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Stability and compatibility of intrathecal admixtures containing baclofen and high concentrations of morphine

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Abstract

We have found that the simultaneous intrathecal infusion of low concentrations of baclofen and morphine are of significant benefit in the treatment of both severe pain and spasticity. To extend the range of drug concentrations for clinical use, the stability and physical compatibility of baclofen and morphine sulphate admixtures containing high concentrations of baclofen and morphine sulphate have been examined. The studies reported demonstrate that baclofen and morphine in the admixtures examined were stable for at least 30 days when stored at 37°C. 4-(4-chlorophenyl)-2-pyrrolidone, a degradation product of baclofen was detected in all admixtures examined. Its concentration remained less than 1% of that of baclofen throughout the period of storage. Morphine-*N*-oxide, a potential degradation product of morphine, could not be detected in any of the admixtures examined. While the use of a highly sensitive and selective liquid chromatographic technique with on-line fluorescence detection revealed the presence of pseudomorphine and its time-dependent increase on storage, its concentration also constituted less than 1% of the parent drug. © 1997 Elsevier Science B.V.

Keywords: Baclofen; Morphine; Pseudomorphine; Admixture; Compatibility; Stability; Intrathecal

1. Introduction

Intrathecal delivery of baclofen has been used for the treatment of spasticity (Penn and Kroin, 1984; 1985; Erickson et al., 1985; Muller et al., 1987; Dralle et al., 1985; Hankey et al., 1987;

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Armstrong et al., 1987; Penn, 1988; Parke et al., 1989; Abel and Smith, 1994). Similarly intrathecal morphine has also been used successfully for the treatment of spasticity (Erickson et al., 1985) and pain (Onofrio et al., 1981; Penn and Paice, 1987; Follett et al., 1992). When used singly, however, tachyphylaxis has been shown to occur with morphine and to a lesser extent baclofen (Ochs et al., 1989; Penn, 1992; Abel and Smith, 1994; Yaksh and Rudy, 1978; Milne et al., 1985; Coombs et al., 1985 and Krames et al., 1985).

In a recent study we acquired pharmaceutical data on the compatibility and stability of baclofen/morphine sulphate admixtures within the concentration range 200–1000 μg/ml baclofen and 1000–1500 μg/ml morphine sulphate to support the clinical use of low concentrations of these drugs in combination for intrathecal infusion (Sitaram et al., 1995). Combinations of the two drugs in intrathecal infusion have proved to be synergistic in clinical practice, resulting in lower doses of both in patients with significant tachyphylaxis to either or both drugs (Rawicki et al., 1994a,b). To support the proposed use of higher concentrations of baclofen and morphine sulphate, we have now extended these studies to admixtures containing baclofen within the range 200–1500 μg/ml and morphine sulphate within the range 7.5–21 mg/ml. In addition to the analysis of the parent drugs, assays for the major degradation products of baclofen and morphine have also been developed. In view of the markedly increased concentrations of morphine sulphate we propose to use, a highly sensitive and selective assay has now been developed to monitor its major degradation product pseudomorphine.

2. Materials and methods

2.1. Materials

All drugs and solvents used for liquid chromatography were obtained from sources previously described (Sitaram et al., 1995).

2.2. Instrumentation

Chromatography was performed using Waters 510 liquid chromatographs (Millipore, Milford, MA). All samples were introduced into the column using Rheodyne 7125 injectors (Rheodyne, Cotati, CA) fitted with a 100 μl loop. The spectroscopic detectors used included a Waters Lamda-Max Model 481 spectrometer and a Perkin Elmer LC 240 fluorescence spectrometer (Perkin Elmer, Buckinghamshire, UK). Outputs were recorded on a BBC Goerz Metrawatt SE 120 dual pen chart recorder. An implantable pump (Infusaid Model 400 infusion pump, Infusaid, Norwood, MA) was donated by Medical Specialities Australia Pty Ltd (Sydney, Australia). Osmolality of the admixtures was determined using a Fiske® ONE-TEN Osmometer (Fiske Associates, Needham Heights, MA).

2.3. Liquid chromatographic analysis of baclofen and morphine

Separation of baclofen and morphine was achieved by cation exchange liquid chromatography as previously described (Sitaram et al., 1995). Detection, using ultraviolet absorption spectroscopy, was routinely performed at a fixed wavelength of 266 nm.

2.4. Liquid chromatographic analysis of pseudomorphine

Analysis of pseudomorphine was achieved by reversed-phase liquid chromatography on a Bondex 10 C18 column, 30 cm × 4.6 mm, 10 μm (Phenomenex®, Torrance, CA). The mobile phase consisted of acetonitrile: 50 mM di-ammonium hydrogen orthophosphate buffer pH 6.2 (12:88 v/v) and was maintained at a flow rate of 2.5 ml/min. Detection was routinely performed using fluorescence spectroscopy (excitation 324 nm:emission 428 nm).

To illustrate the analysis of pseudomorphine using this method, an aliquot (50 μl) of a standard solution containing pseudomorphine (3 μg/ml) in saline was subjected to liquid chromatographic analysis with fluorescence detec-

tion. The chromatographic separation of pseudomorphine from baclofen, morphine and morphine-*N*-oxide was confirmed following the analysis of mixtures containing either 50 μg/ml of baclofen and morphine-*N*-oxide or 50 μg/ml of morphine hydrochloride and pseudomorphine using ultraviolet spectroscopic detection at 266 and 285 nm, respectively.

2.5. Liquid chromatographic analysis of 4-(4-chlorophenyl)-2-pyrrolidone

Analysis of 4-(4-chlorophenyl)-2-pyrrolidone was achieved by reversed-phase chromatography on a Spherisorb ODS 2 column, 25 cm × 4.6 mm 5 μm (Phenomenex®, Torrance, CA. The mobile phase consisted of acetonitrile: ammonium phosphate buffer (30:70 v/v) and was maintained at a flow rate of 1.3 ml/min. The buffer consisted of 0.043 M phosphoric acid adjusted to pH 6.0 with ammonia. Detection, using ultraviolet absorption spectrocopy, was routinely performed at 220 nm.

To illustrate the analysis of 4-(4-chlorophenyl)-2-pyrrolidone using these methods, a sample of admixture B was taken after storage at 37°C for 30 days and prepared for analysis. Aliquots (50 μl) of the admixture and a standard solution containing 1 μg/ml CPP in isotonic saline were subjected to liquid chromatographic analysis.

2.6. Preparation of standard solutions and admixtures containing baclofen and morphine

Standard solutions of baclofen and morphine hydrochloride within the concentration range 0–100 and 0–1200 μg/ml, respectively and pseudomorphine and 4-(4-chlorophenyl)-2-pyrrolidone within the concentration range 0–10 μg/ml were prepared from stock solutions, in isotonic saline in a similar manner to that previously described (Sitaram et al., 1995).

2.7. Determination of the pH, physical compatibility and stability of baclofen and morphine in the admixtures

The pH and the physical compatibility and stability of baclofen and morphine in admixtures was determined in admixtures containing 1500 μg/ml baclofen: 7.5 mg/ml morphine sulphate (admixture A), 1000 μg/ml baclofen: 15 mg/ml morphine sulphate (admixture B), and 200 μg/ml baclofen: 21 mg/ml morphine sulphate (admixture C), prepared in a similar manner to that previously described (Sitaram et al., 1995) and stored in sterile glass vials at 37°C. To assess the physical compatibility of baclofen and morphine sulphate, additional samples of the admixtures were taken at specified intervals and filtered through a 0.45 μm filter to remove any drug present in the admixtures in the form of microparticulate material. The concentrations of baclofen and morphine in the resultant filtrate were directly compared with those present in non-filtered controls.

At specified intervals samples of the admixtures were also removed and prepared for the analysis of the concentrations of baclofen, morphine, pseudomorphine and 4-(4-chlorophenyl)-2-pyrrolidone. The liquid chromatographic methods used for analysis are described above and in our previous publication (Sitaram et al., 1995).

To examine the stability of baclofen and morphine in the Infusaid pump for the likely duration of uninterrupted infusion (up to 30 days), the pump was loaded with a 50 mL sample of admixture B and maintained in an incubator at 37°C. The concentrations of baclofen, morphine and pseudomorphine within samples of the infusion solution (500 μl) withdrawn from the pump between 09:00 and 10:00, were determined by liquid chromatography.

2.8. Determination of osmolality of admixtures

After calibration of the Fiske Osmometer using a Accuref 300 Reference Solution, 10 μl aliquots of admixtures A, B and C were placed in a Fiske 110825 sample tube and subjected to analysis. The results represent mean ± S.E. of three independent analyses.

2.9. Analysis of data

All data is expressed as mean ± S.E. for the number of determinations indicated. All statistical analyses were performed as previously described (Sitaram et al., 1995).

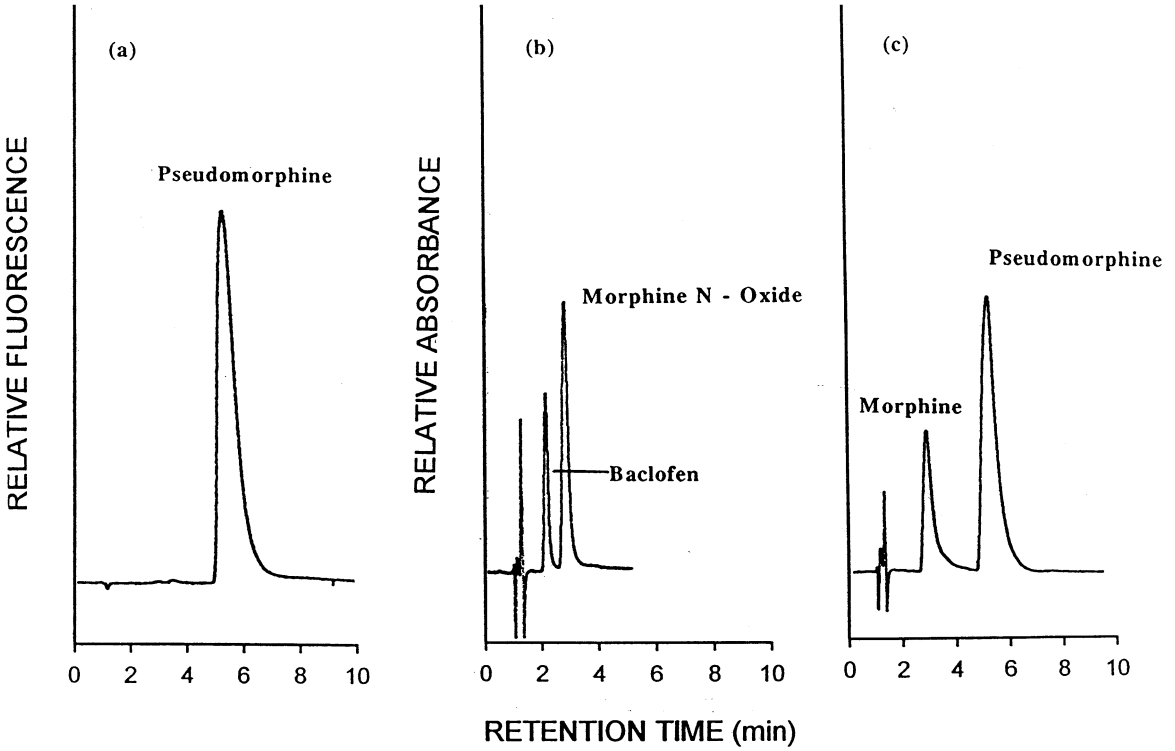

Fig. 1. Chromatogram (a) illustrates the direct analysis of pseudomorphine by reversed-phase liquid chromatography with fluorescence spectroscopic detection. Chromatograms confirming its separation from (b) baclofen and morphine N-oxide and (c) its separation from morphine are also presented.

3. Results

3.1. Liquid chromatographic analysis of baclofen and morphine

Analyses of baclofen and morphine were performed using cation exchange liquid chromatographic techniques we have previously described (Sitaram et al., 1995). These techniques permit the complete separation of baclofen and morphine while ensuring freedom of interference from the known potential degradation products of baclofen (4-(4-chlorophenyl)-2-pyrrolidone) and morphine (morphine-*N*-oxide, and pseudomorphine). Within the range of concentrations of baclofen (0–100 μg/ml) and morphine hydrochloride (0–1200 μg/ml) examined, linear relationships were observed between relative absorbance (peak height) and the concentrations of baclofen ($y = 1.39x + 2.57$; $R = 0.999$) and of morphine hydrochloride ($y = 0.16x + 5.46$; $R = 0.998$).

3.2. Liquid chromatographic analysis of pseudomorphine

A reversed-phase liquid chromatographic method with on-line fluorescence detection was developed for the direct quantitative analysis of trace amounts of pseudomorphine in admixtures A, B and C which contain high concentrations of morphine, within an analysis time of less than 8 min (Fig. 1a). Analyses conducted using on-line ultraviolet absorption spectroscopy demonstrated that under the chromatographic conditions used, pseudomorphine was completely resolved from baclofen and morphine-*N*-oxide (Fig. 1b) and from morphine (Fig. 1c). 4-(4-chlorophenyl)-2-pyrrolidone did not elute from the column under the conditions used. The relative selectivity of fluorescence spectroscopy for the detection of pseudomorphine was confirmed following the chromatographic analysis of equimolar quantities

(50 nmol on column) of morphine, morphine-*N*-oxide and baclofen. In contrast to pseudomorphine, none of these compounds yielded a significant detector response. Under the conditions used the minimum detectable limits for pseudomorphine (signal to noise >2) was 2.15 ng (3.5 pmol) ± 0.02 (5) on column. Within the range of concentrations of pseudomorphine examined (0–10 μg/ml) a linear relationship ($y = 47.37x + 1.64$; $R = 1.000$) was observed between relative fluorescence (peak height) and the concentrations of pseudomorphine.

3.3. Liquid chromatographic analysis of 4-(4-chlorophenyl)-2-pyrrolidone

A reversed-phase liquid chromatographic method with ultraviolet absorption spectroscopic detection was developed for the quantitative analysis of trace amounts of 4-(4-chlorophenyl)-2-pyrrolidone in the presence of concentrations of baclofen within the range 200–1500 μg/ml and morphine within the range 7.5–21 mg/ml. Complete separation of 4-(4-chlorophenyl)-2-pyrrolidone from baclofen, morphine, morphine-*N*-oxide and pseudomorphine was achieved within an overall analysis time of less than 25 min (Fig. 2). Under the conditions used the minimum detectable limits for 4-(4-chlorophenyl)-2-pyrrolidone (signal to noise >2) was 1.84 ± 0.02 ng (4) on column. Within the range of concentrations of 4-(4-chlorophenyl)-2-pyrrolidone examined (0–10 μg/ml) a linear relationship ($y = 26.7x - 0.78$; $R = 0.998$) was observed between relative absorbance (peak height) and the concentration of 4-(4-chlorophenyl)-2-pyrrolidone.

3.4. Stability of baclofen and morphine in admixtures maintained at 37°C

The stability of baclofen and morphine in admixtures A-C was examined for up to 30 days. In admixture A the amount of baclofen and morphine detected following 30 days of storage, represented 103.9 ± 0.78 and $99.2 \pm 1.0\%$ of initial concentrations, respectively (Fig. 3a). No significant time dependent change in the percentage of baclofen remaining, ($y = 98.5 + 0.08x$) or the percentage of morphine remaining ($y = 99.8 + 0.04x$) was detected over the duration of storage. In the case of admixture B the concentrations of baclofen and morphine remaining after 30 days were 101.5 ± 0.55 and $98.1 \pm 0.25\%$ of the initial concentrations, respectively (Fig. 3b). Regression analysis detected no significant time dependent change in the percentage of baclofen remaining ($y = 98.5 + 0.05x$;). In contrast a slight but significant trend towards an increase was detected in the percentage of morphine remaining ($y = 98.7 + -$

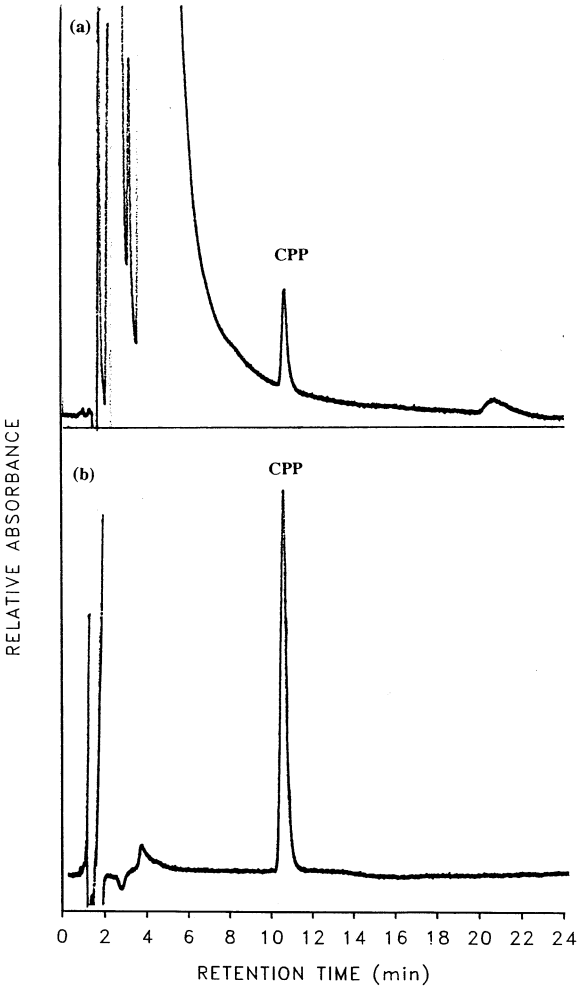

Fig. 2. Chromatograms illustrating the separation on an ODS column of (a) 4-(4-chlorophenyl)-2-pyrrolidone (CPP) present in admixture B with that of (b) an authentic standard.

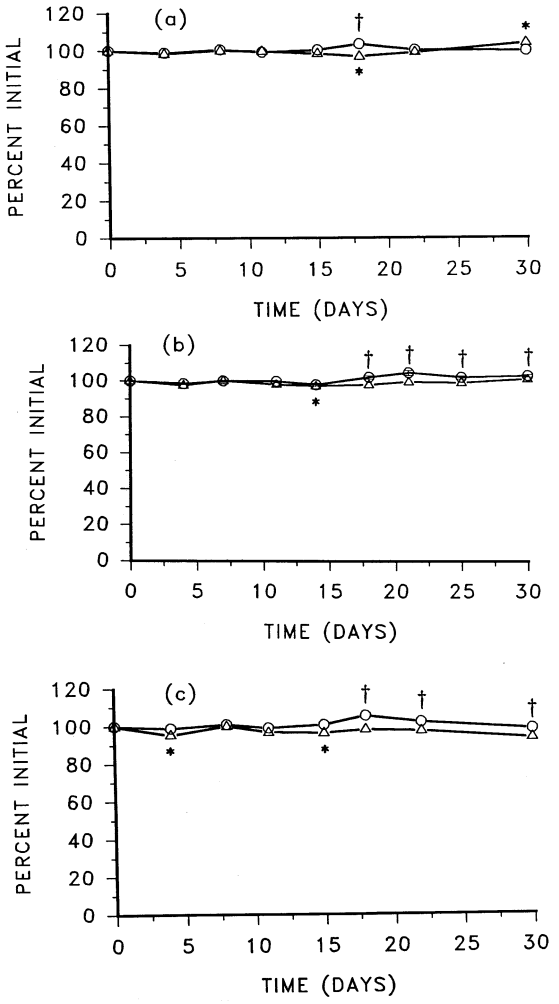

Fig. 3. Profiles for the percentages of (a) baclofen (△) and morphine (○) in admixture A (b) in admixture B and (c) in admixture C stored in sterile glass vials at 37°C. All results are presented as mean ± S.E. for determinations on 5 samples (*$p < 0.05$ baclofen significantly different from initial concentrations; †$p < 0.05$ morphine significantly different from initial concentrations).

$0.17x$; $p < 0.001$). After 30 days the amounts of baclofen and morphine in admixture C, meanwhile, represented 93.1 ± 1.3 and 98.1 ± 0.25% of initial concentrations, respectively (Fig. 3c) While regression analysis detected a slight but significant decrease in the percentage of baclofen remaining ($y = 99.1 - 0.15x$; $p < 0.05$), no time dependent change in the percentage of morphine remaining ($y = 100.2 + 0.02x$) was evident.

The statistically significant trends detected by regression analysis suggest that a small decrease (< 5%) in the concentration of baclofen might occur in admixture C after 30 days of storage at 37°C, whereas a small increase (< 5.2%) in the concentration of morphine might be expected in admixture B.

3.5. Formation of pseudomorphine in admixtures maintained at 37°C

Pseudomorphine was detected in all admixtures immediately after preparation and represented 0.29 ± 0.03% of the morphine present at time zero. The concentrations of pseudomorphine present in admixtures A, B and C at zero time were 24.3, 33.3 and 71.2 μg/ml, respectively. During storage at 37°C the concentration of pseudomorphine in all the admixtures examined was found to increase significantly (Fig. 4a–c). By 30 days the concentration of pseudomorphine initially present in admixture A had increased by 45.4% to 35.3 μg/ml, in admixture B by 66.3% to 55.7 μg/ml and in admixture C by 64.3% to 117 μg/ml. The increase in the concentration of pseudomorphine was accompanied by a slight yellow discoloration in the admixtures, suggesting a polymerisation reaction involving morphine. The observation of a similar degree of discoloration in control solutions containing morphine alone and the absence of discoloration in solutions containing baclofen alone, is consistent with this hypothesis. Despite the slight discoloration of the admixtures observed, no statistically significant reduction in the overall concentration of morphine could be detected in any of the admixtures examined. The percentage of morphine present in the form of pseudomorphine after 30 days represented < 0.56% of initial concentrations. Furthermore < 0.4% of the morphine present as pseudomorphine in the admixtures after 30 days was actually generated during storage.

3.6. Presence of 4-(4-chlorophenyl)-2-pyrrolidone in admixtures maintained at 37°C

4-(4-chlorophenyl)-2-pyrrolidone was detected in all the admixtures examined, immediately after

preparation and represented $0.57 \pm 0.02\%$ w/w of the baclofen present at time zero. The concentrations of 4-(4-chlorophenyl)-2-pyrrolidone present in admixtures A, B and C at zero time were 8.62 μg/ml; 5.36 μg/ml and 1.23 μg/ml respectively. In admixture A the amount of 4-(4-chlorophenyl)-2-pyrrolidone detected following 30 days of storage, represented $89.7 \pm 1.44\%$ of the initial concentrations (Fig. 5). A small but significant time dependent decrease ($y = 96.8 - 0.24x$; $p < 0.005$) in the percentage of 4-(4-chlorophenyl)-2-pyrrolidone remaining, was detected over the duration of storage. In admixture B the amount of 4-(4-chlorophenyl)-2-pyrrolidone detected following 30 days of storage, represented $96.2 \pm 1.32\%$ of the initial concentration. A significant time dependent increase ($y = 98.5 + 0.34x$; $p < 0.005$) in the percentage of 4-(4-chlorophenyl)-2-pyrrolidone remaining, was detected over the duration of storage. In admixture C the amount of 4-(4-chlorophenyl)-2-pyrrolidone detected following 30 days of storage represented $109.1 \pm 1.62x$) of initial concentrations, respectively (Fig. 5). No significant time dependent change in the percent-

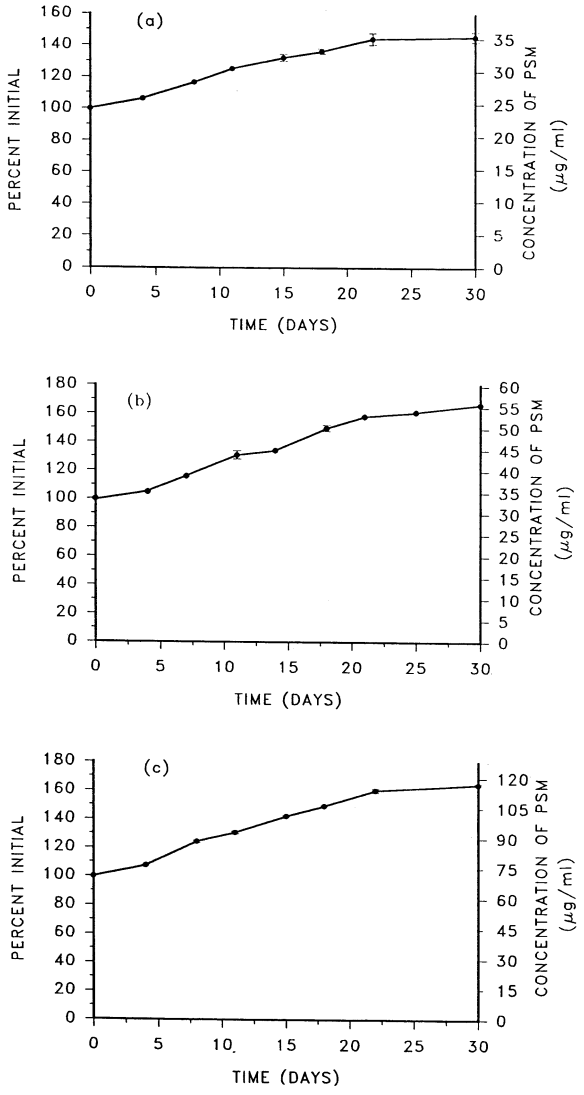

Fig. 4. Profiles for the production of pseudomorphine (PMS) in (a) admixture A (b) admixture B and (c) admixture C stored in sterile glass vials at 37°C.

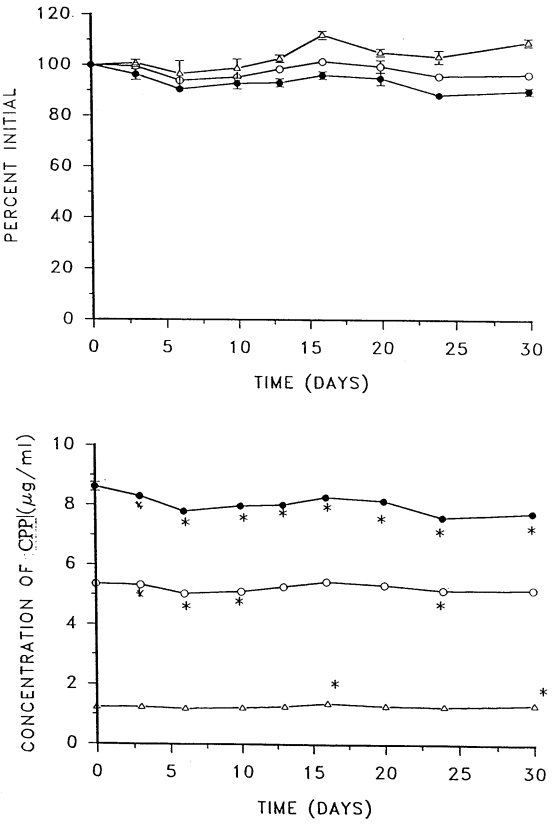

Fig. 5. Profiles of the percentages of 4-(4-chlorophenyl)-2-pyrrolidone (CPP) in admixture A (●), admixture B (○) and admixture C (△) stored in sterile glass vials at 37°C. Results are presented as mean ± S.E. for determinations on 3 samples. *$p < 0.05$ CPP significantly different from initial concentrations.

Table 1
Physical compatibility and pH of admixtures containing baclofen and morphine

Day	Baclofen (percentage ± S.E.)	Morphine (percentage ± S.E.)	Day	pH
Admixture A				
0	96.7 ± 1.4	100.2 ± 0.6	0	5.25 ± 0.01
8	96.7 ± 1.4	96.7 ± 2.4	9	5.23 ± 0.01
15	100.1 ± 1.3	99.7 ± 0.7	14	5.18 ± 0.03
22	101.9 ± 1.6	98.4 ± 0.4	21	5.10 ± 0.06
30	100.2 ± 0.7	101.9 ± 0.1	30	5.01 ± 0.01
Admixture B				
0	99.7 ± 0.4	99.9 ± 0.3	0	4.95 ± 0.04
7	99.4 ± 0.4	99.6 ± 0.3	7	4.81 ± 0.03
14	101.2 ± 0.4	99.9 ± 0.8	14	4.77 ± 0.02
21	98.6 ± 1.2	98.8 ± 1.3	21	4.85 ± 0.06
30	100.7 ± 0.5	98.9 ± 0.6	30	4.75 ± 0.01
Admixture C				
0	100.4 ± 1.1	100.3 ± 1.0	0	3.83 ± 0.04
8	97.7 ± 0.5	97.9 ± 0.9	9	3.82 ± 0.04
15	101.5 ± 1.1	100.8 ± 0.7	14	3.80 ± 0.01
22	100.2 ± 0.3	99.7 ± 0.7	21	3.82 ± 0.03
30	100.0 ± 0.0	99.30 ± 0.05	30	3.64 ± 0.00

The concentrations of baclofen and morphine present following filtration were compared to those present in non-filtered controls. Results are expressed as percent of non-filtered controls. Samples were also taken at specified intervals and the pH determined. All results are presented as mean ± S.E for determinations on five samples.

age of 4-(4-chlorophenyl)-2-pyrrolidone remaining, was detected in admixture C over the duration of storage. The statistically significant trends detected by regression analysis suggest that a small decrease ($< 7.5\%$) in the concentration of 4-(4-chlorophenyl)-2-pyrrolidone might occur in admixture A after 30 days of storage at 37°C whereas an increase ($< 10.5\%$) might be expected in admixture B. It was noted that in all admixures examined the concentrations of 4-(4-chlorophenyl)-2-pyrrolidone remained less than 1% of that for baclofen throughout the duration of storage.

3.7. Physical compatibility of baclofen and morphine sulphate in admixtures maintained at 37°C

No significant loss of either baclofen or morphine accompanied the filtration of any of the admixtures examined at intervals during the period of storage (Table 1). This suggests that no significant physical incompatibilities are likely to occur between baclofen and morphine sulphate within the range of concentrations present in admixtures A–C.

3.8. pH profiles of admixtures containing baclofen and morphine sulphate maintained at 37°C

An examination of the pH profiles for admixtures A–C (Table 1) obtained during the period of storage indicated that only relatively minor changes in the pH of the admixtures were observed between the commencement and the termination of the period of storage. Statistical analysis of the data, performed using regression analysis, detected slight but statistically significant time-dependent reductions in pH in all 3 admixtures examined. The pH of admixture A was reduced from pH 5.25 to 5.01 ($y = 5.28 - 0.008x$; $p < 0.001$); admixture B from pH 4.95 to 4.75 ($y = 4.89 - 0.005x$; $p < 0.05$) and admixture C from pH 3.82 to 3.63 ($y = 3.86 - 0.005x$; $p < 0.05$) by 30 days.

3.9. Osmolality of admixtures

The osmolality of each of the admixtures used in the study were determined. The osmolality of admixture A, B and C was 241.6 ± 0.33, 154.6 ± 0.88 and 190 ± 0.0 mOsmol/kg, respectively.

3.10. Stability of baclofen and morphine in the Infusaid pump

The concentration of baclofen and morphine in the infusion solution obtained from the Infusaid pump after 36 days represented $100.8 \pm 0.67\%$ and $94.9 \pm 0.5\%$ of initial concentrations respectively (Fig. 6). While regression analysis detected no significant time dependent change in the percentage of baclofen remaining ($y = 99.4 + 0.006x$) a significant time-dependent decrease in the percentage of morphine remaining ($y = 97.1 - 0.131x$; $p < 0.007$) was evident over the duration of the study. The statistically significant trend detected by regression analysis suggests that a small but significant decrease ($< 4\%$) may occur in the concentration of morphine during the course of a 30-day infusion.

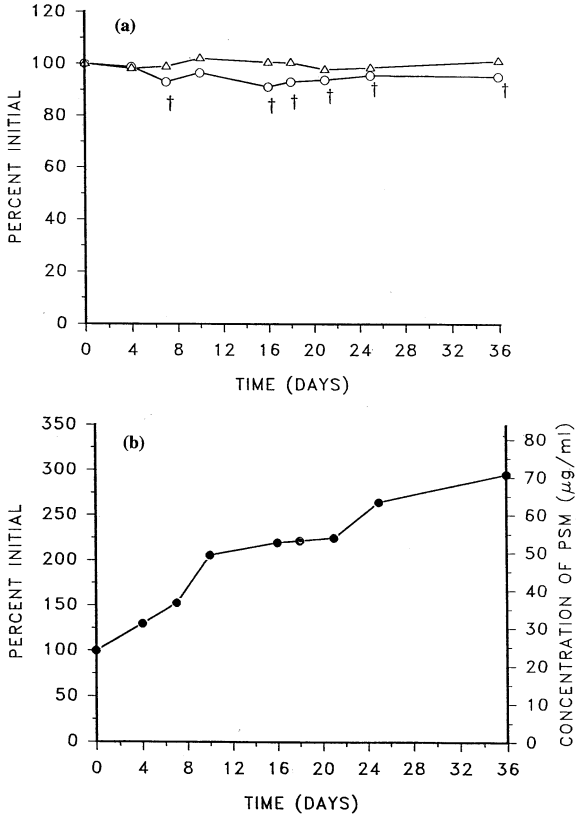

Fig. 6. Profiles (a) for the stability of (△) baclofen and (○) morphine and (b) for the production of pseudomorphine (PMS) (●) from the Infusaid pump. Results are presented as mean ± S.E. for 3 to 4 replicate samples (*$p < 0.05$ baclofen significantly different from initial concentrations; †$p < 0.05$ morphine significantly different from initial concentrations).

The concentration of pseudomorphine present in the infusion solution recovered from the pump at zero time was 23.9 μg/ml. During storage at 37°C the concentration of pseudomorphine was found to increase significantly. Although by 36 days the concentration of pseudomorphine initially present in the infusion solution had increased by 296% to 70.8 μg/ml its concentration still remained at less than 0.7% of that of the parent drug throughout the duration of infusion.

4. Discussion

The aim of our study was to establish the compatibility and stability profiles of baclofen and morphine admixtures containing high concentrations of morphine sulphate. Our studies were conducted at 37°C for up to 30 days, consistent with proposed clinical practice. The liquid chromatographic methods of analysis used (Sitaram et al., 1995) permitted the complete separation of morphine and baclofen from known potential degradation products (Ahuja, 1985; Yeh and Lach, 1961) which might interfere with their analysis. The development of independent methods of analysis was required to facilitate the detection and quantitation of trace amounts of the degradation products pseudomorphine and 4 -(4-chlorophenyl)-2-pyrrolidone, in the present of a large excess of the parent drugs.

In view of the slight discoloration of admixtures observed during our studies, likely to be due to the formation of polymeric degradation products of morphine, a sensitive and selective liquid chromatographic method for the detection of pseudomorphine in the presence of high concentrations of morphine was developed based on its fluores-

cence properties (Darwin and Cone, 1980). Pseudomorphine is a dimeric product and a probable intermediate in the polymerisation of morphine (Yeh and Lach, 1961). Using on-line fluorescence spectroscopy, nanogram quantities of pseudomorphine could be detected without interference from baclofen, morphine or their other degradation products.

The stability and physical compatibility of different admixture concentrations was examined. The concentrations of baclofen and morphine sulphate selected were chosen to reflect possible clinical doses used. Although in some cases regression analysis detected small but statistically significant time dependent changes in the concentration of baclofen and morphine their magnitude and/or direction suggests they are unlikely to be of clinical significance. The absence of a significant change in drug concentrations following filtration, performed at regular intervals throughout the period of storage, suggests that no physical incompatibility developed between these drugs under the conditions examined.

The pH of the admixtures also displayed only minor changes throughout the study. It was noted however that the pH of all of the admixtures examined were acidic, ranging from pH 5.2 for admixture A containing 7.5 mg/ml of morphine sulphate to pH 3.8 for the admixture C containing 21 mg/ml of morphine sulphate. The osmolality of the admixtures ranged from 154 to 242 mOsmol/kg. It has been noted that the pH and the osmolality of the admixtures described differ significantly from the pH (pH 7.35 ± 0.03) and osmolality (292 ± 6 mOsmol/kg) of normal cerebrospinal fluid (van Heijst et al., 1961; Forman and Changus, 1967). Given the flow rates of admixtures during intrathecal infusion (< 0.1 ml/h), the estimated rate of exchange of cerebrospinal fluid of 21 ml/h with a complete exchange of cerebrospinal fluid three to five times per day (Cutler et al., 1968) and the inherent buffering capacity of cerebrospinal fluid, it is unlikely that these differences will result in any sustained perturbations of localised pH or osmolality in the spinal cord.

Pseudomorphine was present in all admixtures immediately after preparation and occurs as a trace impurity in sterile solutions of morphine (Dolezalova, 1992). Despite the time dependent increase in the concentration of pseudomorphine in the admixtures and the appearance of a slight discoloration of the admixtures the overall concentration of morphine was not subject to a statistically significant reduction in any of the admixtures studied. Furthermore the final concentration of pseudomorphine present in the admixtures, even after storage for 30 days at 37°C, represented $< 0.6\%$ of the initial concentration of morphine. Although trace amounts of 4-(4-chlorophenyl)-2-pyrrolidone were also detected in admixtures A-C the concentration present remained at less than 1% of that of baclofen throughout the 30 days of storage at 37°C.

To simulate actual conditions of use, an Infusaid infusion pump was loaded with an infusion solution containing baclofen and morphine sulphate and stability profiles examined. The results indicate that no significant loss of baclofen and only a very small loss of morphine ($< 4\%$) is likely to occur within the infusion pump and that delivery of appropriate concentrations can be expected during intrathecal infusion. Despite a three-fold increase, relative to initial concentrations, pseudomorphine levels remained at less than 1% of the parent drug throughout the proposed period of infusion.

5. Conclusions

Spasticity is a chronic condition affecting the patient's quality of life. In severe cases oral treatments are often limited by systemic side effects. Intrathecal infusion of baclofen and morphine individually are of demonstrable therapeutic value but could also be limited by tachyphylaxis. Based on our earlier studies (Sitaram et al., 1995) the potential benefits of co-administration of baclofen and low concentrations of morphine sulphate ($\leq$ 1.5 mg/ml) are currently being realised. We have extended these studies to admixtures containing morphine sulphate concentrations up to 21 mg/ml. The excellent stability and compatibility of the admixtures demonstrated in our present studies will now further the clinical evaluation of their

possible synergistic benefits in patients, over an extended range of concentrations of morphine sulphate. The trace amounts of pseudomorphine formed in the admixtures on storage and the 4-(4-chlorophenyl)-2-pyrrolidone present, represented less than 1% of the parent drugs and are unlikely to compromise the desired clinical effects.

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References

Abel, N.A., Smith, R.A., 1994. Intrathecal baclofen for treatment of intractable spasticity. Arch. Phys. Med. Rehab. 75, 54–58.

Ahuja, S., 1985. Baclofen. In: Klaus Florey (Ed.), Analytical Profiles of Drug Substances, Academic Press Inc., New York, Vol. 14, pp. 527–548.

Armstrong, R.W., Sykanda, A., Steinbok, P., Farrell, K., 1987. A pilot study of intrathecal baclofen for treatment of spasticity in children. Dev. Med. and Child Neurol. 2 (55), 23–24.

Coombs, D.W., Saunders, R.L., Lachance, D., Savage, S., Ragnarsson, T.S., Jensen, L.E., 1985. Intrathecal morphine tolerance: use of intrathecal clonidine. DADLE and intraventricular morphine. Anesthesiology 62, 358–363.

Cutler, R.P.W., Page, L., Galicich, J., Watters, G.V., 1968. Formation and absorption of CSF in man. Brain 91, 707–720.

Darwin, W.D., Cone, E.J., 1980. Fluorescence properties of pseudomorphine and congeners: structure-activity relationships. J. Pharmaceutical Sci. 69, 253–257.

Dolezalova, M., 1992. Ion-pair high-performance liquid chromatographic determination of morphine and pseudomorphine in injections. J. Pharmaceutics Biomed. Anal. 10, 507–514.

Dralle, D., Muller, J., Zierski, J., Klug, N., 1985. Intrathecal baclofen for spasticity. Lancet, ii, 1003.

Erickson, D.L., Blacklock, J.B., Michaelson, M., Sperling, K.B., Lo, J.N., 1985. Control of spasticity by implantable continuous flow morphine pump. Neurosurgery 16, 215–217.

Follett, K.A., Hitchon, P.W., Piper, J., Kumar, V., Clamon, G., Jones, M.P., 1992. Response of intractable pain to continuous intrathecal morphine: a retrospective study. Pain 49, 21–25.

Forman, D.T., Changus, G.C., 1967. An automated osmometer. Clin. Chem. 38, 38–46.

Hankey, G.J., Stewart-Wynne, E.G., Perlman, D., 1987. Intrathecal baclofen for severe spasticity. Med. J. Aust. 147, 261.

Krames, E.S., Gershow, J., Glassberg, A., Kenefick, T., Lyons, A., Taylor, P., Wilkie, D., 1985. Continuous infusion of spinally administered narcotics for the relief of pain due to malignant disorders. Cancer 56, 696–702.

Milne, B., Cervenko, F., Jhamandas, K., Loomis, C., Sutak, M., 1985. Analgesia and tolerance to intrathecal morphine and norepinephrine infusion via implanted mini-osmotic pumps in the rat. Pain 22, 165–172.

Muller, H., Zierski, J., Dralle, D., Borner, U., Hoffman, O., 1987. The effect of intrathecal baclofen on electrical muscle activity in spasticity. J. Neurol. 234, 348–352.

Ochs, G., Struppler, A., Meyerson, B.A., Linderoth, B., Gybels, J., Gardner, B.P., Teddy, P., Jamous, A., Weinman, P., 1989. Intrathecal baclofen for long term treatment of spasticity: a multicentre study. J. Neurol. Neurosurg. and Psychiatry 52, 933–939.

Onofrio, B.M., Yaksh, T.L., Arnold, P.G., 1981. Continuous low dose intrathecal morphine administration in the treatment of chronic pain of malignant origin. Mayo. Clin. Proc. 56, 516–520.

Parke, B., Penn, R.D., Savoy, S.M., Corcos, D., 1989. Functional outcome after delivery of intrathecal baclofen. Arch. Phys. Med. Rehabil. 70, 30–32.

Penn, R.D., Kroin, J.S., 1984. Intrathecal baclofen alleviates spinal cord spasticity. Lancet, i, 1078.

Penn, R.D., Kroin, J.S., 1985. Continuous intrathecal baclofen for severe spasticity. Lancet, ii, 125–127.

Penn, R.D., Paice, J.A., 1987. Chronic intrathecal morphine for intractable pain. J. Neurosurg. 67, 182–186.

Penn, R.D., 1988. Intrathecal baclofen for severe spasticity. Ann. N.Y. Acad. Sci. 531, 157–166.

Penn, R.D., 1992. Intrathecal baclofen for spasticity of spinal origin: seven years of experience. J. Neurosurg. 77, 236–240.

Rawicki, H.B., Sitaram, B.R., Tsui, M., Lam, S., Courage, P., 1994a. In vivo and in vitro combination of baclofen and morphine for intrathecal use in severe spasticity and chronic pain. Unpublished data, presented at the International Medical Society of Paraplegia (IMSOP) Regional Scientific Meeting, Melbourne 12–13 May 1994.

Rawicki, H.B., Sitaram, B.R., Tsui, M., Lam, S., Courage, P., 1994b. In vivo and in vitro combination of baclofen and morphine for intrathecal use in severe spasticity and chronic pain. Unpublished data, presented at the International Neuromodulation Society Scientific Meeting, Gotberg, Sweden. 2–4 June 1994.

Sitaram, B.R., Tsui, M., Rawicki, H.B., Lam, S., Courage, P., Sitaram, M., Chapman, C.B., 1995. Stability and compatibility of baclofen and morphine admixtures for use in an implantable infusion pump. Intern. J. Pharmaceutics 118, 181–189.

van Heijst, A.N.P., Visser, B.F., Maas, A.H.J., 1961. A micromethod for the determination of pH and P_{CO2} in human cerebrospinal fluid. Clin Chim Acta. 6, 589–590.

Yaksh, T. L, Rudy, T.A., 1978. Narcotic analgesics, CNS sites and mechanisms of action as revealed by intracerebral injection techniques. Pain 4, 299–359.

Yeh, S., Lach, J.L., 1961. Stability of morphine in aqueous solution III. Kinetics of morphine degradation in aqueous solution. J. Pharm. Sci. 50, 35–42.