1976 YEAR BOOK OF DRUG THERAPY

The YEAR BOOK of

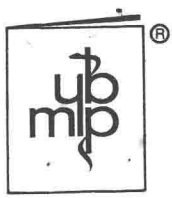
Drug Therapy

1976

Edited by

DALE G. FRIEND, M.S., M.D.

Associate Clinical Professor of Medicine (Emeritus), Harvard Medical School; Member, Revision Committee, U.S. Pharmacopeia, 1960–1970; Chairman, Pharmacy and Therapeutics Committees, Peter Bent Brigham Hospital; Member, Pharmacy and Therapeutics Committee, Veterans Administration Outpatient Clinic, Boston; Member, Pharmacy and Therapeutics Committee, West Roxbury Veterans Hospital, Boston



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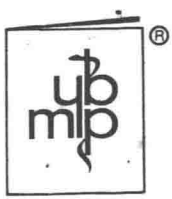

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Introduction

New Developments

The past year has been fruitful for the development of new drugs, new uses for drugs already available and new diagnostic and therapeutic technics.

Mebendazole has been found to be the first really effective drug for the treatment of trichuriasis. Colchicine, for centuries the drug of choice for podagra, has now been found to be useful in controlling Mediterranean fever and has also shown considerable promise in the treatment of psoriasis. Glucagon is of therapeutic value for diverticulitis. Potassium sorbate is a new, effective antifungal agent. Dihydroergotamine has been found useful in combating hypotension. A new β-adrenergic stimulator, terbutaline, relieves bronchospasm with fewer cardiac effects. Zinc effectively relieves acrodermatitis enteropathica, a real breakthrough. Molluscum contagiosum is controlled by methysergide. Metronidazole shows promise in the treatment of Crohn's disease. A new drug, bromocriptine, is useful in controlling acromegaly. Chorea may be helped by trifluoperazine. Propranolol is proving to be useful in relieving glaucoma. Phenoxybenzamine, an α-blocker, relieves nonocclusive bowel ischemia. Phenylpropanolamine is useful in preventing retrograde ejaculation.

Drugs have been altered to give improved action. Para-aminosalicylic acid has been recrystalized with ascorbic acid to give a better-tasting preparation useful in treating elevated cholesterol and triglyceride levels. Testosterone has been shown to be effective when given orally. It is absorbed from the intestine by the lymphatic circulation.

There are many other interesting developments in therapeutics that signify an encouraging trend toward more and better agents and procedures to treat disease.

D.G.F.

General Information

Chloramphenicol-Containing Drugs: Report from Spain. The possible development of aplastic anemia after treatment with chloramphenicol has led to repeated warnings against its indiscriminate use. Sergio Erill, Patricio du Souich and Jesus A. Garcia-Sevilla[1] (Univ. of Barcelona) examined the principal pharmaceutical specialties containing chloramphenicol sold in Spain, particularly the information included in their package inserts. Practically all the formulations recorded in a 1973 publication were examined. Of the 198 chloramphenicol-containing products listed, 13 could not be obtained. The 185 specialties that were analyzed included 169 brands sold by 71 different companies.

Eighty-two agents were to be taken orally, 43 were suppositories, 32 were injectables and 28 were topicals. Only 11 contained chloramphenicol as a single active ingredient. In 51 other products, chloramphenicol was the only antibiotic present. One other antibiotic was present in 78 compounds and two others in 34, whereas 11 compounds contained combinations of chloramphenicol and three or four other antibiotics. Excluding topicals, the usual recommended mean daily dose of chloramphenicol was 15 mg/kg, but in 11 instances it exceeded 30 mg/kg. Eight package inserts did not include a recommended dosage. Indications were not mentioned in 3 instances. The most common indications given were bronchitis and pneumonia. Side effects were not mentioned in 132 of the 185 leaflets. Dose-related bone marrow depression was mentioned 28 times and aplastic anemia 22 times. Contraindications were mentioned in only 53 leaflets, whereas 8 claimed there were no contraindications for the product. Further warnings or other advice about usage was given in 36 leaflets, in 28 under a specific heading. Periodic hematologic tests were recommended in 35. Long-term treatment was cautioned against in 30 leaflets.

These findings emphasize the need for better information and instructions about use in chloramphenicol products. There is evidence that this is a widespread problem. A change in the availability of drug combinations containing chloramphenicol and an improvement in the information accompanying them are urged.

► [What a terrible situation! The thousands of travelers to Spain from the United States, as well as other countries, may be exposed there to a dangerous drug, often without knowing it. It is absolutely essential that physicians warn their patients about taking any foreign medication unless they know the contents or seek expert advice from a reputable physician.—Ed.] ◄

Drugs—Remarkably Nontoxic. Hershel Jick[2] (Boston Univ.) has found that drugs, though responsible for considerable morbidity and

(1) J. Clin. Pharmacol. 15:401-404, May-June, 1975.
(2) N. Engl. J. Med. 291:824-828, Oct. 17, 1974.

mortality, are remarkably nontoxic and as benign as one could reasonably expect. The short-term effects of drugs have been studied in some 19,000 medical inpatients in the Boston Collaborative Drug Surveillance Program. About 30% of hospitalized medical patients manifest at least one adverse drug reaction during hospitalization. Drug-attributed deaths occur in 0.29% of such patients, an annual total in the United States of about 29,000 such deaths. The average medical inpatient receives about nine different drugs per hospitalization. At least 75,000,000 adults take drugs regularly. The rate of life-threatening reactions in hospital patients is about 3%, but the rate per course of drug therapy is only 0.4%. The rate of drug-attributed death per course of drug therapy is currently about 3 per 10,000. Over a third of 46 such deaths have been attributed to hyperkalemia or pulmonary edema. One third of these 46 patients had advanced cancer, and another third had advanced alcoholic liver disease. Hospitalizable illness results from an estimated 1 of every 500 long-term outpatient drug treatments per year.

These estimates ignore drug use in pediatric and surgical practice. Rare adverse drug effects are generally not identified, and the study does not provide for the identification of "delayed" adverse drug effects. Nevertheless, it appears that, despite some alarming gross numbers, most drugs are remarkably nontoxic. Drugs with risks grossly out of proportion to their benefits are not in current use. If the amount of drug toxicity is to be reduced substantially, the number of drugs that people take must be decreased. There appears to be little need for alarm about the problem of drug toxicity, but a need remains to quantitate the toxicity that does occur, to identify the populations at highest risk and to uncover any drugs whose toxicity may be unwarranted in relation to the benefits derived from them.

► [General surveys of this type gather many interesting data and confirm what many have long realized, that in skilled hands, under proper observation, hazard from drugs is far less than many risks faced daily by our society. Most drug deaths occur among seriously ill patients, who require heroic measures in attempts to save or prolong life and who in previous decades would have died from their disease. There is altogether too much loose thinking about drug hazards. Certain concerned groups have become so alarmed that they are making efforts to control drug therapy so completely that medical progress and good therapeutic practice would be inhibited.—Ed.] ◄

Use and Abuse of Intravenous Solutions are discussed by Donald G. Vidt[3] (Cleveland Clinic). Intravenous fluids are used to maintain normal body composition when normal food or fluid intake is impossible, and to correct acute and chronic disturbances of fluid and electrolyte balance. Simple solutions suffice when maintenance problems exist for only several days. High-calorie solutions may be given when patients cannot take nutrition or fluids orally for 3–6 days. If oral feedings must be deferred for weeks or longer, total parenteral nutrition is necessary.

Sufficient nutrients exist in intravenous saline solution to support the growth of gram-negative bacteria. Solutions may be contaminated by airborne microbes. The major hazard of adding drugs to intrave-

(3) J.A.M.A. 232:533–536, May 5, 1975.

nous fluids is microbial contamination. Further, interactions of active drugs with components of solutions are complex and often poorly understood. Drug availability is also a consideration when drugs are added to intravenous solutions. More research is needed to learn the role of particulate matter in lung damage. Volume control sets carry many hazards, including omitted drug doses and admixture errors. Polyvinyl chloride in containers may adversely affect solutions stored in them. The use of high-percentage glucose solutions for total parenteral nutrition may lead to several clinical problems.

The open system with tube containers should be opened only in an aseptic environment to reduce the possibility of microbial contamination. Addition of drugs to intravenous fluids should be discouraged except in emergencies. Only one drug should be added to a fluid, and all additions should be noted in the patient's permanent drug file. Critical attention should be paid to the administration equipment used for intravenous solutions, especially volume control sets. Hospitals should consider establishing a continuous admixture monitoring system and quality control program, which would help indicate sources of contamination and be useful in planning inservice education and training programs pertaining to intravenous therapy preparation and administration.

► [A wise suggestion is given for the proper use of intravenous solutions. Excessive use of such solutions is common. Furthermore, the practice of adding several drugs to such infusions is almost routine in hospital practice. There certainly needs to be a tightening up of technics.—Ed.] ◄

Metabolism of Drugs by Microorganisms in the Intestine is discussed by Peter Goldman, Mark A. Peppercorn and Barry R. Goldin[4] (Harvard Med. School). The metabolism of both exogenous and endogenous compounds can be attributed not only to host enzymes but also to the enzymes of the host's bacterial microflora.

An interesting example is found with salicylazosulfapyridine (SAS), composed of a sulfa drug and a salicylate. Whether it is the intraluminal content of 5-aminosalicylate, the release of sulfapyridine in the colon or the presence of undegraded SAS in the colon that is related to the mechanism of action of SAS is not clear.

Alterations in the flora may alter the distribution of a drug and its metabolites so as to influence its effectiveness. Caffeic acid metabolism can be attributed to a variety of intestinal bacteria and caffeic acid metabolites in the urine can be used as a probe of the activity of various constituents of the flora. There is no obvious correlation between the metabolic transformations made by bacteria in culture and those attributable to the bacteria when associated with a germ-free rat.

It is not clear whether the conversion of dopamine to m-hydroxyphenylacetic acid (m-HPAA) that occurs in conventional animals proceeds through dopac or through m-tyramine. The time course of the appearance of m-HPAA after feeding dopamine suggests that an active conversion of dopamine to m-tyramine occurs in the gastrointestinal tract. Neomycin reduces the urinary excretion of m-tyramine and m-HPAA in patients taking L-dopa, indicating reduced conver-

(4) Am. J. Clin. Nutr. 27:1348–1355, November, 1974.

sion of dopamine to m-tyramine as the result of suppression of the intestinal flora by the antibiotic. The pharmacokinetic argument implicating the flora in the transformation of dopamine to m-HPAA is applicable to food-deprived as well as to fed animals.

Study of the metabolism of both exogenous and endogenous compounds by the flora offers an opportunity to elucidate the effects of these compounds on the host and the possibility that the effects may change with alterations in the flora.

► [This is an important observation. It is forgotten all too often that there may be a considerable difference in drug action between the oral and percutaneous doses of the same drug. Perhaps a variable portion of drug metabolism usually attributed to the liver or other tissues is actually the effect of bacterial enzymes. This subject needs more study.—Ed.] ◄

The Placebo Effect: Neglected Asset in Care of Patients. According to Herbert Benson and Mark D. Epstein[5] (Boston), the placebo effect is a neglected and berated aspect of patient care, the value of which must be recognized so that provision can be made for its incorporation and proper use in evolving health care delivery systems. Any system that fragments the physician-patient relationship will lessen the effects of this asset. Although the placebo effect is disdained in medicine today, throughout much of medical history it was the most a physician could offer his patients.

Most controlled drug studies have failed to assess the placebo effect itself as a therapeutic intervention by not incorporating nontreatment controls. The placebo effect is considered merely as a variable to be controlled and hence is ignored. The existence of the placebo effect in treatment of a variety of diseases is well substantiated. Reactions to placebos may involve practically any organ system.

The placebo effect seems to be derived from a combination of factors involving the patient, the physician and the relationship between the two. The psychologic state of the patient affects his responses to both active and nonactive drugs. The milieu in which drugs are given may also affect the patient's response. The physician exerts much influence on the course of treatment as a result of his own biases, attitudes, expectations and methods of communication. The actual interaction of the physician and patient is probably more responsible for the effect than is the contribution of each.

The placebo effect usually enhances the patient's well-being and is thus an essential aspect of medicine. More emphasis on the potency of the placebo and its positive effects is needed. Research and instruction in efficient methods of establishing the appropriate doctor-patient relationship conducive to the placebo effect should be initiated. The placebo effect must be allowed to survive if medicine is to provide optimal care for patients.

► [A timely, sensible article on placebo therapy is offered here. It must be remembered that physicians have been honored and accepted by society for many centuries for their role in relieving the maladies of mankind. Since extremely few specific remedies were available, it must be obvious that some other factor was operating. I have been amused by the often quoted statement, attributed to Laurence J. Henderson, the biochemist; he reputedly said in regard to medicine in the early years of this century

(5) J.A.M.A. 232:1225–1227, June 23, 1975.

that a patient seeing a physician "had a 50–50 chance of benefiting from the contact." If that were so, it is doubtful if medicine would have survived as a useful profession. What most scientifically trained people fail to realize is the fact that human belief overcomes many obstacles. Therefore, if a physician can instill the necessary confidence, the patient often does the rest.—Ed.] ◄

Effects of a Procaine Preparation (Gerovital H3) in Hospitalized Geriatric Patients: Double-Blind Study. The action of procaine hydrochloride as an anesthetic and vasodilator is well known, but its effect on the aging process is more controversial. Israel Zwerling, Robert Plutchik, Margaret Hotz, Ruth Kling, Leo Rubin, Joel Grossman and Barbara Siegel[6] conducted a 12-week study on the effects of Gerovital H3, a procaine hydrochloride preparation, on geriatric inpatients. Each 5-ml ampule contains 100 mg of 2% procaine plus benzoic acid and potassium metabisulfite; the pH is buffered to 3.3. Nineteen patients with varying levels of organic brain dysfunction were studied 4 weeks after the withdrawal of all drugs. A 5-ml injection of Gerovital H3 was given intramuscularly 3 times a week for 6 weeks; a double dose of 10 ml was then injected for 6 weeks. Control subjects received saline injections. Nine drug and 10 control patients completed the first 6 weeks of study, and 6 drug and 7 control patients completed the second 6 weeks. The mean age of drug patients was 74 years and of controls, 72 years. The respective average hospitalizations were 28 and 33 months.

The Geriatric Rating Scale, Geriatric Interpersonal Evaluation Scale and Brief Psychiatric Rating Scale were utilized. At 6 weeks, there were no significant differences between the groups. At 12 weeks, the only significant difference was greater hostility in the drug group, probably reflecting random variation. No significant differences in change of scores were found for any laboratory values, psychologic measures or psychiatric ratings at 12 weeks. Depressive items were comparable in the two groups. Side effects were also comparable, the most common in both groups being agitation, confusion and difficulty in walking, which are typical in geriatric populations. Overall, there were only small, apparently random differences between the drug and control subjects.

Gerovital H3 had no apparent therapeutic efficacy in this sample of hospitalized geriatric patients with organic symptoms, in agreement with most previous studies. No antidepressant effect of the drug was observed, and there were no changes in ward behavior, cognitive functioning or memory. Gerovital H3 had no ameliorative effect on either psychologic or physiologic functioning among these hospitalized geriatric patients.

► [This needed study supports what medical investigators have long believed. Whether such subjective data will have any impact on those who use Gerovital H3 remains to be seen. Past experience with such agents has shown that they continue to be used as long as a gullible patient is available or until their use is prohibited by law.—Ed.] ◄

Snake Venom Poisoning in the United States: Experiences with 550 Cases. According to Findlay E. Russell, Richard W. Carl-

(6) J. Am. Geriatr. Soc. 23:355–359, August, 1975.