J. Pharm. Pharmacol. 1988, 40: 644–645
Communicated April 7, 1988

The stability of morphine in isobaric and hyperbaric solutions in a drug delivery system

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Abstract—Intrathecal preparations of morphine for use in intractable pain must contain no preservatives. They are generally formulated in saline (isobaric) or dextrose (hyperbaric) which raises questions of stability. The behaviour of morphine in hyperbaric and isobaric solutions stored in a reservoir for implantation has been examined and the effect of temperature and the time of contact of morphine with the different components of the reservoir as well as the sterilization procedure have been investigated. The best stability was observed with a hyperbaric solution in which there was 15 to 20 times less pseudomorphine than in the isobaric solution, which was found to contain 1% pseudomorphine after 1 month of storage at 37 °C in the reservoir. Similar solutions stored in ampoules did not degrade.

Intractable pain can be treated effectively by repeated injections of morphine into the subarachnoid space and this has led to the concept of an extended control of pain by the use of an implanted or portable drug delivery system (Lazorthes et al 1980; Onofrio et al 1981; Coombs et al 1983; Penn et al 1984). Such treatment through a permanent subcutaneous catheter has been found beneficial.

Intrathecal preparations must contain no preservatives (Prognon et al 1982). However, in the absence of antioxidants, morphine is susceptible to oxidative degradation (Fulton 1933; Roksvaag et al 1980). Moreover, the use of drug-reservoirs has raised the problem of its stability in contact with new materials at 37 °C.

The preparations are generally formulated in 0·9% NaCl (saline; isobaric solution) (Leavens et al 1982; Nordberg et al 1984) or in dextrose (hyperbaric solution) (Chauvin et al 1981; Lazorthes et al 1985). Pharmacokinetic studies and clinical results (Lazorthes et al 1980, 1985; Caute et al 1988) obtained in our laboratory showed that morphine in a hyperbaric solution had greater efficacy.

The stability of the two morphine solutions in a drug delivery system has now been investigated.

Materials and methods

Drug delivery system. This was a disc shaped device of moulded plastic: 65 mm in diameter. The back holds a pliable 12 mL fluid reservoir (silicone rubber reinforced with polyester). The recesses in the top surface (polysulphone) contain two push buttons (silicone rubber) and the filling dome (silicone rubber). The push buttons control the operating mechanism through a system of plungers and calibrated valves to administer the medication solution via a catheter (silicone rubber). The device is available as Secor (Cordis Europa).

Morphine solutions. The two intrathecal morphine solutions were an isobaric solution of 10 mg morphine hydrochloride in 1 mL of 0·9% NaCl (saline), pH 5·3 prepared in the Pharmacy Department, Hôpitaux de Paris and a hyperbaric solution of 5 mg morphine hydrochloride with 7% dextrose, pH 5·5 prepared in the Pharmacy Department, CHU Toulouse-Rangueil. The solutions were stored in 1 mL ampoules. The stability of the two solutions in the ampoules stored at 4 °C and 37 °C was examined. These ampoules were used as the control.

Analytical methods. The degradation of morphine was measured using a high pressure liquid chromatographic method (Waters model with U6K injector, M_{440} dual wavelength ultraviolet (UV) detector (280, 254 nm), Photodiode Array M 990). Separations were on a C_{18} μbondapack column (0·39 cm × 30 cm) (Waters). Mobile phase: methanol–50 mM ammonium phosphate (40–60 v/v) pH 6·22 with trifluoroacetic acid. The elution was performed isocratically at a flow rate of 1 mL min^{-1}. Morphine has a retention time of 5·4 min and pseudomorphine 6·4 min. The molar absorbance of pseudomorphine (ε) is 20 times larger than that of morphine at 254 nm. The amounts of morphine and pseudomorphine were quantified from linear curves (peak areas vs concentration using a dual wavelength detector 280/254 nm) constructed by direct injection of samples. Pseudomorphine was identified by mass spectrometry and UV spectroscopy by comparison with a sample prepared according to Bentley & Dyke (1959).

Reagents. Methanol (LC Carloerba), ammonium phosphate (Merck), trifluoroacetic acid (Fluka), morphine hydrochloride (Francopia); pseudomorphine was synthetized in the laboratory by the method of Bentley & Dyke (1959).

Pump. The same experimental procedure was used for the two solutions in the reservoir and for a blank solution. The systems were immersed in saline and stored at 37 °C. The polysulphone and silicone of the pump components were brought into contact with the isobaric morphine solution at 37 °C.

The stability of the silicone and polysulphone sterilized with ethylene oxide gas was investigated at 37 °C with the isobaric solution. The samples were assayed at 0, 3, 5 days and every week for two months, when the solutions were replaced. The study lasted six months.

Results and discussion

Each result is the mean of three assays. In the control ampoules stored at 4 °C and 37 °C, no precipitation or discolouration was seen and the HPLC recordings did not show the formation of a degradation product. These results indicate that morphine in hyperbaric and isobaric solutions are stable in our control. In the reservoir, the isobaric solution underwent a colour change to yellow. Fig. 1 summarises the different HPLC recordings from hyperbaric and isobaric solutions at time 0 and two months later. After 3 days a degradation product identified as pseudomorphine was found in the two solutions. Yeh & Lach (1961) have reported that the degradation products of morphine are

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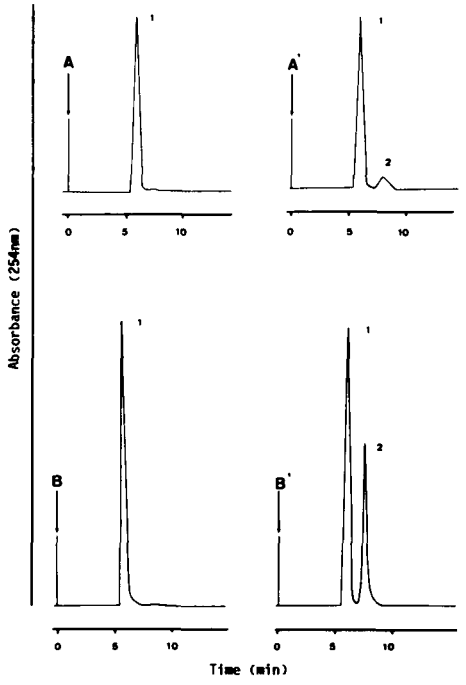

FIG. 1. HPLC Chromatograms of morphine in hyperbaric (A-A') and isobaric (B-B') solutions stored at 37 °C in the pump at time 0 (A-B) and two months later (A'-B').

pseudomorphine and morphine *N*-oxide, together with traces of a base said to be methylamine, and that the deterioration takes place through a condensation process at the phenolic group. This occurs in alkaline or neutral solutions, whereas acidic solutions are relatively stable. The pH values of the two solutions we used were 5·3 for the isobaric solution and 5·5 for the hyperbaric solution and there was no change during the stability investigation. For each collection time, the levels of pseudomorphine were quantified using a calibration curve. The isobaric solution (10 mg morphine HCl) contained 0·1 mg mL^{-1} of pseudomorphine (% of initial dose of morphine) after one month in the reservoir, while the hyperbaric solution (5 mg morphine HCl) contained 15 to 20 times less. A 10 mg hyperbaric morphine solution in the same experimental conditions behaved similarly.

In the case of the isobaric solution, the difference in rate of degradation between the ampoules and the reservoir stored at 37 °C could be attributed to the nature of the different components of the pump, the presence of dissolved oxygen in the system and the sterilization procedure. The rate of degradation in the pump could not be attributed solely to the presence of dissolved oxygen. Isobaric morphine stored at 37 °C in the pump in the same volume was more degraded than in the closed ampoule (0·003 mg mL^{-1} vs 0·1 mg mL^{-1}). We also investigated the different components of the pump: polysulphone and silicone rubber. There was some degradation (about 20 times less than in the intact pump). These results do not allow us to attribute the degradation to the materials studied separately.

We also considered the possible effect of sterilization with ethylene oxide gas on the rate of morphine degradation as it is known that silicone elastomer desorbs poorly (Galtier 1977).

A complementary investigation of the different components of the pump (polysulphone-silicone) sterilized with ethylene oxide has shown a higher rate of degradation (10 times higher) with the silicone parts, than with those of polysulphone, but this was less (0·016 mg mL^{-1}) than with the intact pump.

It seems that the observed degradation of isobaric morphine in the pump is the result of the effects of dissolved oxygen, ethylene oxide, and silicone elastomer.

The results for the morphine in isobaric solution show the formation of 1% of pseudomorphine after one month. However, pseudomorphine is not toxic at these concentrations, so we conclude that morphine in isobaric and hyperbaric solutions has a good stability in this drug delivery system under the experimental conditions used.

The authors wish to thank CORDIS EUROPA, Roden, The Netherlands, for financial support for this work.

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