

HOSPITAL MONITORING OF ADVERSE DRUG REACTIONS IN SINGAPORE

By P. C. Teoh

SYNOPSIS

The serious health hazards posed by adverse drug reactions have long been recognised, but the application of epidemiological principles to their studies is only a recent development. A total of 3160 patients admitted into Medical Unit I, General Hospital, Singapore were kept under surveillance for adverse reactions to drugs for six months in 1972. Fifty three of them (1.7%) were admitted with adverse drug reactions as the sole reason for admission. There were 25 males and 28 females. There were two deaths and ten life-threatening reactions, and hypersensitivity was the most common type of reaction encountered. Among the chief offending drugs were Chinese herbal medicines, digoxin, corticosteroids, antibiotics, phenothiazines, and hypoglycaemic agents. All doctors especially the general practitioners must be fully aware of these hazards so that they can help prevent unnecessary morbidity and mortality and also to avoid taxing heavily on the already over-burdened hospital service in a developing country.

Adverse reactions to drugs pose as serious health hazards and have been observed for as long as the drugs have been used. But the application of epidemiological principles to their studies has been a recent development. It had been found by Seidl *et al* in 1966 that 1 in 20 patients (5%) admitted into the medical wards of Johns Hopkins Hospital in United States were associated with drug reactions and this was the seventh most common cause for admission. Hurwitz in 1969 reported a 2.9% of the 1268 patients admitted into 2 Belfast Hospitals in United Kingdom because of adverse reactions to drugs and a further 2.1% were admitted because of self-poisoning with drugs. It is obvious that adverse reactions to drugs has become a serious problem in the West but the situation is not as clear in Singapore where the control over the safety use of drugs is not as stringent. Therefore a prospective survey of adverse reactions to drugs as the cause of admission into the Medical Unit I of Outram Road General Hospital in Singapore is carried out from June to December 1972 for a period of six months.

METHOD

All patients admitted into the four medical wards of Medical Unit I, General Hospital,

Singapore during the six months period between June, 1972 and December, 1972 were included in this survey. Each ward was visited daily by the author and the doctors in charge were personally questioned to find out those patients admitted with drug-induced adverse reactions. Each suspected patient was interviewed and if possible together with the relatives. Data recorded for each patient included name, age, sex, race and unit number. Inquiry of any previous reaction to drugs and of allergy, hay fever and asthma was also made. Detailed history was taken and careful clinical examination performed. Type of adverse reactions, drugs suspected to cause the adverse reactions with details of dose and route of administration were recorded. These patients under surveillance were treated with withdrawal of the suspected drugs and other appropriate therapy.

For the purpose of this study, adverse reactions to drug was defined as any response to drug in a patient that was unintended and undesired by the doctor who prescribed it. The reactions were classified in terms of probability into three categories as proposed by Seidl, Thornton and Cluff in 1965:—

1. Documented reaction—which occurred commonly with a definite temporal relationship to taking the drug and a positive rechallenge test or laboratory confirmation,
2. probable reaction—which occurred commonly and had a definite temporal relationship and improvement on withdrawal of drug,
3. possible reaction—which was known to occur but the temporal relationship was less clear and other causes were possible

Department of Medicine, University of Singapore, Singapore.

P. C. TEOH, M.B., B.S., M.Med., M.R.C.P., A.M., Senior Lecturer in Medicine.

The mechanisms of the reactions were classified according to the scheme proposed by Rosenheim (1962):

1. Overdosage,
2. Intolerance,
3. Side effects,
4. Hypersensitivity and
5. Idiosyncrasy.

RESULTS

During the six months period under survey, there were a total of 3160 patients admitted into the four medical wards of Medical Unit I. These included 1950 males and 1210 females. Fifty-three of them (1.7%) were admitted because of adverse reactions to drug therapy which was thought to be the entire reason for admission. There were 25 males and 28 females. The age distribution is shown in Fig. 1 with a mean age of 30. The youngest was 12 years old and the oldest was 74 years old. The duration of their stay in hospital is shown in Fig. 2 with a mean duration of 8 days. Most of the reactions were of hypersensitivity type with a total of 26, 5 were due to overdosage and 4 were due to intolerance, and 11 were the results of side effects and the remaining 7 were due to idiosyncrasy. There were 2 deaths and 10 life-threatening reactions and the rest were moderate in severity. All of them required withdrawal of drugs and other treatments for control. When the reactions were classified in terms of the probability of their causation by a drug, 4 were regarded as 'documented' and 6 as 'possible' and the rest were 'probable'.

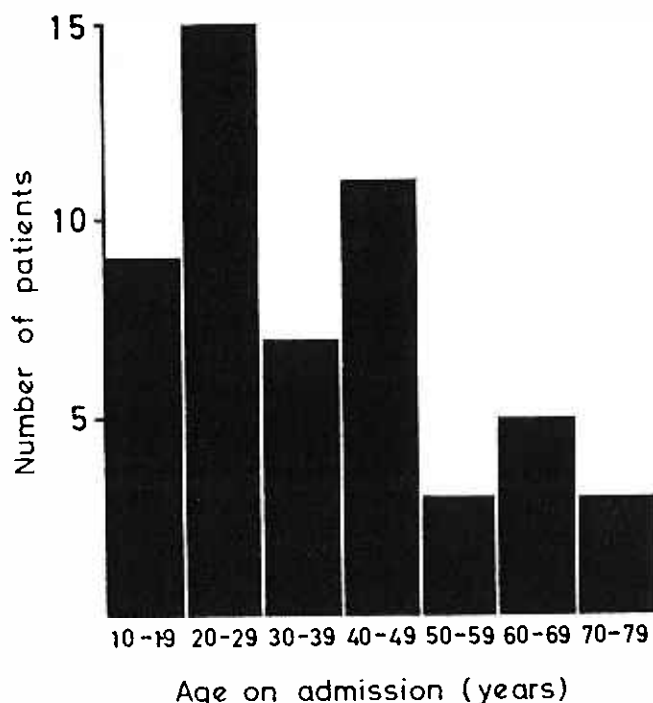


Fig. 1. Age distribution of patients.

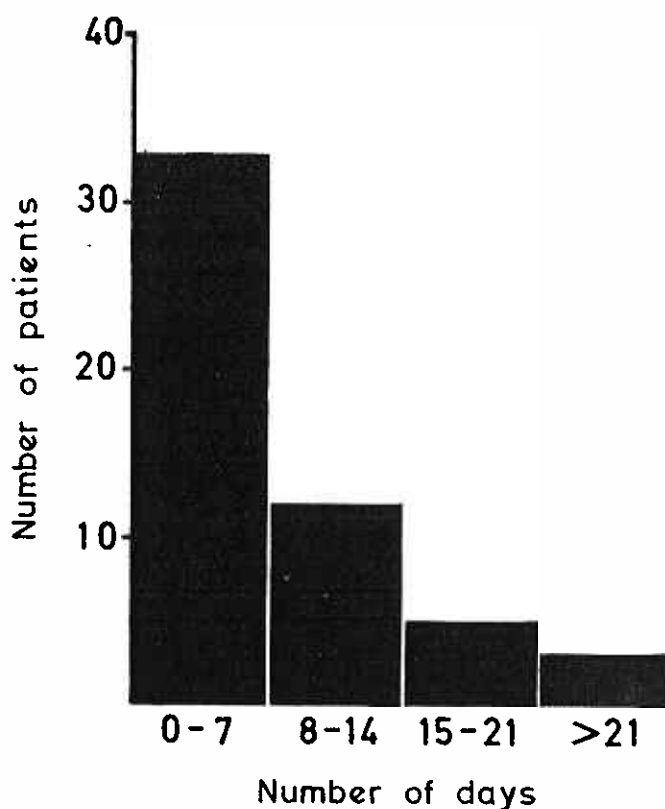


Fig. 2. Duration of stay in hospital.

Overdosage: Five patients were admitted to hospital because of the effects of taking a dose of drug in excess of that prescribed by the doctor. One woman aged 36, impatient of the progress of her weight reduction, decided to take 20 tablets of fenfluramine of 20 mg. each to speed up the process. Few hours later, she became agitated and tremulous and complained of giddiness, palpitation and hearing voices. She was treated with chlorpromazine and discharged well after 3 days in the hospital. One patient took an overdose of digoxin and complained of nausea and vomiting. ECG showed sinus bradycardia with depressed ST segments. Two patients were admitted with hypoglycaemia with one of them having blood sugar level as low as 10 mg. %. They later admitted to taking more than the prescribed dose of long acting insulins. One other interesting case of overdose was admitted not because of physical complication but as a result of severe anxiety after learning from the local newspaper that the Chinese herbal medicine 'Sin Lak Pill' she took for her bronchial asthma could cause skin cancer due to high arsenic content in the pill. On examination, there was no cutaneous keratosis or epithelioma though the level of arsenic in her hair was as high as 2.7 parts per million. This was due to prolonged ingestion of Sin Lak Pill over a period of months. She required parenteral administration of Dimer-caprol for treatment.

Intolerance: Three patients were admitted because of serious cardiac arrhythmia namely coupled beats, nodal bradycardia and ventricular tachycardia as a result of digitalis toxicity while on usual dose of digoxin. One of them was found to have high blood urea and the other patient a low serum potassium of 3 meq. per 100 ml. due to concomitant diuretic therapy. Renal insufficiency could have easily caused toxic serum digoxin level, and low serum potassium was well known to sensitise the heart to a normal level of serum digoxin and hence the cardiac arrhythmia. Unfortunately one of them died on the same day of admission and the other few days later in spite of treatment. Marked postural giddiness was the cause for one admission in one elderly patient who took the prescribed dose of methyldopa for his hypertension. Erect blood pressure was only 80/60 mmHg.

Side effects: Two patients were admitted with Cushingoid features while on prolonged steroid therapy for nephrotic syndrome. They were treated by withdrawal of steroid and replaced by cyclophosphamide. Another complication of steroid therapy was encountered in a female patient with scleroderma and positive lupus erythematosus (LE) cells who was admitted with gastritis and melena, she required blood transfusion for blood loss. A similar case of gastritis and melena was found to be salicylate-induced. Both of them had normal barium meals. One woman came in with cardiac failure and bradycardia while on treatment with propranolol for her angina pectoris. One asthmatic complained of palpitation, tremors of hands and abdominal cramps after receiving a subcutaneous injection of adrenaline for her asthmatic attack. Four other patients had giddiness and hypotension after intramuscular injections of chlorpromazine, promethazine and chlorpheniramine for various reasons at the Casualty Department. They all required admission as the symptoms did not subside on resting. Deep vein thrombosis, though rare among Asians, was found in one young woman taking contraceptive pills.

Hypersensitivity: Out of the 53 patients with adverse reactions to drugs, 26 suffered from hypersensitivity reactions. One patient was admitted because of cholestatic jaundice while on treatment with stelazine which cleared after withdrawal of drugs. Four patients developed full blown Stevens Johnson Syndrome after taking sulphonamide, phenobarbitones and oxytetracycline respectively. Another patient developed the similar syndrome with associated jaundice and hepatomegaly after taking Chinese herbal medicine. All of them were

ill and they required steroid therapy. Another popular Chinese medicine 'Ginseng' together with salicylate, tetracycline and mebhydrolin napadisylate were incriminated in the production of urticaria in four patients. One patient had urticaria and purpura thought to be due to sulphonamide, and the other had urticaria and maculo-papular rashes while taking neomercazole for thyrotoxicosis. Three patients had exfoliative dermatitis attributed to sulphonamide, allupurinol and chlorthiazide respectively. Maculo-papular rashes and swollen eye-lids were the cause of admission for five patients who took Chinese herbal medicines, paracetamol, and dimethyl-chlortetracycline. One female patient aged 33 was given debrisoquine for her hypertension, few days later she developed arthralgia, myalgia and erythema nodosum. Her erythrocyte sedimentation rate was 97 mm. during the first hour but her LE cells and RA factors were negative. She recovered two weeks later after withdrawal of debrisoquine. Though the temporal relationship was quite definite, so far no similar adverse reaction to debrisoquine had been reported in medical literature. However in another female patient aged 16, there was no doubt that she developed systemic lupus erythematosus with positive LE cells and anti-nuclear factors after taking troxidone for two years to control her epilepsy. She also developed hypoplastic anaemia with a haemoglobin of 6 gm.%, white cell count of 2100 per cu.mm. and a platelet count of 10,000 per cu.mm. She was successfully treated with blood transfusion, withdrawal of troxidone and steroid therapy. Two other serious haematological complications were also encountered during this survey. One woman aged 25 developed chill and rigor with leucopenia of 500 per cu.mm. and thrombocytopenia after taking penicillamine for her Wilson's disease. The other was a man of 66 who developed pure red cell aplasia while taking chlorpropamide for his diabetes mellitus. His haemoglobin was as low as 3.7 gm.% with a very low reticulocyte count. Fortunately he responded to withdrawal of chlorpropamide and steroid therapy. This case was earlier reported by Teoh *et al* in 1973.

Idiosyncrasy: Alarming dystonia and oculogyric crisis occurred in three patients after having parenteral administration of prochlorperazine for vomiting. Three others developed Parkinsonian-features after taking reserpine for hypertension and chlorpromazine for schizophrenia. Dyskinesia was brought about by L-Dopa in one patient with Parkinsonism. The writhing movement of his neck disappeared after the withdrawal of L-Dopa.

DISCUSSION

In this present survey, only 53 patients or 1.7% admitted into Medical Unit I of Singapore General Hospital were due to adverse reactions of drugs. This number is small when compared with the 5% reported by Seidl *et al* in 1966 at Johns Hopkins Hospital and 2.9% reported by Hurwitz in 1969 at two Belfast Hospitals. There are probably two reasons to account for the low incidence. Firstly many patients who have mild adverse reactions of drugs are unable to get admission into hospital due to shortage of hospitals beds and this is shown by the fact that all the 53 patients admitted in the survey were either life-threatening or at least moderate in severity; secondly patients in Singapore are not as well aware of the danger of drugs as the patients in Western countries and hence poor drug history is the rule rather than exception, therefore it is not surprising that many drug-induced disorders have been missed even under active surveillance. In spite of its lower incidence the burden of these iatrogenic diseases to the local community is very great indeed as they tax very heavily the already over-burdened medical service especially in a developing country like Singapore. Together with the 67 patients (2.1%) admitted into the Medical Unit I during the same six months period as a result of self-poisoning with drugs, the total number of hospital admissions due to drugs is 120 (3.8%) which can easily be the ninth most common cause for admission into the medical wards. Therefore many valuable beds in the hospital have to be used to treat iatrogenic diseases. The total number of hospital-days spent by the above mentioned 53 patients with adverse reactions is around 400. This is not only expensive but wasteful as they should be better utilised to treat the ever increasing number of natural human maladies. Another reason to take adverse reactions seriously is that they may cause unnecessary human sufferings and even deaths. The serious morbidity and mortality are well proven by the two deaths and ten life-threatening adverse reactions in this survey. Some of them are fortunate enough to have even survived the serious reactions.

One interesting feature which distinguishes this survey from the surveys carried out in the West is the involvement of Chinese herbal medicines which are taken not infrequently by some 75% of the local population. But unfortunately their nature, therapeutic effects, mechanisms of action and the possible adverse reactions are unknown to most of the clinicians. There is no doubt that these herbal medicines, just like the drugs used in Western medical practice, can cause adverse reactions. This is clearly shown by the urticaria, Stevens

Johnson syndrome and the maculo-papular rashes brought about by the Chinese herbal preparations in this study. The recent revelation that some Chinese herbal medicines, like Sin Lak Pills, contain toxic amounts of arsenic causes great concern as cases of arsenic keratosis, and epithelioma have been reported in 1972 by Tay in Singapore. The young asthmatic mentioned in this survey was fortunate to have the complications of arsenic poisoning averted as it was detected early enough to be treated effectively. Another distinguishing feature is that the patient below 50 years of age are more commonly affected by the adverse reactions to drugs in this survey and the majority of them are in the 10 to 29 age groups whereas in the surveys carried out by Seidl and Hurwitz, patients above 50 developed adverse reactions more commonly than younger patients.

The correct diagnosis of iatrogenic diseases can be made only if the clinicians have a high index of suspicion and routinely take a detailed drug history as not many reliable laboratory tests are available at present to confirm the diagnosis. In order to prevent unnecessary morbidity and mortality, the doctors especially those in general practice must be fully aware of these health hazards. They must also make sure that the limited facilities available in the medical service are not over-burdened by the iatrogenic disorders as more of which will be expected in future as more and more potent drugs will be marketed by the pharmaceutical industries. Therefore there is a great need to continue active surveillance and to determine not only the type of adverse reactions but also the incidence of those reactions. If more surveys of adverse reactions to drugs can be performed, more hazards will be identified and investigated, and greater drug safety will be achieved. It is also necessary to set up a body similar to Committee of Safety of Drugs in England to whom any adverse drug reactions should be reported by any doctor who encounters them. The Committee then analyse the information received and subsequently disseminate them to all the practising doctors in Singapore. The awareness of these health hazards, I believe, is the first but the most important step in the prevention of adverse reactions to drug therapy.

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