(1981) Interactions between Drugs and Polyvinyl chloride infusion bags. Am. J. Hosp. Pharm. 38: 1308–1314
Lee, M. G. (1985) The sorption of drugs onto plastics. Br. J. Pharm. Pract. April: 82–87
Ogawa, H., Yasue, H., Nakamura, N., Obata, K., Sonoda, R. (1987) Hemodynamic effects of intravenous diltiazem in patients with acute myocardial infarction. Clin. Cardiol. 10: 323–328
Rusmin, S., Welton, S., DeLuca, P., DeLuca, P. P. (1977) Effect of inline filtration on the potency of drugs administered intravenously. Am. J. Hosp. Pharm. 34: 1071–1074
Sewell, G. J., Forbes, D. R., Murton, T. J. (1985) The stability of sodium nitroprusside infusion during administration by motorized syringe pump. J. Clin. Hosp. Pharm. 10: 351–360
Zannad, F., Amor, M., Karcher, G., Royer-Morrot, M., Bertrand, A., Gilgenkrantz, J., Faivre, G. (1985) Limitation of infarct size: diltiazem in acute myocardial infarction. Preliminary results. In: Abstracts of the International Symposium of Cardiovascular Pharmacotherapy, Geneva, Switzerland, 22–25 Apr. 1985

J. Pharm. Pharmacol. 1989, 41: 275–277
Communicated May 20, 1988

Diamorphine stability in aqueous solution for subcutaneous infusion

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Abstract—The influence of temperature and concentration on diamorphine stability during storage over 8 weeks has been investigated. Ampoules containing diamorphine hydrochloride in concentrations from 0·98–250 mg mL^{-1} have been stored at −20, 4, 21 and 37°C for 8 weeks. Their content of diamorphine, 6-monoacetylmorphine and morphine, on measurement by high performance liquid chromatography after 1, 2, 4, 6 and 8 weeks storage changed to slow degradation of diamorphine at all concentrations at temperatures of 4°C and above. This was accompanied by a corresponding increase in 6-monoacetylmorphine and morphine. There was an associated fall in pH and development of a strong odour characteristic of acetic acid. Precipitation and a white turbidity seen in solutions of 15·6 mg mL^{-1} and above, appeared after 2 weeks incubation.

Parenteral diamorphine hydrochloride in concentrations up to 250 mg mL^{-1} are used in continuous subcutaneous infusions employing portable infusion pumps (Jones & Hanks 1986). However, in solution, the drug is unstable, being degraded to 6-monoacetylmorphine and morphine (Beaumont 1982); 3-monoacetylmorphine is a possible third degradation product (Davey & Murray 1969). The degradation is temperature- and pH-dependent (Cooper et al 1981; Beaumont 1982).

Since solutions of diamorphine may remain in infusion pump reservoirs for days or weeks without renewal (Jones & Hanks 1986), it is necessary to determine its stability under those conditions. In a preliminary study (Jones et al 1987), changes in aqueous solutions of diamorphine hydrochloride containing either 1 *or* 250 mg mL^{-1} were monitored over 8 weeks at room temperature or 37°C. Significant temperature- and concentration-dependent degradation of diamorphine was seen, with a corresponding increase in monoacetylmorphine and morphine levels. This was accompanied by a fall in pH. Precipitation was seen in the 250 mg mL^{-1} solution after storage at 37°C. Because of these findings we have investigated the influence of four temperatures and nine concentrations on diamorphine stability over time, and the associated pH changes.

Material and methods

From a 250 mg mL^{-1} aqueous solution of diamorphine hydrochloride, serial dilutions were made to give final concentrations of 250, 125, 62·5, 31·25, 15·6, 7·8, 3·9, 1·95 and 0·98 mg mL^{-1}. Aliquots (1 mL) of each were sealed in sterile brown glass ampoules which were stored protected from light at −20°C (freezer), 4°C (refrigerator), 21°C (room) and 37°C (body). Ampoules were removed at 1, 2, 3, 4, 6 and 8 weeks for analysis by high performance liquid chromatography (Joel et al 1988). The method was modified as follows:- 500 μL samples were injected by autosampler (Gilson model 231). A Spectroflow 400 pump (Kratos) was used with a μ-Bondapack C18 column in a Waters Z Module radial compression system. Analysis of diamorphine was by UV absorbance at 210 nm using a FS770 LC detector (Schoeffel Instrument Inc) and of 6-monoacetylmorphine and morphine by electrochemical detection using a Coulochem detector (Model 5011A) with a high sensitivity analytical cell (Model 5011) and conditioning cells (Esa Model 5021). Coefficients of variation ranged from 4–7·5% over the concentration range of 1–40 μg mL^{-1} for diamorphine and 10–1000 ng mL^{-1} for 6-monoacetylmorphine and morphine.

Data were analysed by multiple regression analysis using the Minitab program, with the dummy variable technique, to determine the effects of temperature and time on concentrations of diamorphine and its metabolites over 8 weeks. Drug concentrations are given as mg L^{-1} to conform with current clinical conventions, but where appropriate, they have been expressed as μ mol L^{-1} to allow direct comparison of diamorphine, 6-monoacetylmorphine and morphine concentrations.

Results

Detailed analytical data for all concentrations at all times have been presented elsewhere (Omar 1988). Degradation of diamorphine occurred at all the concentrations studied at temperatures of 4°C and above. There was a corresponding increase in 6-monoacetylmorphine and to a lesser extent, morphine (Table 1, Fig. 1). The effect of temperature was significant ($P < 0·025$) at 21 and 37°C (Fig. 2). The percentage fall in diamorphine concentration was directly related to the initial concentration (Fig. 3), the median decline in concentration being approximately 8% of the starting dose per week.

Degradation of diamorphine was associated with a fall in pH (Table 1, Fig. 1), and the development of a strong odour characteristic of acetic acid. Precipitation and a white turbidity appeared after 2 weeks incubation, in solutions of concentration 15·6 mg mL^{-1} and above. No peaks other than diamorphine, 6-monoacetylmorphine and morphine were seen on the chromatograms, suggesting that other possible breakdown products such as 3-monoacetylmorphine were not present in detectable quantities.

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Table 1. Concentrations (μmol L^{-1}) of diamorphine, 6-monoacetylmorphine (6MAM), morphine and pH values, before (c) and after 8 weeks storage under different temperature conditions. Figures in parentheses indicate percentage changes compared with control (C) values.

Starting Concn (mg mL^{-1})	Temp (°C)	pH	Diamorphine	6MAM	Morphine
250	c	4·33	675·14 (100)	9·35 (100)	0·0
	−20	4·24	672·20 (1)	11·57 (23)	0·0
	4	3·44	649·77 (4)	21·69 (133)	0·73
	21	2·75	579·62 (14)	86·27 (828)	8·97
	37	2·25	229·37 (66)	231·00 (2384)	203·13
31·2	c	5·20	87·23 (100)	0·98 (100)	0·0
	−20	4·91	85·24 (2)	1·60 (63)	0·0
	4	4·05	83·20 (5)	3·85 (293)	0·09
	21	3·55	72·45 (18)	15·75 (1507)	1·05
	37	3·17	39·66 (54)	29·66 (2926)	8·39
7·81	c	5·70	21·13 (100)	0·30 (100)	0·0
	−20	5·57	20·34 (5)	0·32 (7)	0·0
	4	5·15	18·52 (12)	1·25 (317)	0·02
	21	4·38	18·04 (15)	3·03 (910)	0·02
	37	3·80	12·50 (41)	5·94 (1880)	0·75
0·98	c	6·45	2·65 (100)	0·05 (100)	0·0
	−20	6·32	2·58 (3)	0·06 (20)	0·0
	4	6·29	2·26 (15)	0·20 (300)	0·01
	21	5·86	1·90 (28)	0·57 (1040)	0·03
	37	4·70	1·30 (51)	0·60 (1100)	0·07

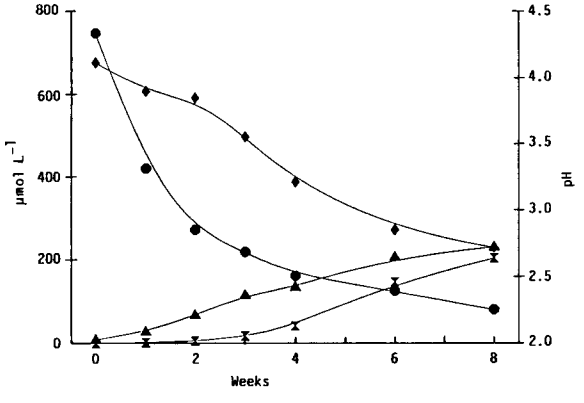

FIG. 1. Concentrations (μmol L^{-1}) of diamorphine hydrochloride (- ◆ -), 6-monoacetylmorphine (- ▲ -) and morphine (- ⧗ -), and pH values (●) before and over 8 weeks storage at 37°C. The initial solution contained diamorphine 250 mg mL^{-1} (675·14 μmol L^{-1}).

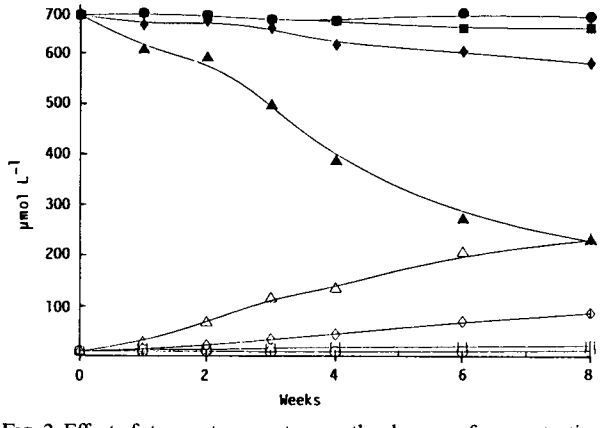

FIG. 2. Effect of storage temperature on the changes of concentration (μmol L^{-1}) of diamorphine, and 6-monoacetylmorphine (6MAM) over 8 weeks, the initial solution containing diamorphine 250 mg mL^{-1} (675·14 μmol L^{-1}). The decreasing diamorphine concentrations are shown by closed symbols and the increasing 6MAM concentrations by open symbols. (−20°C; circles, 4°C; squares, 21°C; diamonds and 37°C; triangles).

Discussion

This study, as well as confirming the observations of Cooper et al (1981), Beaumont (1982) and Jones et al (1987), that degradation of diamorphine in aqueous solutions over time is temperature-dependent, clearly shows the instability to occur under conditions of concentration, time and temperature at which the drug is used for subcutaneous infusion to control pain. Concentrations of 15·6 mg mL^{-1} and above showed turbidity or even a white crystaline precipitate after 2 weeks storage at 21° and 37°C, confirming our earlier finding (Jones et al 1987). (The chemical identify of the precipitate is not known because it could not be dissolved for examination without excluding the possibility that hydrolysis to morphine and 6-monoacetylmorphine had occurred.)

The temperature of a solution in a syringe driver pump may be assumed to be between room and body temperature and will

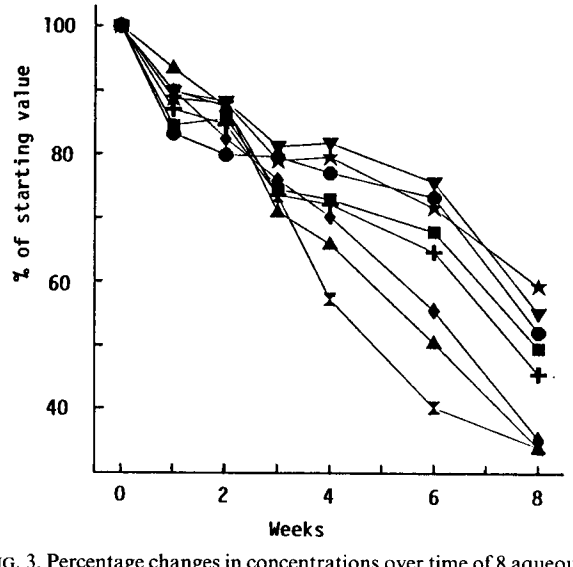

FIG. 3. Percentage changes in concentrations over time of 8 aqueous solutions of diamorphine hydrochloride at 37°C, where initial concentrations ranged from: 1·95 - ● -, 3·91 - ▼ -, 7·81 - ★ -, 15·63 - ■ -, 31·2 - + -, 62·6 - ◆ -, 25 - ▲ - to - ⧗ - 250 mg mL^{-1}.

depend on the proximity of the pump to the patient's body, and the effect of bedclothes and other coverings. It is possible that precipitation may occur in the syringe driver or the infusion pump. This could result in loss of pain control because of inadequate delivery of diamorphine. Clinical experience with *long-term* infusion of diamorphine is limited but we have experienced no problems with infusions maintained for up to two weeks (Jones & Hanks 1986).

The observed changes in pH and liberation of acetic acid may also have clinical implications. Local irritation at the site of infusion is well recognized and may be more common when high doses of diamorphine are used (Regnard & Newbury 1983).

In general, diamorphine solutions for infusion are freshly made up and used within 24 h. There is increasing interest in the use of longer-term infusions both by the subcutaneous route and by the spinal route, where the implications of precipitation and local irritation are potentially more serious. The results of the present work demonstrate the need for caution in using high concentrations of diamorphine in this way. Careful regular examination of the syringe for signs of precipitation is recommended.

P. J. H. was supported by the Cancer Research Campaign and A. J. by the Synthelabo Foundation.

References

Beaumont, I. M. (1982) Stability study of aqueous solutions of diamorphine and morphine using HPLC. Pharm. J. 229: 39–41

Cooper, H., Metha, A. C., Calvert, R. T. (1981) Stability of diamorphine in chloroform water mixture. Ibid. 226: 682–683

Davey, E. A., Murray, J. B. (1969) Hydrolysis of diamorphine in aqueous solutions. Ibid. 203: 737

Joel, S. P., Osbourne, R. J., Slevin, M. L. (1988) An improved method for the simultaneous determination of morphine and its principle glucuronide metabolites. J. Chromat. 430: 394–399

Jones, V. A., Hanks, G. W. (1986) New portable infusion pump for prolonged subcutaneous administration of opioid analgesics in patients with advanced cancer. Br. Med. J. 292: 1496

Jones, V. A., Hoskin, P. J., Omar, O. A., Johnston, A., Hanks, G. W., Turner, P. (1987) Diamorphine stability in aqueous solution for subcutaneous infusion. Br. J. Clin. Pharmacol. 23: 651p

Omar, O. A. (1988) Development of analytical methods for morphine and diamorphine and their application to pharmacokinetic studies in man. Ph.D. Thesis. University of London

Regnard, C., Newbury, A. (1983) Pain and the portable syringe pump. Nursing Times. 79: 25–28

J. Pharm. Pharmacol. 1989, 41: 277–278
Communicated March 18, 1988

Evidence for α_1-adrenoceptor subtype predominance in the rat seminal vesicle

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Abstract—Noradrenaline (0·6–19 μM) and phenylephrine (2–130 μM) induced contractions in the rat seminal vesicle that were competitively antagonized by the α_1-adrenoceptor-selective antagonist corynanthine (120–920 nM). Yohimbine (60–450 nM), an α_2-adrenoceptor-selective antagonist, produced a non-competitive antagonism of noradrenaline responses, suggesting that the responses were not α_2-adrenoceptor mediated. It is concluded that the rat seminal vesicle has a predominance of α_1-adrenoceptors.

The presence in the rat seminal vesicle of post junctional α-adrenoceptors has been well demonstrted (Saxena 1970; Castelli & Genedani 1982; Hib et al 1984). It is widely believed that post-junctional α-adrenoceptors exist as two subtypes, namely the α_1- and α_2-adrenoceptors (Moulds & Jauernig 1977; Drew & Whiting 1979; Docherty & McGrath 1980; Adenekan & Tayo 1982, 1985). The studies on the rat seminal vesicle have provided little or no information about the subtype(s) of post-junctional α-adrenoceptors present in the preparation. I have examined the interactions of noradrenaline and phenylephrine with antagonists in the rat seminal vesicle in an attempt to characterize the α-adrenoceptor subtypes.

Methods

Male albino rats, 200–250 g were stunned and exsanguinated. Both seminal vesicles were isolated, desheathed and the lumen well flushed out with Tyrode solution. Each seminal vesicle was mounted under a resting tension of 1·0 g in a 15 mL organ bath containing Tyrode solution of the following composition (mmol L^{-1}): NaCl 136·9, KCl 2·7, $CaCl_2$ 1·8, $MgCl_2$ 0·9, NaH_2PO_4 0·3, $NaHCO_3$ 11·9 and glucose 5·6. The Tyrode solution was maintained at 36°C and gassed with air while the tissue was connected through an Ugo Basile DY2 force-displacement transducer to a 'Gemini' recorder. After 60 min equilibration, during which the Tyrode solution was replaced at 15 min intervals, non-cumulative concentration-response curves were constructed repeatedly in the absence (control) or presence of three increasing antagonist concentrations. A tissue-drug contact time of 30 s was allowed and the tissue rested for 4 min between contractions. Each antagonist concentration was allowed 25 min equilibration time with the tissue before the agonist was added. Control tissues showed no significant changes in the concentration-response curves over the period of experiment. All experiments were carried out in the presence of cocaine (1·3 μM) to block neuronal uptake. The pA_2 values of the antagonists were estimated by Schild regression plots and antagonism was regarded as competitive when the slope of the Schild regression line was not significantly different from unity (Arunlakshana & Schild 1959). The significance of the differences was analysed with Student's *t*-test and the accepted level of significance was $P < 0.05$.

Drugs used were: Noradrenaline hydrochloride, phenylephrine hyrochloride, yohimbine hydrochloride, corynanthine hydrochloride (Sigma) and cocaine hydrochloride (Krakowski Zargad, Poland). Concentrations refer to base.

Results

Noradrenaline (NA) (0·6–19 μM) and phenylephrine (PE) (2–130 μM) produced concentration related contractions of the rat seminal vesicle unlike UK-14, 304–18 (0·3–76 μM), B-HT 920 (2-amino-6-allyl-5,6,7,8-tetrahydro-4*H*-thiazolo[5,4-*d*]azepine dihydrochloride) and B-HT 933 (2-amino-6-ethyl-4,5,7,8-tetrahydro-6*H*-oxazolo-[5,4-*d*] azepine dihydrochloride) (3·6–920 μM) which did not evoke any contractions. Corynanthine (120–920 nM) produced competitive antagonism of NA and PE as revealed by the Arunlakshana and Schild (A–S) plots. It had pA_2 values of