. Results and discussion

3.1. Solubility

Although the solubility of M in water at room temperature was reported by Budavari et al. (1989) to be 57 mg/ml, solubility problems are common during the preparation and storage of concentrated M solutions for subcutaneous infusion. In daily practice injectables are commonly prepared by dissolving the drug in 0.9% NaCl or 5% dextrose solutions and stored at 4°C until use. Therefore the solubility of M in water, 0.9% NaCl and 5% dextrose solutions was investigated as a function of temperature. For all the solutions tested the adsorption of M to the filters was below 3%. From Fig. 1 it can be seen that dextrose 5% had no influence on the solubility of M, whereas 0.9% NaCl markedly reduced its solubility. As expected the solubility of M is strongly dependent on the temperature. The maximal M concentration that could be dissolved at room temperature (22°C) was...
Table 2
Percentage of the theoretical morphine hydrochloride concentration in solutions of morphine hydrochloride (30 mg/ml) during storage in PVC containers at 4, 22 and 40°C

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Storage time (days)</th>
<th>4°C</th>
<th>22°C</th>
<th>40°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>1</td>
<td>95.0</td>
<td>102.4</td>
<td>101.8</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>100.5</td>
<td>94.0</td>
<td>104.4</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>100.0</td>
<td>101.0</td>
<td>112.0</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>100.0</td>
<td>101.0</td>
<td>113.1</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>99.4</td>
<td>105.0</td>
<td>189.2</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>100.0</td>
<td>110.6</td>
<td>100.0</td>
</tr>
<tr>
<td>Water with NaCl</td>
<td>1</td>
<td>100.9</td>
<td>101.0</td>
<td>101.3</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>96.9</td>
<td>103.0</td>
<td>102.8</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>96.6</td>
<td>98.5</td>
<td>108.4</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>96.9</td>
<td>102.7</td>
<td>110.0</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>96.0</td>
<td>102.6</td>
<td>131.0</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>97.3</td>
<td>106.4</td>
<td>173.7</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>97.5</td>
<td>108.6</td>
<td>--</td>
</tr>
<tr>
<td>Water with dextrose</td>
<td>1</td>
<td>97.8</td>
<td>101.9</td>
<td>101.9</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>100.3</td>
<td>101.2</td>
<td>100.7</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>98.5</td>
<td>99.5</td>
<td>104.4</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>99.7</td>
<td>101.0</td>
<td>106.2</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>100.7</td>
<td>105.2</td>
<td>124.2</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>101.0</td>
<td>104.3</td>
<td>168.6</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>102.1</td>
<td>112.0</td>
<td>--</td>
</tr>
</tbody>
</table>

approximately 50 mg/ml in water and 5% dextrose and 30 mg/ml in 0.9% NaCl. At 4°C the maximal solubility of M was decreased to 30 mg/ml in water and 5% dextrose and 20 mg/ml in 0.9% NaCl.

3.2. Isotonisation

It is well-known that the injection of isotonic solutions is less painful and reduces tissue irritation (DeLuca and Boylan, 1984). To isotonise solutions the osmolality of drug solutions in pure water needs to be known. To our knowledge, for M these data have not been reported in literature. Therefore the osmolality of different M concentrations in water was measured.

The osmolality was plotted against the M concentration and linear regression resulted in the following equation: \( y = ax + b \) with \( y = \text{osmolality (mOsm/kg)}, \ x = \text{M concentration (mg/ml)}, \ a = 3.94 \) and \( b = 10.64 \) \( (r^2 = 0.998) \). Using this equation the concentration of an isotonic solution \( (y = 285 \text{ mOsm/kg}) \) was calculated as 69.59 mg/ml M in water. The percentage (v/v) of isotonic solution (0.9% NaCl or 5% dextrose) required to obtain an isotonic solution at a concentration of \( x \) mg/ml M, was calculated using equation 2:

\[
\%	ext{ isotonic concentration} = \left( \frac{\text{concentration M to be prepared (mg/ml)}}{69.59 \text{ (mg/ml)}} \right) \times 100
\]

Equation 2: % isotonic concentration = (concentration M to be prepared (mg/ml) / 69.59 (mg/ml)) × 100
3.3. HPLC analysis

Methods for the analysis of morphine and its congeners have been reported by Roksvaag et al. (1980); Deeks et al. (1983); Lee (1984); Hung et al. (1988); Dolezalova (1992) and Salem and Galan (1993). These reports, however, do not provide sufficient information on the separation and quantification of the four compounds of interest in the present study. Hence, as a part of this investigation, an HPLC assay for the quantitation of these solutes in aqueous medium was developed. The organic modifier concentrations, the pH and the ionic strength of the eluent were empirically optimized. Fig. 2 shows a representative chromatogram obtained under optimal chromatographic conditions. The sensitivity and reproducibility of the HPLC method are summarized in Table 1. All standard curves were linear with correlation coefficient values > 0.99. Over a period of 6 months the relative standard deviation of the regression coefficient was below 2.5% (n = 15) for all components.

3.4. Stability study

Visual inspection of freshly prepared M solutions showed for increasing concentrations of M an increase in colour intensity from colourless to pale yellow. Visually no difference was detected between the solutions prepared in the different solvents. During storage the colour of the solutions increased progressively to dark yellow and brown. The discoloration was most evident when the solutions were stored at 40°C. In all M solutions above 20 mg/ml stored at 4°C for 1 day or longer a white precipitate was detected. The amount of this precipitate increased with increasing M concentration and with the use of NaCl for isotonisation as compared to the use of dextrose and solutions in pure water. The larger amount of precipitate in the solutions isotonised with NaCl can be explained by the common ion effect. The precipitate formed at 4°C causes problems in daily practice as it is difficult to redissolve. A white precipitate was formed in all solutions after 1 month of storage in PVC containers at 22 and 40°C, and in the solutions at a concentration above 40 mg/ml yet after 14 days. Due to this precipitate is was impossible to take samples from the solutions stored for 3 months at 40°C in PVC containers. It is thought that this precipitate is due to the evaporation of water vapour through the PVC wall of the container, thus increasing the concentration of M above its solubility limit.

The initial pH of the M solutions in water decreased with increasing concentration, and ranged from 5.30 to 4.58 for a concentration of

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**Fig. 3.** Influence of the type of reservoir (borosilicate glass (□), polypropylene syringes (○) and PVC containers (◇)) on the occurrence of pseudomorphine during storage at 4°C (——), 22°C (— — —) and 40°C (— — —) in a solution of morphine hydrochloride (30 mg/ml) isotonised with NaCl.
Fig. 4. Influence of the type of reservoir (borosilicate glass (□), polypropylene syringes (○) and PVC containers (◇)) on the occurrence of morphine-N-oxide during storage at 4°C (——), 22°C (— —) and 40°C (—— —) in a solution of morphine hydrochloride (30 mg/ml) isotonised with NaCl.

10–50 mg/ml, respectively. For the isotonic M solutions the pH was lower than for the solutions in water, and was almost constant for increasing M concentrations. The pH ranged from 4.29 to 4.63 and from 4.18 to 4.66, for the solutions isotonised with NaCl and dextrose, respectively and did not alter during 3 months of storage at 4°C. The pH of the solutions showed a slight decrease after storage for 3 months at 22 and 40°C. This pH decrease was noticeably higher for the solutions stored in PVC containers.

The initial osmolality of M solutions in water increased from 49 to 215 mOsm/kg with increasing concentrations of M (10–50 mg/ml). The initial osmolality of the isotonic M solutions ranged from 285 to 305 mOsm/kg and was independent of the M concentration. Storage did not influence the osmolality of the solutions, except for the solutions stored in PVC containers at 22 and 40°C, where an important increase in osmolality was detected, due to water vapour evaporation.

Although Pohjola et al. (1985) reported that M solutions are stable during freeze-thaw cycles, in this study the long term stability of M solutions at −20°C was investigated over a period of 1 year. In all solutions the concentration of morphine-N-oxide and pseudomorphine remained unchanged during 1 year of storage at −20°C. The actual samples were stored for a maximum period of 8 months at −20°C, and therefore no degradation occurred before analysis. Table 2 shows the percentage of the theoretical M concentration (30 mg/ml) during storage in PVC containers. For all concentrations the M content increased to 105% of the theoretical concentration after storage in PVC containers for 1 month at 22°C and for 1 week at 40°C, which is in agreement with the findings of Landersjö and Nyhammar (1989) and Roos et al. (1992). This increase in M concentration could explain the larger decrease in pH in these solutions. In all samples as degradation products morphine-N-oxide and pseudomorphine were found. In none of the samples apomorphine hydrochloride was detected, which is in disagreement with the observations of Orr et al. (1982) who identified apomorphine as a degradation product in morphine solutions stored for 20 min in plastic syringes. The findings of Osol and Hoover (1975) that the degradation of morphine to apomorphine chemically requires hydrochloric acid and a temperature of 60–65°C for 2.3 h and that apomorphine readily oxidizes to form a blue-green color, make it unlikely that the product found by Orr et al. (1982) was indeed apomorphine. In the freshly prepared M solutions the concentration of morphine-N-oxide was less than 0.2% (w/v). After 3 months the
Fig. 5. Influence of the concentration of morphine hydrochloride (10 mg/ml (●), 20 mg/ml (△), 30 mg/ml (○), 40 mg/ml (□) and 50 mg/ml (○)) on the occurrence of pseudomorphine in morphine hydrochloride solutions isotonised with NaCl during storage in borosilicate glass at 40°C.

concentration of morphine-N-oxide remained below 0.2% (w/v) when stored at 4 and 22°C, but increased to concentrations below 0.4% (w/v) when stored at 40°C. Fennessey and Fearn (1969) found that in mice, morphine-N-oxide is a weak analgesic with intravenous and subcutaneous toxicities 3.2 and 8 times less than those of morphine and that morphine-N-oxide has no carcinogenic or teratogenic effects in mice and rats. The freshly prepared M solutions contained less than 0.2% (w/v) pseudomorphine. After storage for 3 months at 4, 22 and 40°C the pseudomorphine concentration was below 0.2, 0.4 and 2% (w/v), respectively. Misra and Mule (1972) demonstrated that in rats pseudomorphine, unlike morphine, does not penetrate the blood-brain barrier. Travell (1932), Schmidt and Livingston (1993) and Misra and Mule (1972) reported that pseudomorphine causes an acute circulatory depression after intravenous administration but not after oral or subcutaneous administration. It can therefore be concluded that M solutions containing low concentrations of morphine-N-oxide and pseudomorphine can be used safely for subcutaneous infusion. In the freshly prepared M solutions similar concentrations of pseudomorphine and morphine-N-oxide were found. During storage, however, the pseudomorphine concentration exceeded by far the levels found for morphine-N-oxide, which confirms the findings of Yeh and Lach (1961), that pseudomorphine is the major degradation product of morphine. The effect of the reservoir on the formation of pseudomorphine and morphine-N-oxide during storage for 3 months at 4, 22 and 40°C is shown in Figs. 3 and 4, respectively. These figures illustrate the higher concentrations of both degradation products during storage at 40°C in the polypropylene syringes and the PVC containers than in borosilicate glass. During storage at 4 and 22°C there was no influence of the type of reservoir on the formation of the degradation products. During storage at 4 and 22°C no influence of the solvent on the formation of pseudomorphine and morphine-N-oxide was observed. When stored at 40°C the pseudomorphine and morphine-N-oxide concentrations tended to be lower in the solutions isotonised with dextrose as compared with the solutions isotonised with NaCl and the solutions prepared in water. The effect of the M concentration on the formation of pseudomorphine and morphine-N-oxide during storage at 40°C in borosilicate glass is shown in Figs. 5 and 6, respectively. These data indicate that at 40°C the
Fig. 6. Influence of the concentration of morphine hydrochloride (10 mg/ml (○), 20 mg/ml (△), 30 mg/ml (◇), 40 mg/ml (□) and 50 mg/ml (◇)) on the occurrence of morphine-N-oxide in morphine hydrochloride solutions isotonised with NaCl during storage in borosilicate glass at 40°C.

degradation rate of M increased with increasing concentration, while no influence of the concentration was seen during storage at 4 and 22°C.

From this study it can be concluded that after storage for 3 months, under all conditions investigated M solutions are safe to be used for subcutaneous infusion. Isotonic M solutions are to be preferred. To avoid precipitation, M solutions should be stored at 22°C. To avoid a potentially dangerous increase in M concentration, solutions in PVC containers should not be stored for longer than 1 month. Investigations on the compatibility of M with other drugs frequently used in the palliative setting and on the stability of these admixtures are ongoing.

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