Epidemiology of Adverse Drug Reactions

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There is a similarity in the approach taken by Dr. Wolf (Dr. Stewart G., the 1967 Stoneburner Lecturer) and Col. Moser to the one I will present to you. Dr. Wolf is interested in why some people die suddenly and why others do not. What are the factors responsible for predisposition? The major theme of our studies on the epidemiology of adverse drug reactions has been to gain understanding of why some people will have trouble and others will not when given the same drugs in essentially the same way and for the same reasons. Col. Moser spoke to the problem of adverse drug reactions, i.e., their recognition, identification, and documentation. Epidemiological methods allow us to identify reactions, when they occur, and to establish the risk involved in administration of drugs to patients.

In any epidemiological study there are two pieces of information that must be accumulated. One is denominator data and the other is numerator data. When we began our studies about five years ago, our initial attention was directed toward assembling denominator data. How many drugs are used? What patients receive them? Under what circumstances? These data identified the population at risk. One should also know the dosage form in which the drug is administered, and have information on the duration of therapy. Unfortunately, the latter two pieces of information are difficult to obtain, because, as Col. Moser has pointed out, the accumulation of masses of information on patients at risk and the drugs they receive is an overwhelming task requiring automatic data processing. At present, in most hospitals, it is impossible to retrieve information on dosage form or duration of therapy, although in most instances it is possible to identify the population at risk receiving given groups of drugs.

Drug Usage in Hospitals

I will summarize some of the pertinent observations that we have made during the course of our investigations.

The most frequently used drugs in a hospital, as you might expect, are tranquilizers and sedatives. It is interesting, however, in reference to Col. Moser's paying particular attention to tetracycline, that in one survey at the Johns Hopkins Hospital, five of the ten most commonly prescribed drugs were antimicrobial agents.

The studies that I will speak about were confined largely to an evaluation of drug usage and adverse reactions to drugs on a medical service at the Johns Hopkins Hospital. This included an evaluation of private and public patients. The results were in essence identical, so there is no point in differentiating them.

On the medical service at the Johns Hopkins Hospital the average number of drugs given to a patient during hospitalization was 11. This ranged from zero to 42 different drugs. We have identified only one patient who received no medication during hospitalization. It is interesting to evaluate the kinds of drugs patients receive. In one study, evaluating all the patients in the hospital receiving methicillin, we identified a patient who received 37 different drugs, and this patient received five different antimicrobial agents during the course of hospitalization. In other university medical centers, the average number of drugs administered to patients on medical services is about 10 to 14 different medications during hospitalization.

Examining drug usage can be a useful exercise. It's not just a collection of meaningless data. I would like to point out one example of how this was important at Johns Hopkins Hospital.

During the initial phase of our study on drug usage, we became aware that the surgical service used the most chloramphenicol in the hospital. We investigated the patients on the surgical service who received chloramphenicol. Most of the patients received the drug prophylactically, in an attempt to prevent wound infections. But the interesting thing was to determine *why* chloramphenicol was being used as a prophylactic drug, when this is not considered advisable. Two years before, one of the surgeons on the staff had done a study

of the effectiveness of chloramphenicol in prevention of postoperative wound infections. He had instituted a study with a double-blind placebo and the housestaff administered the drugs in random fashion to the patients on the service, some getting chloramphenicol and some getting placebo. The study was conducted for six months. The surgeon evaluated his data, found no difference in the frequency of wound infections, and terminated his study. By this time, the surgical staff had become accustomed to using chloramphenicol prophylactically, however, and the practice was perpetuated. When this was brought to the attention of the surgeon-in-chief, some curtailment in the use of chloramphenicol was possible.

Detection of Adverse Drug Reactions

Identification of adverse drug reactions, when patients receive 11 different drugs, is a problem. When a reaction occurs or when some anticipated illness develops how can the physician 1) be certain that it is an adverse reaction to a drug, and 2) identify the specific drug responsible for the adverse effect. When a patient develops a febrile reaction or granulocytopenia during hospitalization, and he is receiving 42 different drugs, you tell me which one is involved! We can go to the literature and identify those drugs incriminated previously, but we may overlook the one that is specifically involved.

Methods of Detection

What are some of the methods that can be employed for detection of adverse reactions? The AMA Registry on Drugs and the Food and Drug Administration are using voluntary reporting, the system we initially adopted. In epidemiological studies, however, one needs a complete numerator and denominator. Otherwise incidence and rates cannot be accurately determined. We instituted a voluntary reporting system throughout the Johns Hopkins Hospital for one year. The average number of adverse reactions reported initially was 15 per month. It gradually went up to 25 per month at the end of the year. We thought this was under-reporting, so an effort was made to examine the records of patients upon whom reports had been obtained, as well as those on whom reports had not been obtained. Only one-tenth of all significant adverse reactions had been reported voluntarily. Obviously voluntary reporting is incomplete. Its greatest usefulness is in the identification of previously unrecognized ill effects of a drug.

The only way to collect complete data is by personalized surveillance. This can be done, prospectively or retrospectively, and we have done both. A retrospective analysis is notoriously inadequate. To evaluate this we selected the records of patients who had been given Warfarin. The ill effects of anticoagulant drugs are readily identifiable. In a retrospective analysis 10% of the patients who received this anticoagulant drug had some manifestation of bleeding, gross or microscopic. The commonest site of bleeding, of course, was in the urine. Most commonly the bleeding was microscopic. Occasionally, blood was found in the feces, but subarachnoid hemorrhage and massive bleeding into the pleural space following thoracentesis was demonstrable. This method too, however, was an inadequate way of obtaining data, because doctors are not good at recording reactions in patients' charts. This is illustrated by the fact that the majority of the patients receiving Wafarin had one urinalysis and had one stool examination for occult blood done during hospitalization and that was the day of admission. Generally these examinations were not repeated. The necessary tests were not done to detect the most common sites of bleeding in patients receiving anticoagulants.

Personalized prospective surveillance was the only way to obtain complete information. Three methods have been evaluated: 1) surveillance of all patients receiving a particular drug in the hospital; 2) surveillance of all patients with a particular disease in the hospital, the drugs they receive, and the reactions they may develop; 3) surveillance of groups of patients, such as those on a medical service or surgical service. The latter is the one that has proven, in our hands, the most useful in uncovering information relevant to the factors that predispose patients to reactions.

Definition of a Reaction

Another problem is the definition of a reaction. It can be defined by mechanism involved, clinical features, or in terms of severity or probability. Severity is relatively easy to note: 1) fatal or life-threatening; 2) requiring an antidote or long hospitalization; and 3) an annoyance. The real difficulty is documenting the probability of a reaction. These are the systems that we have employed: 1) A documented reaction is one known to occur, with a clear temporal association with the administration of the drug; on re-challenge the patient has a recurrence of the reaction; or there is some confirmatory laboratory test establishing that the drug is incriminated in the patient's illness. 2) Probable reactions that have a temporal relationship, are known to occur and disappear on withdrawal of the medication. We have ignored other reactions which are possible, because we cannot in those instances establish this as an adverse drug effect.

I would like to show you examples of problems in identifying drug reactions. A 6-year-old boy with a tetralogy of Fallot was seen in the hospital for surgical cor-

rection of his cardiac defect. He was put on penicillin and streptomycin prophylactically. Following operation he developed progressively increasing fever, leukocytosis, mild anemia, weight loss, and anorexia. He had multiple blood cultures taken which were negative. He had no splenomegaly, nor did he have microscopic hematuria or petechiae, but the surgeons felt that he must have a post-cardiotomy infection. The dosages of the anti-microbial drugs were increased, and others were added. The therapy was continued for seven weeks at which time I was called in consultation. It was suggested that the patient might have drug fever. Streptomycin, tetracycline, and erythromycin were stopped without any termination in the patient's course. Eight hours after the penicillin was stopped, the patient was afebrile and left the hospital four days later. This boy had fever as the only manifestation of the ill effects of a drug, and this was confused with infection. A young woman was seen in the emergency room because of a streptococcal sore throat. She was given penicillin. Within 48 hours, she returned to the emergency room with a florid confluent erythematous rash, and a diagnosis of scarlet fever was made. The girl did not have scarlet fever. Following recovery, after discontinuing her treatment, she was given penicillin again and had a recurrence of the reaction. Again identification of a reaction and differentiating it from a naturally occurring disease complicated the identification of a drug reaction.

Adverse Reactions Occurring in Hospitals

With this as background, let's look at the overall problem of adverse drug reactions in the hospital. On the medical service of the Johns Hopkins Hospital 5% of all the patients are admitted to the hospital with an adverse drug reaction. Four percent of the patients are admitted to the medical service, because of adverse effects of drugs. Adverse drug reactions as a cause of hospitalization represent the seventh most common reason for admission to the medical service. Of those patients admitted to the hospital who have a reaction at the time of admission, 30% will have a reaction to another drug during the course of hospitalization. This contrasts with an overall rate of reactions to drugs of 10% in all patients on the medical service. This means that the patient who has had a reaction to a medication has a three-fold greater likelihood of having a reaction to another drug during the course of hospitalization. This identifies patients with a pronounced predisposition to the occurrence of reactions.

A patient with miliary tuberculosis who was comatose when admitted to the hospital, was put on INH, PASA, and streptomycin. During the course of the first five or six days of hospitalization she defervesced, and regained consciousness. She developed an exfoliative rash and because of this it was necessary to stop all of her medication. At that time her temperature declined and her exfoliative rash disappeared. She still had her miliary tuberculosis, so she was put back on INH, but this time she developed a folicular rash over the face. An industrious intern aspirated one of these and grew a Staphylococcus albus. He was alarmed that the patient might be developing staphylococcal sepsis, and gave the patient an injection of penicillin. She went into anaphylactic shock, requiring hydrocortisone and norepinephrine. All drugs were again stopped, except that steroid and digitalis were continued. Again, the patient required treatment for her tuberculosis. While on prednisone she was given a single dose of PASA and had a frank chill with a prompt rise in temperature. Subsequently, she was given a single dose of streptomycin, and again had a prompt chill and recurrence of fever. During the course of these 70 days of hospitalization, this patient had documented reactions, to paraminosalicylic acid, penicillin, streptomycin, and INH.

I would like to return briefly to the problem of severity. Not all reactions to drugs seen in hospitals are mild. Mild reactions account for almost half of those observed. Correspondingly almost half of the patients had reactions sufficiently severe to warrant the physician's giving an antidote, prolong hospitalization or to threaten life. Seven percent of the patients with adverse reactions had life-threatening or fatal reactions.

Gastrointestinal reactions to drugs are particularly common in women. In a report by Jordan and Dingle, women with colds also have an increased frequency of nausea, vomiting, and diarrhea. Whether this is a specific effect of drug reactions or whether it is a peculiarity of females, I don't know. Nevertheless, in all of our subsequent studies we have eliminated the minor gastrointestinal reactions, because we cannot be certain of the relationship to the drug itself. It should be emphasized, however, that adverse effects of drugs frequently mimic natural disease.

Tranquilizers and sedatives rank far above any other drugs as causes of ill effects in patients. Antimicrobial and cardiac drugs, however, are near in importance of ill effects in hospitalized patients. There is wide variation in rates of reactions to different drugs. The range was from 27% (probenecid) down to 3.1% (mercaptomerin). Col. Moser made the point that before the physician can significantly weigh benefit with risk, he must have such data as this, citing incidence as well as severity. Unfortunately, such data is usually lacking at the present time. In contrast to Col. Moser, however, I do not believe the present systems of the

AMA Council on Drug and the Food and Drug Administration will get us to the point of determining the exact risk.

Severity of Reactions

Patients do die of drug reactions in the hospital. During one three-month period on the medical service of the Johns Hopkins Hospital, there were five deaths due to drugs in hospitalized patients. It is possible for the physician to avoid some of these lethal effects as illustrated by these patients. A middle-aged man admitted to the hospital with chronic pulmonary disease had a coin lesion in his lung. During the course of his hospitalization it was decided that he should be bronchoscoped. The pre-bronchoscopic medications were promazine, pentobarbital, and morphine. This medication was given and he was taken to the endoscopy room where he developed respiratory arrest. He was given artificial respiration and returned to the ward without bronchoscopy with the advice of the endoscopist that the patient should not be bronchoscoped because of the problem of premedication. Two weeks later there was a change of physicians on the ward. They were fully aware that the patient shouldn't be bronchoscoped, but they needed a study to identify the nature of his pulmonary disease. A bronchogram was decided upon. The pre-medications for bronchography were promazine, pentobarbital, and morphine, of which the physicians on the ward were unaware. The premedication was given, and within a very short time the man went into shock, cardiac arrest, respiratory depression, and died. Another patient was a young woman who during her prepartum period on the obstetrical service had been found to have a minor urinary tract infection and was given sulfisoxazole. Her bacteriuria cleared, but she developed an urticarial and erythematous rash. A note was written in the progress notes by the obstetrician that the patient was allergic to sulfonamides and the drug was discontinued. Following delivery, the woman was again found to have bacteriuria. She was now no longer an obstetrical patient and was referred to the medical clinic for evaluation. The obstetrical records were kept in a different part of the chart from the medical records. Frequently the internist doesn't read the obstetrician's notes. Nevertheless, the internist recognized the bacteriuria and re-prescribed sulfisoxazole. Very shortly thereafter she had gross hematuria. She was admitted to the hospital hypertensive, had sulfonamide crystalluria, and died in renal failure. Autopsy revealed she had typical sulfonamide crystals in the tubules of her kidney. She undoubtedly died of sulfonamide-induced allergic vasculitis. This illustrates some of the settings in which lethal effects of drugs can be observed and how they can be avoided.

We have been unable to confirm any relationship in the patient with atopy and the subsequent development of allergic or other reactions to drugs. However, history of an adverse reaction to any drug is associated with a significant increase in the frequency of reactions to other drugs subsequently administered. So there is something peculiar about people who have trouble with drugs. Whether this is heritable or what the factors are that are particularly involved remains to further study.

Number of Drugs Administered

An important factor related to the occurrence of adverse reactions to drugs in hospitalized patients is the number of drugs administered. When one exceeds a total of six drugs there is a logarithmic increase in the likelihood of the patient's having an adverse reaction to at least one drug. Of the patients receiving 16 drugs during the period of hospitalization, 45% of them will have an adverse reaction to at least one drug that they have during the period of hospitalization. If I were to recommend one thing that would significantly reduce the problem of the ill effects of drugs, it would be to curtail the use of innumerable drugs. This is undoubtedly the most important factor we have thus far identified. Why this curve is logarithmic I don't know. Our present feelings are that much of this is a problem of drug interaction, interactions that conceivably have not been identified and are unrecognized. As you would expect, of course, there is a relationship between the number of drugs administered and the mortality rate and period of hospitalization, indicating that people who get lots of drugs are generally the sickest.

In studies of pneumonia the rate of allergic reaction to penicillin rarely is less than 10%. Yet in patients receiving penicillin in V.D. clinics, the rate is usually less than 1%. Is there a relationship between the presence of infection and the occurrence of allergic reactions to drugs? We have shown such a relationship which I think deserves further study. It's our present supposition that a severe infection may serve as an adjuvant to an immunological response to a simple chemical agent.

Over three times more men than women receiving penicillin in the hospital will have allergic reactions to this drug. By history the men in this study had received penicillin in the past no more frequently than women.

Conclusion

I would like to conclude by citing two other rather interesting observations we have made. Three-quarters of all the patients in all our surveillance who have allergic reactions to drugs have had peptic ulcer, ulcerative colitis, or neo-

plastic disease of the gastrointestinal tract. Of these patients, three-quarters of the drugs producing allergic reactions are administered orally. The rates of allergic reactions to individual drugs in patients with gastrointestinal disease as opposed to those without gastrointestinal disease receiving the same medication, are significantly increased. What the impact is of inflammatory gastrointestinal disease 1) upon the absorption of the drug, 2) upon its metabolism, and 3) upon its antigenicity has not been investigated before. But from these studies it is suggested that inflammatory disease of the gastrointestinal tract may be an important factor predisposing patients receiving oral drugs to occurrence of allergic reactions. It has commonly been supposed that patients with autoimmunological disorders, e.g., systemic lupus erythematosus, may have a predisposition to multiple allergic reactions to drugs. In our evaluation of this problem, there is no significant increase in the occurrence of allergic reactions to drugs in these patients.

I would like to end with some unresolved questions. We obviously need more information on rates of reactions to drugs. Without this the physician is ill prepared in estimating risk as opposed to benefit. As Col. Moser pointed out, we can go 20 years before identification of a possible relationship of thrombocytopenia to tetracycline. It took six years to identify aplastic anemia in relation to chloramphenicol. There must be some better way to identify the ill effects of drugs than just by the casual, incidental, periodic reporting in the literature by physicians who suspect or identify relationships. I happen to think this is the greatest value of the Food and Drug Administration and the AMA Council on Drugs Registry on adverse reactions. Unfortunately, however, most of the reactions reported are those that we know exist. As far as I am aware, in the FDA program in operation in a multiplicity of hospitals voluntarily reporting adverse effects of drugs has not identified a single previously unrecognized ill effect of a drug that would not have been detected as promptly otherwise. We need a great deal more information about how drugs are used outside of the hospital by patients who can buy them in the drug store without prescription. I was recently amazed when a pharmaceutical representative came into my office, and I commented about how many drugs patients kept in their cabinets at home. The pharmaceutical representative was intrigued and came back the following day having counted the number of drugs in his cabinet—90! It is my impression that most of the patients who developed Fanconi syndrome from outdated tetracycline were children whose mothers had been given tetracycline by the physician, had kept it on the shelf, and then when the child got ill had given it to him. I think it's critically important that the public be informed as much about the problem of drugs as the medical profession. We do it poorly. We let journalists write about how horrible hospitals are, but I have yet to see anybody in the medical profession make any exertion to inform the public about the use of non-prescription drugs. We need a great deal more information about what heritable factors cause reactions to drugs. I have indicated some factors that suggest this may be far more important than we have previously recognized. We need more information on other factors—diseases and organ function—which influence predisposition to drug reactions. Most studies done on the metabolism, absorption, and excretion of drugs are performed in normal people. They are not comparable to patients in the hospital who have fever, renal failure, minor abnormalities of liver function, who have respiratory embarrassment and are in heart failure. We need a great deal more information about the reactions to drugs in patients who are sick, as well as we need increasing information about the problems of drugs in people who are well. Thank you.