Absorption Rates Vary

Brand, Generic Drugs Differ In Man

Comparison of brand and generic forms of three drugs, tested in healthy volunteers, shows several significant differences in amount and rate of absorption, investigators at Georgetown University School of Medicine report.

"These differences do not make it possible, in any sense, to say that product A is better than product B," said Christopher M. Martin, MD, director of the Georgetown Laboratory of Clinical Pharmacology.

"What we have found, when drugs are tested in man, are differences between brand and generic forms that may or may not be significant in the actual treatment of disease. It is only inferential evidence that something may be wrong," Dr. Martin emphasized.

Chloramphenicol, sulfisoxazole, and diphenylhydantoin are the first of ten drugs to be studied by the team, headed by Dr. Martin. The study began in 1967.

The investigation, requested and supported by the Food and Drug

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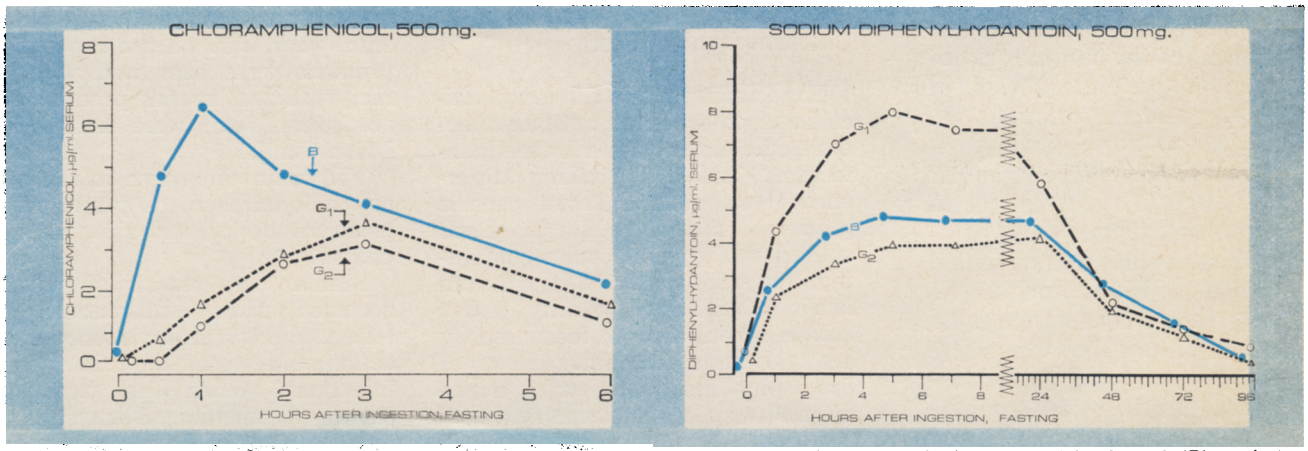

Chart at left compares mean serum levels of microbiologically active chloramphenicol produced by brand (B) and two generic (G_1 and G_2) products. Brand chloramphenicol was absorbed significantly more quickly. The other chart shows wide differences in absorption rates for brand and two generic diphenylhydantoins. One of the generic products was absorbed faster and in greater quantity than the brand or the other generic.

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Medical News This Week

Recent studies suggest that one male in 300 may be born with the XYY chromosomal abnormality which has been associated with criminal behavior... *page 28.*

Two California physicians report successful cryosurgical treatment of 20 patients with vulvar warts... *page 26.*

"Radiography of breast biopsies is indispensable to the pathologic diagnosis of very early breast cancers," says an Emory University radiologist... *page 31.*

Elevated levels of blood histamine may cause some symptoms associated with polycythemia vera, according to a team of New York physicians... *page 27.*

Looking Ahead

Rene Dubos, PhD, distinguished Rockefeller University microbiologist, has in recent years turned his attention to the complex problems of the interaction of biology and environment. He has shown that subtle variations in the environment, if present at birth, can affect an organism throughout life—a phenomenon he has called Biological Freudianism. The long range consequences of this for man and the prospect of studying epidemiological problems in the laboratory are discussed next week in MEDICAL NEWS.

Brand, Generic Drugs Differ In Man

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Administration, indicates that the absorption of these oral drugs is affected by manufacturing processes determining tablet hardness, crystal size, and capsule composition.

Dr. Martin reported his work at the Minneapolis meeting of the American Society for Pharmacology and Experimental Therapeutics.

Twelve Volunteers

Twelve healthy, adult male volunteers served as their own controls and were given each drug in the study at separate times. After fasting, each subject received single oral doses of either the brand or one of two generic products. Intervals between doses ranged from 2 to 14 days.

Dr. Martin said that brand drugs in the study were the first products in a drug classification that were patented. Generic drugs were any of the subsequent products that met the content requirements.

Generic products for the study were chosen largely at random from the many available products, he said. In some cases, however, prior reports of a product's ineffectiveness prompted the investigators to include particular generics in the study.

Before and at intervals following each ingestion, blood samples were analyzed for active drug and drug plus metabolite levels. Drug levels were also determined on 24 hour urine collections. Dr. Martin said doses were selected which would involve minimum risk but produce measurable blood levels in the volunteers.

Chloramphenicol Study

Experiments with chloramphenicol, a broad-spectrum antibiotic recommended mainly for salmonella infections, revealed striking differences between brand and generic products, said Dr. Martin. Each subject was given capsules containing 500 mg of the drug. Serum levels of microbiologically active chloramphenicol were measured by an agar plate technique; levels of drug plus metabolite were determined by spectrophotometry.

Mean serum levels of chloramphenicol plus metabolites, measured hourly, showed that the brand drug was absorbed significantly more quickly than the two generics.

Comparison of the mean serum levels of microbiologically active chloramphenicol showed nearly the same absorption rate differences. After twenty-four hours, however, the amount absorbed was similar for all three products.

Brand chloramphenicol produced serum concentrations exceeding the generally accepted therapeutic level of 2 micrograms per milliliter at one time or another in all 12 volunteers, Dr. Martin noted. However, one of the generic products failed to produce the level in one case, and the other generic in two cases, he said. "There is a chance, therefore, that these generic chloramphenicols may not be effective in 10% of people," Dr. Martin said.

Urinary recoveries of the drug and metabolites at 24 hours were not significantly different. Dr. Martin said this "indicates that the generic chloramphenicols are absorbed by the body slowly over a prolonged period and accumulate with successive doses."

Absorption Differences

Further studies by the Georgetown investigators showed that absorption rate differences did not exist when three volunteers were given aqueous solutions of the various product contents. The rate difference was reproduced when the brand chloramphenicol was dissolved in alcohol, recrystallized, and pulverized to produce coarser crystal sizes similar to the two generic products. The recrystallized brand product produced statistically significant absorption delay in four volunteers when compared with the unchanged brand chloramphenicol. And, when data on the two generic products were compared with the recrystallized brand product, the absorption rates were similar, Dr. Martin said.

The main difference in the various chloramphenicol products appears to be crystal size, he concluded.

Similar, but less striking results occurred when sulfisoxazole was tested. Sulfisoxazole is one of the sulfonamides used for urinary tract infections. When the "free," or chemically unchanged drug, and the total sulfonamide content in serum and urine were assayed by standard methods for sulfa levels, it was found that one of two generics tested was

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Three Regions Affected

Heat Waves Cited In Excess Deaths

Three weeks with weather temperatures in the 80s and 90s apparently pushed mortality in three regions of the United States over limits projected by the National Communicable Disease Center.

Statisticians at the Atlanta facility, who draw on data of the past five years to produce a curve of expected deaths, noticed increases in the New England, Middle Atlantic, and Pacific regions.

The increases coincided with heat waves in these areas in the last three weeks of July.

The pneumonia-influenza mortality rate, often the cause of summer mortality peaks, was conspicuously low.

An NCDC spokesman said the excess was not solely a function of heat. Factors such as humidity or air pollution could have been involved. Some areas, he said, had comparable temperatures without reflecting it in their mortality figures.

The most significant effect was seen in the Pacific region. The predicted figures for deaths from all causes in the weeks ending July 13, July 20 and July 27 were 1,465, 1,461 and 1,457 respectively. Deaths actually reported during those weeks were 1,697, 1,594, 1,631.

"Excess mortality was not solely a function of heat . . . , humidity or air pollution might have been involved."

Two Other Regions

In the Middle Atlantic region the predicted deaths were 3,150, 3,133 and 3,117. Actual deaths were 3,582, 3,516 and 3,502. And in New England, where the predictions were 704, 701 and 698, reported deaths were 766, 711 and 704.

In Boston, for example, 231 persons died during the week ending July 13. Of these, 129 were over 65 and eight were under a year old. Seventeen of the total died of pneumonia or influenza.

In New York city during the following week of July 20, 1,687 persons died. Of these, 1,037 were over 65, 53 were under one year, and 73 were pneumonia and influenza victims.

During the third week (July 27), 512 persons died in Los Angeles, 294 of whom were 65 and over, and 26 were under one year. Fifteen were pneumonia and influenza victims.

Similar episodes of excess mortality occurred in two other recent summers; the Middle Atlantic division during 1963 and the Middle Atlantic and West North Central divisions in 1966.

Revision Of Standards For Generic Drugs?

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absorbed significantly more slowly than the brand product.

"The therapeutic significance of this difference is questionable," Dr. Martin explained, "because the cumulative 24-hour urinary excretions of total sulfisoxazole plus metabolites did not differ significantly with the three products."

Tablet Friability

Experiments indicated that tablet friability was a major reason for absorption differences among the three sulfisoxazole products. Tablets of the brand drug and the slower generic product were crushed into fine powder, made into capsules, and administered to four volunteers. The generic product then produced a mean serum concentration which came very close to that attained by the crushed brand.

In sulfisoxazole, at least, the tabletting process is probably the key to why the various products act differently, Dr. Martin said.

The third drug in the study was diphenylhydantoin, an anticonvulsant for major motor and psychomotor seizures. Mean serum concentrations of diphenylhydantoin were measured in duplicate by gas-liquid-chromatography. Volunteers ingested 500 mg of the drug in capsules.

Wide differences in the absorption rates were seen for the three diphenylhydantoin products.

One of the generic diphenylhydantoins was absorbed faster and in greater quantity than the brand or the other generic.

"Current evidence suggests that particle size and differences in solubility of the capsule seem to be the reasons for absorption differences," Dr. Martin said.

"We cannot draw firm conclusions from these studies," said Dr. Martin. "We can, however, draw some reasonable inferences. These data raise the question of whether or not a thorough revision of standards of certification of the generic drugs will have to be made."

Continuing Study

The continuing Georgetown study will include seven other drugs. They are diphenhydramine, tripelennamine, prednisone, ferrous sulfate, meprobamate, isoniazid, and aminosalicylic acid (PAS).

Dr. Martin is also professor of medicine and pharmacology. His co-workers include Martin Rubin, PhD, professor of biochemistry; William E. O'Malley, MD, PhD, assistant professor of neurology; Vincent F. Garagusi, MD, assistant professor of medicine; and Charles E. McCauley, MD, PhD, assistant professor of physiology and biophysics.

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