During the last several years there has been continued pressure from consumers, legislators, and health administrators to mandate generic prescribing. It has been proposed that requiring physicians to prescribe by generic rather than brand name and allowing pharmacists to substitute generically equivalent drug products would save consumers millions of dollars. These assumptions and the following events have stimulated the American Academy of Pediatrics to bring this issue to the attention of its membership.

1. The report of the Office of Technology Assessment, Drug Bioequivalence Study Panel, entitled "Drug Bioequivalence," concluded that current standards and regulatory practices do not ensure bioequivalence for drug products, although most of the analytical methodology and experimental procedures for the conduct of bioavailability studies in man are available. Additional work may be required to develop the means of applying them to certain drugs and to special situations of drug use.

2. The Drug Research Board of the National Academy of Sciences (October 25, 1974) recommended that the physician "should be required to delegate to the pharmacist, or explicitly to retain to himself, selection of the particular drug product to be dispensed."2

3. The Maximum Allowable Cost Proposal published in the Federal Register (November 15, 1974) would establish a system to fix a "maximum allowable cost" for reimbursement for drugs dispensed under health financing and service programs of the Department of Health, Education, and Welfare which have multiple sources and are deemed bioequivalent. Other provisions of this proposal call for a fixed dispensing fee and supplying comparative price information to physicians and pharmacists.

Analysis of the Problem

The Committee on Drugs recognizes, and is in agreement with the validity of, attempts to provide safe and efficacious medications at the lowest possible cost. Unfortunately, few drug products have been appropriately studied for bioavailability or therapeutic equivalence in infants and children. Such products often differ in formulation from drug products used for adults.

The bioavailability of a drug product has been defined as the rate and extent (efficiency) of absorption and distribution of the active substance to the site of action in the body. In vitro tests do not suffice for the determination of bioavailability. Data must be derived from testing in man in order to determine physiologic availability of the drug. Differences in bioavailability may be accentuated in infants and children where there is evidence of age-related changes in the rate and extent of gastrointestinal absorption—as well as changes in volume of distribution, rates of metabolism, and excretion.

The term bioavailability is often confused with bioequivalence, but these are not interchangeable terms. Bioequivalence is achieved when two chemically equivalent drug products exhibit similar bioavailability characteristics.

One cannot assume that specific products will be equivalent in therapeutic effect until they have been evaluated in vivo. The clinical efficacy of a drug may be greatly modified by the rate and extent of absorption of a drug into systemic circulation. Changes in physical state, such as crystal form or particle size, can affect the dissolution of a drug. The addition of inert ingredients used in tablet or capsule formulations can have pronounced effects on drug absorption; and variations in tablet structure formulation and other aspects of manufacturing have been found to have a significant effect on bioavailability. A number of generically equivalent products have been demonstrated to vary appreciably in their rate and extent of absorption, concentrations of drug produced in the body, and clinical response. These differences in bioequivalency usually occur because of variations in the foregoing pharmaceutical factors. Such ingredients differ from one product to another and are not usually specified in official compendia.

These differences have been demonstrated in
adults. The lack of data on bioavailability and bioequivalence in children precludes blanket support of generic prescribing for infants and children.

With some drugs, for example antibiotics—where (1) initial studies on bioavailability are carried out in adults with comparison to "the standard" product of that particular drug, (2) batch certification of biologic potency is carried out, and (3) therapeutic endpoints or serum levels can be more or less accurately defined—generic prescribing may be used with relatively more confidence.

The current trend in drug development is toward more specific agents, thereby amplifying the need for bioavailability data. These data must be established in infants and children as well as in adults.

Although some lists evaluating risk potential (as related to relative bioequivalence) have been made, these lists are inconclusive because they are prepared from incomplete information presently available and reflect no significant data from the pediatric population.

Pharmacists' professional fees, acquisition costs, overhead, profit margin (which depends on neighborhood and other local factors), the number of tablets in a prescription, and insurmountable other variables may determine the cost to the patient more than the wholesale list price of a drug. Assistance in product availability, quality, and price can be obtained from community pharmacists to enable the physician to prescribe the drug product most suitable for his patient.

The Committee on Drugs of the American Academy of Pediatrics strongly supports the use of the least expensive medication which provides effective therapy. However, the physician's duty to the patient is to prescribe reliable drugs with reproducible therapeutic effects at a given dose. Therefore, until suitable bioavailability data in children are determined and therapeutic importance recognized, the physician should continue to prescribe the products which have shown significant clinical effectiveness in his hands or in published clinical trials.

The variation in drug handling in the infant and child resulting from his various stages of development, as well as the alterations produced by the disease, accentuates the fact that therapy with many drugs is individualized; and, differences existing between patients are often more significant than those existing between drug products. Some situations require careful "titrations" of drug therapy. In these cases and those in which blood levels closely correlate with therapeutic and/or toxic effects, care should be used to ensure that the patient maintains therapy with the same product (the same brand).

The physician is ultimately responsible for care; therefore, authority for prescribing must remain his prerogative. To exercise this prerogative, he now demands increased efforts to judge critically if there is a need for any drug therapy; and, having so decided, to select the right drug, drug product, dose, and dose schedule. To make these decisions, the pediatrician needs heightened awareness, continuing education, and consultation with peers and other health professionals. The prescribing pediatrician should insist that data on bioavailability be made available to him to choose the product most suitable for his patient.

RECOMMENDATIONS

The Committee on Drugs of the American Academy of Pediatrics feels strongly that cost alone should not receive the highest priority in the choice of drug or drug product. Drug disposition in the sick infant and child has not been adequately investigated at this time; and the data which would allow the pediatrician to prescribe generically and expect consistent therapeutic results does not exist. Therefore, the pediatrician must acquaint himself with dose-response relationships of known entities and not prescribe products with which he has no familiarity.

The Committee also recommends that the Department of Health, Education, and Welfare dedicate fiscal and manpower resources to the solution of the many pressing questions and problems which stand in the way of rational drug therapy for pediatric patients.

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## Generic Prescribing


*Pediatrics* 1976;57:275

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