ELSEVIER

International Journal of Pharmaceutics 177 (1999) 53–67

international journal of pharmaceutics

Compatibility and stability of ternary admixtures of morphine with haloperidol or midazolam and dexamethasone or methylprednisolone

A. Vermeire, J.P. Remon *

Laboratory of Pharmaceutical Technology, University of Gent, Harelbekestraat 72, 9000 Gent, Belgium

Received 1 September 1998; accepted 6 October 1998

Abstract

The concentration range over which compatible admixtures of morphine hydrochloride with haloperidol lactate (Haldol®) or midazolam hydrochloride (Dormicum®) and dexamethasone-21-sodium phosphate (Decadron® and Decadron® Pack) or methylprednisolone-21-sodium succinate (Solu-Medrol®) can be prepared was determined by visual evaluation of the solutions at 22°C. The compatibility was evaluated for admixtures prepared in a ratio morphine hydrochloride (D_1)/drug 2 (D_2)/drug 3 (D_3) in a ratio 10/1/1 to 10/1/10 (v/v/v). The solutions of morphine hydrochloride used were 10, 20, 30, 40 and 50 mg/ml prepared in water and isotonized with sodium chloride or dextrose. The drug solutions were used undiluted and diluted 1/5 (v/v) in water. All admixtures were prepared by adding the corticosteroid as D_2 and as D_3 in order to evaluate the influence of the order of mixing on the compatibility. The stability of the drugs in the compatible admixtures was evaluated during storage for 28 days at 22°C and protected from light. Visual inspection, high performance liquid chromatography (HPLC) analysis, pH and osmolality determinations were performed. For each drug combination incompatibility was observed with increasing ratio and/or concentration of the drug solutions. Within the range of compatibility the concentrations of the three drugs could be increased so to allow adequate symptom control with all drug combinations. For a similar admixture a higher concentration of corticosteroid could be obtained using dexamethasone-21-sodium phosphate versus methylprednisolone-21-sodium succinate and a higher concentration of dexamethasone-21-sodium phosphate could be obtained without incompatibility using Decadron® Pack versus Decadron®. The admixtures for which the stability was evaluated were stable for 28 days ($>95\%$ of the initial concentration). None of these admixtures showed any visual changes during storage, except for some of the admixtures prepared using undiluted Decadron®, in which small crystals were seen after 1–28 days. The initial pH of the admixtures ranged from 3.99 to 6.06 and varied less than 0.10 during storage. The initial osmolality of the admixtures ranged from 170 to 323 mOsm/kg and remained almost constant during storage.

Keywords: Incompatibility; Morphine hydrochloride; Midazolam hydrochloride; Haloperidol lactate; Dexamethasone-21-sodium phosphate; Methylprednisolone-21-sodium succinate; Stability

* Corresponding author. Tel.: +32-9-264-80-54; fax: +32-9-222-82-36; e-mail: jeanpaul.remon@rug.ac.be.

0378-5173/99/$ - see front matter
PII: S0378-5173(98)00324-X

1. Introduction

Terminally ill cancer patients commonly suffer from several symptoms at the same time, such as pain, nausea and anxiety (Vianio et al., 1996). To treat the severe pain, morphine remains the opioid of first choice (WHO, 1990). Adjuvant drugs frequently used are anti-emetics, anxiolytics and corticosteroids. Haloperidol is commonly added to morphine infusions in order to reduce the opioid induced nausea, and is well-tolerated when infused subcutaneously (Twycross, 1986; Storey et al., 1990). To treat anxiety, restlessness and agitation, subcutaneous infusion of midazolam has been found a safe and effective treatment (De Sousa and Jepson, 1988; Amesburry and Dunphy, 1989; Bottomley and Hanks, 1990; Burke et al., 1991). Corticosteroids seem to be beneficial for the treatment of pain (especially pain due to invasion of nerves or stretching of an organ capsule) and to treat nausea and weakness (Needham et al., 1992; Twycross, 1992; Watanabe and Bruera, 1994).

Many patients with advanced disease have great difficulties in taking drugs orally. In these patients portable infusion pumps offer the possibility of continuous parenteral drug administration, which compared to intermittent injections, give a more constant plasma concentration and is less painful for the patient (Bruera, 1990; Storey et al., 1990).

To avoid the use of different intravenous or subcutaneous needles, it may be beneficial to mix different drugs in one single infusor. Combination of morphine hydrochloride with adjuvant drugs in solutions for subcutaneous infusion is now commonplace in palliative care, but is based largely on anecdotal evidence of drug compatibility and/or stability, especially the absence of physical changes. The compatibility of morphine hydrochloride with some drugs in binary admixtures was studied by Vermeire and Remon (1998), but from daily practice there is a need for additional research on the compatibility of these drugs in ternary admixtures.

The aim of this study was to investigate the compatibility and the stability of ternary admixtures of morphine hydrochloride with four drugs frequently used in palliative care: midazolam, haloperidol, dexamethasone and methylprednisolone. As the pH and the osmolality might play a major role in the prevalence of local skin irritation (Lewis and Hecker, 1985; Fransson and Espander-Jansson, 1996; 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 in a concentration of 10, 20, 30, 40 and 50 mg/ml the 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 & 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 equivalent to 100 mg/ml

methylprednisolone. Dexamethasone-21-sodium phosphate solutions were prepared from Decadron® (Merck Sharp & Dohme, Brussels, Belgium) containing 3.33 mg/ml dexamethasone (equivalent to 4 mg/ml dexamethasone phosphate) as dexamethasone-21-sodium phosphate and Decadron® Pack (Merck Sharp & Dohme, Brussels, Belgium) containing 20 mg/ml dexamethasone as dexamethasone-21-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 (1 mg/ml) and sodium hydroxide (ad pH 7–8.5). Next to the above mentioned additives in Decadron® Pack disodium edetate (0.5 mg/ml) is present as an additive (Trissel et al., 1992).

2.2. Compatibility study

To determine the compatibility of morphine hydrochloride in ternary admixtures with the different drug solutions tested the following strategy was used. The ratio in which admixtures were prepared ranged from morphine hydrochloride solution (D_1)/drug solution secondly added (D_2)/drug solution thirdly added (D_3): 10/1/1 to 10/1/10 (v/v/v). Admixtures were prepared with morphine hydrochloride solutions in five concentrations (10, 20, 30, 40 and 50 mg/ml) and the drug solutions at two concentrations (maximal concentration available or soluble and its dilution 1/5 (v/v) (for methylprednisolone diluted to 5 mg/ml). Admixtures were prepared using either both drug solutions (D_2 and D_3) at maximal concentration or both diluted 1/5 (v/v) in water or one (D_2 or D_3) undiluted and the other (D_2 and D_3) diluted. For the evaluation of the influence of the order of mixing on the compatibility either the corticosteroid solution (dexamethasone-21-sodium phosphate or methylprednisolone-21-sodium succinate) was added as the second drug and the haloperidol or midazolam solution as the third drug or vice versa. In order to determine the influence of isotonization of the morphine hydrochloride solutions and the isotonization agent used on the compatibility all admixtures were prepared using the morphine hydrochloride solutions prepared in water and isotonized with sodium chloride and dextrose.

For the preparation of the admixtures 5 ml of the morphine hydrochloride solution were added to a borosilicate tube. Then 0.5 ml of D_2 was added and the admixture was gently shaken. Consequently the required volume of D_3 was added, the admixture was gently shaken and inspected visually. The compatibility was evaluated by visual inspection of the admixtures immediately after preparation and daily during storage for 1 week at 22°C and protected from light. In a first screening all admixtures were prepared only once. Afterwards the admixtures were prepared again in duplicate in order to determine more precisely the compatibility limits. An admixture was considered compatible if no physical change was noticed during this week for any of the three admixtures.

2.3. Stability study

The stability was evaluated for compatible admixtures in which the concentration of the three drugs is above the minimal effective concentration for subcutaneous administration at an infusion rate of 1 ml/h. The minimally effective doses for the different drugs were obtained from daily practice and literature data (Twycross, 1986; Bottomley and Hanks, 1990; Needham et al., 1992; Clément and Schrooten, 1997) and are 2 mg/day for haloperidol and midazolam, 1.5 mg/day for dexamethasone and 8 mg/day for methylprednisolone.

The stability was only studied for the following admixtures: admixtures with the undiluted drug solutions prepared in a ratio $D_1/D_2/D_3$:10/1/1 (v/v/v) and admixtures with the diluted drug solutions prepared in a ratio $D_1/D_2/D_3$:10/1/10 (v/v/v). The stability of compatible admixtures prepared using one of both drug solutions undiluted and the other drug solution diluted, was not evaluated. The stability study was only performed for admixtures prepared using morphine hydrochloride solutions at two concentrations (10 and 50 mg/ml) isotonized with dextrose.

For the stability study the admixtures were prepared under aseptic conditions using sterile drug solutions: the morphine hydrochloride solu-

tions 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 Solu-Medrol® powder was dissolved in water for injection. The admixtures were prepared by adding the drug solution to the morphine hydrochloride solution in the order indicated, filled in sterile borosilicate tubes (Corning glassware, Novolab, Belgium) and closed with 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 30 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. The samples were stored at −20°C prior to analysis. High performance liquid chromatography (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).

For the determination of the stability of the drugs present in the admixtures the stability indicating validated HPLC assays described by Vermeire and Remon (1998) were evaluated for their suitability. The assay for the stability determination of morphine allowed quantification of morphine as well as of its degradation products, namely pseudomorphine (MacFarlan Smith, Edinburgh, UK), morphine-*N*-oxide (MacFarlan Smith, Edinburgh, UK) and apomorphine (as the hydrochloride salt; Sigma-Aldrich, Bornem, Belgium). For the stability of midazolam only midazolam was quantified. Its main fotodegradation products, *N*-desalkylflurazepam, 6-(8-chloro-1-methyl-4,5-dihydro-2,5,10b-tri-azabenzo [e]azu-len-6-ylidene)cyclohexa2,4-dienone, 6-chl-oro-2-methyl-4-(2-fluorophenyl)quinazoline and 6-chloro-2-methyl-4(1H)-quinazolinone (Pharmaceutical Chemistry Division, Department of Pharmacy, University of Helsinki, Finland) were only identified because of the insufficient amount available. The occurrence of any other possible degradation products was checked by visual inspection of the chromatogram. The HPLC assay for the evaluation of the stability of haloperidol was shown to be stability indicating, but no degradation products were identified. In order to evaluate the stability of haloperidol, the drug concentration was determined and the chromatograms were inspected visually for any additional peaks. Using the stability indicating assay for dexamethasone-21-sodium phosphate, the parent drug as well as its main degradation product, dexamethasone were quantified. For none of the drugs or their degradation products any interference with the other compounds in the admixtures was present (Figs. 1–4). For all 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) and an autoinjector (Autoinjector 234, Gilson, Analis, Gent, Belgium) with an electrically actuated Rheodyne valve (Type 7010, Analis, Gent, Belgium) fitted with a 20 μl sample loop.

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 (concentration of parent drug + concentration of degradation product(s)).

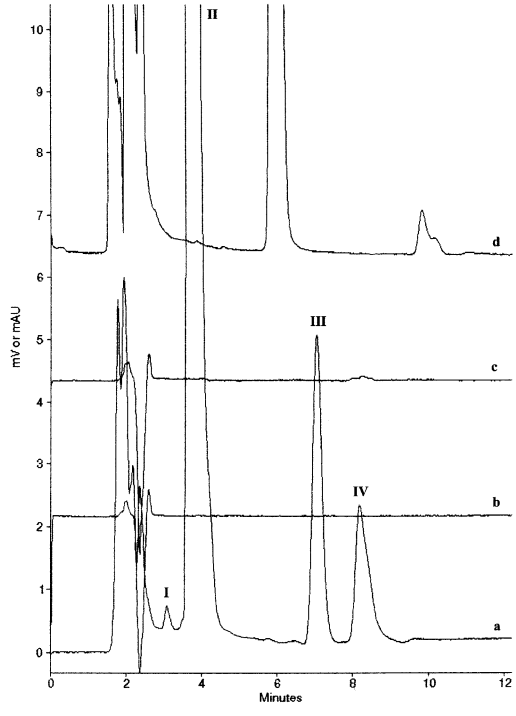

Fig. 1

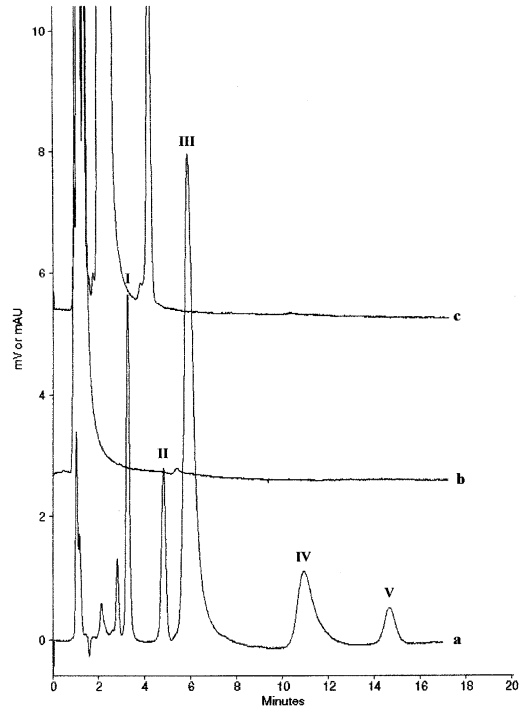

Fig. 2

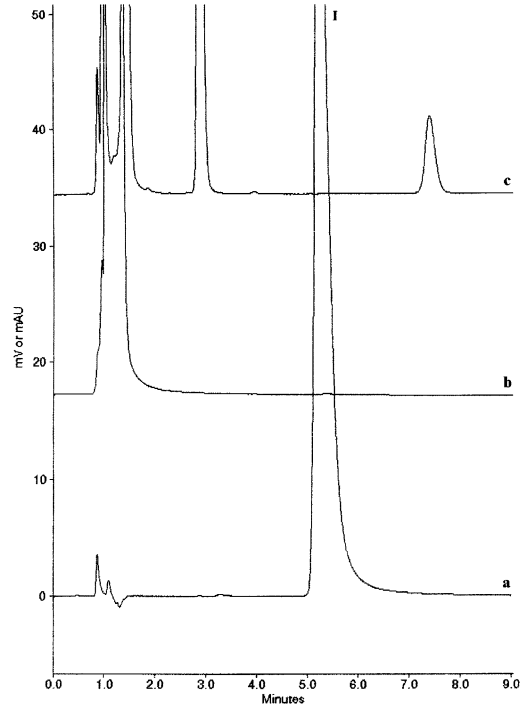

Fig. 3

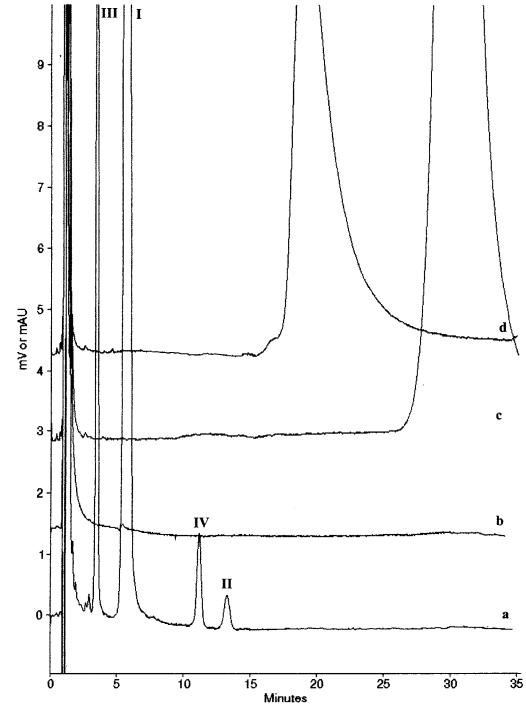

Fig. 4

Figs. 1,2,3 and 4.

3. Results

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

The compatibility of all ternary admixtures is summarized in Tables 1–4 and Figs. 5 and 6.

The results of the compatibility study with methylprednisolone-21-sodium succinate at concentrations above 15 mg/ml are not shown here as using these concentrated solutions incompatibility was observed at all ratios tested.

From Tables 1–4 it can be noticed that, as expected, higher ratios were compatible for the admixtures prepared with one or both drug solutions diluted 1/5 (v/v) in water than with the undiluted drug solutions. The maximal ratio in which a compatible admixture was obtained increased with increasing morphine hydrochloride concentration, except for the admixtures with the undiluted dexamethasone-21-sodium phosphate solution added thirdly. There was no influence of the solvent used to prepare the morphine hydrochloride solution on the compatibility. When comparing the compatibility of the admixtures prepared in a ratio $D_1/D_2/D_3$:10/1/1 (v/v/v) with the same composition, but with a different order of mixing no differences in compatibility were observed. When for all drug combinations the maximal compatible concentration of corticosteroid in the admixtures prepared using methylprednisolone-21-sodium succinate solutions versus dexamethasone-21-sodium phosphate solutions were compared, admixtures with higher corticosteroid concentrations could be prepared using the dexamethasone-21-sodium phosphate solutions.

When comparing the maximal compatible concentration of dexamethasone-21-sodium phosphate in the ternary admixtures prepared using Decadron® with those prepared using Decadron® Pack, higher concentrations of dexamethasone-21-sodium phosphate could be obtained without incompatibility problems using Decadron® Pack only (Fig. 5).

3.2. Stability of ternary admixtures of morphine hydrochloride with midazolam hydrochloride or haloperidol lactate and dexamethasone-21-sodium phosphate or methylprednisolone-21-sodium succinate

The composition of the compatible admixtures for which the stability was evaluated is shown in Tables 5 and 6. The stability of admixtures with methylprednisolone was not studied because for only a few of the compatible admixtures with

Fig. 1. Chromatograms of: (a) a mixture containing 1000 μg/ml morphine hydrochloride (II), 10 μg/ml morphine-*N*-oxide (I), 10 μg/ml pseudomorphine (III) and 5 μg/ml apomorphine hydrochloride (IV); (b) midazolam (2 μg/ml) and its degradation products; (c) Haldol® diluted in water to a concentration of 100 μg/ml haloperidol stored for 28 days at 60°C; and (d) Decadron® Pack diluted in water to a concentration of 100 μg/ml dexamethasone stored for 28 days at 22°C injected under optimal chromatographic conditions used for the quantification of morphine and its degradation products.

Fig. 2. Chromatograms of: (a) midazolam (III) (2 μg/ml) and its degradation products (I = 6-chloro-2-methyl-4(1H)-quinazolinone (2 μg/ml), II = *N*-desalkylflurazepam (0.2 μg/ml), IV = 6-(8-chloro-1-methyl-4,5-dihydro-2,5,10b-tri-azabenzo[e] azulen-6-ylidene)cyclohexa-2,4-dienone (concentration unknown) and V = 6-chloro-2-methyl-4-(2-fluorophenyl)quinazoline (concentration unknown); (b) a solution containing morphine hydrochloride (1000 μg/ml) and its degradation products; and (c) Decadron® Pack diluted to a concentration of 100 μg/ml dexamethasone (as the sodium phosphate salt) stored for 28 days at 22°C injected under optimal chromatographic conditions used for the determination of the stability of midazolam.

Fig. 3. Chromatograms of: (a) Haldol® diluted to 100 μg/ml haloperidol (I); (b) a solution containing morphine hydrochloride (1000 μg/ml) and its degradation products; and (c) Decadron® Pack diluted to a concentration of 100 g/ml dexamethasone (as the sodium phosphate salt) stored for 28 days at 22°C injected under optimal chromatographic conditions used for the quantification of haloperidol.

Fig. 4. Chromatograms of: (a) Decadron® Pack diluted in water to 100 μg/ml dexamethasone as dexamethasone-21-sodium phosphate (I = dexamethasone-21-sodium phosphate, II = dexamethasone, III = methylparaben and IV = propylparaben); (b) a solution containing morphine hydrochloride (1000 μg/ml) and its degradation products; (c) midazolam (2 μg/ml) and its degradation products; and (d) Haldol® diluted in water to a concentration of 100 μg/ml haloperidol stored for 28 days at 60°C injected under optimal chromatographic conditions used for the determination of the stability of dexamethasone-21-sodium phosphate.

Table 1
Maximal ratio $D_1/D_2/D_3$ (v/v/v) in which morphine hydrochloride is compatible with midazolam hydrochloride (Dormicum®) and dexamethasone-21-sodium phosphate (Decadron® and Decadron® Pack) for 7 days at 22°C when prepared as described

2nd drug solution added	3rd drug solution added	Morphine hydrochloride (mg/ml)				
		10	20	30	40	50
Decadron®	Dormicum®	–[a]	–	10/1/1	10/1/2	10/1/2
	Dormicum® (1/5)	10/1/2	10/1/3	10/1/4	10/1/5	10/1/6
Decadron® (1/5)	Dormicum®	10/1/10[b]	10/1/10[b]	10/1/10[b]	10/1/10[b]	10/1/10[b]
	Dormicum® (1/5)	10/1/10[b]	10/1/10[b]	10/1/10[b]	10/1/10[b]	10/1/10[b]
Decadron® Pack	Dormicum®	–	–	–	–	–
	Dormicum® (1/5)	10/1/2	10/1/3	10/1/4	10/1/5	10/1/6
Decadron® Pack (1/5)	Dormicum®	10/1/10	10/1/10	10/1/10	10/1/10	10/1/10
	Dormicum® (1/5)	10/1/10	10/1/10	10/1/10	10/1/10	10/1/10
Dormicum®	Decadron®	–	–	10/1/1	10/1/1	10/1/1
	Decadron® (1/5)	10/1/2	10/1/3	10/1/4	10/1/5	10/1/7
Dormicum® (1/5)	Decadron®	10/1/1	10/1/1	10/1/1	10/1/1	10/1/1
	Decadron® (1/5)	10/1/10[b]	10/1/10[b]	10/1/10[b]	10/1/10[b]	10/1/10[b]
Dormicum®	Decadron® Pack	10/1/1	10/1/1	10/1/1	10/1/1	10/1/1
	Decadron® Pack (1/5)	10/1/10[b]	10/1/10[b]	10/1/10[b]	10/1/10[b]	10/1/10[b]

[a] (–) Incompatible at all ratios evaluated.
[b] Resulted in admixtures for which the concentration of dexamethasone-21-sodium phosphate or midazolam hydrochloride are below the minimal therapeutic concentration and for which the maximal ratio resulting in effective concentrations of these drugs is $D_1/D_2/D_3$:10/1/1 (v/v/v).

methylprednisolone the concentration of methylprednisolone (as the 21-sodium succinate salt) and/or that of midazolam or haloperidol was above the minimally effective concentration to allow adequate symptom control when administered at an infusion rate of 1 ml/h. Moreover, methylprednisolone-21-sodium succinate is reported to degrade rapidly as a function of time (Nahata et al., 1994 Vermeire and Remon, 1998).

No visual change was noticed during storage for any of the admixtures studied except for some of the admixtures with undiluted Decadron® 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 formation of these crystals depended on small changes of the ambient temperature and the presence of dust in the solutions, acting as crystallization seeds.

The concentration of the parent drug, the pH and the osmolality of the admixtures containing morphine hydrochloride, midazolam hydrochloride or haloperidol lactate and dexamethasone-21-sodium phosphate recorded during storage for 28 days at 22°C and protected from light are shown in Tables 5 and 6. The concentration of midazolam and haloperidol remained in all admixtures above 96 and 98% of the initial concentration, respectively. No degradation products of midazolam and haloperidol were detected in any of the admixtures. Dexamethasone-21-sodium phosphate also showed an excellent stability ($>97\%$ of the initial concentration) in all admixtures studied. No degradation products of dexamethasone-21-sodium phosphate were present in any of the admixtures, except dexamethasone. This was confirmed by the fact that the concentration of dexamethasone-21-sodium phosphate in these formulations decreased to the same extent as the increase in dexamethasone concentration. Little chemical loss of morphine occurred in all admixtures evaluated. Pseudomorphine and morphine-*N*-oxide, two degradation products of morphine, were always observed but their concentration remained below 0.5% of the total morphine concentration during the entire period studied. Apomorphine was not detected in any of the admixtures studied.

The initial pH of the admixtures prepared using

Table 2
Maximal ratio $D_1/D_2/D_3$ (v/v/v) in which morphine hydrochloride is compatible with haloperidol lactate (Haldol®) and dexamethasone-21-sodium phosphate (Decadron® and Decadron® Pack) for 7 days at 22°C when prepared as described

2nd drug solution added	3rd drug solution added	Morphine hydrochloride (mg/ml)				
		10	20	30	40	50
Decadron®	Haldol®	10/1/1	10/1/2	10/1/3	10/1/4	10/1/4
	Haldol® (1/5)	10/1/10	10/1/10	10/1/410	10/1/10	10/1/10
Decadron® (1/5)	Haldol®	10/1/10[a]	10/1/10[a]	10/1/10[a]	10/1/10[a]	10/1/10[a]
	Haldol® (1/5)	10/1/10[a]	10/1/10[a]	10/1/10[a]	10/1/10[a]	10/1/10[a]
Decadron® Pack	Haldol®	–[b]	–	–	–	–
	Haldol® (1/5)	10/1/1	10/1/1	10/1/1	10/1/1	10/1/2
Decadron® Pack (1/5)	Haldol®	–	–	–	10/1/1	10/1/2
	Haldol® (1/5)	10/1/10	10/1/10	10/1/10	10/1/10	10/1/10
Haldol®	Decadron®	10/1/1	10/1/1	10/1/1	10/1/1	10/1/1
	Decadron® (1/5)	10/1/10	10/1/10	10/1/10	10/1/10	10/1/10
Haldol® (1/5)	Decadron®	10/1/1	10/1/1	10/1/1	10/1/1	10/1/1
	Decadron® (1/5)	10/1/10[a]	10/1/10[a]	10/1/10[a]	10/1/10[a]	10/1/10[a]
Haldol®	Decadron® Pack	–	–	–	–	–
	Decadron® Pack (1/5)	–	–	–	10/1/1	10/1/2
Haldol® (1/5)	Decadron® Pack	10/1/1	10/1/1	10/1/1	10/1/1	10/1/1
	Decadron® Pack (1/5)	10/1/10[a]	10/1/10[a]	10/1/10[a]	10/1/10[a]	10/1/10[a]

[a] Resulted in admixtures for which the concentration of dexamethasone-21-sodium phosphate or haloperidol lactate are below the minimal therapeutic concentration and for which the maximal ratio resulting in effective concentrations of these drugs is $D_1/D_2/D_3$:10/1/1 (v/v/v)
[b] (–) Incompatible at all ratios evaluated.

the undiluted drug solutions ranged from 5.48 to 6.06 and varied by less than 0.1 during storage. The pH of the admixtures prepared using the diluted drug solutions ranged from 3.99 to 5.83 and varied not more than 0.05 over the study period. The initial osmolality of the admixtures with the undiluted drug and corticosteroid solutions ranged from 308 to 323 mOsm/kg and that of the admixtures with the diluted drug solutions ranged from 170 to 189 mOsm/kg. In all admixtures the osmolality remained almost constant during storage.

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 cancer 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. The compatibility and the stability of binary admixtures of morphine hydrochloride with some drugs frequently used in palliative care was investigated (Vermeire and Remon, 1998), but these data do not give any information on the compatibility of these drugs in a ternary admixture with morphine hydrochloride and another drug. In daily practice ternary admixtures of morphine with a corticosteroid and another adjuvant drug are frequently prescribed. Therefore in this study the compatibility and the stability of ternary admixtures of morphine hydrochloride with Dormicum® or Haldol® and Decadron® (Pack) or Solu-Medrol, was investigated.

It should be emphasized that the results of the compatibility study are based on evaluation of the admixtures at a temperature of 22 ± 2°C during 1 week after their preparation. Small changes in temperature might significantly influence the com-

Table 3
Maximal ratio $D_1/D_2/D_3$ (v/v/v) in which morphine hydrochloride is compatible with midazolam hydrochloride (Dormicum®) and methylprednisolone-21-sodium succinate (Solu-Medrol®) for 7 days at 22°C when prepared as described

2nd drug solution added	3rd drug solution added	Morphine hydrochloride (mg/ml)				
		10	20	30	40	50
Methylprednisolone (15 mg/ml)	Dormicum®	–[a]	–	–	–	–
	Dormicum® (1/5)	–	–	10/1/1	10/1/1	10/1/2
Methylprednisolone (5 mg/ml)	Dormicum®	–	–	10/1/1	10/1/1	10/1/2
	Dormicum® (1/5)	10/1/10[b]	10/1/10[b]	10/1/10[b]	10/1/10[b]	10/1/10[b]
Dormicum®	Methylprednisolone (15 mg/ml)	–	–	–	–	–
	Methylprednisolone (5 mg/ml)	–	–	10/1/1	10/1/1	10/1/2
Dormicum® (1/5)	Methylprednisolone (15 mg/ml)	–	–	10/1/1	10/1/1	10/1/2[c]
	Methylprednisolone (5 mg/ml)	10/1/10[c]	10/1/10[c]	10/1/10[c]	10/1/10[c]	10/1/10[c]

[a] (–) Incompatible at all ratios evaluated.
[b] Resulted in admixtures for which the concentration of methylprednisolone-21-sodium succinate is below the minimal therapeutic concentration and for which the maximal ratio resulting in an effective concentration of the drug is $D_1/D_2/D_3$:10/1/4 (v/v/v).
[c] Resulted in admixtures for which the concentration of midazolam hydrochloride is below the minimal therapeutic concentration and for which the maximal ratio resulting in an effective concentration of the drug is $D_1/D_2/D_3$:10/1/1 (v/v/v).

patibility, and visual inspection is thus recommended. Immediately after preparation larger concentrations seemed compatible, but after some days small suspected particles were observed. Late crystallization was also observed in binary admixtures of these drugs (Vermeire and Remon, 1998).

It should also be stressed that the compatibility limits presented here are only valid for the admixtures prepared as indicated. Although there was no influence of the order of mixing on the compatibility of admixtures prepared in a ratio $D_1/D_2/D_3$:10/1/1 (v/v/v), this does not imply that the order of mixing can be inverted without compatibility problems for admixtures prepared in another ratio. Methods of preparation which are not mentioned are not evaluated and could cause precipitation within the compatibility limits indicated.

From the compatibility data (Tables 3 and 4 and Fig. 6) it is clear that for only few of the compatible admixtures with methylprednisolone-21-sodium succinate the final concentration of methylprednisolone-21-sodium succinate and/or that of haloperidol or midazolam was sufficiently high to obtain adequate symptom control when using an infusion rate of 1 ml/h. For the admixtures with both dexamethasone-21-sodium phosphate solutions it was possible to prepare compatible admixtures within the therapeutic range used in palliative care for most of the combinations tested (Tables 1 and 2 and Fig. 5). Therefore if a corticosteroid is needed in combination with morphine hydrochloride and midazolam hydrochloride or haloperidol lactate, dexamethasone-21-sodium phosphate should be preferred.

As for the compatibility of both dexamethasone-21-sodium phosphate solutions in binary admixtures (Vermeire and Remon, 1998) the maximal compatible concentration of dexamethasone-21-sodium phosphate was higher in the ternary admixtures prepared using Decadron® Pack versus Decadron® (Fig. 5). Thus if high concentrations of corticosteroid are needed Decadron® Pack should be preferred over Decadron® because of its compatibility over a higher concentration range.

For most of the admixtures the maximal drug concentration resulting in a compatible ternary admixture was lower than the maximal compatible concentration in a binary admixture with morphine hydrochloride alone (Vermeire and Remon, 1998). This suggested that in most cases the incompatibility observed in the ternary admix-

Table 4
Maximal ratio $D_1/D_2/D_3$ (v/v/v) in which morphine hydrochloride is compatible with haloperidol lactate (Haldol®) and methylprednisolone-21-sodium succinate (Solu-Medrol®) for 7 days at 22°C when prepared as described

2nd drug solution added	3rd drug solution added	Morphine hydrochloride (mg/ml)				
		10	20	30	40	50
Methylprednisolone (15 mg/ml)	Haldol®	–[a]	–	–	–	–
	Haldol® (1/5)	–	–	–	–	–
Methylprednisolone (5 mg/ml)	Haldol®	–	–	–	–	–
	Haldol® (1/5)	10/1/1	10/1/1	10/1/1	10/1/2	10/1/2
Haldol®	Methylprednisolone (15 mg/ml)	–	–	–	–	–
	Methylprednisolone (5 mg/ml)	–	–	–	–	–
Haldol® (1/5)	Methylprednisolone (15 mg/ml)	–	–	–	–	–
	Methylprednisolone (5 mg/ml)	10/1/3[b]	10/1/3[b]	10/1/3[b]	10/1/4[b]	10/1/5[b]

[a] (–) Incompatible at all ratios evaluated.
[b] Resulted in admixtures for which the concentration of haloperidol lactate is below the minimal therapeutic concentration and for which the maximal ratio resulting in an effective concentration of the drug is $D_1/D_2/D_3$: 10/1/1 (v/v/v).

tures is due to incompatibility between both admixed drugs rather than to an incompatibility with morphine hydrochloride. Additional admixtures prepared by mixing either of both corticosteroid solutions with the haloperidol or midazolam solution resulted indeed in a white precipitate immediately after mixing for the diluted (1/5 (v/v) in water) as well as for the undiluted drug solutions.

Although one would expect that the maximal volume of the third drug that can be added without compatibility problems decreased with increasing morphine hydrochloride concentration, in most of the admixtures the maximal volume of the third drug solution that could be added increased with increasing concentration of morphine hydrochloride. This could be due to the fact that morphine interacts with the drug added secondly which is then less available for interaction with the drug added thirdly. The fact that for the admixtures where the undiluted Decadron® solution was added as the third drug the ratio remained constant can be explained since 1 ml was the maximal volume compatible with 10 ml of the morphine hydrochloride solutions at all concentrations in binary admixtures (Vermeire and Remon, 1998).

Although it has been shown that isotonized infusion solutions reduced the prevalence of irritation (Sykes and Oliver, 1987), in daily practice it is not possible to optimize the tonicity of each particular admixture (ratio, drug solution used,…). Isotonizing the morphine hydrochloride solutions, however, could partially solve this problem and can be easily performed. The choice of the diluent, however, might affect the drug solubility. In this study the compatibility of morphine hydrochloride solutions prepared in water was compared with that of morphine hydrochloride solutions isotonized with sodium chloride and dextrose. As for the binary admixtures (Vermeire and Remon, 1998) there was no influence of isotonizing the morphine hydrochloride solutions or the isotonizing agent used on the compatibility range observed. Therefore isotonization of the morphine hydrochloride solutions is advisable. Dextrose is to be preferred as isotonizing agent as sodium chloride might cause precipitation in some cases at higher drug concentrations (Outman and Monolakis, 1991; Fraser and Riker, 1994). For the stability study morphine hydrochloride solutions were always isotonized with dextrose.

From the osmolality measurements it can be concluded that the preparation of the admixtures using isotonized morphine hydrochloride solutions did not result in an isotonic admixture. The osmolality of the admixtures prepared using undiluted drug solutions in a ratio $D_1/D_2/D_3$:10/1/1 (v/v/v) did not deviate a lot from isotonicity (285 mOsm/kg). For the admixtures prepared using the

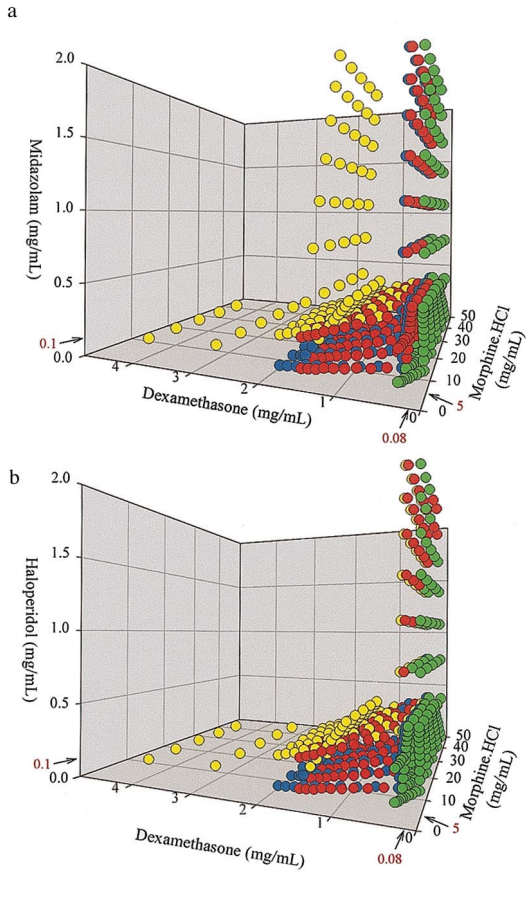

Fig. 5

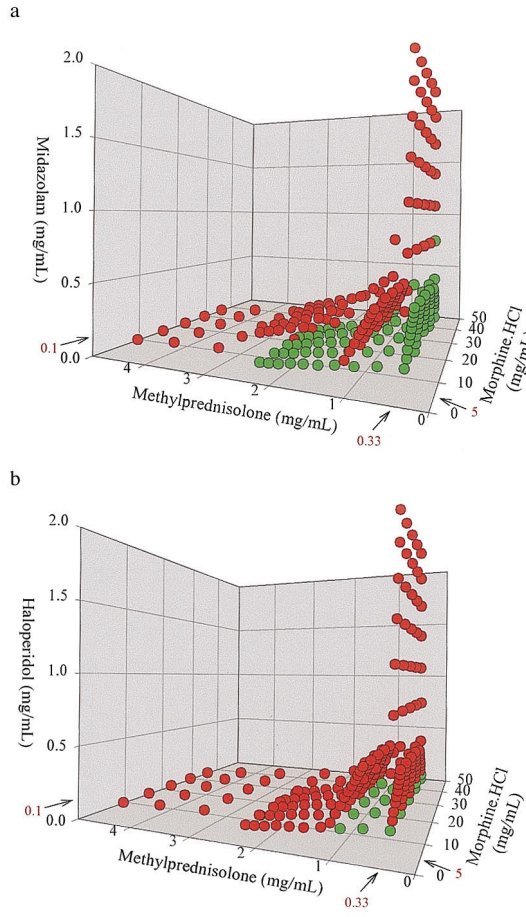

Fig. 6

Fig. 5. Concentrations of morphine hydrochloride, dexamethasone (as sodium phosphate salt) and (a) midazolam (as hydrochloride salt) or (b) haloperidol (as lactate salt) in compatible admixtures prepared using Decadron® green and Decadron® Pack blue and incompatible admixtures prepared using Decadron® red and Decadron® Pack yellow. The compatible admixtures with the maximal compatible concentration and the incompatible admixtures with the minimal incompatible admixtures are shown. The arrows indicate the minimal therapeutic concentration.

Fig. 6. Concentrations of morphine hydrochloride, methylprednisolone (as 21-sodium succinate salt) and (a) midazolam (as hydrochloride salt) or (b) haloperidol (as lactate salt) in compatible green and incompatible red admixtures. The compatible admixtures with the maximal compatible concentration of each drug and the incompatible admixtures with the minimal incompatible concentration of each drug are shown. The arrows indicate the minimal therapeutic concentration.

diluted drug and corticosteroid solutions in a ratio $D_1/D_2/D_3$:10/1/10 (v/v/v), however, the osmolality never increased above 200 mOsm/kg although isotonized morphine hydrochloride solutions were used. This can be explained by the low osmolality of the commercially available drug solutions, the dilution in water and the large percentage of the diluted solutions in the admixtures. These low osmolalities show the importance of using isotonized morphine hydrochloride solutions. The pH of the admixtures decreased with increasing volume of haloperidol or midazolam solution and increased with an increasing volume of corticosteroid solution in the admixture. The pH of some of the admixtures was much lower than the physiological pH. The pH of haloperidol

Table 5
Stability of morphine hydrochloride, midazolam hydrochloride, haloperidol lactate and dexamethasone-21-sodium phosphate, pH and osmolality of the admixtures prepared using the undiluted drug solutions during storage for 28 days at 22°C and protected from light

Composition of admixture				% Of initial drug concentration after 28 days	pH		Osmolality (mOsm/kg)	
Drug	Conc. (mg/ml)	Volume (ml)	Final conc. (mg/ml)		Initial	After 28 days	Initial	After 28 days
MorphineHCl	10	10	8.33	99.93	5.68	5.66	314	312
+ Haloperidol	5	1	0.42	102.32				
	3.33	1	0.28	99.82				
+ Dexamethasone[a]								
MorphineHCl	50	10	41.66	99.97	5.49	5.51	315	316
+ Haloperidol5	1	0.42	99.20					
	3.33	1	0.32	98.98				
+ Dexamethasone[a]								
MorphineHCl	10	10	8.33	100.00	5.64	5.65	309	311
	3.33	1	0.28	99.83				
+ Dexamethasone[a]								
+ Haloperidol	5	1	0.42	99.95				
MorphineHCl	50	10	41.66	99.95	5.48	5.49	310	312
	3.33	1	0.28	98.92				
+ Dexamethasone[a]								
+ Haloperidol	5	1	0.42	103.21				
MorphineHCl	50	10	41.66	99.93	6.02	6.03	321	323
+ Midazolam	5	1	0.42	97.26				
	3.33	1	0.28	97.53				
+ Dexamethasone[a]								
MorphineHCl	50	10	41.66	99.94	5.98	6.06	318	317
	3.33	1	0.28	97.38				
+ Dexamethasone[a]								
+ Midazolam	5	1	0.42	100.31				

[a] Prepared from Decadron®.

Table 6
Stability of morphine hydrochoride, midazolam hydrochloride, haloperidol lactate and dexamethasone-21-sodium phosphate, pH and osmolality of the admixtures prepared using the diluted drug solutions during storage for 28 days at 22°C and protected from light

Composition of admixture				% Of initial drug concentration after 28 days	pH		Osmolality (mOsm/kg)	
Drug	Conc. (mg/ml)	Volume (ml)	Final conc. (mg/ml)		Initial	After 28 days	Initial	After 28 days
MorphineHCl	10	10	4.76	99.99	5.81	5.83	187	189
	4	1	0.19	98.97				
+ Dexamethasone[a]								
+ Midazolam	1	10	0.48	97.37				
MorphineHCl	50	10	23.81	99.98	5.57	5.62	188	189
	4	1	0.19	98.76				
+ Dexamethasone[a]								
+ Midazolam	1	10	0.48	101.07				
MorphineHCl	10	10	4.76	99.86	4.03	4.05	170	171
	4	1	0.19	96.97				
+ Dexamethasone[a]								
+ Haloperidol	1	10	0.48	101.33				
MorphineHCl	50	10	23.81	100.01	3.99	4.04	174	175
	4	1	0.19	99.64				
+ Dexamethasone[a]								
+ Haloperidol	1	10	0.48	98.15				

[a] Prepared from Decadron® Pack.

lactate, midazolam hydrochloride and morphine hydrochloride solutions is below the physiological range and are reported to be well-tolerated when infused subcutaneously (Bottomley and Hanks, 1990; Bruera, 1990; Storey et al., 1990). The low pH as well as the low osmotic values of some of these admixtures, however, are more likely to cause pain and irritation (Sykes and Oliver, 1987; Fransson and Espander-Jansson, 1996). Careful inspection of the infusion site is therefore recommended when administering these admixtures.

Data on the stability of these admixtures would allow patients to take their medication home for a longer period of time and it would also permit the hospital pharmacy to prepare some frequently prepared admixtures in advance. Therefore, in this study the stability of some compatible admixtures that are therapeutically effective was studied over a period of 28 days.

Visual evaluation of the admixtures during storage for 28 days revealed that the admixtures with diluted Decadron® Pack remained clear for the entire study period, while in some of the admixtures prepared using undiluted Decadron® sometimes a small amount of precipitate occurred. Since even small amounts of precipitate could block the catheter, visual inspection of these admixtures is recommended.

All drugs in the admixtures evaluated remained stable ($>96\%$ of initial concentration) during 28 days storage at 22°C and protected from light.

It can be concluded that under the conditions tested midazolam hydrochloride or haloperidol lactate and dexamethasone-21-sodium phosphate are compatible with morphine hydrochloride, prepared in the three solvents, tested over a dose range covering those usually prescribed in palliative care. In the compatible admixtures with methylprednisolone, however, the concentration of methylprednisolone-21-sodium succinate and/or that of midazolam or haloperidol was only slightly higher than the concentration that allowed to administer a daily dose within the therapeutic range. The low pH and osmolality of some of the admixtures prepared using diluted drug solutions careful inspection of the infusion site is advisable. From the stability study it could be concluded that the admixtures prepared using diluted drug and corticosteroid solutions were all physically stable for 28 days. In the admixtures prepared using undiluted Decadron® small crystals sometimes occurred on the bottom and thus visual inspection of these admixtures is recommended. In the admixtures for which the stability was evaluated over 28 days at 22°C morphine hydrochloride, midazolam hydrochloride and haloperidol lactate showed a good stability.

Acknowledgements

We wish to thank Roche (Brussels, Belgium) for supplying Dormicum®, and Dr R. Andersin (Pharmaceutical Chemistry Division, Department of Pharmacy, University of Helsinki, Finland) for supplying the degradation products of midazolam. We wish to thank Pharmacia & Upjohn (Puurs, Belgium) for supplying the Solu-Medrol®. We are also grateful to Baxter (Brussels, Belgium) for supplying the isotonic sodium chloride and dextrose solutions. This study was supported by a grant of the Research Fund of the University of Gent.

References

Amesburry, B.D.W., Dunphy, K.P., 1989. The use of subcutaneous midazolam in the home care setting. Pall. Med. 3, 299–301.

Bottomley, D.M., Hanks, G.W., 1990. Subcutaneous midazolam infusion in palliative care. J. Pain Symptom Manage. 5, 259–261.

Bruera, E., 1990. Ambulatory infusion devices in the continuing care of patients with advanced diseases. J. Pain symptom Manage. 5, 287–296.

Burke, A.L., Diamond, P.L., Hulbert, J., Yeatman, J., Farr, E.A., 1991. Terminal restelessness—its management and the role of midazolam. Med. J. Aust. 155, 485–487.

Clément, A., Schrooten, P., 1997. Corticoiden: volg de gids. Patient care, speciale uitgave 41–42.

De Sousa, E., Jepson, B.A., 1988. Midazolam in terminal care. Lancet 9, 67–68.

Fraser, G.L., Riker, R.R., 1994. Visual compatibility of haloperidol lactate with injectable solutions. Am. J. Hosp. Pharm. 51, 905–906.

Fransson, J., Espander-Jansson, A., 1996. Local tolerance of subcutaneous injections. J. Pharm. Pharmacol. 48, 1012–1015.

Lewis, G.B.H., Hecker, J.F., 1985. Infusion thrombophlebitis. Br. J. Anaesth. 57, 220–233.

Nahata, M.C., Morosco, R.S., Hipple, T.F., 1994. Stability of diluted methylprednisolone sodium succinate injection at two temperatures. Am. J. Hosp. Pharm. 51, 2157–2159.

Needham, P.R., Daley, A.G., Lennard, R.F., 1992. Steroids in advanced cancer: survey of current practice. Br. Med. J. 305, 999.

Outman, W.R., Monolakis, J., 1991. Visual compatibility of haloperidol lactate with 0.9% sodium chloride injection or injectable critical-care drugs during simulated Y-site injection. Am. J. Hosp. Pharm. 48, 1539–1541.

Storey, P., Herbert, H.H., St. Louis, R.H., Tarver, E.E., 1990. Subcutaneous infusions for control of cancer symptoms. J. Pain Symptom Manage. 5, 33–41.

Sykes, N.P., Oliver, D.J., 1987. Isotonic methotrimeprazine by continuous infusion in terminal cancer care. Lancet 1, 393.

Trissel, L.A., Allwood, M.C., Haas, D.P., Hale, K.N., 1992. Handbook on Injectable Drugs, 7th Edn. American Society of Hospital Pharmacists, Washington, DC, pp. 594–601.

Twycross, R.G., 1986. Care of the dying, Symptom control, Br. J. Hosp. Med. 244–249.

Twycross, R., 1992. Corticosteroids in advanced cancer. Br. Med. J. 305, 969–970.

Vermeire, A., Remon, J.P., 1997. The solubility of morphine and the stability of concentrated morphine solutions in glass, polypropylene syringes and PVC containers. Int. J. Pharm. 146, 213–223.

Vermeire, A., Remon, J.P., 1998. Compatibility and stability of morphine in binary admixtures with haloperidol, midazolam, dexamethasone or methylprednisolone. Int. J. Pharm. 174, 157–177.

Vianio, A., Auvinen, A., Members of the Symptom Prevalence Group, 1996. Prevalence of symptoms among patients with advanced cancer: an international collaborative study. J. Pain Symptom Manage. 12, 3–10.

Watanabe, S., Bruera, E., 1994. Corticosteroids as adjuvant analgesics. J. Pain Symptom Manage. 9, 442–445.

WHO Expert Committee, 1990. WHO Technical Report Series: Cancer pain Relief and palliative care, Geneva.