The Effect of Dosage Forms on the Duration and Continuity of Action Of Belladonna Alkaloids

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Present day therapy is fast becoming one of specific medication and specialized dosage forms. However, one of the problems associated with the formulation of these specialized forms has been the development of quantitative tests which measure the effectiveness of their design. This work reports a quantitative method for measuring the intensity and duration of action of belladonna alkaloids in human beings and compares the duration of action of specialized dosage forms of these drugs. Further aims of the work were to determine the variation of human response following the administration of belladonna at four-hour intervals and to measure the reproducibility of response to several lots of a particular sustained release dosage form. Intensity and uniformity of response over a period of time were measured as a function of salivary suppression.

The duration of action of a drug is determined by its chemical structure, its rate of absorption, degradation, and excretion, its concentration in and affinity for certain tissues, and the rate at which physiologic antagonists are formed at its site[s] of action. Collectively, these can be called intrinsic factors since they are related to the drug itself. Altering any of them should, theoretically, produce a change in the drug’s duration of activity. Other factors, unrelated to the drug, also affect its duration of action. These concern the amount of drug that is given, its route of administration, and the design of its dosage form.

Changes in chemical structure have been made that alter the

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duration of action of certain drugs when they are used clinically. This is illustrated, for example, with derivatives of sulfanilamide,\textsuperscript{1,3a} d-lysergic acid,\textsuperscript{2} and barbituric acid.\textsuperscript{3b} Dosage forms have also been altered in an attempt to prolong the action of drugs.\textsuperscript{4,50} These changes, if successful, permit less frequent administration of the drug and, by minimizing fluctuations in the tissue concentrations of the drug, may result in more uniform therapeutic effects.

The current study is concerned with the effect of the dosage form and dosage regimen on the onset, duration, and intensity of action of belladonna alkaloids. A sustained release dosage form\textsuperscript{*} has been compared with the placebo and with a conventional belladonna dosage form administered one or three times a day. The sustained release form used in this study is characterized by capsules containing hundreds of minute, lipid-coated spheroids which, when ingested, release the medication over an extended period, so that useful pharmacological effects last for approximately twelve hours. Utilizing the Mushin Salivary Suppression Test,\textsuperscript{11} Thomson\textsuperscript{12} quantitatively measured the onset and intensity of action of this sustained release preparation. Grossman\textsuperscript{13} has shown that, following the administration of an anticholinergic agent, there is a definite correlation between salivary suppression and gastric secretion when tested by the Mushin Test and aspiration, respectively. Since Thomson failed to consider all of the factors that can influence the results of a salivary suppression study, this placebo-controlled, statistically designed, double-blind evaluation was undertaken. Using the Mushin Test, onset, intensity, continuity, and duration of action have been measured.

**MATERIAL AND METHOD**

Eight hospitalized, ambulatory women patients took part in the evaluation. They ranged in age from 39 to 77 years and had been hospitalized for conditions that did not interfere with the use of this preparation or the criteria used for judging results. All patients participated in each of the drug regimen tests and placebo tests and thereby served as their own controls.

The exact amounts of each of the belladonna alkaloids contained in each of the dosage forms are given in Table 1. All the capsules

\\textsuperscript{14} 'Prydon', 'Spanule capsules, trademark, Smith Kline and French Laboratories, Philadelphia, Pa.