STABILITY OF DIAMORPHINE HYDROCHLORIDE WITH HALOPERIDOL IN PREFILLED SYRINGES FOR CONTINUOUS SUBCUTANEOUS ADMINISTRATION

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In order to improve the control of pain in the terminally ill continuous subcutaneous administration of diamorphine, using motorized syringes, has become increasingly popular. Haloperidol is often added to the diamorphine solutions, in the syringe, as an antiemetic.

The solutions in regular use at Princess Margaret Hospital contain diamorphine hydrochloride 50 or 100mg/8ml with haloperidol 2.5mg/8ml, and are administered over 24 hours. Because of the large number of requests for these aseptically filled syringes, it has become necessary to consider keeping them as a stock item. Prior to administration a useful storage period would be 2 days, to cover weekend usage, or more ideally at least 7 days.

Gove et al (1985) found that plain diamorphine hydrochloride solutions, filled into syringes, were most stable when stored under refrigeration. Allwood (1984) reported that diamorphine hydrochloride, up to 50mg/ml, was stable for at least 24 hours when mixed with haloperidol at room temperature, but was unable to determine the stability of the haloperidol.

This study examines the stability of both diamorphine and haloperidol, when mixed in plastic syringes, at the concentrations shown above. The solutions were prepared from commercially available injections and 8mls of each was filled aseptically into 10ml polypropylene plastic syringes, through a 0.2µm filter. After sealing them with blank caps the syringes were then either kept at room temperature (22-24°C), as during administration, or stored under refrigeration (4-8°C). The syringes at room temperature were stored both protected and unprotected from light, as haloperidol can discolour and degrade on exposure to sunlight.

HPLC has previously been used to determine diamorphine (Gove et al 1985; Allwood 1984) and haloperidol (Olszewski et al 1980) in formulations and so was the method of choice for this study.

A suitable separation of diamorphine and haloperidol, with respective retention times of 3.0 and 7.1 minutes, was obtained using the following conditions :- flow-rate 2.0mls/min of the solvent (0.005M heptane sulphonic acid sodium salt in 60/40% v/v methanol/water, adjusted to pH 3.5 with glacial acetic acid), a Technopak C18 column and UV detection using a photodiode array detector (Hewlett-Packard HP-1040A), monitoring 277nm for diamorphine and 245nm for haloperidol. Peak height calibration graphs were linear for diamorphine from 0 to 100mg/8ml (r=0.9999) and for haloperidol 0 to 2.5mg/8ml (r=0.9993), when injected directly using a 20µl loop. Replicate assay (n=4) relative standard deviations were diamorphine 0.82% and haloperidol 0.73%.

The degradation products of diamorphine, 6-monoacetylmorphine and morphine, were found to elute before diamorphine at 2.5 and 2.3 minutes respectively. An acid hydrolysis product of haloperidol, prepared in this laboratory, was found to elute after haloperidol at 9.3 minutes. Throughout the study peak purity was examined, using the photodiode array detector, by spectral overlay and signal ratio plot techniques.

From the assay results it was found that haloperidol showed no loss, and diamorphine only a loss of 1.5%, during storage under refrigeration for 7 days. The solutions kept at room temperature for 24 hours showed no significant loss of diamorphine or haloperidol, either protected or unprotected from light. None of the solutions showed any signs of discolouration or precipitation.

Gove, L.F. et al (1985) Pharm. J. : 378-379

Allwood, M.C. (1984) Br. J. Pharm. Prac. 6 : 88-90

Olszewski, L.T. et al (1980) Analytical Profiles of Drug substances. 9 : 362-363, Academic Press, London