TRANSDERMAL NICOTINE PATCHES

IS THE STOWIC PATCH A SIGNIFICANT TECHNICAL ADVANCE AND IS IT LIKELY TO BE DEVELOPED INTO A SALABLE PRODUCT FOR MASS MARKETS?

Background

The technology for transdermal administration of ethical pharmaceuticals has been is use for over ten years. Transdermal nicotine patches (TNP's) are a refinement of this technology. TNP's are marketed as a major advance in smoking cessation therapy. They were first introduced in Europe in 1990 and were introduced in the US in late 1991. TNP's provide the nicotine that would be otherwise obtained from the use of tobacco products. In the US, they are available only by prescription; however, in Ireland and Italy, they are available as over-the counter (OTC) products. TNP's are available in thirty-seven countries.

The Stowic patch may represent a advance over other TNP's based upon its claimed ability to deliver nicotine at a constant (zero order) rate that is independent of its concentration in the patch. This is claimed to be achieved through the use of an aqueous nicotine gel (hydrophilic) against a hydrophobic membrane that is in contact with the skin. It appears that the hydrophobic membrane serves as a barrier to control release of nicotine to skin at a constant rate.

Current Market

It is important to note that TNP's are marketed specifically as an aid for smoking cessation along with significant patient support programs that include access to trained smoking cessation specialists via a toll-free hotline, referrals to smoking cessation clinics, educational materials for families of smokers, and audio tapes. Likewise there is substantial promotional activities for physicians and pharmacists including sample kits and educational materials. There are also joint programs with the American Medical Association and the American Lung Association.

The three major firms in the US market are Ciba-Geigy (Habitrol brand, technology licensed from Alza), Marion Merrell Dow (Nicoderm brand, technology also licensed from Alza), and Lederle Laboratories Division of American Cyanamid (Prostep brand, technology licensed from Elan). A fourth firm, Warner-Lambert, is expected to launch its Nicotrol brand (technology licensed from Cygnus/Kabi Pharmacia), once FDA approval is granted later this year. Besides the promotional activities that were mentioned above, each of these companies has very aggressive advertising budgets. Estimated current annual expenditures for advertising for TNP's are $20 million.

US sales of TNP's to date have been above expectations and manufacturers have had difficulty meeting the unforcasted demand. Initial US sales projections were $300 million (approximately 100 million units) for 1992. Current retail price is about $3.50 per unit. Total manufacturing costs are believed to be $0.23 to $0.27 per unit.

Estimated first quarter sales were reportedly in excess of $200 million (Habitrol, $150 million; Nicoderm, $50 million; and Prostep, $15 million). By year end, annualized sales are expected to be $650 million. By the year 2000, annual sales are projected to be $2 billion. This should be compared to the sales of Nicorette gum, which was introduced in 1984, and had 1991 sales of only $129 million.

DOES THE PATCH (TNP) REPRESENT A SIGNIFICANT THREAT TO THE TOBACCO INDUSTRY?

The product appears to represent a potential threat. The magnitude of the threat still remains to be determined. The extent of the threat will depend upon the degree of the patch's success in enhancing long term cigarette abstinence and the extent of its availability and use. Based on the current sales projection for TNP's and an estimate that 25% of the smokers who use TNP's will quit smoking, US industry volume will only be minimally affected for the next few years. However, TNP's could reduce industry volume by 6% by 1997 and 20% by the year 2000.

The Product's Performance

The dosage forms are typically 10, 20 or 30 mg delivered nicotine per patch. Absorption is slow and continuous. Peak blood levels are attained after about 2 hours following application (see attachment A). Blood nicotine levels are maintained at a range of 17 to 24 ng/mL.

The average 24-hour blood nicotine concentrations resulting from use of a 21 mg patch are somewhat lower but comparable to smoking a pack of cigarettes. The pattern of the blood nicotine concentrations attained by smoking vs the patch, however, are different. With smoking, blood nicotine absorption is very rapid. Blood nicotine concentrations go through a series of peaks and troughs with successive cigarette smoking throughout the day (see attachments B-1 & B-2). With the patch, nicotine absorption is relatively slow and continuous and peak blood levels are not as high as with cigarette smoking. A major advantage of cigarette smoking over the nicotine patch system is the ability for the smoker to have very flexible control over titrating his desired dose of nicotine. It has been suggested that these differences in blood nicotine patterns could result in significant differences in preference.

At least 6 controlled double blind clinical trials of the nicotine patch have been conducted. Short term (6-week) smoking cessation rates are generally about 25% to 75% using transdermal skin patches. This compares with success rates of about half this rate in placebo groups within the same studies. Longer term (one year) abstinence rates drop substantially and range from 15% to 35%. These long term success rates are comparable to that of traditional behavioral modification therapies for smoking cessation. While plasma nicotine levels are linearly related to nicotine patch dose, this appears to have less than expected effects on long term smoking cessation.

Skin irritation appears to be a persistent problem associated with use of the patch for greater than 4 weeks. This could be a limiting factor in the prolonged use of the skin patch, however, skin irritation can be overcome by rotation of the site of patch application or by modification of the nicotine vehicle. Currently, clinical trials extending beyond three months have not been conducted. Its long-term success rate as a smoking cessation device therefore remains to be determined.

The fact that people use snuff and chewing tobacco indicates that administration routes other than the inhalation route can deliver tobacco satisfaction (see attachment C). Moreover, enhanced cognitive performance has been reported in non-smokers following subcutaneous administration of nicotine. It is therefore reasonable to assume that such effects would be produced by transdermal administration of nicotine.

WHAT SHOULD BE THE REACTION, IF ANY, BY B.A.T. INDUSTRIES?

There is currently a void in the market for a product that provides tobacco satisfaction in a form that is acceptable and available to many segments of the market. The tobacco industry currently does not have such a product.

A critical turning point for the nicotine patch will be whether the current product fulfills the regulatory requirements to become available over the counter. This event will substantially effect the mass marketing aspects and opportunities for the product from control through a physician to end consumer selection or through a recommendation of a pharmacist.

We should closely monitor all technical, marketing, and regulatory developments related to the skin patch and other nicotine delivery systems such at the nasal spray and the vapor inhaler. This should include ongoing business analyses based on new information as it becomes available.

We should be looking for opportunities to fill the void for products that provide tobacco satisfaction in a format that is acceptable to market segments that find currently available tobacco products unacceptable.

We should evaluate potential mergers or joint ventures between BAT and other businesses involved in the sale of nicotine based products.

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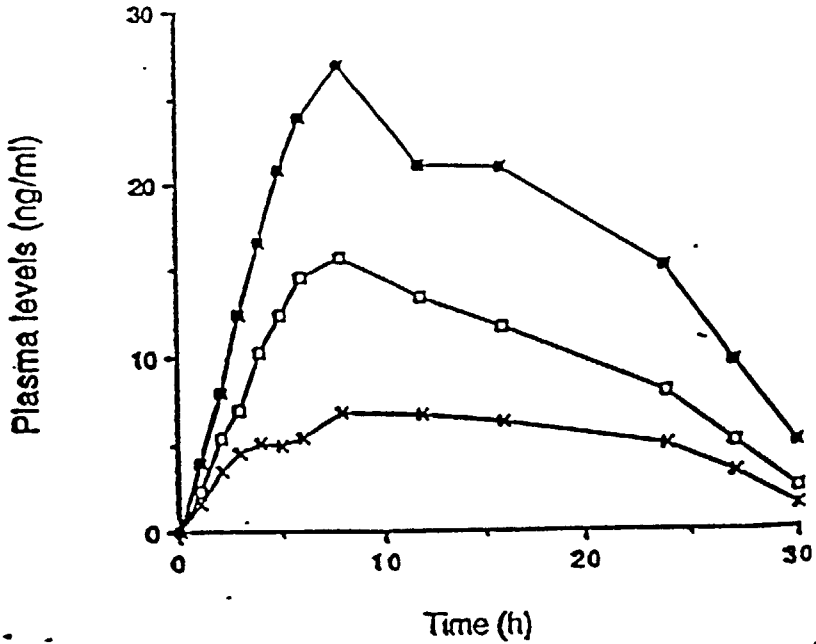

Fig.1. Plasma nicotine levels following 24 h single application of × 15 mg, □ 30 mg and ■ 60 mg transdermal patches

SOURCE: BANNON, ET.AT., 1989

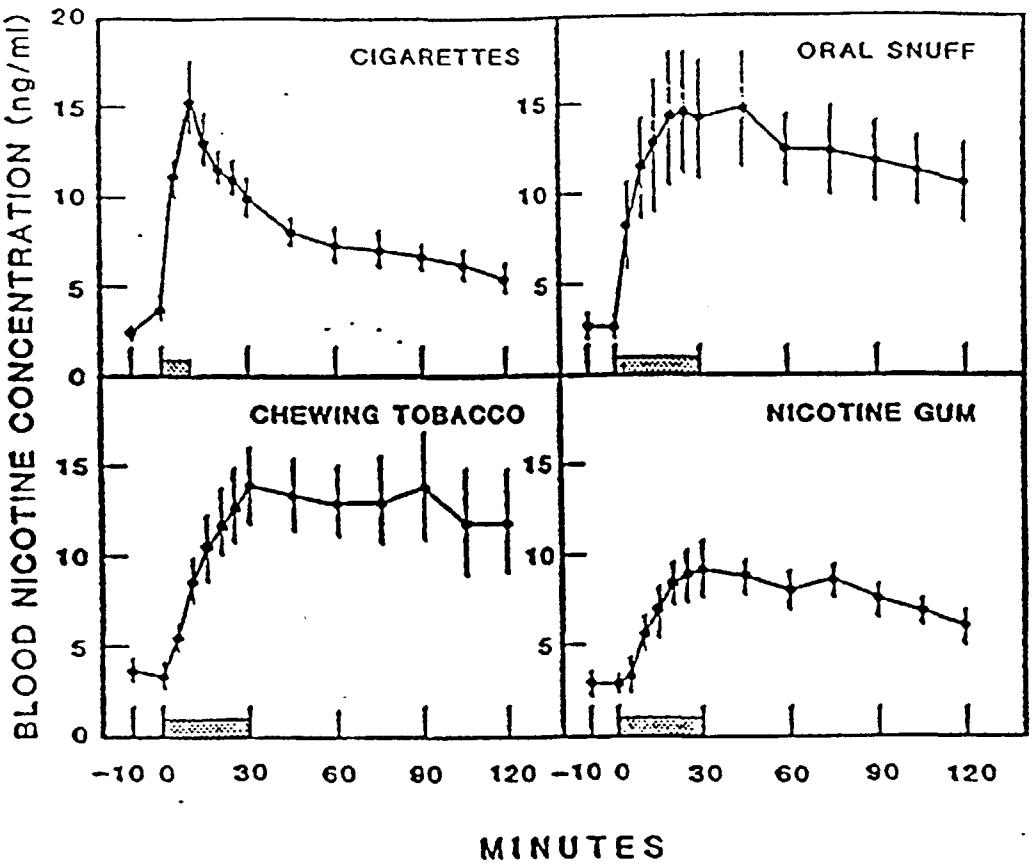

Fig. 1. Blood nicotine concentrations during and after cigarette smoking, oral snuff, chewing tobacco, and nicotine gum (two 2 mg pieces). Data represent average values for 10 subjects; vertical bars indicate SE. Shaded bars above time axis indicate period of tobacco or nicotine gum exposure.

SOURCE: BENOWITZ, ET.AL., 1988

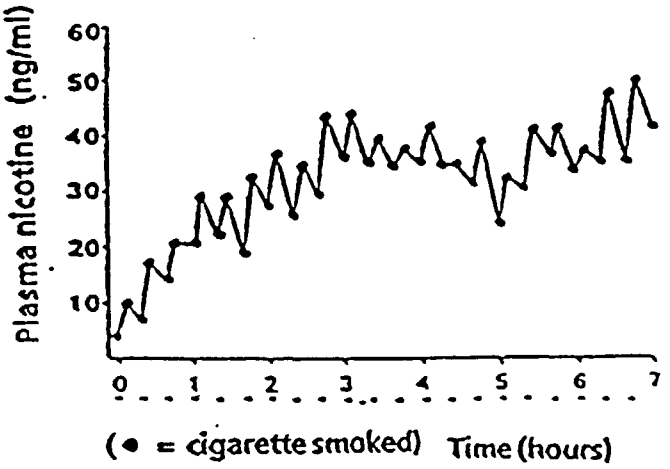

Fig. 3. Blood nicotine levels of a heavy smoker, smoking three cigarettes an hour. From Russell & Feyerabend (1978).

SOURCE: RUSSELL ET.AL., 1987

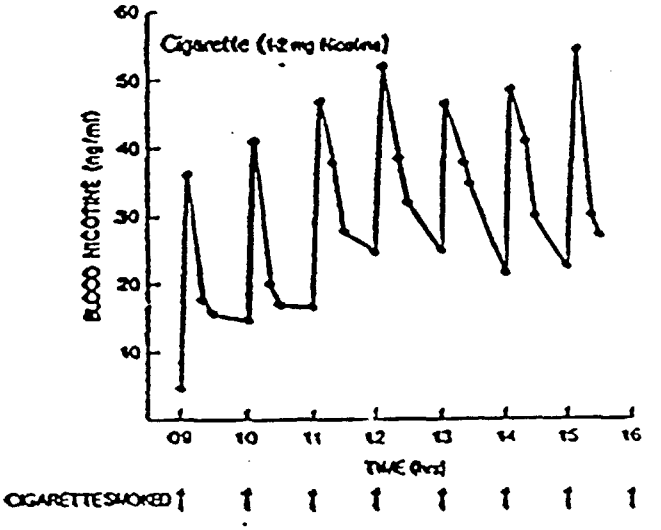

Fig. 2. Blood nicotine levels of an inhaling smoker, smoking one cigarette an hour. From Russell et al. (1976).

SOURCE: RUSSELL ET.AL., 1987

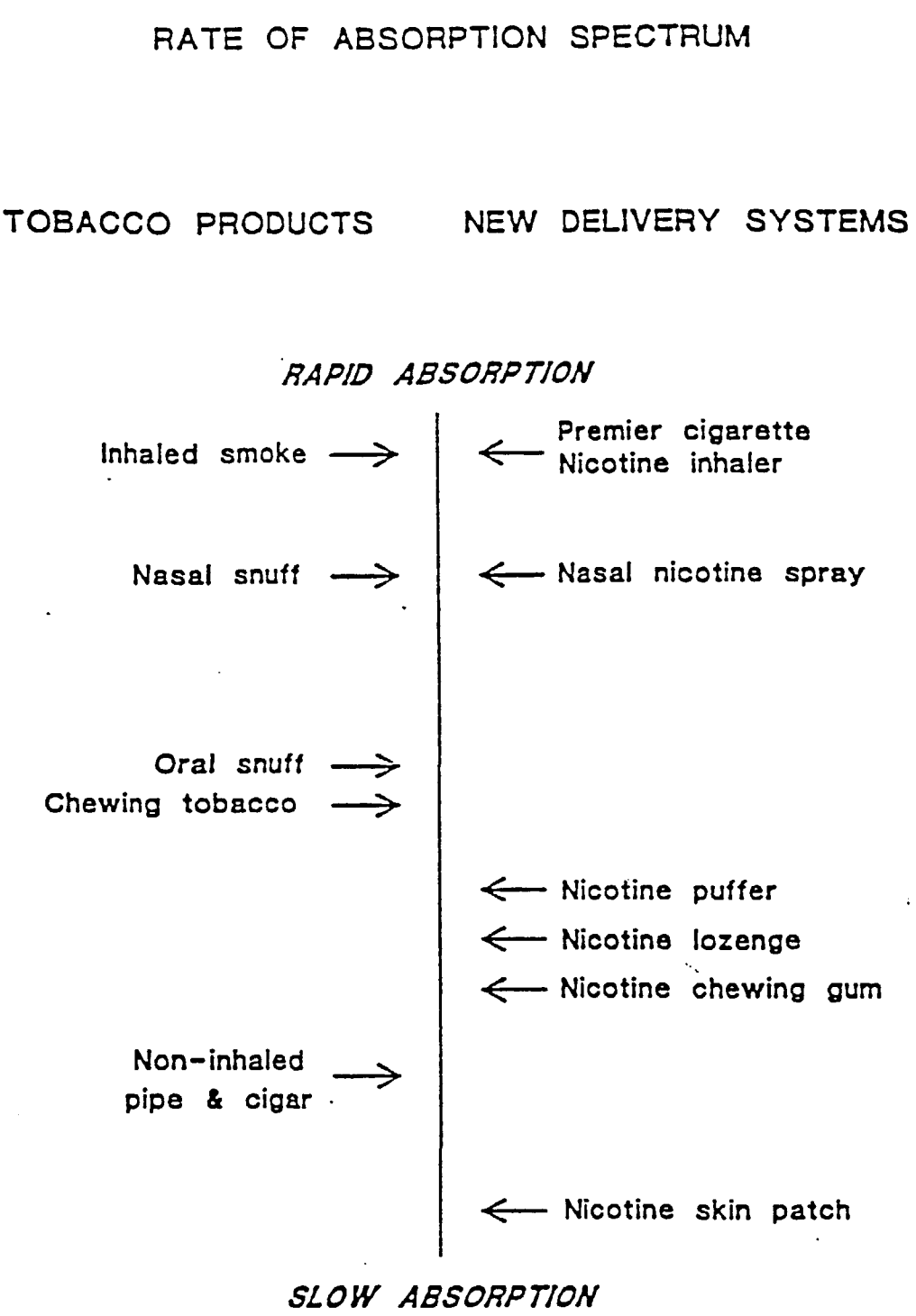

Figure 1. *Tobacco products and new nicotine delivery systems can be positioned roughly on a spectrum based on the rate of nicotine absorption obtained from their use.*