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Comparison of in vitro release of prostaglandin E_2 from various pessary bases

D.J. Morton

Department of Pharmacy, University of Zimbabwe, Mount Pleasant, Harare (Zimbabwe)

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In recent years prostaglandin E_2 (PGE_2) has become a popular labour-inducing agent (Sims, 1980). The fact that it is effective intravaginally has simplified administration and increased patient acceptability. Preliminary reports used a gel base (MacKenzie and Embrey, 1977, 1978) and more recently tablets and pessaries have also been used (Gordon-Wright and Elder, 1979; Shepherd et al., 1979). It has been suggested that a wax-based pessary would be a desirable dosage form for PGE_2 (Gordon-Wright and Elder, 1979) and Witepsol S55 (Dynamit Nobel) has been adopted for this purpose (Shepherd et al., 1979; Pearce et al., 1979).

The aim of this study was to examine the rate of release of PGE_2 from various bases in order to ascertain which vehicle was most suitable for clinical use.

The various bases were melted on a water bath and [^{3}H]PGE_2 (5.92 TBq/mmol), Amersham PLC, Bucks.) was added. Once molded the pessaries were inserted into a length of dialysis tubing (6 mm diameter) and suspended in 100 ml distilled water at 37°C. At set time intervals 500 μl of water was removed and radioactivity present quantitated by scintillation spectrometry. The rate of diffusion of [^{3}H]PGE_2 through the dialysis membrane was taken as an indication of the relative rate of release from the base. All results were obtained in triplicate.

All the bases used slowed release of PGE_2 when compared to water (Fig. 1). The addition of surfactants and lipids to cocoa butter further retarded release of PGE_2 (Table 1).

Extrapolation of the results using a double logarithmic plot allowed calculation of the time to total release for each base (Table 2).

As the length of labour varies up to 10.6 ± 5.1 h (Shepherd et al., 1979) it would seem pointless to use a preparation which had not released most of its content by this time and the ideal situation would be a vehicle which gave steady release over

Correspondence: D.J. Morton, Department of Pharmacy, University of Zimbabwe, P.O. Box MP 167, Mount Pleasant, Harare, Zimbabwe.

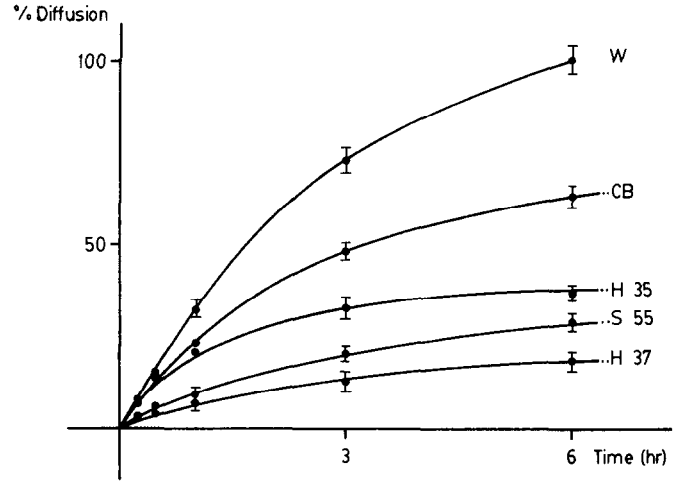

Fig. 1. Graph illustrating % diffusion of PGE_2 from various pessary bases with time. W = water, CB = cocoa butter, H35, S55 and H37 = Witepsol H35, S55 and H37, respectively.

TABLE 1

EFFECT OF ADDITIVES ON RELEASE RATE OF PGE_2 FROM COCOA BUTTER

	% diffusion after 6 h
cocoa butter	67 ± 7%
cocoa butter + 5% Span 80	58 ± 6%
cocoa butter ± 5% Tween 80	53 ± 6%
cocoa butter ± 5% liquid paraffin	48 ± 7%

TABLE 2

TIME TAKEN FOR TOTAL RELEASE OF PGE_2 FROM VARIOUS BASES (EXTRAPOLATED FROM DOUBLE LOGARITHMIC PLOTS). COEFFICIENT OF DETERMINATION (r^2) GIVEN TO ILLUSTRATE THE LINEARITY OF THE PLOTS USED

	Time to 100% diffusion (h)	r^2
Water	5.18	0.9842
Witepsol S55	38.23	0.9964
Witepsol H35	39.84	0.9207
Witepsol H37	100.59	0.9979
Cocoa butter	10.74	0.9885

this time. Of the bases tested cocoa butter appears to be the most suitable with total release occuring in under 11 h (Table 2). Witepsol S55, the base used clinically to date, is unsuitable in this respect in that total release would only occur after 38 h and less than 45% of the PGE_2 would be released within the maximum labour period. Theoretically on this basis the 3 mg PGE_2 Witepsol pessaries used (Shepherd et al., 1979) could probably be substituted by 1.5 mg PGE_2 cocoa butter pessaries with the same level of activity over 11 h.

It appears from these results that cocoa butter would be the most suitable vehicle for PGE_2 pessaries for use in induction of labour although this would have to be confirmed clinically. At present work is being conducted to evaluate the clinical efficacy of PGE_2 cocoa butter pessaries and to assess their stability.

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