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Compatibility and stability of morphine in binary admixtures with haloperidol, midazolam, dexamethasone or methylprednisolone

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Abstract

The concentration range over which compatible admixtures of morphine hydrochloride with haloperidol lactate (Haldol®), midazolam hydrochloride (Dormicum®), dexamethasone sodium phosphate (Decadron® and Decadron® Pack) or methylprednisolone-21-sodium succinate (Solu-Medrol®) can be prepared was determined by visual evaluation of the solutions. Compatibility was investigated either by mixing the drug solution with the morphine hydrochloride solution or by adding morphine hydrochloride powder to the drug solution. The precipitate and the supernatant in the incompatible admixtures were analyzed by high performance liquid chromatography (HPLC) and NMR. The stability of the drugs in the compatible admixtures and of the drug solutions used to prepare the admixtures was evaluated during storage for 28 days at 22°C and protected from light. Visual inspection, HPLC analysis, pH and osmolality determinations were performed. Addition of Dormicum®, Haldol® or Decadron® (Pack) to the morphine hydrochloride solution (50 mg/ml) resulted in compatible admixtures up to a volume ratio drug/morphine hydrochloride: 10/10, 5/10, 1/10 (v/v), respectively. Addition of methylprednisolone (100 mg/ml) to the morphine hydrochloride solution (50 mg/ml) resulted in an incompatible admixture in a volume ratio drug/morphine hydrochloride: 1/10 (v/v). Inverting the order of mixing resulted in incompatibility for admixtures that were compatible when prepared by the addition of drug solution to the morphine hydrochloride solution, except for the admixtures prepared with Dormicum® for which the order of mixing did not affect compatibility. The concentration range over which compatibility was observed could not be extended by using the powder addition technique, except for the admixtures with Dormicum®. The maximal amount of morphine hydrochloride that could be dissolved in Dormicum® was 30 mg/ml and increased to 50 mg/ml in its dilution 1/10 (v/v). For all admixtures tested no visual incompatibility was observed during the period studied, except for the admixtures prepared with undiluted Decadron® (Pack) solutions in which occasionally precipitation occurred. HPLC analysis revealed that all drugs remained stable ($< 10\%$ degradation) in the admixtures and drug solutions studied, except for methylprednisolone-21-sodium

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succinate and dexamethasone sodium phosphate in the admixtures prepared using Decadron®.

Keywords: Dexamethasone sodium phosphate; Haloperidol lactate; Incompatibility; Methylprednisolone sodium succinate; Midazolam hydrochloride; Morphine hydrochloride; Stability

1. Introduction

More than 50% of cancer patients experience moderate to severe pain during the terminal stage of their disease (Vianio et al., 1996) which is usually treated with an opioid analgesic. For the treatment of opioid induced nausea and/or vomiting, occuring in about 40% of the patients with terminal cancer (Twycross, 1986), haloperidol has been found extremely effective, causing less sedation than other anti-emetics and little if any irritation during subcutaneous infusion (Storey et al., 1990; Lord and Clarke, 1995). Anxiety, restlessness and agitation are also common symptoms in terminally ill patients, and may cause considerable distress. For this, subcutaneous infusions of midazolam have been found to be a well-tolerated, safe and effective treatment (De Sousa and Jepson, 1988; Amesburry and Dunphy, 1989; Bottomley and Hanks, 1990; Burke et al., 1991). Terminally ill patients also commonly suffer from numerous other symptoms for which corticosteroids have been proven to be effective (Needham et al., 1992; Twycross, 1992; Watanabe and Bruera, 1994). With their specific anti-inflammatory effects corticosteroids are used in raised intracranial pressure, compression of the spinal cord and obstruction of the superior vena cava or other hollow organs. With their general effects corticosteroids are reported to be effective for the treatment of anorexia and weakness, symptoms occurring in 30–50% of the terminally ill cancer patients (Vianio et al., 1996).

Since, in most of these patients oral administration is no longer possible and regular intramuscular injections are painful for the patient, terminally ill patients commonly receive their opioid analgesics by continuous subcutaneous infusion. The subcutaneous infusion of drugs using a portable syringe driver provides major benefits in palliative care, allowing comfortable parenteral treatment of pain and other cancer related symptoms when the oral route of administration is no longer available (Bruera, 1990; Storey et al., 1990). In order to avoid separate injections of different drugs, admixtures of opioids with other drugs used in palliative care, such as anti-emetics, sedatives and corticosteroids, are frequently prescribed. Moreover addition of corticosteroids to the solutions infused subcutaneously is reported to be useful for the treatment and prevention of local skin irritation, occasionally occurring at subcutaneous infusion sites (Shvartzman and Bonneh, 1994).

The aim of this study was to investigate the compatibility and the stability of admixtures of morphine hydrochloride, still the opioid of choice in palliative care (WHO, 1990), with four drugs frequently prescribed in terminally ill patients: midazolam, haloperidol, methylprednisolone and dexamethasone. Combinations of morphine hydrochloride with these drugs in solutions for subcutaneous infusion is now commonplace in palliative care, however, to our knowledge no useful data concerning the compatibility and/or stability of these admixtures are available. The compatibility of morphine hydrochloride with midazolam hydrochloride was studied by Swart et al. (1995), but at concentrations far below the doses prescribed in palliative care. Data on the compatibility of these drugs with morphine sulphate have been reported by several authors (Forman and Souney, 1987; Pugh et al., 1991; Johnson et al., 1994; Lebelle et al., 1995). In all these studies the concentration of morphine was also very low and since in Belgium only the hydrochloride salt is used to prepare the infusion solutions this information is of no practical use. As the pH and the osmolality may play a major role in the prevalence of local skin irritation (Lewis and

Hecker, 1985; Sykes and Oliver, 1987), both parameters were determined and the influence of isotonizing agents such as sodium chloride and dextrose on the compatibility was also investigated.

2. Materials and methods

2.1. Preparation of the solutions

Morphine hydrochloride solutions (max. 50 mg/ml) were prepared from morphine hydrochloride powder (Belgopia, Louvain-la-Neuve, Belgium). Solutions were prepared in freshly distilled water or isotonized using either 0.9% sodium chloride (Baxter, Brussels, Belgium) or 5% dextrose solutions (Baxter, Brussels, Belgium). To obtain isotonic morphine hydrochloride solutions at a concentration of 10, 20, 30, 40 and 50 mg/ml the appropriate amount of morphine hydrochloride powder was dissolved in a mixture containing 85.6, 71.2, 56.8, 42.5 and 28.0% (v/v) dextrose 5% or sodium chloride 0.9% in water, respectively as described by Vermeire and Remon (1997). Midazolam hydrochloride solutions were prepared from Dormicum® (Roche, Brussels, Belgium) containing midazolam (5 mg/ml), sodium chloride, hydrochloric acid, sodium hydroxide ad pH 3.3 and water for injection. Haloperidol lactate solutions were prepared using Haldol® (Janssen Cilag, Berchem, Belgium) containing haloperidol (5 mg/ml), lactic acid and water for injection. Methylprednisolone-21-sodium succinate solutions were prepared using the lyophilized powder from the Solu-Medrol® vial (Solu-Medrol®, 1 g, Pharmacia and Upjohn, Brussels, Belgium) containing 67.57% methylprednisolone as methylprednisolone-21-sodium succinate, monosodium phosphate monohydrate and disodium phosphate. The maximal concentration of methylprednisolone-21-sodium succinate that could be dissolved in water was determined as 100 mg/ml methylprednisolone. Dexamethasone sodium phosphate solutions were prepared from Decadron® (Merck Sharp and Dohme, Brussels, Belgium) containing 3.33 mg/ml dexamethasone (equivalent to 4 mg/ml dexamethasone phosphate) as dexamethasone sodium phosphate and Decadron® Pack (Merck) containing 20 mg/ml dexamethasone as dexamethasone sodium phosphate. Both dexamethasone solutions contain creatinine (8 mg/ml), methylparaben (1.5 mg/ml), propylparaben (0.2 mg/ml), sodium citrate (10 mg/ml), sodium bisulfite (7 mg/ml) and sodium hydroxide (ad pH 7–8.5). Next to the the above mentioned additives in Decadron® Pack disodium edetate (0.5 mg/ml) is present as an additive (Trissel, 1994).

2.2. Compatibility study

For the compatibility study of the different drug solutions with morphine hydrochloride the same strategy was followed (Fig. 1). In a first approach the compatibility was investigated for admixtures prepared by mixing morphine hydrochloride solutions with the drug solutions and secondly the compatibility of admixtures prepared by adding morphine hydrochloride powder to the drug solutions was investigated.

For the determination of the compatibility of admixtures prepared by mixing solutions, first an admixture was prepared in a volume ratio drug solution (D)/morphine hydrochloride solution (M) of 1/10 using both solutions at maximal concentration. These maximal concentrations of the drug solutions used to prepare the admixtures were either the maximal concentration soluble or the maximal concentration available: morphine hydrochloride 50 mg/ml, midazolam 5 mg/ml, haloperidol 5 mg/ml, methylprednisolone 100 mg/ml, dexamethasone 3.33 mg/ml (Decadron®) and dexamethasone 20 mg/ml (Decadron® Pack).

If this admixture was incompatible, additional admixtures were prepared in the same ratio but using lower concentrations of both the drug and morphine hydrochloride till minimally 20% of the maximal concentration or till compatibility was observed. Dilutions of the drug solutions were prepared in water and less concentrated morphine hydrochloride solutions were prepared in water or isotonized with sodium chloride or dextrose. If compatibility was observed in a ratio D/M:1/10 (v/v) at a certain concentration additional admixtures were prepared to determine whether the concentration of morphine hydrochloride or the

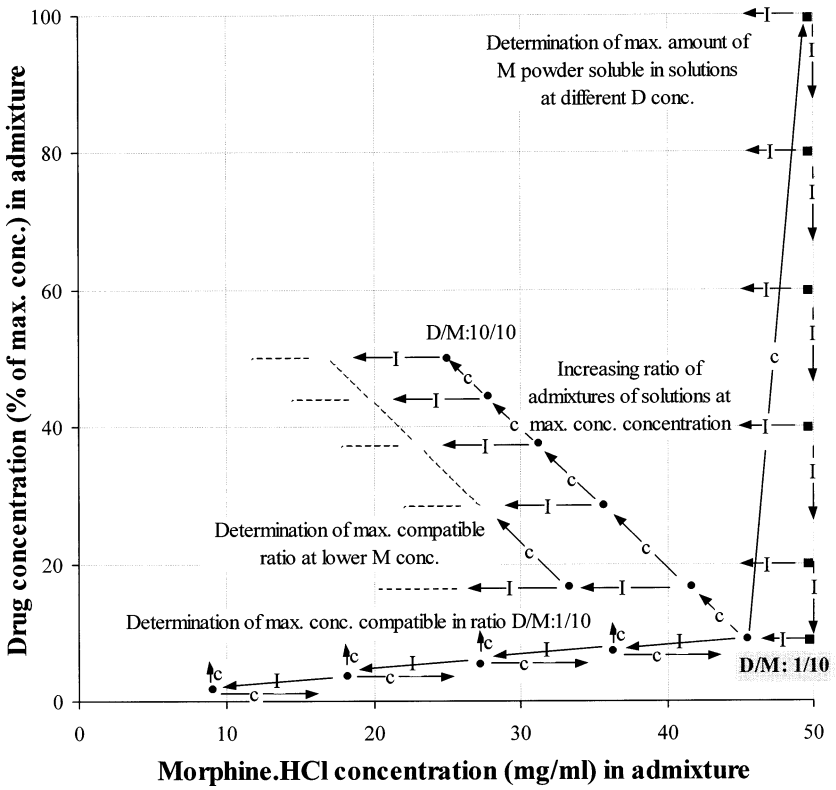

Fig. 1. Flow-chart for the determination of the compatibility range of morphine hydrochloride in binary admixtures. (●) Admixtures prepared by mixing the drug solution with the morphine hydrochloride solution. (■) Admixtures prepared by addition of morphine hydrochloride powder to the drug solution. -c→ Indicates the admixtures prepared if compatibility was observed. -I→ Indicates the admixtures prepared if incompatibility was observed. M = morphine hydrochloride, D = drug. D/M:1/10. Admixture prepared by mixing morphine hydrochloride and the drug solution at maximal concentration in a ratio D/M:1/10 (v/v).

drug was the limiting factor. These admixtures were prepared in the same ratio using either the solution of morphine hydrochloride at the concentration for which compatibility was observed and the drug solution at a higher concentration or the drug solution at the concentration for which compatibility was observed and the morphine hydrochloride solution at a higher concentration.

If the admixture of both drugs at maximal concentration in a ratio D/M:1/10 (v/v) was visually compatible, additional admixtures were prepared with both solutions at maximal concentration but in a gradually increasing D/M ratio from 2/10 up to 10/10 (v/v) or until incompatibility was observed. If incompatibility was observed at a ratio less than D/M:10/10 (v/v) additional admixtures were prepared by mixing the drug solution at the maximal concentration with solutions of morphine hydrochloride at a lower concentration (minimally 10 mg/ml) until compatibility was observed up to a ratio D/M:10/10 (v/v).

This compatibility test was performed with morphine hydrochloride solutions prepared in water and isotonized with sodium chloride and dextrose. In this case the admixtures were always prepared by adding the drug solution to the morphine hydrochloride solution. As the order of mixing is known to have an influence on the compatibility, the admixtures were also prepared by adding morphine hydrochloride solution to the drug solution and evaluated for their compatibility.

Although admixtures are most frequently prescribed in a ratio D/M of approximately 1/10 (v/v), sometimes high doses of morphine hydrochloride as well as the other drug are prescribed. By mixing solutions it is not possible to obtain admixtures

with high concentrations of both the admixed drug and morphine hydrochloride. These high concentrations can be obtained by dissolving morphine hydrochloride powder in the drug solution. When no incompatibility was observed for the admixtures prepared with both solutions at maximal concentration in a ratio D/M:1/10 (v/v), the maximal amount of morphine hydrochloride powder that can be dissolved per ml drug solution at different concentrations was determined. Therefore 50 mg of morphine hydrochloride powder was added per ml of drug solution at maximal concentration. If this admixture was found to be visually incompatible the same experiment was performed using a drug solution at lower concentration till 50 mg/ml morphine hydrochloride was soluble or till minimally 10% of the maximal drug concentration. Then the maximal amount of morphine hydrochloride that can be dissolved per ml of the drug solution at the higher concentrations was determined. This approach permitted a determination of the concentration range where morphine hydrochloride was compatible with each of the drugs tested.

Each admixture was first prepared only once. After this first screening all admixtures near the compatibility limits were prepared and evaluated again in duplicate. Immediately after preparation the admixtures were evaluated by visual inspection (color, clarity, presence of particles and evolution of gas). All admixtures were evaluated daily during a one week storage period at 22°C and protected from light in order to detect any delayed crystallization. Solutions were considered visually compatible if after one week no physical change was observed as compared to the pure drug solutions. If a precipitate was observed, it was analyzed as well as the supernatant. A large amount of precipitate was prepared by adding 500 mg morphine hydrochloride to 10 ml of the drug solution at maximal concentration. After addition of the morphine hydrochloride powder the admixture was shaken, sonicated for 15 min and stored for 1 week at 22°C protected from light. Next the solution was centrifuged for 15 min at 5000 rpm. and the supernatant was transferred to another tube. The precipitate was isolated by filtration under vacuum and dried by lyophilization (GT4, Amsco Finn Aqua, Germany). The supernatant was analyzed by HPLC analysis, the precipitate by HPLC and NMR.

2.3. Stability study

For each drug combination the stability of six compatible admixtures in a ratio D/M:1/10 (v/v) and of the drug solutions used to prepare the admixtures was evaluated. These six admixtures of each drug combination were prepared with morphine hydrochloride solutions at two concentrations (10 and 50 mg/ml) and drug solutions at three concentrations compatible with each of the morphine hydrochloride solutions. The stability study was only performed for admixtures prepared using morphine hydrochloride solutions isotonized with dextrose. For the stability study the admixtures were prepared under aseptic conditions using sterile drug solutions: the morphine hydrochloride solutions were sterilized by filtration (Minisart NML, 0.22 μm, Sartörius, Göttingen, Germany), commercially available sterile drug solutions were diluted in sterile water and the sterile methylprednisolone powder was dissolved in sterile water. The admixtures were prepared by adding the drug solution to the morphine hydrochloride solution, filled in sterile borosilicate tubes (Corning glass ware, Novolab, Belgium) and closed with sterile polyethylene caps (Böttger, Bodenmais, Germany). In order to eliminate any influence of oxygen on the stability of the solutions, the tubes were gassed with sterile N_2 for 15 s before closing.

All tubes were stored at 22°C and protected from light for 28 days. Samples were taken immediately and 1, 3, 7, 14 and 28 days after preparation and evaluated visually for any changes. As methylprednisolone solutions are described to have a limited stability when stored at room temperature (Nahata et al., 1994) the stability of the admixtures containing methylprednisolone was also investigated during storage for 0, 1, 3 and 7 days at 4°C followed by a 1 day storage at 22°C. The samples were stored at -20°C prior to analysis. HPLC analysis was done at each sampling point, the pH and osmolality were measured immediately after preparation and at the end of

the storage period. The pH was measured using a Consort pH-meter (P601, Consort, Turnhout, Belgium), osmolality measurements were performed using an osmometer (Type M, measuring cell 150 μl, Knauer, Berlin, Germany).

2.4. HPLC analysis

The concentrations of each drug and, where possible, its degradation products were quantified using stability indicating validated HPLC assays. For the analysis of methylprednisolone-21-sodium succinate the chromatographic equipment constisted of a UV-detector (Waters 441, Waters, Brussels, Belgium), a gradient pump (Waters 590, Waters, Brussels, Belgium), an autoinjector (Spectraphysics 8880, Thermo Separation Products, Wilrijk, Belgium) and an integrator (Millenium, Waters, Brussels, Belgium). For the other HPLC determinations the following chromatographic equipment was used: an isocratic pump (L-7100, Lachrom, Merck, Overijse, Belgium), a variable wavelenght detector (UV 2000, Spectra System, Thermo Separation Products, Wilrijk, Belgium), an autoinjector (Autoinjector 234, Gilson, Analis, Gent, Belgium). Both systems used an electrically actuated Rheodyne valve (Type 7010, Analis, Gent, Belgium) fitted with a 20 μl sample loop. The determination of morphine hydrochloride and its degradation products (pseudomorphine (MacFarlan Smith, Edinburgh, UK), morphine-*N*-oxide (MacFarlan Smith, Edinburgh, UK) and apomorphine (as the hydrochloride salt; Sigma-Aldrich, Bornem, Belgium) was performed according to the method described by Vermeire and Remon (1997) using an Ultrasphere RP-18 (5 μm, 250×4.6 mm) column (Beckman Instruments, Fullerton, US). This method was slightly modified in order to obtain a good separation from all other compounds present in the admixtures. Therefore the pH of the mobile phase (buffer (ammonium acetate 0.08 M, sodium dodecyl sulphate 5 mM)/acetonitrile: 62.5/37.5 (v/v)) was adjusted to 4.70 instead of 4.95. Using this mobile phase at a flow rate of 1 ml/min a good separation was obtained of morphine, its degradation products and the other compounds present in the admixtures, except for the interfering peak with apomorphine which was observed in the chromatogram of methylprednisolone solutions (Fig. 2). DAD analysis of these interfering peaks during sample analysis however revealed that no apomorphine was present in these admixtures. For the determination of midazolam and its degradation products the HPLC assay of Andersin and Tammilehto (1995) was slightly modified and validated. The ratio phosphate buffer (pH = 3.5)/methanol was decreased from 65/35 to 60/40

Fig. 2. Chromatograms of (a) a mixture containing 1000 μg/ml morphine hydrochloride (I), 10 μg/ml morphine-*N*-oxide (II), 10 μg/ml pseudomorphine (III) and 5 μg/ml apomorphine hydrochloride (IV) μg/ml; (b) midazolam and its degradation products; (c) Haldol® stored for 28 days at 60°C; (d) Solu-Medrol® stored for 7 days at 22°C; and (e) Decadron® Pack stored for 28 days at 22°C injected under optimal chromatographic conditions used for the quantification of morphine and its degradation products as indicated in the text.

Fig. 3. Chromatograms of (a) midazolam (2 μg/ml) and its degradation products ((I = midazolam, II = desalkylflurazepam (0.2 μg/ml), III = 6-(8-chloro-1-methyl-4,5-dihydro-2,5,10b-tri-azabenzo[e] azulen-6-ylidene)cyclohexa-2,4-dienone (concentration unknown), IV = 6-chloro-2-methyl-4-(2-fluorophenyl)quinazoline (concentration unknown) and V = 6-chloro-2-methyl-4(1H)-quinazolinone (2 μg/ml)); and (b) morphine hydrochloride, and its degradation products injected under optimal chromatographic conditions used for the determination of the stability of midazolam as indicated in the text.

Fig. 4. Chromatograms of (a) Haldol® diluted to 50 μg/ml haloperidol stored for 28 days at 60°C; and (b) morphine hydrochloride injected under optimal chromatographic conditions used for the quantification of haloperidol as indicated in the text.

Fig. 5. Chromatograms of (a) Decadron® Pack diluted to 100 μg/ml dexamethasone as dexamethasone sodium phosphate (I = dexamethasone sodium phosphate, II = dexamethasone, III = methylparaben and IV = propylparaben; and (b) morphine hydrochloride and its degradation products injected under optimal chromatographic conditions used for the determination of the stability of dexamethasone sodium phosphate as indicated in the text.

Fig. 6. Chromatograms of (a) methylprednisolone-21-sodium succinate (450 μg/ml) (I), methylprednisolone-17-sodium succinate (45 μg/ml) (II), methylprednisolone (25 μg/ml) (III) and fluorometholone (= internal standard, 200 μg/ml) (IV); and (b) morphine hydrochloride and its degradation products injected under optimal chromatographic conditions used for the determination of the stability of methylprednisolone-21-sodium succinate as indicated in the text.

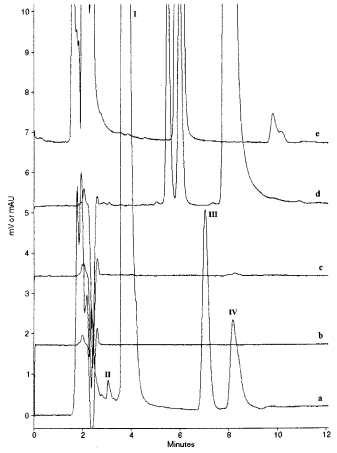

Fig. 2

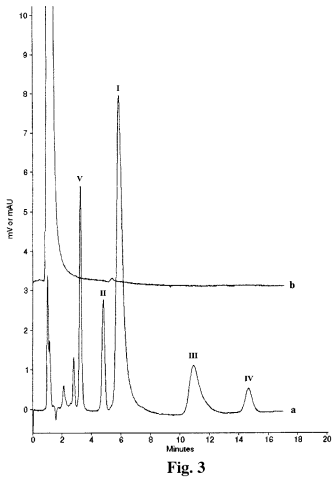

Fig. 3

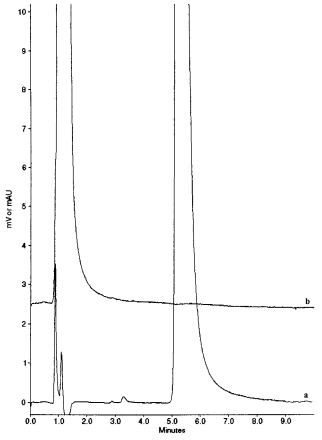

Fig. 4

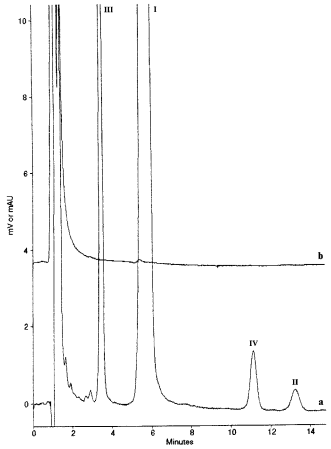

Fig. 5

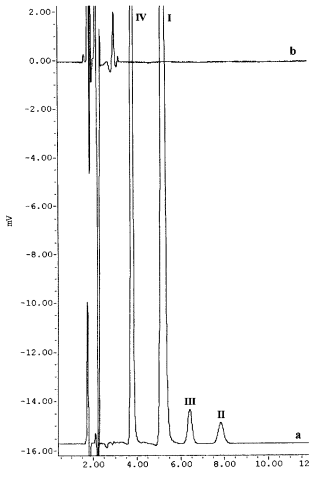

Fig. 6

Figs. 2–6.

(v/v). This mobile phase was used at a flow rate of 1 ml/min on a Lichrospher RP-18 (125 × 4 mm, 5 μm) column (Merck, Darmstadt, Germany) and the detection wavelength was set at 245 nm. Under these chromatographic conditions midazolam was well separated from the four main degradation products: desalkylflurazepam, 6-(8-chloro-1-methyl-4,5-dihydro-2,5,10b-tri-azabenzo[e]azulen-6-ylidene)cyclohexa-2,4-dienone, 6-chloro-2-methyl-4-(2-fluorophenyl)quinazoline and 6-chloro-2-methyl-4(1H)-quinazolinone (Pharmaceutical Chemistry Division, Department of Pharmacy, University of Helsinki, Finland) (Fig. 3a). Injection of a morphine hydrochloride solution (1 mg/ml) also containing morphine-*N*-oxide (10 μg/ml), pseudomorphine (10 μg/ml) and apomorphine hydrochloride (5 μg/ml) under the same chromatographic conditions indicated there was no interference with the compounds of interest (Fig. 3b). Good linearity was obtained for midazolam over the entire calibration range (1–50 μg/ml) with determination coefficients >0.999. The within and between day coefficients of variation for midazolam (1–50 μg/ml, $n=5$) were 2.90% ($\pm$ 1.31) and 3.22% ($\pm$ 1.26), respectively. For the determination of haloperidol a new method was developed and validated. A Lichrospher RP-18 (125 × 4 mm, 5 μm) column (Merck, Darmstadt, Germany) was used with a mobile phase consisting of monosodium phosphate (0.1 M)/acetonitrile in a ratio 65/35 (v/v) (pH 4.95) at a flow rate of 1 ml/min; the detection wavelenght was set at 254 nm. The stability indicating capacity of the method was evaluated by comparing the chromatograms of haloperidol lactate solutions (50 μg/ml) of different pH (2.0, 3.9 and 6.5) stored under three different circumstances: at 22 and 60°C unprotected from light and at 60°C protected from light for 28 days with the chromatogram of a freshly prepared haloperidol lactate solution (50 μg/ml haloperidol) in water (pH 3.9). During storage additional peaks were observed mainly in the solutions stored in the presence of light, but none of these peaks interfered with the peaks of interest. Injection of a morphine hydrochloride solution (1 mg/ml) containing also morphine-*N*-oxide (10 μg/ml), pseudomorphine (10 μg/ml) and apomorphine hydrochloride (5 μg/ml) under optimal chromatographic conditions indicated that these compounds did not interfere with the quantification of haloperidol (Fig. 4). For haloperidol a good linearity ($r^2>0.999$) was observed over the entire calibration range (1–50 μg/ml). The within- and between-day coefficients of variation for haloperidol (1–50 μg/ml, $n=5$) were 1.23% ($\pm$ 0.46) and 1.16% ($\pm$ 0.79). For the determination of dexamethasone sodium phosphate and its main degradation product, dexamethasone, the method of Das Gupta (1979) was slightly modified and validated. The detection wavelength was set at 239 nm, the absorption maximum of dexamethasone and the composition of the mobile phase was changed. During preparation of the eluent as described by Das Gupta (1979) crystals were observed immediately after preparation. When the monopotassium phosphate (0.01 M) was substituted by oxalic acid (0.01 M) no crystals were observed after mixing the buffer with methanol in the same ratio (50/50, v/v) and adjusting the pH to 6. Using this mobile phase at a flow rate of 1 ml/min on a Lichrospher RP-18 (125 × 4 mm, 5 μm) column (Merck, Darmstadt, Germany) a good separation of dexamethasone sodium phosphate and its main degradation product, dexamethasone (Sigma-Aldrich, Bornem, Belgium), was obtained. The stability indicating capacity of the method was evaluated by HPLC analysis of dexamethasone sodium phosphate solutions (100 μg/ml) prepared in water, sodium hydroxide (2 M) and hydrochloride (2 M) immediately after preparation and after 0.5, 1, 2, 7 and 14 days storage at 60°C. In all solutions dexamethasone was the main degradation product formed, minor other peaks were also detected but these peaks did not interfere with the peaks of interest. From Fig. 5 it can be seen that neither the additives present in the dexamethasone formulation or morphine and its degradation products interfered with the peaks of interest. The within- and between-day coefficients of variation for dexamethasone sodium phosphate (10–500 μg/ml, $n=5$) were 1.51% ($\pm$ 0.35) and 2.19% ($\pm$ 0.51) and for dexamethasone (0.2–25 μg/ml, $n=5$) 3.79% ($\pm$ 1.48) and 3.75% ($\pm$ 1.33), respectively. For both components the determination

coefficients were >0.998 over the entire calibration range (dexamethasone sodium phosphate: 10–500 μg/ml and dexamethasone 0.2–25 μg/ml). The concentration of methylprednisolone-21-sodium succinate and its main degradation products (free methylprednisolone and methylprednisolone-17-sodium succinate, both from Upjohn and Pharmacia, Kalamazoo, US) was performed using a validated HPLC assay. Therefore a Microporasil column (silicagel, 10 μm, 300 × 3.9 mm, Waters, Brussels, Belgium) was used. The mobile phase consisted of 50% water saturated *n*-butylchloride/tetrahydrofuran/methanol/glacial acid (950/70/35/30, v/v/v/v). The flow rate was set at 1.8 ml/min and a detection wavelength at 254 nm was used. Using these chromatographic conditions a good separation of mehylprednisolone-21-sodium succinate and its main degradation products was obtained and there was no interference of morphine or its degradation products with the peaks of interest (Fig. 6). The residual standard ($n=6$) deviation was 0.23% for methylprednisolone-21-sodium succinate 800 μg/ml and 1.36% for methylprednisolone 40 μg/ml. For methylprednisolone-21-sodium succinate 30 to 1200 μg/ml and methylprednisolone 3 to 120 μg/ml the determination coefficients were above 0.999. The concentration of methylprednisolone-17-sodium succinate was calculated from the calibratiocurves of methylprednisolone-21-sodium succinate.

All HPLC determinations were performed only once. The purity of the quantified drug substance peaks in the admixtures stored for 28 days was checked by diode array detection (DAD) analysis (Hewlet Packard, 1040A HPLC detection system) and indicated no interference from the degradation products or the other substances present in the admixtures.

For the evaluation of the stability the concentration of the parent drugs was expressed as the percentage of the initial drug concentration and the concentration of the degradation products was expressed as the percentage of the total drug concentration (drug + degradation product(s)).

3. Results

3.1. Compatibility of morphine hydrochloride with midazolam hydrochloride, haloperidol lactate, dexamethasone sodium phosphate or methylprednisolone-21-sodium succinate

The compatibility range of morphine hydrochloride with midazolam hydrochloride is shown in Fig. 7. Dormicum® was visually compatible with morphine hydrochloride (50 mg/ml) up to a ratio D/M:10/10 (v/v). There was no influence of isotonizing the morphine hydrochloride solution or the order of mixing on the compatibility. The maximal amount of morphine hydrochloride that can be dissolved per ml Dormicum® and its dilutions 4/5, 3/5, 2/5, 1/5 and 1/10 (v/v) in water was 30, 32.5, 40, 42.5, 45 and 50 mg, respectively. HPLC analysis of the supernatant and the precipitate in the admixture prepared by adding 50 mg/ml morphine hydrochloride powder to Dormicum® revealed that mainly morphine precipitated, as confirmed by NMR analysis.

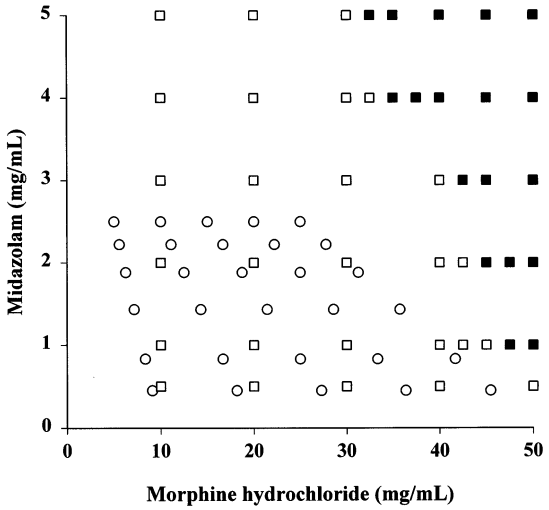

Fig. 7. Compatibility range of morphine hydrochloride with midazolam hydrochloride: final concentrations of compatible (○) and incompatible (●) admixtures prepared by adding Dormicum® to morphine hydrochloride solutions, compatible (□) and incompatible (■) admixtures prepared by the addition of morphine hydrochloride powder to the drug solution.

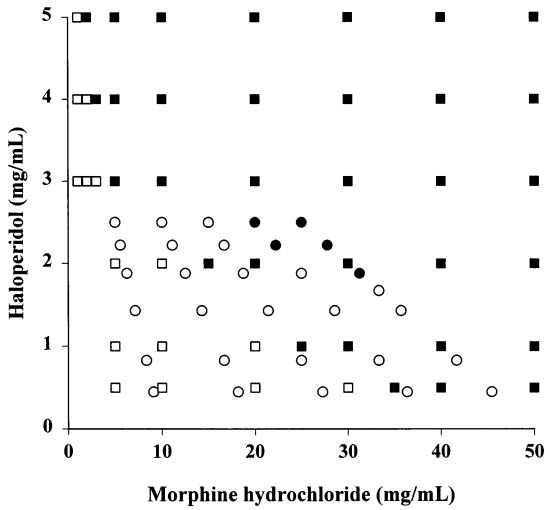

Fig. 8. Compatibility range of morphine hydrochloride with haloperidol lactate: final concentrations of compatible (○) and incompatible (●) admixtures prepared by adding Haldol® to morphine hydrochloride solutions, compatible (□) and incompatible (■) admixtures prepared by the addition of morphine hydrochloride powder to the drug solution.

The compatibility range of morphine hydrochloride with haloperidol lactate is shown in Fig. 8. Compatible admixtures of Haldol® with morphine hydrochloride 10, 20, 30, 40 and 50 mg/ml were obtained up to a ratio D/M: 10/10, 10/10, 10/10, 6/10 and 5/10 (v/v), respectively. There was no influence of isotonizing the morphine hydrochloride solutions with sodium chloride or dextrose. For admixtures with haloperidol the compatibility was clearly influenced by the order of mixing. When adding the morphine hydrochloride solution to the haloperidol solutions, precipitation was observed at a lower ratio drug/morphine hydrochloride than for the admixtures prepared by adding the haloperidol solution to the morphine hydrochloride solution. The maximal amount of morphine hydrochloride that can be dissolved per ml Haldol® and its dilutions 4/5, 3/5, 2/5, 1/5 and 1/10 (v/v) in water was 1, 2, 3, 10, 20 and 30 mg, respectively. Larger amounts seemed to be soluble immediately after preparation but precipitation occurred after some days. HPLC analysis of the supernatant and the precipitate in the admixture prepared by adding 50 mg/ml morphine hydrochloride to Haldol® revealed that mainly haloperidol precipitated as confirmed by NMR analysis. In the NMR spectrum only peaks corresponding to morphine and haloperidol were found; no peak corresponding to the lactate was present.

The compatibility range of morphine hydrochloride with methylprednisolone-21-sodium succinate is shown in Fig. 9. In a ratio corticosteroid solution/morphine hydrochloride solution:1/10 (v/v) the maximal concentration of methylprednisolone compatible decreased from 100 to 15 mg/ml for increasing morphine hydrochloride concentrations from 10 to 50 mg/ml. There was no influence isotonizing the morphine hydrochloride solutions on the compatibility, but the order of mixing did influence the compatibility. When adding the morphine hydrochloride solution to the methylprednisolone solution in the same concentration and ratio precipitation it was seen for admixtures that were compatible when prepared by adding the methylprednisolone-21-sodium succinate solution to the morphine hydrochloride solution. HPLC analysis of the supernatant and the precipitate in the admixture prepared by adding 50 mg/ml morphine hydrochloride to the methylprednisolone solution

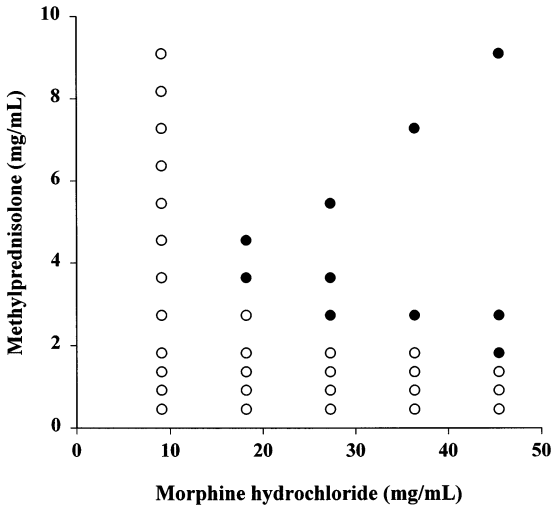

Fig. 9. Compatibility range of morphine hydrochloride with methylprednisolone-21-sodium succinate: final concentrations of compatible (○) and incompatible (●) admixtures prepared by adding the methylprednisolone-21-sodium succinate solution to the morphine hydrochloride solution.

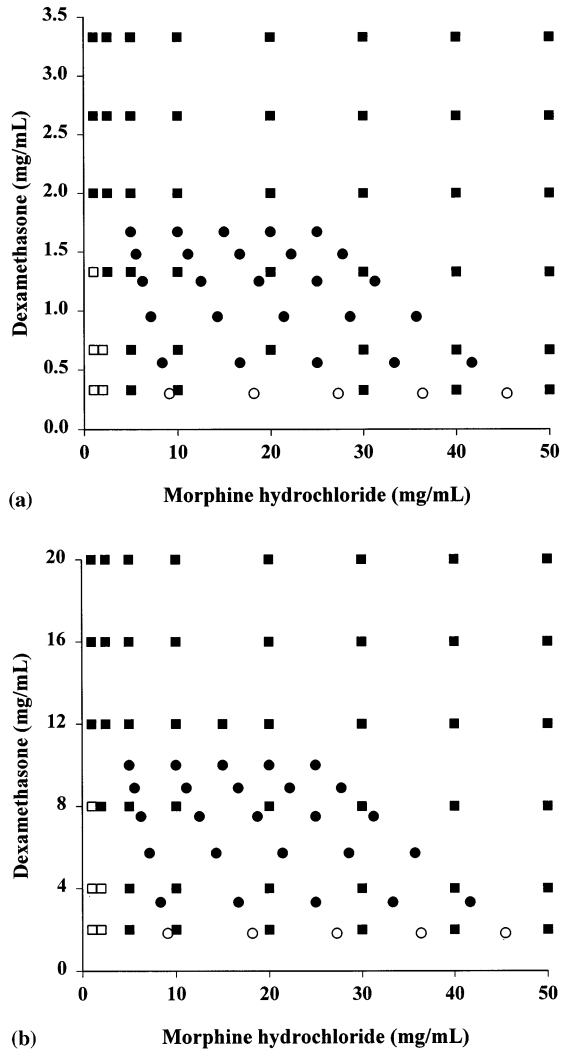

Fig. 10. Compatibility of morphine hydrochloride with dexamethasone sodium phosphate using (a) Decadron® and (b) Decadron Pack®: final concentrations of compatible (○) and incompatible (●) admixtures prepared by adding the dexamethasone sodium phosphate solution to the morphine hydrochloride solution, compatible (□) and incompatible (■) admixtures prepared by the addition of morphine hydrochloride powder to the dexamethasone sodium phosphate solutions.

100 mg/ml (as the 21-sodium hemisuccinate salt) in water indicated that the precipitate consisted mainly of morphine, but also methylprednisolone was precipitated, as confirmed by NMR analysis.

The compatibility range of morphine hydrochloride with dexamethasone sodium phosphate (Decadron® and Decadron® Pack) is shown in Fig. 10. Morphine hydrochloride solutions (10–50 mg/ml) prepared in water and isotonized with sodium chloride or dextrose were visually compatible with undiluted Decadron® and Decadron® Pack up to a ratio corticosteroid solution/morphine hydrochloride solution 1/10 (v/v). When adding Decadron® Pack to the morphine hydrochloride solutions at high concentrations the solution should be shaken immediately in order to avoid precipitation. Mixing morphine hydrochloride solutions with Decadron® Pack in a ratio 2/10 (v/v) resulted immediately in the formation of a fine white precipitate that could not be dissolved by shaking. Increasing this ratio for Decadron® did not result in the immediate formation of precipitate, but within 3 days small crystals were formed on the bottom of the tube. The compatibility of both dexamethasone solutions was also clearly influenced by the order of mixing, and incompatibility was observed for admixtures that were compatible when prepared by adding the dexamethasone solution to the morphine hydrochloride solution. The maximal amount of morphine hydrochloride powder that could be dissolved per ml Decadron® and Decadron® Pack and its dilutions 4/5 and 3/5 (v/v) was less than 1 mg and was 1, 2 and 2 mg in its dilutions 2/5, 1/5 and 1/10 (v/v), respectively. When exceeding these limits clear solutions could be obtained by sonication, but after a few days (1–7 days) small yellow spots sticking to the bottom of the tube were formed. As large differences were seen between the compatibility range as determined by mixing solutions versus that obtained by dissolving morphine hydrochloride in the dexamethasone solutions, this was further investigated. When heating the admixture of morphine hydrochloride 50 mg/ml with both undiluted dexamethasone solutions in a ratio D/M:1/10 (v/v), a comparable amount of precipitate was formed as in the admixture prepared by adding 50 mg/ml morphine hydrochloride to both dexamethasone solutions diluted 1/11 (v/v) in water. HPLC analysis of the supernatant and the precipitate in the admixture prepared by dissolving 50 mg/ml morphine hydrochloride in Decadron® and Decadron® Pack indicated that both drugs precipitated. In the admixtures with Decadron® however only traces of dexamethasone were

present, whereas in the admixtures with Decadron® Pack both drugs were present in substantial amounts. NMR analysis of the precipitates confirmed these results and showed that next to morphine and dexamethasone also the additives were present in the precipitate.

3.2. Stability of the admixtures containing morphine hydrochloride and midazolam hydrochloride, haloperidol lactate, dexamethasone sodium phosphate or methylprednisolone-21-sodium succinate

The three concentrations of midazolam and haloperidol mixed with morphine hydrochloride (10 and 50 mg/ml isotonized with dextrose) were 1, 2.5 and 5 mg/ml for midazolam and haloperidol, 0.83, 1.67 and 3.33 mg/ml for dexamethasone prepared from Decadron® and 4, 10 and 20 mg/ml for dexamethasone prepared from Decadron® Pack. The three concentrations of methylprednisolone mixed with 10 mg/ml morphine hydrochloride were 10, 50 and 100 mg/ml and with 50 mg/ml morphine hydrochloride 5, 10 and 15 mg/ml.

In none of the admixtures and the drug solutions used to prepare the admixtures any visual change was noticed during storage, except for some of the admixtures prepared using undiluted Decadron® and Decadron® Pack in which small crystals were formed on the bottom of the tubes after a storage period ranging from 1 to 28 days. Further investigation of this late crystallization showed that the rate of formation of these crystals depended on small changes of ambient temperature and the presence of dust in the solutions, acting as crystallization seeds.

The concentration of the parent drug and of the degradation products, the pH and the osmolality of the solutions and admixtures containing midazolam hydrochloride, haloperidol lactate, methylprednisolone-21-sodium succinate or dexamethasone sodium phosphate recorded during storage are shown in Tables 1–3. The concentration of midazolam and haloperidol remained above 95% of the initial concentration in all admixtures and solutions studied. In none of the admixtures or solutions with haloperidol or midazolam were any degradation products of midazolam or haloperidol detected.

The concentration of methylprednisolone-21-sodium succinate in the solutions stored at 22°C decreased to less than 90% of the initial drug concentration after 7 and 28 days for a concentration of 5 and 100 mg/ml, respectively. In the admixtures stored at 22°C the concentration of methylprednisolone remained above 90% of the initial concentration for 3 to 7 days and decreased with 20 to 50% after 28 days. In the admixtures stored at 4°C for 1 week followed by a 1 day storage at 22°C the concentration of methylprednisolone-21-sodium succinate remained above 90% of the initial concentration during the entire storage period.

The concentration of dexamethasone sodium phosphate in undiluted and diluted Decadron® Pack solutions remained above 99% of the initial concentration. The Decadron® solutions also showed an excellent stability ($>99\%$ of initial concentration), but in the dilutions of Decadron® containing 0.83 and 1.67 mg/ml dexamethasone the percentage of the initial concentration of dexamethasone sodium phosphate remaining after 28 days of storage was 90.06 and 98.67%, respectively. In the admixtures of morphine hydrochloride with Decadron® undiluted and diluted to 1.67 and 0.83 mg/ml dexamethasone the concentration of dexamethasone sodium phosphate remained above 90% of the initial concentration for 28, 14 and 7 days, respectively. In the admixtures of morphine hydrochloride (10 and 50 mg/ml) with undiluted and diluted Decadron® Pack solutions the concentration of dexamethasone sodium phosphate remained above 95 and 90% of the initial drug concentration, respectively after 28 days of storage at 22°C. In all solutions containing dexamethasone sodium phosphate, free dexamethasone was found as a major degradation product and its concentration increased to the same extent as the decrease in dexamethasone sodium phosphate concentration. Besides the peaks of the exipients present in the dexamethasone formulation no additional peaks were seen on the chromatograms of all solutions analyzed.

In all admixtures the concentration of morphine hydrochloride remained above 99% of the initial concentration. The two major degradation products, morphine-*N*-oxide and pseudomorphine, were present in all solutions and increased during

Table 1
Stability of morphine hydrochloride, midazolam hydrochloride and haloperidol lactate, pH and osmolality of the solutions and admixtures during storage for 28 days at 22°C protected from light

Solutions used to prepare admixture			Ratio (D/M)	Final concentration (mg/ml)		Percentage remaining after 28 days at 22°C[a]		pH		Osmolality (mOsm/kg)	
Name	D (mg/ml)	M (mg/ml)		D	M	D	M	0 days	28 days	0 days	28 days
Haldol®	0.5	—	—	0.50	—	101.78	—	3.67	3.72	26	26
		10	1/10	0.05	9.09	94.76	99.96	4.46	4.44	274	283
		50	1/10	0.05	45.45	99.86	99.86	4.21	4.34	275	274
	2.5	—	—	2.50	—	97.83	—	3.46	3.48	60	63
		10	1/10	0.23	9.09	97.81	99.90	3.79	3.82	287	279
		50	1/10	0.23	45.45	100.01	99.79	3.72	3.74	282	276
	5.0	—	—	5.00	—	95.37	—	3.49	3.49	84	78
		10	1/10	0.45	9.09	97.21	99.90	3.63	3.66	284	282
		50	1/10	0.45	45.45	101.33	99.77	3.58	3.61	277	278
Dozmicum®	0.5	—	—	0.50	—	99.05	—	4.48	4.54	71	70
		10	1/10	0.05	9.09	99.65	100.00	5.57	5.58	286	290
		50	1/10	0.05	45.45	102.31	99.90	5.34	5.01	286	287
	2.5	—	—	2.50	—	97.78	—	3.53	3.50	165	159
		10	1/10	0.23	9.09	102.88	100.01	4.53	4.50	291	287
		50	1/10	0.23	45.45	99.18	99.88	4.42	4.35	286	292
	5.0	—	—	5.00	—	102.22	—	3.35	3.36	288	292
		10	1/10	0.45	9.09	103.39	99.92	4.15	3.97	302	297
		50	1/10	0.45	45.45	100.81	99.89	3.85	4.05	302	300

D = drug M = morphine hydrochloride.
[a] Concentration expressed as percentage of the initial concentration.

Table 2
Stability of morphine hydrochloride and methylprednisolone-21-sodium succinate, pH and osmolality of the solutions and the admixtures during storage for 28 days at 22°C and for 7 days at 4°C followed by 1 day storage at 22°C and protected from light

Storage conditions	Solutions used to prepare admixtures		Ratio (D/M)	Final concentration (mg/ml)		Percentage remaining after storage				pH		Osmolality (mOsm/kg)	
	D (mg/ml)	M (mg/ml)		D	M	MP21[a]	MP[b]	MP17[b]	M[a]	Initial	Final	Initial	Final
28 days at 22°C	5	—	—	5.00	—	72.08	23.07	10.73	—	7.97	6.51	52	51
		10	1/10	0.45	9.09	66.20	9.08	25.53	99.99	6.26	4.38	273	273
		50	1/10	0.45	45.45	78.68	2.81	23.68	99.93	5.64	3.65	269	273
	10	—	—	10.00	—	74.87	21.24	9.48	—	7.88	6.50	78	76
		50	1/10	0.91	45.45	60.14	7.10	37.67	99.96	5.90	3.53	272	274
	15	—	—	15.00	—	74.76	21.58	8.74	—	7.83	6.52	108	110
		50	1/10	1.36	45.45	47.64	17.20	37.50	99.96	6.07	3.70	272	276
	50	—	—	50.00	—	84.20	14.56	6.70	—	7.68	6.55	264	1263
		10	1/10	4.45	9.09	77.82	12.96	11.09	100.02	7.03	6.41	272	274
	100	—	—	100.00	—	85.10	19.78	12.50	—	7.56	6.50	>400[c]	>400[c]
		10	1/10	9.09	9.09	77.29	14.79	10.08	100.00	7.18	6.79	325	330
7 days at 4°C+1 day at 22°C	5	10	1/10	0.45	9.09	94.50	2.14	1.96	100.00	6.26	6.27	273	274
		50	1/10	0.45	45.45	95.51	3.25	2.70	99.96	5.64	5.68	270	272
	10	50	1/10	0.91	45.45	95.27	3.95	3.00	99.97	5.90	5.95	273	273
	15	50	1/10	1.36	45.45	94.55	3.88	3.39	99.95	6.07	6.12	273	274
	60	10	1/10	5.45	9.09	92.36	3.69	1.71	100.10	7.03	7.01	272	273
	100	10	1/10	9.09	9.09	92.37	3.88	2.09	100.11	7.18	7.10	325	327

D = drug M = morphine hydrochloride.
[a] Concentration of morphine hydrochloride (M) and methylprednisolone-21-sodium succinate (MP21) expressed as percentage of the initial concentration.
[b] Concentration of methylprednisolone-17-sodium succinate (MP17) and methylprednisolone (MP) expressed as percentage of the total methylprednisolone concentration.
[c] Exceeds measuring range of apparatus (0–400 mOsm/kg).

Table 3
Stability of morphine hydrochoride and dexamethasone sodium phosphate, pH and osmolality of the solutions and the admixtures during storage for 28 days at 22°C and protected from light

Solutions used to prepare admixtures			Ratio (D/M)	Final concentration (mg/ml)		Percentage remaining after 28 days at 22°C			pH		Osmolality (mOsm/kg)	
Formulation	D (mg/ml)	M (mg/ml)		D	M	Dex. Phosph.[a]	Dex.[b]	M[a]	0 days	28 days	0 days	28 days
Decadron®	0.83	—	—	0.83	—	90.06	10.36	—	7.74	7.43	61	62
		10	1/10	0.08	9.09	79.96	22.57	99.97	6.40	4.58	273	278
		50	1/10	0.08	45.45	81.51	20.75	99.98	5.87	3.70	267	270
	1.67	—	—	1.67	—	98.67	1.59	—	7.69	7.60	118	119
		10	1/10	0.15	9.09	86.52	15.41	99.92	6.60	5.65	274	286
		50	1/10	0.15	45.45	89.39	12.86	99.96	6.00	5.09	278	281
	3.33	—	—	3.33	—	99.99	0.27	—	7.69	7.52	234	232
		10	1/10	0.30	9.09	97.22	3.95	99.81	6.73	6.42	294	286
		50	1/10	0.30	45.45	99.89	1.35	99.95	6.18	6.13	284	287
Decadron® Pack	4	—	—	4.00	—	99.24	0.84	—	7.97	7.88	75	75
		10	1/10	0.36	9.09	96.41	4.26	100.02	6.55	4.50	269	272
		50	1/10	0.36	45.45	92.71	8.05	99.98	5.97	4.02	267	272
	10	—	—	10.00	—	99.78	0.28	—	8.06	8.02	178	177
		10	1/10	0.91	9.09	97.79	2.64	99.83	6.75	5.23	284	288
		50	1/10	0.91	45.45	91.84	8.62	99.98	6.20	4.82	274	276
	20	—	—	20.00	—	100.00	0.06	—	8.11	8.04	341	345
		10	1/10	1.81	9.09	96.56	3.68	99.89	6.93	6.38	295	297
		50	1/10	1.81	45.45	99.60	0.67	99.91	6.38	6.32	293	293

D = drug M = morphine hydrochloride.
[a] Concentration of morphine hydrochloride (M) and dexamethasone sodium phosphate (Dex. Phosph.) expressed as the percentage of the initial concentration.
[b] Concentration of dexamethasone (Dex.) expressed as the percentage of the total dexamethasone concentration.

storage but their concentration remained below 0.6% of the total morphine concentration. In none of the admixtures apomorphine was detected.

The initial pH of the admixtures with haloperidol or midazolam ranged from 3.5 to 5.6, and that of the admixtures with the corticosteroids from 5.5 to 7.5. The pH of the admixtures and the solutions containing haloperidol or midazolam remained almost constant over the period studied, whereas that of the admixtures and solutions with dexamethasone or methylprednisolone decreased during storage to reach a final pH ranging from 3.5 to 6.5. The pH of the admixtures and of the solutions with methylprednisolone decreased (decrease < 2.5) during storage for 28 days at 22°C, but remained constant for 1 weeks storage at 4°C followed by 1 days storage at 22°C. For the admixtures with the dexamethasone solutions the decrease in pH was higher in the admixtures with the diluted Decadron® and Decadron® Pack solutions (decrease < 2.5) than in the admixtures with the undiluted Decadron® and Decadron® Pack solutions (decrease < 0.6) but higher in the admixtures than in the solutions.

The initial osmolality of the drug solutions indicated that some of the commercially available solutions (Haldol® (84 mOsm/kg), Decadron® (234 mOsm/kg) and Decadron® Pack (341 mOsm/kg)) were not isotonic. This was also the case for the methylprednisolone solution at maximal concentration (100 mg/ml) which was strongly hypertonic (> 400 mOsm/kg). This explains why the admixtures prepared using isotonic morphine hydrochloride solutions were not isotonic but slightly hypotonic or hypertonic (270–330 mOsm/kg). In all solutions and admixtures the osmolality remained constant during the period studied.

4. Discussion

The subcutaneous infusion of drugs by a syringe driver provides major benefits in palliative care, allowing comfortable parenteral treatment of pain and other symptoms frequently occurring in terminally ill patients. In many cases, combinations of drugs are administered, resulting in possible drug incompatibility or loss of stability. Incompatibility might cause drug precipitation or crystallization resulting in the blockage of the cannula, skin irritation and poor absorption. Although admixtures of morphine hydrochloride with other drugs are frequently prescribed for subcutaneous infusion in terminally ill patients, to our knowledge no useful data are available neither on the compatibility nor on the stability of these admixtures. In this study the stability and the compatibility of admixtures of morphine hydrochloride with Dormicum®, Haldol®, Decadron® (Pack) or Solu-Medrol®, drugs frequently combined in palliative care, was investigated.

From the compatibility data (Figs. 7–10) it can be calculated that at an infusion rate of 0.5 ml/h a daily dose of 20 mg haloperidol can be administered together with 400 mg morphine hydrochloride using the admixture of both drug solutions at maximal concentration in a ratio D/M:5/10 (v/v). A daily dose of 30 mg midazolam can be administered together with 300 g morphine hydrochloride using the admixture of the drug solutions at maximal concentration in a ratio D/M:10/10 (v/v) infused at 0.5 ml/h. The maximal daily dose of dexamethasone that can administered together with 545 mg morphine hydrochloride at 0.5 ml/h is 3.6 or 22 mg using the admixture in a ratio D/M:1/10 (v/v) prepared with 50 mg/ml of morphine hydrochloride and Decadron® or Decadron® Pack, respectively. A daily dose of 109 mg methylprednisolone can be administered together with 109 mg morphine hydrochloride, using the admixture prepared by mixing methylprednisolone 100 mg/ml with morphine hydrochloride 10 mg/ml in a ratio D/M:1/10 (v/v) infused at 0.5 ml/h. This is within the dose limits usually prescribed in terminally ill patients (Twycross, 1986; Bottomley and Hanks, 1990; Needham et al., 1992; Clément and Schrooten, 1997).

Forman and Souney (1987) and Lebelle et al. (1995) who studied the compatibility of midazolam hydrochloride (5 mg/ml) with morphine sulphate (10 mg/ml) also reported compatibility of the admixture prepared in a ratio D/M:10/10 (v/v), admixtures prepared with higher concentrations of morphine sulphate were not evaluated. The compatibility of midazolam hydrochloride with low concentrations of morphine sulphate was also re-

ported by Johnson et al. (1994). This however does not imply that the results on the compatibility with morphine hydrochloride at higher concentrations can be extrapolated to similar admixtures with morphine sulphate, since the salt form used can play an important role in the compatibility observed.

The admixtures of midazolam hydrochloride with diamorphine hydrochloride that were reported to be compatible (Allwood et al., 1994) were within the compatibility range of midazolam hydrochloride with morphine hydrochloride. The fact that mainly morphine precipitated in the admixtures prepared by adding 50 mg/ml of morphine hydrochloride to Dormicum®, as shown by HPLC and NMR analysis of the precipitate and the supernatant, could be explained by the fact that morphine hydrochloride at 45 mg/ml is near its saturation concentration, whereas the concentration of midazolam remained far below its solubility limits at this pH (Janknegt et al., 1986). As the solubility of morphine hydrochloride has been described to be lower in sodium chloride 0.9% vs water (Vermeire and Remon, 1997), the sodium chloride present in the midazolam solution could cause the precipitation of morphine hydrochloride of which the concentration was very near its solubility limits in water.

Lebelle et al. (1995) who studied the compatibility of Haldol® with morphine sulphate reported incompatibility for admixtures prepared by mixing Haldol® and morphine sulphate (10 mg/ml). These differences in compatibility range could be due to the different salt form used or to the parabens present in the Haldol® solution used in that study which were not present in the Haldol® solutions used for this study.

NMR analysis of the precipitate in admixtures prepared by adding 50 mg/ml of morphine hydrochloride to Haldol® indicated that in these admixtures haloperidol precipitated not as the haloperidol lactate, since no lactate peak was observed. The precipitation of haloperidol lactate in the presence of high concentrations of morphine hydrochloride is possibly due to the formation of haloperidol hydrochloride, which has a much lower solubility than haloperidol lactate (Olçer and Hakyemez, 1988). Similar incompatibilities of haloperidol lactate with diamorphine hydrochloride (Regnard et al., 1986; Allwood, 1991) and hydromorphone hydrochloride (Huang and Anderson, 1994) in dilutions with 0.9% NaCl (Outman and Monolakis, 1991; Fraser and Riker, 1994) have been reported.

The compatibility range found for admixtures of morphine hydrochloride with methylprednisolone-21-sodium succinate was in agreement with the data reported by Pugh et al. (1991), who reported compatibility for an admixture containing 1.25 mg/ml methylprednisolone-21-sodium succinate and 0.5 mg/ml morphine sulphate.

The compatibility range of dexamethasone sodium phosphate with morphine hydrochloride was smaller than was published for admixtures with hydromorphone hydrochloride (Walker et al., 1991). In this study however another formulation of dexamethasone sodium phosphate was used and the compatibility was evaluated at slightly higher temperatures and only for 24 h. As all these factors were shown to have an important influence on the compatibility observed, comparisons can hardly be made. Pugh et al. (1991) reported that low concentrations of dexamethasone sodium phoshate were also compatible with low concentrations of morphine sulphate. The compatibility range of dexamethasone was always higher for Decadron® Pack than for Decadron® and could be explained by the higher additive concentration for a certain dexamethasone concentration in Decadron® vs Decadron® Pack. The fact that the additives present in the dexamethasone formulation played a major role in the compatibility was confirmed by the presence of these additives in the precipitate as determined by HPLC and NMR analysis.

It should be emphasized that our results of the compatibility study are based on evaluation of the admixtures for 1 week after their preparation at a temperature of 22 ± 2°C. Small changes in temperature might significantly influence the compatibility, and visual inspection is therefore recommended. Immediately after preparation higher concentrations of morphine hydrochloride and the drug seemed compatible, but after some days small suspect particles were observed. The phenomenon of late crystallization was also reported by Lebelle et al. (1995) in admixtures of midazolam hy-

drochloride and haloperidol lactate with morphine sulphate and by Regnard et al. (1986) in admixtures of diamorphine hydrochloride with haloperidol lactate. In this study delayed precipitation was also observed in the admixtures with both corticosteroids.

It should also be stressed that the compatibility limits presented here are based on the compatibility data as determined by adding drug solution to the morphine hydrochloride solution, other methods of preparation resulted in precipitation within these compatibility limits, except for the admixtures with midazolam hydrochloride. Using the admixture prepared by dissolving 50 mg/ml morphine hydrochloride powder in the midazolam solution (3 mg/ml) a daily dose of 360 mg midazolam can be administered together with 600 mg morphine hydrochloride. The fact that for admixtures with haloperidol, dexamethasone and methylprednisolone the way of preparation influenced the compatibility is possible on short term. However, finally all admixtures with the same composition, although prepared in different ways, should all become either compatible or incompatible. Acceleration of the aging process by heating the admixtures caused precipitation and revealed that the admixtures of these drugs prepared by adding the drug solution to the morphine hydrochloride solution were compatible only for a limited period of time. By adding morphine hydrochloride solution or powder to the drug solution, the ratio D/M is varying from 1/0 over 1/1 to 1/10 (v/v). The high concentrations of morphine hydrochloride occurring when preparing the admixtures by adding the morphine hydrochloride solution or powder to the drug solution also probably accelerate the incompatibility process. By adding the drug solution to the morphine hydrochloride solution this combination of concentrations is never obtained and incompatibility is not induced immediately. The results of the stability study showed that, when prepared in this way, the admixtures remained visually stable for 28 days, although visual inspection is recommended.

As the choice of the diluent might affect the drug solubility the compatibility was investigated with morphine hydrochloride solutions prepared with water and isotonized morphine hydrochloride solutions. Isotonization of morphine hydrochloride solutions did not result in an isotonic admixture, but in daily practice it is not possible to optimize the tonicity of each particular admixture (ratio, drug solution used,…) and the osmolality of the admixtures prepared using isotonized morphine hydrochloride solutions did not deviate a lot from isotonicity (270–330 mOsm/kg) since the main part of the solution always consisted of morphine hydrochloride solution. Although Outman and Monolakis (1991) and Fraser and Riker (1994) showed that haloperidol (as the lactate salt) at a concentration of 1 mg/ml or above precipitated in sodium chloride 0.9%, in our study no influence of isotonization of the morphine hydrochloride solutions on the compatibility was seen. This can be explained by the lower concentrations of sodium chloride present in the admixtures. The maximal concentration of haloperidol obtained in an admixture prepared in a ratio D/M:10/10 (v/v) was 2.5 mg/ml but the concentration of sodium chloride in that admixture was below 0.4%. For the other drugs also the isotonization of the morphine hydrochloride solutions did not affect the compatibility. Therefore isotonization of the morphine hydrochloride solutions is advisable to reduce the risk of irritation during subcutaneous administration. Dextrose is to be preferred as isotonizing agent as sodium chloride might cause precipitation in some cases at higher drug concentrations.

The initial pH values of the admixtures with haloperidol or midazolam and the final pH of all admixtures were far below the physiological pH of 7.4. Solutions with a low pH are described to have a higher irritation potential when infused intravenously (Lewis and Hecker, 1985), and cause more pain when injected subcutaneously (Fransson and Espander-Jansson, 1996). Increasing the pH of these drug solutions would cause precipitation of the drugs since at physiological pH both drugs exist in the base form. Moreover both drug solutions are reported to be well tolerated when infused subcutaneously (Bottomley and Hanks, 1990; Storey et al., 1990).

In the home care settings patients often receive their medication for a longer period of time, therefore in this study the stability of the admix-

tures was studied over a period of 28 days. As from our experience the admixtures seemed to be most frequently prescribed at a ratio D/M:1/10 (v/v), the stability of these admixtures was evaluated.

Comparison of the percentage of initial drug concentration remaining after 28 days in undiluted Dormicum® and Haldol® with that of their dilutions shows that there was no influence of the dilution on the stability of both drugs. These results are in agreement with the findings of Pramar et al. (1997) and Janicki and Ko (1980) who showed that midazolam and haloperidol are stable after dilution for a period of at least 25 days.

Both drugs also showed a good stability in all admixtures studied. The pH of the admixtures (>4) with midazolam was slightly higher as in the solutions (<4) used to prepare the admixtures. Above pH 4 the drug exists mainly in the closed ring form, which is more susceptible to degradation (Andersin, 1991). Comparison between the stability of in the solutions used to prepare the admixtures and the admixtures with morphine hydrochloride however, revealed that this small differences in pH did not affect its stability during the period studied. Data currently available on the stability of similar admixtures containing diamorphine hydrochloride and haloperidol lactate (Allwood, 1991) for 45 days or diamorphine hydrochloride and midazolam hydrochloride (Allwood et al., 1994) for 14 days, also reported no stability problems.

In all solutions and admixtures methylprednisolone-21-sodium succinate rapidly degraded as a function of temperature and time confirming the data previously reported by Nahata et al. (1994) on the stability of diluted methylprednisolone solutions. The data suggested that solutions and admixtures containing methylprednisolone-21-sodium succinate should be stored at 4°C rather than at room temperature. It should however be emphasized that the storage at 4°C causes solubility problems for solutions containing morphine hydrochloride at concentrations of 30 mg/ml and above (Vermeire and Remon, 1997). The major problem of the morphine hydrochloride precipitation was the difficulty to redissolve the precipitate. Therefore admixtures of morphine hydrochloride at high concentrations with methylprednisolone-21-sodium succinate should be stored at 22°C, although the stability is limited to 3 or 7 days, depending on the composition of the admixtures. The degradation rate of methylprednisolone sodium-21-hemisuccinate increased with a decreasing drug concentration. In the solutions without morphine hydrochloride methylprednisolone was the major degradation product formed, whereas in all admixtures methylprednisolone-17-sodium succinate was formed more rapidly as compared to methylprednisolone. This difference in degradation rate could be explained by a difference in pH: the initial pH of the solutions was above 7.56, whereas that of the admixtures ranged between 5.64 and 7.18. Anderson et al. (1984) studied the degradation process of methylprednisolone-21-sodium succinate and showed that the rate of hydrolysis and of the $21 \rightarrow 17$ acyl migration were pH dependent. Hydrolysis of methylprednisolone-21-sodium succinate is slightly faster than the $21 \rightarrow 17$ acyl migration above pH 7.4, while $21 \rightarrow 17$ acyl migration dominates between pH 3.6 and 7.4. Below pH 3.6 the rate of hydrolysis is faster than the $21 \rightarrow 17$ acylmigration.

From Table 3 it is clear that there is an important difference between the stability of dexamethasone sodium phosphate in solutions and admixtures prepared from Decadron® versus Decadron® Pack. All these data suggest that if admixtures of morphine hydrochloride with corticosteroids are to be prepared this should preferably be done using Decadron® Pack because of its compatibility over a broader dose range and its higher stability in comparison with Decadron® and methylprednisolone, although visual inspection of these admixtures is advisable. Decadron® Pack solutions, however, contain additives such as sodium bisulfite, methylparaben and propylparaben, which are reported to cause allergic reactions and should therefore be avoided in parenteral preparations (Weiner and Bernstein, 1989). These additives are not present in Solu-Medrol® but on the contrary methylprednisolone-21-sodium succinate has a more limited compatibility and a poor stability of only 3 days at room temperature. Morphine hydrochloride showed good stability in all admixtures.

It can be concluded that midazolam hydrochloride, haloperidol lactate, methylprednisolone-21-sodium succinate and dexamethasone sodium phosphate are compatible with morphine hydrochloride over a dose range covering those usually prescribed in palliative care. Morphine hydrochloride, midazolam hydrochloride and haloperidol lactate showed an excellent stability, but corticosteroids have a more limited stability ranging from 3 to 28 days depending on the type of corticosteroid and of the formulation used.

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