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Stability and compatibility of baclofen and morphine admixtures for use in an implantable infusion pump

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Abstract

The simultaneous intrathecal infusion of baclofen and morphine may be of significant benefit in the treatment of both severe pain and spasticity. The stability and physical compatibility of baclofen and morphine admixtures, at a range of concentrations relevant to their use for intrathecal administration, 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. In addition, it was shown that admixtures can be introduced into an Infusaid® implantable infusion pump, used clinically for the intrathecal delivery of drugs, and appropriate concentrations of both baclofen and morphine maintained for a duration of up to 30 days. The data presented indicate that admixtures of baclofen and morphine can be successfully prepared and delivered using an Infusaid® pump for periods consistent with proposed clinical practice.

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

1. Introduction

Intrathecal medication has been used in the treatment of chronic (mostly malignant) pain since 1981 and severe spasticity since 1985.

Intrathecal delivery of medications, namely, baclofen (Penn and Kroin, 1984, 1985; Dralle et al., 1985; Erickson et al., 1985; Armstrong et al., 1987; Hankey et al., 1987; Muller et al., 1987; Penn, 1988; Parke et al., 1989) for the treatment of spasticity and morphine for the treatment of spasticity (Erickson et al., 1985) and pain (Onofrio et al., 1981; Penn and Paice, 1987; Follett et al., 1992) allows the effective delivery of high local concentrations of medications to the spinal cord, circumventing the blood brain barrier and resulting in a significant reduction in the symptoms of spasticity with few or no systemic side effects. Both morphine and baclofen have been shown repeatedly to be safe, effective treatments with few and usually self-limited side effects.

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Tachyphylaxis has been shown to occur with both morphine and to a lesser extent baclofen (Ochs et al., 1989; Penn, 1992) With morphine a number of experimental studies (Yaksh and Rudy, 1978; Milne et al., 1985) have explained the mechanism for tachyphylaxis, whilst clinical work (Coombs et al., 1985; Krames et al., 1985) has also revealed significant tachyphylaxis in patients using this drug.

The possibility of using a baclofen and morphine admixture to improve the degree of response in patients with significant tachphylaxis to either or both drugs has been considered. The combination may prove synergistic in action and it may be possible to maintain lower doses of both.

Since no pharmaceutical data on the compatibility/stability of baclofen/morphine admixtures are currently available, we undertook to determine the compatibility and stability profiles of baclofen and morphine admixture in the infusion pump to support the proposed clinical use of these drugs in combination.

2. Materials and methods

2.1. Materials

Baclofen (reference standard) was purchased from Sigma (St Louis, MO, USA) and its potential degradation product 4-(4-chlorophenyl)-2-pyrrolidone was kindly donated by Ciba-Geigy (Basle, Switzerland). Morphine hydrochloride and its potential degradation products morphine *N*-oxide and pseudomorphine were kindly donated by Glaxo Pty Ltd (Melbourne, Australia). Sterile solutions of baclofen (Lioresal Intrathecal® 10 mg/20 ml in ampoules) were obtained from Ciba-Geigy (Basle, Switzerland). Isotonic saline (sodium chloride injection 0.9% w/v B.P) was supplied by Astra Pharmaceuticals (Sydney, Australia). Sterile solutions of morphine sulphate (morphine 10 mg/ml in ampoules) were obtained from David Bull Laboratories (Melbourne, Australia). All solvents used for chromatography were of liquid chromatographic standard. Water was purified using a Milli Q RO 4® water purifier (Millipore Pty Ltd, Melbourne, Australia).

2.2. Instrumentation

Chromatography was performed using a Hewlett Packard 1050® Series modular HPLC unit (Hewlett Packard GmbH, Waldbronn, Germany). All samples were introduced into the column using an autosampler. Detection was achieved using ultraviolet spectroscopy at 266 nm for baclofen and 285 nm for morphine using a timed-programmed wavelength interchange. Outputs were recorded on a Shimadzu CR.4A Chomatopac® calculating integrator (Schimadzu Kyoto, Japan). An implantable pump (Infusaid Model 400 infusion pump (Infusaid Inc., Norwood, MA, USA) was kindly donated by Medical Specialities Australia Pty Ltd (Sydney, Australia).

2.3. Liquid chromatography

Separation of baclofen and morphine was achieved by cation exchange liquid chromatography on a Whatman Partisil® 10 SCX column, 25 μm $\times$ 4.6 mm 10 μm (Whatman International, Maidstone, UK) protected by a cation pre-column cartridge (Brownlee Laboratories, Santa Clara, CA, USA). The mobile phase consisted of methanol-0.043 M phosphoric acid/ammonia buffer pH 3.0 (25:75 v/y) and was maintained at a flow rate of 3.00 ml/min.

2.4. Preparation of standard solutions

Stock solutions (100 μg/ml) of baclofen and morphine and morphine *N*-oxide were prepared in isotonic saline. Pseudomorphine (100 μg/ml) was prepared in isotonic saline containing 0.01 M HCl and 4-(4-chlorophenyl)-2-pyrrolidone (2 mg/ml) was prepared in methanol and diluted in isotonic saline to a final concentration of 100 μg/ml immediately prior to use. Standard solutions of baclofen and morphine within the concentration range 0–100 μg/ml were prepared from the stock solution in isotonic saline.

2.5. Preparation of admixtures containing baclofen and morphine

Admixtures containing 800 μg/ml baclofen: 1500 μg/ml morphine sulphate (admixture A);

800 μg/ml baclofen:1000 μg/ml morphine sulphate (admixture B); 200 μg/ml baclofen:1500 μg/ml morphine sulphate (admixture C) and 200 μg/ml baclofen:1000 μg/ml morphine sulphate (admixture D) were prepared in a laminar flow cabinet from sterile solutions of baclofen (Lioresal®) and morphine sulphate. Normal saline injection diluent was added to a 50 ml sterile vial via a 5 μm filter. Samples of the sterile solutions of baclofen and morphine were then added through the filter to achieve the final specified concentrations in the admixture. After gentle shaking to ensure uniform mixing, aliquots of the admixture (10 ml) were dispensed into five individual 10 ml sterile vials.

2.6. Conditions of storage

Admixtures containing baclofen and morphine were stored in a Selsius Solid State incubator (FSE, Melbourne, Australia) maintained at 37 ± 1.5°C. The admixtures were placed on storage at 12:00 h and all samples were routinely taken and prepared for analysis between 12:00 and 12:30 h.

2.7. Determination of the compatibility / stability of baclofen and morphine in the admixtures

2.7.1. Stability of baclofen and morphine

A sample of the admixture was withdrawn from each of the vials on storage at specified intervals using sterile 1 ml Terumo® syringes (Terumo Medical Corp., Elkton, MD, USA). A 250 μl aliquot of the sample was added to a 5 ml volumetric flask and diluted to volume with isotonic saline. A 50 μl sample was then subjected to liquid chromatographic analysis as described above.

2.7.2. Physical compatibility of baclofen and morphine

To assess the physical compatibility of the baclofen and morphine 0.5 ml samples of the admixture were withdrawn at specified intervals and filtered through an Activon PDVF® filter; 0.45 μm, 4 mm diameter (Activon Scientific Products Pty Ltd, Melbourne, Australia). The first 100 μl of filtrate was discarded. Aliquots (250 μl) were taken from the remaining filtrate and added to a 5 ml volumetric flask and diluted to volume with isotonic saline. A 50 μl sample was then subjected to liquid chromatographic analysis. The concentrations of baclofen and morphine remaining after filtration were compared to those in non-filtered controls.

As a further measure of the development of potential physical incompatibilities, the limit test for particulate matter was performed according to procedures outlined in the USP XXII for small-volume injections (US Pharmacopeia, 1992) Samples of the admixtures (1 ml) were withdrawn at 7, 14, 21 and 28 days and subjected to particle analysis using a Hiac/Ryco Model 4100 particle counter (Hiac/Ryco Instruments, USA).

2.7.3. Determination of pH of admixtures

The pH of the admixtures was examined at specified intervals during the period of storage. The pH of samples of admixtures were determined using a Micro-combination pH electrode M410/MI415® (Microelectrodes Inc., NH, USA) linked to a Metrohm 654 pH meter (Metrohm Ltd, Herisau, Switzerland).

2.8. Determination of the stability of baclofen and morphine in the Infusaid pump

To examine the stability of baclofen and morphine the Infusaid pump was loaded with admixture D. The pump was then maintained in an incubator at 37°C. The concentrations of baclofen and morphine within samples of the solution collected over 24 h intervals for up to 8 days were determined by liquid chromatographic analysis.

To examine the stability of the baclofen and morphine within the Infusaid pump, for the likely duration of uninterrupted infusion (up to 30 days), a pump containing admixture A was maintained at 37°C for 30 days. The outlet catheter was sealed with a surgical clamp. On the days of analysis the surgical clamp was released and samples of the infusion solution (500 μl) were collected between 09:00 and 15:00 h.

2.9. Analysis of data

All data are expressed as mean ± S.E. for the number of determinations indicated. All statisti-

cal analyses involving the comparison of concentrations of baclofen and morphine with those initially present were performed by the one-way analysis of variance, on dependent groups of data, using the computer program Sigmastat® ($^{*}p < 0.05$ baclofen significantly different from initial concentrations; $^{\dagger}p < 0.05$ morphine significantly different from initial concentrations). Data were also subjected to linear regression analysis. The regression equation was calculated by minimising the sum of squares to obtain the line of best fit and the significance of the gradient was then computed.

3. Results

3.1. Liquid chromatographic analysis of baclofen and morphine

Cation exchange liquid chromatographic procedures were developed for the analysis of baclofen and morphine in the admixtures. The spectral characteristics of baclofen and morphine were recorded on-line following separation by cation exchange chromatography.

Absorption maxima for baclofen and morphine were observed at 266 and 285 nm, respectively. Detection was routinely performed by ultraviolet absorption at these wavelengths using a time-programmed wavelength change from 266 to 285 nm (initiated at 7 min) following the elution of the baclofen peak.

The use of cation exchange liquid chromatography permitted the complete separation of baclofen and morphine with overall analysis times of less than 12 min. Freedom of interference from the known potential degradation products of baclofen (4-(4-chlorophenyl)-2-pyrrolidone) and morphine (morphine *N*-oxide, and pseudomorphine) was also demonstrated. Both 4-(4-chlorophenyl)-2-pyrrolidone (CPP) and morphine *N*-oxide were completely seperated from baclofen and morphine during the analysis (Fig. 1). No interference is expected from pseudomorphine since it did not elute from the strong cation-exchange column under the chromatographic conditions used.

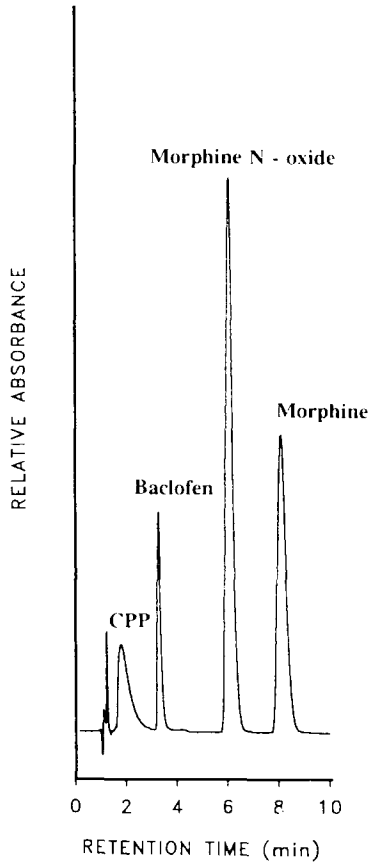

Fig. 1. Chromatogram illustrating the separation of baclofen and morphine and their potential degradation products on an SCX column. An aliquot (20 μl) of a mixture containing 100 μg/ml of baclofen, morphine hydrochloride, morphine *N*-oxide and CPP in isotonic saline was applied to the SCX column and analysed by ultraviolet spectroscopy.

Identification of baclofen and morphine in the admixtures was routinely based on a comparison of retention time characteristics with those of authentic standards. In addition, sequential analyses of 20 μl aliquots of standard solutions of baclofen and morphine (25 μg/ml in isotonic saline) performed by cation-exchange chromatography yielded coefficients of variations of less than 2%. Linear relationships were observed between relative absorbance (peak area) and the concentration of baclofen ($y = 168.16x - 160.8$; $R = 0.999$) and morphine hydrochloride ($y = 644.78x - 0.457$; $R = 0.999$) within the range of concentrations examined (0–100 μg/ml).

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

The stability of baclofen and morphine was initially examined in samples of admixture A (containing 800 μg/ml baclofen:1500 μg/ml morphine) stored at 37°C for 7 days. The study indicated that no significant degradation of either baclofen or morphine occurred in admixture A over this duration of time. The amount of baclofen and morphine present in the admixture on day 7 represented 98.0 ± 1.3 and 99.1 ± 0.85% of initial concentrations, respectively (Fig. 2). Statistical analysis was performed using regression analysis. No statistically significant time-dependent change in the percent baclofen ($y = 99.14 + 0.04x$) or the percent morphine remaining ($y = 99.53 + 0.10x$) was detected during the duration of storage.

In subsequent studies the stability of baclofen and morphine in admixtures A–D was examined for up to 30 days. In admixture A the amount of baclofen and morphine detected following 29 days of storage, represented 104.4 ± 3.9 and 99.5 ± 2.3% of initial concentrations, respectively (Fig. 3a). Regression analysis detected a small but significant trend towards an increase in the percent baclofen remaining, over the duration of storage ($y = 99.6 + 0.17x$; $p < 0.01$). However, no significant time-dependent change in the percent morphine remaining ($y = 99.5 + 0.05x$) was detected. In the case of admixture B the concentrations of baclofen and morphine remaining after 29 days were 102.4 ± 0.44 and 93.5 ± 0.5% of the initial concentrations, respectively (Fig. 3b). Regression analysis detected a small but significant trend towards an increase in the percent baclofen remaining ($y = 99.3 + 0.16x$; $p < 0.001$). In contrast a slight but significant trend towards a decrease in the concentrations was detected in the percent morphine remaining ($y = 98.7 - 0.10x$; $p < 0.05$). After 30 days the amounts of baclofen and morphine in admixture C, meanwhile, represented 99.5 ± 0.35 and 96.5 ± 1.5% of initial concentrations, respectively (Fig. 4a) While regression analysis failed to detect a significant time-dependent change in the percent baclofen remain-

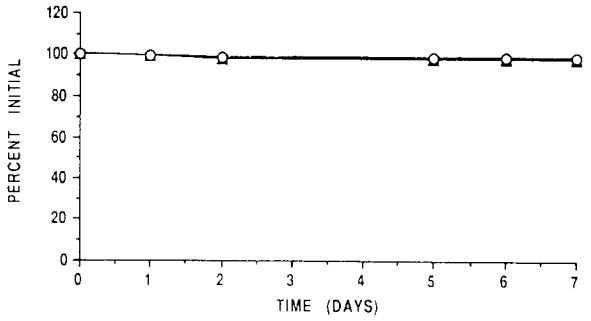

Fig. 2. Stability profiles for (△) baclofen and (○) morphine in admixture A. Samples of admixture A containing baclofen (800 μg/ml) and morphine sulphate (1500 μg/ml) were stored in sterile glass vials at 37°C. At specified intervals samples of the admixture were removed and subjected to analysis. Results are presented as mean ± S.E. for determinations on five samples.

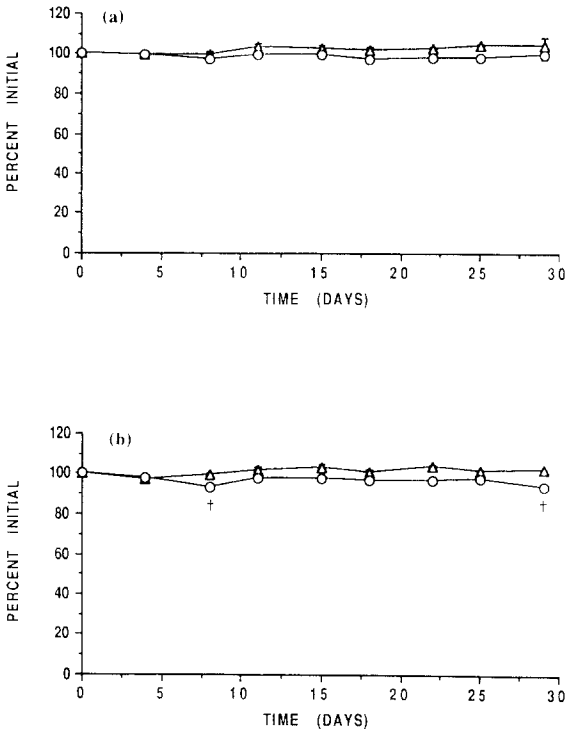

Fig. 3. Stability profiles for (△) baclofen and (○) morphine in (a) admixture A containing baclofen (800 μg/ml) and morphine sulphate (1500 μg/ml) and (b) admixture B containing baclofen (800 μg/ml) and morphine sulphate (1000 μg/ml) stored in sterile glass vials at 37°C. At specified intervals samples of the admixture were removed and subjected to analysis. Results are presented as mean ± S.E. for determinations on five samples.

ing ($y = 100.8 - 0.04x$). a small but significant trend towards a decrease in the percent morphine remaining ($y = 99.7 - 0.04x$; $p < 0.001$) was evident. After 30 days the amounts of baclofen and morphine in admixture D represented 96.6 ± 0.9 and $100.3 \pm 0.8\%$ of initial concentrations (Fig. 4b). Following regression analysis no time-dependent change in either the percent baclofen ($y = 100.34 + 0.02x$) or the percent morphine remaining ($y = 99.7 - 0.02x$) was evident.

The statistically significant trends detected by regression analysis suggest that small increases ($< 5\%$) in the concentration of baclofen might occur in admixture A and in admixture B after 30 days of storage at 37°C whereas small ($< 3\%$) decreases in the concentration of morphine might be expected in admixture B and admixture C.

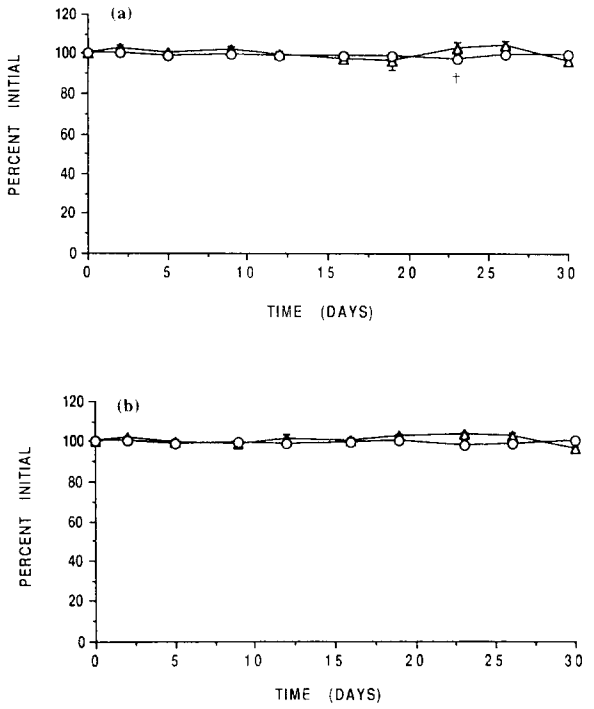

Fig. 4. Stability profiles for (△) baclofen and (○) morphine in (a) admixture C containing baclofen (200 μg/ml) and morphine sulphate (1500 μg/ml) and (b) admixture D containing baclofen (200 μg/ml) and morphine sulphate (1000 μg/ml) stored in sterile glass vials at 37°C. At specified intervals samples of the admixtures were removed and subjected to analysis. Results are presented as mean ± S.E. for determinations on five samples.

Table 1
Physical compatibility of admixtures containing baclofen and morphine

Day	Admixture A		Admixture B	
	Baclofen	Morphine	Baclofen	Morphine
8	101.4 ± 3.0	98.1 ± 0.8	101.8 ± 0.7	98.1 ± 0.3
15	101.9 ± 1.2	98.6 ± 0.3	98.4 ± 0.8	101.2 ± 1.1
22	98.5 ± 1.5	100.3 ± 1.2	98.0 ± 1.3	98.7 ± 1.4
29	93.5 ± 2.9	98.1 ± 2.1	98.4 ± 1.2	101.9 ± 1.9
	Admixture C		Admixture D	
	Baclofen	Morphine	Baclofen	Morphine
9	95.8 ± 2.1	100.8 ± 0.7	106.3 ± 4.5	100.1 ± 0.1
16	102.1 ± 3.2	100.4 ± 0.3	105.8 ± 3.1	99.8 ± 0.2
23	102.8 ± 1.5	100.5 ± 0.7	99.2 ± 3.6	99.4 ± 0.7
30	102.2 ± 1.5	99.9 ± 0.3	100.4 ± 1.1	100.5 ± 0.2

Samples (0.5 ml) of admixtures A–D were taken at specified intervals and filtered through a 0.45 μm filter. Aliquots (20 μl) of the resultant filtrates were then subjected to analysis. The concentrations of baclofen and morphine present following filtration were compared to those present in non-filtered controls. All results are presented as mean ± S.E. for five determinations.

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

To assess the physical compatibility of baclofen and morphine additional samples of the admixtures were also 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. The results obtained indicated that 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 within the range of concentrations present in admixtures A–D. Limit tests for particulate matter were also performed on the admixtures. At all intervals examined during the period of storage (7, 14, 21 and 28 days) the admixtures A–D were found to contain < 1500 particles/container with dimensions ≥ 10 μm and < 100 particles/container

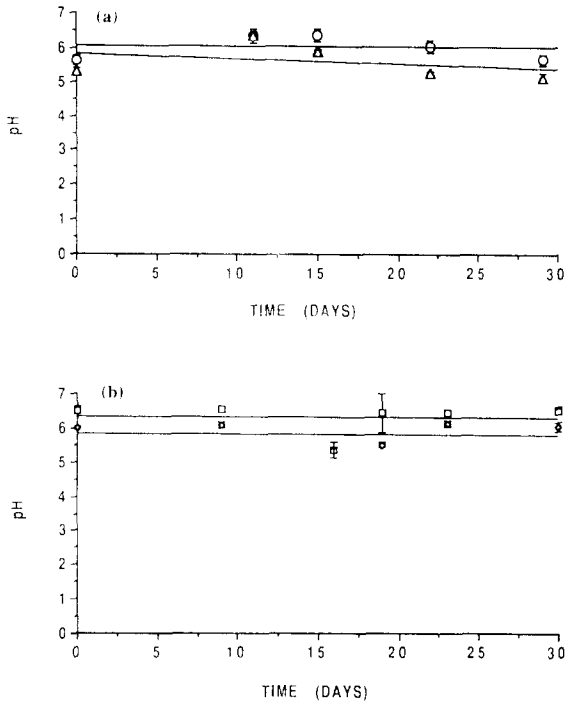

Fig. 5. pH profiles for (a) admixtures A (△) and admixture B (○) and (b) admixtures C (□) and admixture D (◇) containing baclofen and morphine sulphate stored in sterile glass vials at 37°C. At specified intervals samples of the admixtures were removed and the pH determined. Results are presented as mean ± S.E. for determinations on five samples.

with dimensions of 25 μm, well within the limits of 10000 and 1000 particles/container, respectively, imposed by the USP. The data obtained again confirm that no physical incompatibilities are likely to occur in admixtures containing baclofen and morphine.

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

An examination of the pH profiles for admixtures A–D (Fig. 5) obtained during the period of storage indicated that only relatively minor variations in the pH of the admixtures were observed between the commencement and the termination of the period of storage. Statistical analysis of the data was performed using regression analysis. No statistically significant time-dependent change in pH was detected for any of the admixtures examined.

3.5. Infusion profile for baclofen and morphine from the Infusaid pump

To examine the infusion profile from the Infusaid pump admixture D (containing 200 μg/ml baclofen:1000 μg/ml morphine) was loaded into the pump and the infusion solution was collected continuously for 8 days. The concentrations of the drugs in 24 h aliquots of the emergent infusion solution were compared with that present in the admixture prior to its introduction into the pump. The results obtained indicate concentrations of baclofen and of morphine remained similar to the initial concentration, throughout the period of infusion. The concentrations of baclofen and morphine present in the infusion solution on day 8 represented 97.8 ± 0.7 and 101.2 ± 0.5% of initial concentrations, respectively (Fig.

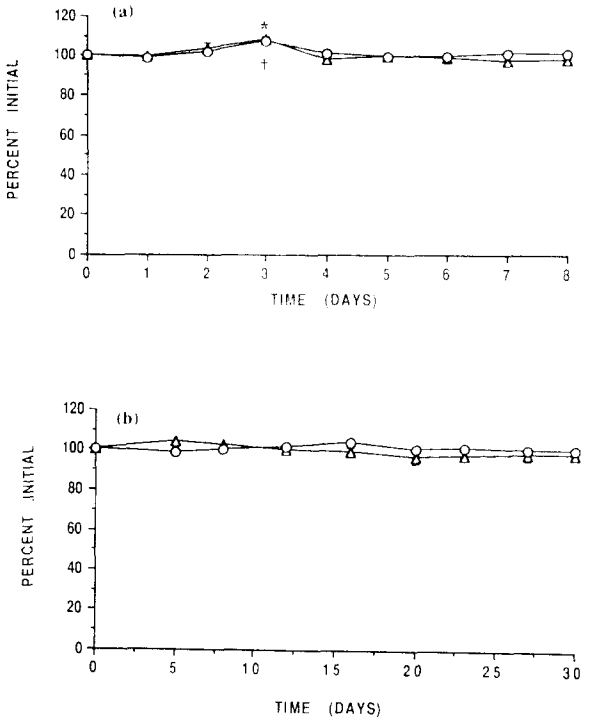

Fig. 6. Infusion and stability profiles for (△) baclofen and (○) morphine sulphate from the Infusaid pump. A 50 ml sample of admixture D containing baclofen (200 μg/ml) and morphine sulphate (1000 μg/ml) sample was introduced into the Infusaid pump. Samples of the infusion solution were collected at specified intervals and subjected to analysis. Results are presented as mean ± S.E. for five replicate analyses.

6a). Following regression analysis no detectable time-dependent change in either the percent baclofen remaining ($y = 102.5 - 0.57x$) or the percent morphine remaining was evident ($y = 101.3 + 0.003x$).

3.6. Stability of baclofen and morphine in the Infusaid pump

To examine the stability of baclofen and morphine in the infusion pump over an extended period admixture D was loaded into the pump and the infusion solution was collected from the outlet at specified intervals over a 30 day period. The concentration of baclofen and morphine in the infusion solution after 30 days represented 98.5 ± 2.3 and $101.3 \pm 0.4\%$ of initial concentrations, respectively (Fig. 6b). Regression analysis detected a small but significant reduction in the percent baclofen remaining ($y = 102.48 - 0.18x$; $p < 0.002$). However, no detectable time-dependent change in the percent morphine remaining ($y = 100.27 + 0.062x$) was evident over the duration of the study. The statistically significant trend detected by regression analysis suggests that a small decrease ($< 5.5\%$) may occur in the concentration of baclofen during the course of a 30 day infusion.

4. Discussion

The aim of our study was to establish the compatibility and stability profiles of baclofen and morphine admixtures at clinically relevant parameters. Implantable infusion pumps are sited subcutaneously in the abdomen wall and thus exposed to body temperature. The pump reservoir is usually replenished percutaneously with the drug at monthly intervals. Thus, our studies were conducted at 37°C for up to 30 days. The methods of analysis of morphine and baclofen in the admixtures were carefully validated. Complete separation of morphine and baclofen from known potential degradation products (Yeh and Lach, 1961; Ahuja, 1985) which might interfere with their analysis, was achieved using the liquid chromatographic techniques described.

The studies we have described were performed in two stages. The first stage was to determine the stability and physical compatibility of different admixture concentrations. The concentrations 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 change in drug concentrations following filtration, performed at regular intervals throughout the period of storage, together with the compliance with the USP particulate limit tests 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. The admixtures examined exhibited good physical and chemical stability.

Experience has shown that drugs can be incompatible with the components of administration devices. To simulate actual conditions of use an Infusaid infusion pump was loaded with the minimum concentrations of baclofen and morphine selected for use clinically (200 μg/ml baclofen:1000 μg/ml morphine) and infusion and stability profiles were examined. The results obtained indicate that no clinically significant loss of either baclofen or morphine is likely to occur within the infusion pump and that the delivery of appropriate concentrations of these drugs can be expected during intrathecal infusion.

5. Conclusions

The therapeutic importance of our studies is clear. Spasticity is a chronic condition requiring protracted treatment. While the intrathecal infusion of baclofen and morphine individually are of demonstrable therapeutic value, the potential benefits of coadministration have yet to be realised. The excellent stability and compatibility of baclofen and morphine admixtures demonstrated in our studies will now facilitate a clinical evaluation of their possible synergistic benefits in patients.

Acknowledgements

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References

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

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

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

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

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

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

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

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

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

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

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

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

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

Penn, R.D., Intrathecal baclofen for severe spasticity. *Ann. NY Acad. Sci.*, 531 (1988) 157–166.

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

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

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

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

US Pharmacopeia, 22nd Edn, US Pharmacopeial Convention, Rockville, 1992, pp. 1596–1598.

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

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