A CONTROLLED RELEASE PAPAVERINE TABLET (PAPACONTIN): A STUDY IN NORMAL VOLUNTEERS

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- 1 A controlled release tablet containing 300 mg of papaverine hydrochloride was compared with a capsule containing the same dose.
- 2 The *in vitro* release pattern showed a steady dissolution of the tablet, with release of the papaverine over 10 h, whereas the capsule release time was 40 min.
- 3 Plasma levels in volunteers who were given the tablet showed a rapid rise to therapeutic levels (150–300 ng/ml) within 1 h, and maintenance of these levels for 10–12 h, with no accumulation on repeated 12 hourly dosage. Administration of the capsule produced early peaking and a subsequent rapid fall in plasma levels.

Introduction

Papaverine hydrochloride is the classic non-specific smooth muscle relaxant, but its therapeutic use has been limited by its short half-life when given orally. The half-life has been reported as 100 min by Axelrod, Shofer, Inscoc, King & Sjoerdsma (1958) and as 90–120 min by Ritter, Nail, Tatum & Blazi (1971). In an attempt to overcome the need for frequent dosage, 300 mg papaverine hydrochloride B.P. was incorporated in a specially formulated controlled release tablet and the subsequent papaverine plasma level concentrations obtained were compared with those obtained from a capsule presentation containing 300 mg papaverine hydrochloride B.P. The principles of the tablet formulation with the technology of this particular controlled bioavailability mechanism have been reported previously, as have the results with a similar tablet containing aminophylline (Boroda, Miller, Leslie, Nicol & Thomson, 1973).

Methods

In vitro studies

The *in vitro* disintegration of the tablets was studied using a Manesty Tablet Disintegration Test Unit.

The tablets were first submitted to a 1h disintegration appraisal in a buffer solution (pH 1.6) at 37°C. The solutions were collected and allowed to cool to ambient temperature. After suitable dilution with buffer the papaverine hydrochloride content of each solution was determined by U.V. spectrophotometry with reference to suitable standard solutions of papaverine hydrochloride.

The disintegration appraisal was continued during

the second and third hours with buffer solutions (pH 2.6 and pH 4.6 respectively). The papaverine hydrochloride content of each solution was determined by U.V. spectrophotometry after suitable dilutions with the appropriate buffer.

Thereafter the disintegration appraisal was carried out in a buffer solution (pH 6.5). At the end of each 60 min interval an aliquot (5 ml) was withdrawn, filtered and a sample of filtrate (1 ml) diluted to 50 ml with hydrochloric acid (0.25% w/v). The papaverine hydrochloride content of the solution was determined by U.V. spectrophotometry with reference to suitable standard solutions. Each aliquot withdrawn for filtration was replaced by a corresponding volume of buffer (pH 6.5). The appraisal was continued until complete disintegration of the tablet had been obtained. The *in vitro* dissolution results are recorded within Table 1. It should also be noted that all the papaverine hydrochloride contained within the capsule presentation was in solution by 40 min in the test solution *viz* buffer solution pH 1.6.

In vivo studies

In view of the *in vitro* results, studies were undertaken to compare papaverine plasma levels attained in volunteers after a single dose of either the controlled release tablet or the capsule presentation.

Dosage and sampling

Controlled release tablet One 300 mg controlled release papaverine hydrochloride tablet was ad-

ministered to each of nine subjects at 0 h, 12 h and 24 h. A premedication blood sample was taken to serve as a baseline and a further fourteen samples were taken at intervals after the first and third doses.

Papaverine hydrochloride B.P.

One 300 mg papaverine hydrochloride capsule was administered to each of three subjects after removal of a baseline blood sample. Six further samples were taken at intervals over the subsequent 8 h.

Estimation of papaverine

To a sample (5 ml) of citrated plasma, contained in a 35 ml stoppered centrifuge tube, was added water (5 ml) and 1M sodium hydroxide (1 ml). The solution was extracted with *n*-heptane containing 2% iso-amyl alcohol (2 × 20 ml) (Axelrod *et al.*, 1958), by shaking mechanically for 15 min and separating the phases by centrifugation. The organic extracts were combined in a 100 ml separating funnel and washed with 0.1M hydrochloric acid (3 × 10 ml). The organic phase was discarded and the acid extracts combined in another 100 ml separating funnel. The aqueous phase was made alkaline by the addition of 1M sodium hydroxide (5 ml) and extracted with chloroform-isopropanol (5:1 v/v; 3 × 10 ml). The organic extracts were combined, taken to dryness under a stream of warm air and 5 α -cholestan-3 β -ol (4.68 μ g) added.

The final residue was dissolved in chloroform-isopropanol (5:1 v/v; 25 μ l) and 1 μ l of this solution was injected into the gas chromatograph.

A Perkin-Elmer F17 Gas Chromatograph equipped with a flame ionisation detector was employed. The column was Pyrex glass, 6 feet × $\frac{1}{4}$ " o.d., packed with Chromosorb W (AW-DMCS; 100–120 mesh) coated with 3% Silicone OV-17. The following operating conditions were used for analysis: carrier gas (oxygen free nitrogen) flow rate, 45 ml/min; hydrogen flow rate, 36 ml/min; air flow rate, 400 ml/min; oven temperature, 270°C; injection block temperature, 275°C.

The amount of papaverine in 5 ml of citrated plasma was obtained by calculating the peak area ratio of the drug to that of the internal standard, and relating this to the ratio obtained for a standard reference solution of the drug and the internal standard. The standard reference solution of papaverine and 5 α -cholestan-3 β -ol was prepared based on a plasma papaverine level of 300 ng/ml and an addition of internal standard to the test extract of 4.68 μ g. The peak area ratio of the standard reference solution was determined daily. The amount of papaverine detected in the test extract was converted to ng/ml plasma by determining the actual volume of plasma taken for analysis. From the whole blood sample, volume and erythrocyte-plasma splits of 60:40 for males and 65:35 for females (Documenta Geigy, 1970), a value for the volume of plasma obtained was calculated and this was converted to the true volume of plasma taken for analysis after making due allowance for the volume of anti-coagulant added to each sample.

Extraction of blank plasma samples revealed no interfering peaks in the region of the retention time of either papaverine or 5 α -cholestan-3 β -ol. Blank plasma was seeded with papaverine hydrochloride over the range 100–1500 ng/ml plasma. The analysis procedure was shown to be linear over the range studied with a recovery efficiency of 98% (s.d. 1.63%). Plasma samples obtained from a preliminary volunteer on papaverine hydrochloride therapy were subjected to the analytical procedure. The samples taken for analysis were put through the procedure a second time and gas chromatographic examination of the second extract showed no further presence of papaverine. The values obtained for the amounts of papaverine in the plasma of the subjects given the controlled release papaverine hydrochloride formulation, and the encapsulated papaverine hydrochloride were taken to be the true figures and no correction was made for extraction efficiency because of the evidence obtained from the samples taken from the preliminary volunteer.

All solvents used in the analysis were purified by distillation. Papaverine base was prepared from the

Table 1 *In vitro* dissolution data

Time (h)	Disintegration conditions	Papaverine HCl released (mg)	Total papaverine HCl released (mg)	Total percentage released
1	pH 1.6	43.20	43.20	14.33
2	pH 2.6	45.90	89.10	29.56
3	pH 4.6	34.20	123.30	40.90
4	pH 6.5	27.00	150.30	49.86
6	pH 6.5	28.50	202.89	67.31
8	pH 6.5	19.80	243.39	80.75
11	pH 6.5	18.10	301.39	99.99

Figure 1 Plasma papaverine levels in nine subjects after dosage with 300 mg controlled release papaverine HCl (Papacontin) at 0, 12 and 24 h.

Figure 2 Plasma papaverine levels in three subjects who received one capsule of 300 mg papaverine HCl B.P.

hydrochloride and recrystallised from ethyl alcohol (melting point 146–147°C; literature value [The Merck Index, 1968] 147°C) 5 α -cholestan-3 β -ol (BDH Chemicals Limited) was used as supplied.

Results and Discussion

The individual results and subsequent mean values obtained are as recorded in Figures 1, 2 and 3.

From the plasma concentration levels obtained with the three subjects on the encapsulated papaverine hydrochloride a very rapid peaking and equally rapid decline in plasma levels is noted. In order to maintain therapeutic plasma levels it is obviously apparent that a four hourly dosage regime would be required. It is equally apparent from such plasma profiles that, if the therapeutic efficacy of a presentation be evaluated from the period of time during which drug plasma concentrations are maintained within desired therapeutic range, then such a presentation would realise a low therapeutic efficiency. If we now consider the plasma concentration levels obtained from the subjects on the controlled release tablet presentation we find that not only are therapeutic levels (150–300 ng papaverine/ml plasma) rapidly attained in all subjects within the first hour after administration but that plasma levels are maintained for a period of 10–12 h within the desired plasma therapeutic levels. It is also worth recording that at the end of each 12 h period that the plasma concentrations had fallen to the lower limit of therapeutic activity with no danger of drug accumulation. It should also be noted that no side effects whatsoever were observed or reported at any period of the investigation.

Figure 3 Average plasma papaverine levels in nine subjects who received at 0, 12 and 24 h 300 mg controlled release papaverine HCL (Papacontin) (●) and three subjects who received one 300 mg papaverine HCl B.P. capsule (○).

In conclusion the usefulness of controlled release tablet presentations is obviously most marked in potentially useful drugs with well known pharmacological activity and valuable therapeutic benefit whose clinical use has previously been restricted by a short half life. Such a drug is papaverine hydrochloride, the therapeutic activity of which we

feel has been markedly improved upon by inclusion within the Continus (R) controlled release tablet system. The above work confirms similar findings, using the Continus controlled release system as previously reported by the authors with aminophylline (Boroda *et al.*, 1973).

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