16 Effect of Single versus Multiple Dosing in Percutaneous Absorption

Howard I. Maibach
University of California, San Francisco, California

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16.1 INTRODUCTION

Standard pharmacokinetic practice is to first do a single-dose application to determine bioavailability. This standard application is no different for percutaneous absorption, and most absorption values are for single doses. But think of topical application (or any drug dosing), and the procedure is repeated, whether once per day for several days (or longer) or multiple times during the day, which also can go on for several days (or longer). There are few one-dose magic bullets in pharmaceutics. Therefore, it becomes important to view multiple topical dosing, especially if that is the standard procedure with which a topical drug is used or if such exposure occurs for a hazardous environmental chemical.

16.1.1 Single Daily Dose Application Over Many Days: Human

Figure 16.1 illustrates the method used in this type of study (1, 2). [^{14}C]malathion was applied to the skin of human volunteers on day 1. For days 2 to 7, nonradioactive malathion was applied once per day to the same skin site. The radioactivity excretion curve for days 1 to 7 represents the single first daily dose. On day 8, the [^{14}C] malathion was applied again (note that malathion had been applied the previous seven days). The radioactivity–excretion curve for days 8 to 14 represents the multiple daily dose. Figure 16.1 shows no difference in the percutaneous absorption of malathion in man for single daily dose (exposure) over several days. This same method was used by Bucks et al. (3) to study several steroids in humans. Table 16.1 shows no difference in the absorption of a single daily topical steroid dose over several days. The results are exactly like that with malathion (Figure 16.2).

There is an exception to the clear results presented earlier. Azone (l-dodecylazacycloheptan-2-one) is an agent that has been shown to enhance the percutaneous absorption of drugs. It is believed to act on the stratum corneum (SC) by increasing the fluidity of the lipid bilayers. Because