J. Pharm. Pharmacol. 1989, 41: 273–275
Communicated September 12, 1988



# The availability of diltiazem: a study on the sorption by intravenous delivery systems and on the stability of the drug

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**Abstract**—The stability and the sorption by intravenous delivery systems of the calcium antagonist diltiazem dissolved into either 5% dextrose or 0·9% sodium chloride solutions have been investigated, under conditions simulating current clinical practice. Static experiments showed an excellent stability and no sorption after 48 h. Dynamic experiments, at a perfusion rate of 20 mg $h^{-1}$, showed no sorption of the drug by infusion fluid containers, burettes or administration sets. For end-line filters a temporary decrease of the recovered amount of diltiazem was observed but only with the 0·9% NaCl solution. It is concluded that the stability and the sorption of diltiazem offers no problem with regard to clinical efficacy.

Several authors have studied the problem of sorption of drugs by different kinds of infusion bags, administration sets and end-line filters. The presence of sorption has been reported for a wide variety of drugs such as nitroglycerin, isosorbide dinitrate, nimodipine, diazepam, to name but a few (Rusmin et al 1977; Cossum & Roberts 1981; Kowaluk et al 1981; Illum & Bundgaard 1982; D'Arcy 1983; Lee 1985; Jakobsen & Mikkelsen 1986; De Rudder et al 1987; De Muynck et al 1988). Cutie & Lordi (1980) reported that verapamil, a calcium antagonist, was not sorbed by commonly used infusion fluid containers. Other investigators have demonstrated degradation of drugs in solution, for instance while exposed to normal daylight. This appears to be the case for drugs such as nifedipine, nimodipine, nitroprusside (Sewell et al 1985; Jakobsen & Mikkelsen 1986; Al-Turk et al 1988). Regardless of the cause, the overall decrease in availability may range from 10 to 90% of the initial drug concentration. From a clinical viewpoint it is therefore important that drugs that may be administered by continuous intravenous infusion, should be tested for sorption phenomena and stability under conditions simulating current clinical practice.

The present paper reports on the sorption by infusion bags, administration sets and end-line filters as well as on the stability of diltiazem dissolved into either 5% dextrose or 0·9% sodium chloride solution.

Diltiazem is a potent calcium antagonist (Chaffman & Brogden 1985). Diltiazem i.v. (Tildiem I.V.) is used experimentally in unstable angina and in different aspects of cardioprotection. (Hermann et al 1983; Hagemeijer et al 1984; Zannad et al 1985; Ogawa et al 1987).

## Materials and methods

*Materials.* Diltiazem i.v. vials (Synthélabo Benelux N.V./S.A.) containing 25 or 100 mg of lyophilized drug (batch nos. A 6001 02 and SAP 01-01 A, respectively) were used in all experiments. Drug dilutions of 1 mg $mL^{-1}$ were made using either 5% dextrose or 0·9% sodium chloride solutions. Four infusion bags (A–D), three burettes (E–G), four administration sets (H–K) and four end-line filters (L–O) were examined. The main specifications of all these materials are outlined in Table 1. Static as well as dynamic experiments were performed in twofold under conditions simulating current clinical practice meaning at room temperature ($21 \pm 1$°C) and under normal daylight exposure.

*Analysis.* The HPLC method described by Abernethy et al (1985) was modified. The system consisted of a solvent pump (Waters Associates, model 6000 A), a septumless syringe loaded injector-loop of 1 mL (Valco, Instr. Corp., Houston, USA), a reversed phase column (5 μm Lichrosorb RP 18, 125 mm × 4 mm, Merck, Darmstadt, F.R. Germany), a variable wavelength UV detector (Merck Hitachi, L 4000) set at 238 nm and a chromato-integrator (Merck Hitachi, D 2000).

The mobile phase consisted of acetonitrile–water–methanol (15·0:47·5:37·5:v/v) containing 10 mM heptanesulphonic acid. Glacial acetic acid was added to adjust the pH of the final solution to 3·5. The flow rate was 1·0 mL $min^{-1}$. In all experiments 500 μL were sampled using a glass syringe, and were a hundred times diluted with distilled water. Desacetyldiltiazem was used as the internal standard in a final concentration of 8·5 μg $mL^{-1}$. 40 μL of the sampled and diluted solution were injected in the chromatograph. Calibration curves (peak height

Table 1. Specifications of containers, burettes, administration sets and end-line filters

| Code | Device | Material | Manufacturer |
|---|---|---|---|
| A | 500 mL container | Glass | NPBI bv. Emmer Compascuum, Holland |
| B | 500 mL container | High dens. polyeth. | Braun, Melsungen, W. Germany (Plasco) |
| C | 500 mL container | PVC | Baxter, Travenol Laboratories, Lessen, Belgium (Viaflex) |
| D | 500 mL container | Polyamide (as inner wall) | Braun, Melsungen, W. Germany (Soluflex) |
| E | Burette | Cellulose propionate (CP) | Abbott NV; Ottignies, Belgium (Venisystems Soluset) |
| F | Burette | Butadiene styrene (BS) | Braun, Melsungen, W. Germany (Dosifix) |
| G | Burette | Metacrylate butadiene styrene (MBS) | Avon Medicals, U.K. (Sureset A 2001) |
| H | Administration set | PVC | Abbott NV, Ottignies, Belgium (Venisystems Vented pump set) |
| I | Administration set | PVC | Travenol Laboratories, Lessen, Belgium |
| J | Administration set | Double polymer (PVC/PE) | Abbott NV, Ottignies, Belgium (Venisystems Nitroglycerin pump set) |
| K | Administration set | Polybutadiene (PBD) | Avan Medicals, U.K. (Sureset A261) |
| L | End-line filter | Cellulose ester | Braun, Melsungen, W. Germany (Sterifix) |
| M | End-line filter | Cellulose ester | Millipore, 67 Molsheim, France (IVEX-HP) |
| N | End-line filter | Polyamide (Nylon 66) | Pall, Fajardo, USA (FAE-020 LL) |
| O | End-line filter | Polyamide (Nylon 66) Positively charged‡ | Pall, Fajardo, USA (ELD-96 LL) |

‡ Hydrophylic membrane

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ratio diltiazem versus desacetyldiltiazem) for diltiazem concentrations between 2·5 and 12·0 $\mu$g mL$^{-1}$ showed excellent correlation ($y = 8{\cdot}483\ X - 0{\cdot}00093$ with $r^2 = 0{\cdot}9999$). The standard deviation calculated on the slope of the calibration curve was $4{\cdot}3 \times 10^{-3}$.

*Static experiments.* Diltiazem was added to each of the infusion bags (A–D) and burettes (E–G) containing either a 5% dextrose or a 0·9% NaCl solution. No experiments were performed on polyamide containers with 5% dextrose solution since no such containers appear to be commercially available. The final drug concentration was 1 mg mL$^{-1}$. Samples were taken from the infusion bags after 1, 8, 24 and 48 h. From the polyamide infusion bag and the burettes, samples were taken every hour for 6 h and finally after 24 h.

*Dynamic experiments*: (i) *Administration sets.* Each of the different administration sets was connected to infusion bags containing a solution of diltiazem 1 mg mL$^{-1}$ in either 5% dextrose or 0·9% NaCl. A delivery rate of 20 mL h$^{-1}$ (= 20 mg h$^{-1}$) was assured by a peristaltic infusion pump (Terufusion, infusion pump model STL-503, Terumo Corporation, Tokyo, Japan). The effluent from the administration sets was sampled at 20 or 30, 40, 60, 120, 180, 240 and 300 min.

(ii) *Administration sets and end-line filters.* The dynamic experiment was repeated with the additional attachment of four different end-line filters (L–O) to the delivery system. A sample was taken from the first effluent of the end-line filter and then at 1, 2, 3, 4, 10, 20, 30, 60, 120 to 150 and 300 min thereafter.

## Results and discussion

The time of 48 h was chosen for the static experiments to correspond with the time that the materials tested are used in current clinical practice. For infusion fluid containers in either glass, high density polyethylene or polyvinylchloride no degradation or sorption occurred after 48 h. The amount of diltiazem recovered ranged from 98·9 to 103·4%. Similar results were obtained for a polyamide bag with a 0·9% NaCl solution after 24 h. For the three burettes studied, the quantity of diltiazem recovered after 24 h ranged from 98·0% to 102·3%. All these results were independent of the vehicle. The dynamic experiments relate mainly to the sorption of the drug. In a first series of tests different administration sets in either polyvinylchloride, double polymer (PVC/PE) or polybutadiene were connected to one of the previously tested infusion bags. The recovery of diltiazem after 5 h using a dextrose 5% or a 0·9% NaCl solution, ranged from 95·0% to 103·1% indicating that these tubings do not sorb the drug. In a second series of tests four end-line filters, containing a hydrophilic membrane with the same surface, were connected distally to one of the previously tested combinations of infusion bags and administration sets. End-line filters irrigated by a 5% dextrose solution did not show any adsorption over the period of investigation. With a 0·9% NaCl solution all filters showed a decrease in diltiazem concentration in the first minutes after being linked to the administration set. However, when using a cellulose ester filter this temporary adsorption was reduced to a minimum (Fig. 1). Possibly, when the infusion is started, diltiazem is bound to the surface of the hydrophilic membrane and once all binding sites are saturated, no more drug is adsorbed from the solution. The difference in adsorption pattern between polyamide and cellulose ester filters could be explained by a difference in adsorption capacity of both materials. Nevertheless the two cellulose ester filters, having a greater dead volume (8·5–6·0 mL) than the polyamide filters (5·5–2·0 mL), it is possible that initial adsorption of diltiazem to the cellulose ester filters might not have been detected.

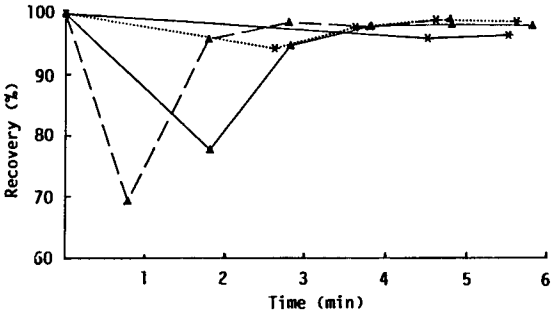


FIG. 1. Recovery (in %) of diltiazem in 0·9% NaCl after administration through 4 types of end-line filters, linked to an infusion set (initial concentration 1 mg mL$^{-1}$; delivery rate 120 mL h$^{-1}$). Each point is the mean of two experiments. -*———*-: L; · * · · * · ·: M; -▲-▲-▲-▲-: N; —▲—▲—▲—▲: O

*Conclusion.* In conditions simulating current clinical practice there is no sorption of diltiazem by the infusion bags, burettes and administration sets tested in this study regardless whether 5% dextrose or 0·9% NaCl solutions were used. Although the four end-line filters show a temporary decrease in diltiazem concentration after being linked to the infusion set, this occurs only in the first minutes and when a 0·9% NaCl solution is used. The static experiments have further demonstrated that the stability of diltiazem is excellent and that no degradation occurs when the drug solution is exposed to normal daylight. Thus the sorption and the stability of diltiazem offers no problem with regard to clinical efficacy.

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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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