Available online at www.sciencedirect.com
SCIENCE DIRECT
International Journal of Pharmaceutics 307 (2006) 278–284
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Morphine, haloperidol and hyoscine *N*-butyl bromide combined in s.c. infusion solutions: Compatibility and stability Evaluation in terminal oncology patients

S. Negro [a,*], R. Reyes [a], M.L. Azuara [b], Y. Sánchez [b], E. Barcia [a]

[a] *Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad Complutense de Madrid, Ciudad Universitaria s/n, Madrid 28040, Spain*

[b] *Unidad de Cuidados Paliativos, Asociación Española contra el Cáncer, Hospital "La Paz", Madrid, Spain*

Received 15 July 2005; received in revised form 6 October 2005; accepted 15 October 2005
Available online 16 November 2005

Abstract

The administration of drugs by subcutaneous infusion is routinely practiced in palliative medicine for the management of patients who are no longer able to take oral medication. It is common for two or more drugs to be combined in subcutaneous solutions. The combination of an opioid with other drugs (haloperiol lactate and hyoscine *N*-butyl bromide) can be very valuable. Unfortunately, the compatibility and stability of morphine hydrochloride, haloperidol lactate and hyoscine *N*-butyl bromide combined in the same solution has not yet been determined. Therefore, this study examined the stability of ternary solutions containing morphine HCl, haloperidol lactate and hyoscine *N*-butyl bromide at different dose ranges. Twelve different solutions were assessed for 15 days after preparation in polypropylene syringes using 0.9% saline as diluent. Triplicate syringes were stored at 25 °C. HPLC was the analytical technique used to measure morphine HCl, haloperidol lactate and hyoscine *N*-butyl bromide. Initial concentration ranges were 1.67–10.0 mg/ml for morphine HCl, 0.417–0.625 mg/ml for haloperidol lactate and, 5.0–6.67 mg/ml for hyoscine *N*-butyl bromide. All three drugs were very stable (>92.5%) when stored at 25 °C. The clinical performance of the admixture was retrospectively assessed in 21 terminal oncology patients. Total symptom control was achieved in 17 out of 21 patients with very good local tolerance.

Keywords: Subcutaneous; Stability; Morphine hydrochloride; Hyoscine *N*-butyl bromide; Haloperidol lactate; Palliative care

1. Introduction

Cancer is among the most feared chronic illnesses and terminally ill cancer patients commonly experience moderate to severe pain as well as several other symptoms. When patients are no longer able to take oral medication the parenteral administration of drugs is often required (Moulin et al., 1992). Alternatives to the oral route of administration may be necessary in protracted nausea and vomiting, bowel obstruction, malabsorption, mucositis, and inadequate pain relief in spite of large oral doses. Among alternate routes, continuous subcutaneous infusion is the most common medication delivery modality for symptom control in these patients.

Subcutaneous infusions have several advantages over intravenous infusions; venous access is not required, close supervision is unnecessary, and infection is unlikely (Hanks et al., 2001). While site changes usually require between five and seven days, continuous subcutaneous infusion may be more manageable for hospice or home practitioners compared to the necessity to change i.v. sites, on average, every one to three days. Another positive attribute of continuous subcutaneous infusion is the ability to infuse small amounts of concentrated drug into the s.c. compartment (Herndon and Fike, 2001).

When combinations of drugs are administered via subcutaneous infusion, drug incompatibility or loss of stability can occur. Incompatibility might cause drug precipitation or crystallization resulting in the blockage of the cannula, skin irritation and poor absorption (Grassby, 1997).

In a survey of hospital practice, a clear deficit of information was found pertaining to the compatibility and stability of

* Corresponding author. Tel.: +34 91 394 1739; fax: +34 91 394 1736.
E-mail address: soneal@farm.ucm.es (S. Negro).

0378-5173/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2005.10.017

agents combined in infusions that were, at the time of the survey, already being used in combination in infusion solutions (Herndon and Fike, 2001). Fortunately, an increasing number of reports are being published in which infusion solutions, reflective of those used in palliative care, are being assessed for drug compatibility and stability. Most of these studies take into account the need to make assessment for more than 24 h but fail to assess how drug stability may be affected by different temperatures to which solutions are exposed during storage and use.

The symptom most frequently associated with terminal cancer patients is pain. At least two-thirds of cancer patients in the final stages of their disease will report significant pain. Often accompanying this pain are problems with depression, anxiety, hostility, and decreased level of activity. Adequate pain control can clearly result in an improved overall quality of life. The opioid analgesics most commonly administered by the s.c. route are hydromorphone, diamorphine and morphine. Morphine is the benchmark "step 3" opioid and in 1996 guidelines were published for its use in cancer pain management (WHO, 1996).

To treat other symptoms commonly experienced by these patients as agitation, with or without pain, nausea and/or vomiting of central origin, intestinal obstruction, sometimes drowsiness and dizziness, the use of a neuroleptic agent such as haloperidol has been found to be very efficient causing less sedation than other neuroleptics and little if any irritation during s.c. infusion (Storey et al., 1990; Lord and Clarke, 1995). Delirium is one of the most common psychiatric disorders in terminally ill cancer patients. Different studies revealed that 28–44% of cancer patients demonstrate delirious symptoms on admission to palliative care units, and 68–88% are delirious just before death (Lawlor et al., 2000; Chiu et al., 2001; Ripamonti et al., 2001; Viano et al., 1996). Olofsson et al. (1996) demonstrated that 66% of delirious patients were adequately managed by haloperidol alone, and 28% required additional benzodiazepines.

Hyoscine *N*-butyl bromide has been successfully used as an antisecretory drug in combination with haloperidol (Ventafridda et al., 1990). It is also useful in controlling vomiting due to malignant GI obstruction.

The compatibility of morphine hydrochloride (morphine HCl) combined with other drugs has been previously studied by Vermeire and Remon (1998) and Vermiere and Remon (1999), but there are no reports on the compatibility and stability of ternary admixtures including morphine HCl, haloperidol lactate and hyoscine *N*-butyl bromide.

Therefore, the aim of this study was to investigate the short-term compatibility and stability of a wide range of concentrations of morphine HCl in combination with haloperidol lactate and hyoscine *N*-butyl bromide in polypropylene syringes stored at 25 °C for 15 days. Specifically the intention was to develop stability-indicating assay procedures, utilizing high-performance liquid chromatography (HPLC) to quantify the drugs included in the admixtures. The clinical outcome of the ternary admixture was retrospectively evaluated in 21 terminal oncology patients.

2. Methods

2.1. Reagents

The reagents used were ampoules of 0.02 g/ml morphine HCl (volume of ampoule = 1 ml) (Oglos, Grünenthal, Spain) and morphine HCl powder (Grünenthal Andrómaco S.A., Spain); ampoules of 5 mg/ml haloperidol lactate (volume of ampoule = 1 ml) (Haloperidol, Esteve, Spain) and haloperidol lactate powder (Sigma–Aldrich, USA); and ampoules of 20 mg/ml hyoscine *N*-butyl bromide (volume of ampoule = 1 ml) (Buscapina, Boehringer Ingelheim, Spain) and hyoscine *N*-butyl bromide powder (Sigma–Aldrich, USA); and sodium chloride for injection 0.9% (Antibióticos Pharma, Spain). Other solvents and reagents were of analytical grade and obtained from Merck (Germany). Water used in the preparation of solutions was purified by Milli-Q Gradient A-10 system (Millipore, France).

2.2. Experimental design

Twelve different drug admixtures were prepared including morphine HCl, haloperidol lactate and hyoscine *N*-butyl bromide. The doses assayed in the study were chosen taking into consideration those more frequently used by our palliative care unit for symptom control of terminal oncology patients. The following doses were assayed: 20, 60 and, 120 mg/day for morphine HCl; 5 and 7.5 mg/day for haloperidol lactate and, 60 and 80 mg/day for hyoscine *N*-butyl bromide (Table 1).

The experimental design involved preparing polypropylene syringes (Icogamma plus, Novico Med., Spain) with infusion solutions, using volumes reflecting those of 5-day infusion pumps (60 ml). The contents of the morphine HCl, haloperidol lactate and hyoscine *N*-butyl bromide ampoules were transferred into 15 ml syringes and made up to a volume of 10 ml, with 0.9% sodium chloride solution. All the procedures were done under aseptic conditions in laminar flow hoods and using sterile drug solutions.

Three syringes of each drug admixture were prepared and stored at $25 \pm 0.5\,^{\circ}C$ (stove), being all the samples protected from direct light exposure. Aliquots from each syringe were stored and analyzed at each time interval. Doses are expressed as the active moiety, not the weight of the salt. To assess loss of volume during storage three extra syringes were prepared for each drug admixture and checked at times 0 and 15 days by measuring their volumes in Hamilton syringes.

Concentrations of morphine HCl, haloperidol lactate and hyoscine *N*-butyl bromide in each syringe were determined in duplicate on the day of preparation and at 5, 7 and 15 days thereafter. At each time point, the solutions were also examined for any loss of volume, the development of colour, cloudiness (i.e. turbidity), precipitation and gas production. This macroscopic determination was performed by transferring the unfiltered admixtures to 5 ml glass test tubes and examining the samples against black and white backgrounds. Microscopic evaluation consisted of transferring two drops of each admixture to a glass slide followed by observation at 100× magnification with an Olympus optical microscope (model CH40). Crystallization

Table 1
Drug admixtures assayed at 25 °C

Admixture	Morphine HCl		Haloperidol lactate		Hyoscine *N*-butyl bromide	
	Dose (mg/day)	*C* (mg/ml)	Dose (mg/day)	*C* (mg/ml)	Dose (mg/day)	*C* (mg/ml)
1	20	1.67	5	0.417	60	5.00
2	20	1.67	7.5	0.625	60	5.00
3	20	1.67	5	0.417	80	6.67
4	20	1.67	7.5	0.625	80	6.67
5	60	5.00	5	0.417	60	5.00
6	60	5.00	7.5	0.625	60	5.00
7	60	5.00	5	0.417	80	6.67
8	60	5.00	7.5	0.625	80	6.67
9	120	10.00	5	0.417	60	5.00
10	120	10.00	7.5	0.625	60	5.00
11	120	10.00	5	0.417	80	6.67
12	120	10.00	7.5	0.625	80	6.67

for both macroscopic and microscopic evaluation was recorded as present or absent.

Moreover, the pH of the solutions was determined on the first day and last day of the study using a calibrated digital pH meter (Crison GLP-22).

2.3. Analytical method

Morphine HCl, haloperidol lactate and hyoscine *N*-butyl bromide concentrations were determined by high-performance liquid chromatography (HPLC). Chromatography was performed using a Gilson HPLC system equipped with a Model 305 piston pump, a Model 118 UV detector, a 506C system interface, a 712 system controller software and, an 831 temperature regulator (Gilson Medical Electronics Inc., Middleton, WI, USA).

For the determination of morphine HCl the method described in the USP 26 (2003a) for the assay of morphine sulphate injections was used. A Lichrospher RP-C18 column (250 mm × 4 mm, 5 μm) (Tecnokroma, S. Coop., Spain) was utilised with an isocratic mobile phase consisting of 720 ml of a solution of 0.73 g sodium 1-heptane sulfonate in water and 280 ml of methanol and 10 ml of glacial acetic acid. The flow rate was 1 ml/min and the detection wavelength was set at 284 nm.

Validation was performed according to the guidelines defined in CDERs Reviewer Guidance on Validation of Chromatographic Methods (FDA, 1994; ICH, 1995). Validation was run on three consecutive days and included calibration curves processed in triplicate. In order to determine the intra-day and inter-day precision and accuracy, a series of three standards were tested six times on the same day and on three different days, respectively.

For morphine HCl the stock solutions were prepared as indicated in a previous paper (Barcia et al., 2005) as well as the standard calibration solutions (concentration range: 5–250 μg/ml). Moreover, three standard samples were prepared containing 100 μg/ml of morphine HCl, 200 μg/ml of hyoscine *N*-butyl bromide and 7.5 μg/ml haloperidol lactate to determine resolution between peaks after HPLC analysis. Retention time for morphine HCl was 9.1 min with no interfering peaks obtained from the other two compounds. Quantification and detection limits of the method were 0.75 and 0.2 μg/ml, respectively.

For the determination of haloperidol lactate, the method described in the USP 26 (2003b) for analysis of haloperidol in tablets was used. A Lichrospher RP-18 column (250 mm × 4 mm, 5 μm) (Tecnokroma, S. Coop., Spain) was used with a mobile phase consisting of 60 parts of methanol and 40 parts of a solution of 0.05 M potassium dihydrogen phosphate buffer adjusted to pH 3.0 with 85% orthophosphoric acid. The flow rate was 1 ml/min and the detection wavelength was set at 254 nm.

For haloperidol lactate the stock solutions were prepared as indicated in a previous paper (Barcia et al., 2003) as well as the standard calibration solutions (concentration range: 0.75–30 μg/ml). Moreover, three standard samples were prepared containing 150 μg/ml of morphine HCl, 30 μg/ml of hyoscine *N*-butyl bromide, and 25 μg/ml of haloperidol lactate to determine resolution between both drug peaks after HPLC analysis. Retention times were 3.6 min. for hyoscine *N*-butyl bromide and 5.4 min for haloperidol lactate ($R = 2.9$). Quantification and detection limits of the method were 0.1 and 0.05 μg/ml, respectively.

For the determination of hyoscine *N*-butyl bromide the method developed by Plank et al. and slightly modified by us was used (Barcia et al., 2003). Briefly, a Lichrospher RP-C18 column (250 mm × 4 mm, 5 μm) (Tecnokroma, S. Coop., Spain) was used with an isocratic mobile phase consisting of 400 ml of an aqueous solution of 0.2% phosphoric acid, adjusted to pH 7.25 with triethylamine, and 600 ml of methanol. The flow rate was 1 ml/min and the detection wavelength was set at 220 nm.

For hyoscine *N*-butyl bromide the stock solutions were prepared as indicated in a previous paper (Barcia et al., 2003) as well as the standard calibration solutions (concentration range: 5–75 μg/ml). Moreover, three standard samples were prepared containing 120 μg/ml of morphine HCl and 40 μg/ml of hyoscine *N*-butyl bromide and 50 μg/ml haloperidol lactate to determine resolution between both drug peaks after HPLC analysis. Retention times were 6.8 min for morphine HCl, 4.8 min for hyoscine *N*-butyl bromide, and 26.8 min for haloperidol lactate ($R = 2.1$ morphine and hyoscine *N*-butyl bromide; and $R = 8.7$ hyoscine *N*-butyl bromide and haloperidol). Quantification and

detection limits of the method were 2.5 and 1.0 μg/ml, respectively.

Preliminary tests were performed to determine the effect of exposing solutions containing the drugs to 70 °C for 10 days. The solutions were prepared in quadruplicate and, under those circumstances, all the solutions underwent less than 5% decomposition with no detectable changes in chromatography resulting from other interfering peaks. Previously, tests were carried out exposing the solutions to extreme pH values, light and higher temperatures for 3 months in order to detect changes in chromatography as indicative of degradation products.

All mobile phases were filtered through 0.45 μm membrane filters (Whatman International Ltd., England) and degassed by sonication before use. Injection volumes of samples and standards were 20 μl and the temperature of the chromatographic system was 35 °C.

For each analytical method, forced degradation experiments were conducted in order to validate that the methods were stability indicating. Preliminary studies were therefore performed to determine the effect of exposing one set of quality control samples prepared with morphine HCl, haloperidol lactate or hyoscine *N*-butyl bromide in each mobile phase and in quadruplicate at 40 °C for 10 days. Under these circumstances, the solutions underwent less than 3% decomposition with no detectable changes in chromatography.

2.4. Statistical evaluation of data

Samples prepared in triplicate for injection gave results consistently within 5% of their mean and data manipulation and statistical tests were therefore performed on the mean values. For each of the admixtures prepared, a two-way analysis of variance (with replicates to account for triplicate syringes) was used to determine whether significant variance occurred which could be attributed to effects of temperature or time and whether any significant interaction between these sources of variation existed (Bolton, 1984).

2.5. Patients

The study was performed in 21 terminally ill cancer patients followed at home by the Palliative Care Unit (AECC), "La Paz" Hospital, Madrid. The study period extended from January 1999 to January 2005. Mean age of the patients was 71.5 ± 8.07 years (47–81). All patients were in an advanced state of their disease exhibiting Karnofsky's indexes ranging from 10 to 40%. The most frequent primary tumors were tumors of the lung (19%), liver (9.5%) and larynx (9.5%). The most frequent symptoms were inminent death (61.9%) followed by pain (33.3%), death rattles (33.3%), dellirium (23.8%), vomiting (23.8%), dyspnea (19%) and dyspfagia (4.8%). To treat these symptoms mean doses used for s.c. infusion were 30.12 mg/day (7.5–140 mg/day) for morphine HCl, 2.78 mg/day (1.6–5 mg/day) for haloperidol lactate and, 57.14 mg/day (30–80 mg/day) for hyoscine *N*-butyl bromide. The duration of the s.c. infusion ranged from 1 to 5 days in all the patients. Pectoral insertion of the butterfly needle was performed in 61.9% of the patients and in the left arm for the rest of the patients (38.1%).

3. Results and discussion

This study developed stability-indicating assay procedures and examined the physicochemical stability of mixtures of proprietary formulations of morphine HCl, haloperidol lactate and hyoscine *N*-butyl bromide, when stored in polypropylene syringes at 25 °C for 15 days. The drugs and concentrations studied were selected after consulting with several palliative care centres, in order to ensure that the results will have clinical utility.

This study used the morphine HCl (commonly used in Europe) rather than morphine sulphate (the only morphine salt available in the US).

It is well known that compatibility and stability is influenced by the relative concentrations of the admixture constituents, but other factors may be involved, including pH changes, ionic concentrations of the vehicles, and storage conditions.

Evaluation of the drug admixtures assayed did not reveal any colour changes associated with admixing. One study of morphine combined in solution with clonidine showed that when the samples were stored at 37 °C a slight discoloration was obtained likely due to formation of small amounts of oxidation products: pseudomorphine and morphine *N*-oxide (Hildebrand et al., 2003).

No precipitation and loss of volume were observed in any of the admixtures tested during the 15-day storage period at 25 °C. No significant changes in the pH of morphine HCl, haloperidol lactate and hyoscine *N*-butyl bromide solutions stored in polypropylene syringes 15 days were noticed. All drug admixtures were acidic with pH values ranging from 3.37 to 4.31 at the beginning of the study. At the end of the storage period (15 days) the pH values ranged from 3.43 to 4.61. A maximum increase of 0.4 pH units was detected.

The pH of all the admixtures was much lower than the physiological pH (pH 7.4). The pH of morphine HCl (pH 4.47), haloperidol lactate (pH 3.28), and hyoscine *N*-butyl bromide (pH 4.4) solutions are all below the physiological range. Although intravenously infused solutions with low pH values are described to have a higher irritation potential (Lewis and Hecker, 1985), however, when infused subcutaneously, binary combinations of drugs with acidic pH values have been previously reported to be well tolerated (Fransson and Espander-Jansson, 1996).

The concentrations of morphine HCl, haloperidol lactate and hyoscine *N*-butyl bromide determined at each time point were estimated in triplicate and expressed as percentage of the drug concentrations contained in the theoretical starting solutions. Mean values obtained from the samples are shown in Table 2 for morphine HCl, haloperidol lactate and hyoscine *N*-butyl bromide, respectively, after storage at 25 °C. Mixtures were considered stable if there was less than 10% degradation.

Concentrations measured for morphine HCl, haloperidol lactate or hyoscine *N*-butyl bromide in syringes at time of preparation were within 2% of the target value.

Table 2
Mean percentages of morphine HCl, haloperidol lactate and hyoscine *N*-butyl bromide remaining in the admixtures

Time (days)	Admixtures											
	1	2	3	4	5	6	7	8	9	10	11	12
Morphine HCl												
0	101.45	101.53	101.57	101.65	101.29	100.01	101.29	101.01	101.21	101.07	101.06	101.02
5	101.10	100.90	101.20	101.30	100.95	101.08	101.09	100.95	101.06	101.04	100.97	100.94
7	100.80	100.60	101.00	100.70	100.57	100.47	100.59	100.38	100.41	100.65	100.51	100.48
15	100.06	99.87	100.25	99.96	100.03	100.04	100.00	99.98	100.04	99.97	99.98	99.92
Haloperidol lactate												
0	101.02	101.16	100.70	101.10	100.76	100.90	101.00	100.78	100.81	100.89	100.95	101.02
5	99.50	98.20	99.20	98.10	98.13	99.00	98.99	98.77	98.90	98.71	98.91	99.84
7	96.70	96.30	97.20	96.40	96.88	96.71	97.04	97.03	96.89	96.53	96.35	96.33
15	95.30	95.10	96.20	95.60	96.07	95.01	95.45	95.04	95.15	95.25	95.51	95.12
Hyoscine *N*-butyl bromide												
0	101.64	101.42	101.09	101.46	101.42	101.65	101.68	101.19	100.89	101.71	101.47	100.96
5	98.80	99.16	97.69	97.18	97.47	97.32	98.07	97.79	98.07	98.08	98.13	98.19
7	96.87	97.54	96.34	96.26	96.89	96.74	96.70	96.63	96.66	96.61	96.92	97.10
15	93.18	93.64	92.66	93.03	94.08	93.95	94.14	93.84	92.66	92.54	93.12	92.78

After 15 days of storage in polypropylene syringes, the percentages of morphine HCl remaining in the drug mixtures were approximately 100% with non-statistically significant differences found between admixtures and sampling times. Moreover, no degradation products of morphine HCl were found (Table 2).

Factors that can influence the degradation of morphine are pH and temperature, oxygen, UV-irradiation, sunlight and impurities. Increasing the pH of the solution results in an increase in the degradation rate of the drug (Vermeire and Remon, 1998). However, in our case, the pH values of the drug mixtures did not change significantly with respect to that of the commercial ampoule of morphine HCl (4.47).

Regarding temperature, several studies (Altman et al., 1990; Vermiere and Remon, 1997) have indicated that concentrated morphine solutions should not be stored at low temperatures in order to avoid precipitation (4 °C). In our case, the storage temperature tested was 25 °C since previous studies performed by ourselves demonstrated that incompatibility occurred at 4 °C when haloperidol lactate was combined in infusion solution with hyoscine *N*-butyl bromide (Barcia et al., 2003). When the solutions containing morphine HCl, haloperidol lactate and hyoscine *N*-butyl bromide were stored at 25 °C no precipitation was obtained since the solubility of morphine HCl was 5.5 times higher than that of the maximum concentration of morphine HCl assayed in our study (10 mg/ml) (Vermiere and Remon, 1997).

All mixtures retained at least 95% of their initial haloperidol lactate after 15 days of storage at 25 °C (Table 2). Previous studies performed by ourselves (Barcia et al., 2003) have indicated that haloperidol lactate might precipitate in the presence of hyoscine *N*-butyl bromide as a result of the formation of haloperidol bromide, which would have a lower solubility than haloperidol lactate. Similar incompatibilities of haloperidol lactate have also been reported with morphine HCl, diamorphine HCl, and hydromorphone HCl (Olcer and Hakyemez, 1988; Grassby and Hutchings, 1997; Huang and Anderson, 1994). However, in the present study the highest concentration of haloperidol lactate assayed in the admixtures was 0.625 mg/ml, lower than 1 mg/ml at which precipitation occurred.

Sunlight is an important factor that affects the stability of haloperidol. In our study and to avoid this instability source, all samples were protected from light exposure. Also, previous studies have demonstrated that haloperidol lactate precipitates in solution when combined with other drugs, such as dexamethasone sodium phosphate and hyoscine *N*-butyl bromide as a consequence of pH modification (Barcia et al., 2003; Negro et al., 2002). In the present study no significant modification of the pH was observed after 15 days when haloperidol lactate and hyoscine *N*-butyl bromide were combined together in solution.

Regarding hyoscine *N*-butyl bromide, all the admixtures retained at least 92.5% of the drug at the end of the study when stored at 25 °C (Table 2). Therefore, relatively little degradation of any of the drugs in either mixture was evident after 15 days when stored in plastic syringes at 25 °C.

In summary, maximum losses of 1%, 6% and 7% were obtained for morphine HCl, haloperidol lactate and hyoscine *N*-butyl bromide, respectively, after storage at 25 °C for 15 days. In all cases, standard deviations ranged from 0.02 to 0.85.

It was not the purpose of this study to determine a precise expiry period but merely to examine the stability over a prolonged period of time. However, based on the findings and bearing in mind that the study only examined physicochemical stability and did not take into account microbial contamination, it would seem reasonable to refill syringes for subcutaneous infusion of these drugs in palliative care patients at intervals of up to one week, assuming that syringes are stored protected from light exposure and stored at 25 °C. This would result in savings in pharmaceutical costs and preparation time, particularly when it might otherwise entail nurses making frequent visits to patients at home. Previous studies have confirmed that the risk of microbial contamination of prefilled syringes is low (Jäppinen et al., 2003).

According to the results of the compatibility and chemical stability study it thus can be recommended that in clinical practice, the morphine HCl, haloperidol lactate and hyoscine *N*-butyl bromide admixtures prepared in polypropylene syringes can be stored for 15 days at 25 °C. We have to emphasize that these results are only valid for the type of syringes tested in this study and for the specific commercial preparations tested.

The performance of morphine resulted in a complete dissapearance of pain and/or dyspnea in eight patients, in 10 patients both symptoms were controlled (absent) with the admixture until death and, in the other three patients only a control 2 was achieved (in a 0–3 scale). Haloperidol was included in the admixture to control vomiting and delirium. In five patients exhibiting vomiting the control obtained was complete. Delirium was controlled in four of the five patients experiencing this symptom since in one patient a control 2/3 was obtained. Hyoscine *N*-butyl bromide was included in the admixture to treat death rattles with complete disappearance in all the patients (seven cases). When hyoscine *N*-butyl bromide was used to prevent death rattles (12 patients), complete disappearance of the symptoms was achieved in 10 cases and in the other two patients a control 2/3 was ontained. Hyoscine *N*-butyl bromide was also very useful in reducing intestinal secretions and cholic pain in two patients suffering from gastrointestinal obstruction.

In summary, symptom control rated in a 0–3 scale (0 = no control and, 3 = complete control) was as follows: 3/3 in 17 cases, 2/3 in three cases and, 1/3 in one patient.

The patient population studied exhibited Karnofsky's indexes of 10% in 14 patients, 20% in four patients and, 40% in three cases. Six of the patients receiving the admixture achieved longer life expectancy and in those cases exhibiting a Karnofsky's index of 40%, the route of administration could be switched to oral.

Local tolerance to subcutaneous infusion of the admixture was very good only exhibiting slight induration in two cases.

Acknowledgement

The authors wish to express their gratitude to Grünenthal Andrómaco S.A., Madrid, Spain for their kind supply of morphine hydrochloride.

References

Altman, L., Hopkins, R.J., Ahmed, S., Bolton, S., 1990. Stability of morphine sulphate in Cormed III (Kalex) intravenous bags. Am. J. Hosp. Pharm. 47, 2040–2042.

Barcia, E., Reyes, R., Azuara, M.L., Sánchez, Y., Negro, S., 2003. Compatibility of haloperidol and hyoscine-*N*-butyl bromide in mixtures for subcutaneous infusion to cancer patients in palliative care. Support. Care Cancer 11, 107–113.

Barcia, E., Reyes, R., Azuara, M.L., Sánchez, Y., Negro, S., 2005. Stability and compatibility of binary mixtures of morphine hydrochloride with hyoscine *N*-butylbromide. Support. Care Cancer 13, 239–245.

Bolton, S., 1984. Pharmaceutical statistics. In: Practical and Clinical Applications. Marcel Dekker Inc., New York, pp. 218–253.

Chiu, T.Y., Hu, W.Y., Lue, B.H., Cheng, S.Y., Chen, C.Y., 2001. Sedation for refractory symptoms of terminal cancer patients. Taiwan J. Pain Symptom Manage. 21, 467–472.

FDA, 1994. Reviewer Guidance: Validation of Chromatographic Methods.

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

Grassby, P.F., Hutchings, L., 1997. Drug combinations in syringe drivers: the compatibility and stability of diamorphine with cyclizine and haloperidol. Palliat. Med. 11, 217–224.

Hanks, G.W., De Conno, F., Cherny, N., Hanna, M., Kalso, E., McQuay, H.J., Mercadante, S., Meynadier, J., Poulain, P., Ripamonti, C., Radbruch, L., Roca i Casas, J., Sawe, J., Twycross, R.G., Ventafridda, V., 2001. Morphine and alternative opioids in cancer pain: the EAPC recommendations. Br. J. Cancer 84, 587–593.

Herndon, C.M., Fike, D.S., 2001. Continuous subcutaneous infusion practices of United States hospices. J. Pain Symptom Manage. 22, 1027–1034.

Hildebrand, K.R., Elsberry, D.D., Hassenbuch, S.J., 2003. Stability and compatibility of morphine-chloride admixtures in an implantable infusion system. J. Pain Symptom Manage. 25, 464–471.

Huang, E., Anderson, R.P., 1994. Compatibility of hydromorphone hydrochloride with haloperidol lactate and ketorolac tromethamine. Am. J. Hosp. Pharm. 51, 2963.

ICH Q2B, 1995. Validation of Analytical Procedures: Methodology.

Jäppinen, A., Turpeinem, M., Kokki, H., Rasi, A., Ojanen, T., Pelkonen, O., Naaranlahti, T., 2003. Stability of sufentanil and levobupivacaine solutions and a mixture in a 0.9% sodium chloride infusion stored in polypropylene syringes. Eur. J. Pharm. Sci. 19, 31–36.

Lawlor, P.G., Ganon, B., Mancini, I.L., 2000. Occurrence, causes, and outcome of delirium in patients with advanced cancer. A prospective study. Arch. Intern. Med. 160, 786–794.

Lewis, G., Hecker, J., 1985. Infusion thrombophlebitis. Br. J. Anaesth. 57, 220–223.

Lord, M., Clarke, R., 1995. Palliative care. Controlling gastrointestinal symptoms. Pharm. J. 254, 511–514.

Moulin, D.E., Johnson, N.G., Murray-Parsons, N., Geoghegan, M.F., Goodwin, V.A., Chester, M.A., 1992. Subcutaneous narcotic infusions for cancer pain treatment: outcome and guidelines for use. Can. Med. Assoc. J. 146, 891–897.

Negro, S., Azuara, M.L., Sánchez, Y., Reyes, R., Barcia, E., 2002. Physical compatibility and in vivo evaluation of drug mixtures for subcutaneous infusion to cancer patients in palliative care. Support. Care Cancer 10, 65–70.

Olcer, M., Hakyemez, G., 1988. Investigations of some physicochemical properties of haloperidol which may affect its activity. J. Clin. Pharmacol. Ther. 13, 341–349.

Olofsson, S.M., Weitzner, M.A., Valentine, A.D., Baile, W.F., Meyers, C.A., 1996. A retrospective study of the psychiatric management and outcome of delirium in the cancer patient. Support. Care Cancer 4, 351–357.

Ripamonti, C., Baines, R., Bozzetti, F., Capri, S., De Conno, F., Mercadante, S., 2001. Clinical practice recommendations for the management of bowel obstruction in patients with end-stage cancer. Support. Care Cancer 9, 223–233.

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.

The United States Pharmacopoeia and The National Formulary 26/21, 2003a. The United States Pharmacopoeia Convention, pp. 1254–1255.

The United States Pharmacopoeia and The National Formulary 26/21, 2003b. The United States Pharmacopoeia Convention, pp. 893–894.

Ventafridda, V., Ripamonti, C., Careceni, D., Spoldi, E., Messina, E., De Conno, F., 1990. The management of inoperable gastrointestinal obstruction in terminal cancer patients. Tumori 76, 389–393.

Vermiere, A., Remon, J.P., 1997. The solubility of morphine and the stability of concentrated morphine solution 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.

Vermiere, A., Remon, J.P., 1999. Compatibility and stability of ternary admixtures of morphine with haloperidol or midazolam and dexamethasone or methylprednisolone. Int. J. Pharm. 177, 53–67.

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

WHO, 1996. Cancer Pain Relief. Report of a WHO Expert Committee. World Health Organization, Geneva, Switzerland.