

# OBSERVATION OF 100 CASES OF ADVERSE DRUG REACTIONS IN GENERAL PRACTICE

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## INTRODUCTION

Adverse drug reactions are commonly seen in general practice and they can be diagnostic problems. The beneficial effects of drugs are invariably coupled with the inescapable ill-effects which can cause much morbidity and discomfort to the patients, and to the acute and painful embarrassments of the prescribing and dispensing doctors. Sometimes adverse drug reactions can lead to unnecessary fatalities. Any death is a catastrophe to the general practitioner.

The problem of adverse effects of drugs is compounded by the fact that most of our patients consume drugs from more than one doctor. This is made worse by self-medications and the regular consumption of traditional herbal medications. Many of our patients are also taking over-the-counter and under-the-counter medications. All these make the problems of adverse drug reactions more complicated.

Every drug can produce untoward consequences. Even the most unlikely drug can produce the most severe adverse reaction.

## EPIDEMIOLOGY

Adverse reactions to drugs are common enough to pose as diagnostic problems to the general practitioners. Patients come from different sources. A general practitioner can see adverse drug reactions in patients who have been discharged from hospital. He also sees patients who have been treated by Government OPD doctors; patients who have been treated by other doctors; patients who self-medicated; and patients of his own. So the presentation of adverse drug reactions is from various sources.

In this analysis, the sources of patients' adverse drug reactions are very varied as outlined above. Like most studies, a small group of widely used drugs like aspirin and anti-microbials account for a disproportionate number of reactions.

## ETIOLOGY

Most adverse reactions to drugs may be classified into two groups:

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1. Exaggeration of the Intended Pharmacologic effects.
2. Reactions unrelated to a drug's primary pharmacologic activity — the so called idiosyncratic reactions.

The majority of the observations in this analysis are idiosyncratic reactions.

## DIAGNOSIS

Adverse drug reactions are great mimics. They are not easily recognisable and their manifestations are protean. This is made more difficult if a patient has multiple drug reactions and cross-reactions. Recognition of a single drug responsible for a reaction can then be very difficult. However a doctor's familiarity with the possible adverse drug manifestations helps in pin-pointing the culprit. It is important to realise that any drug should be suspected in causing an adverse reaction.

The diagnosis is purely clinical observation. No general practitioner should risk confirming his clinical suspicion by challenging the patient with the suspected drug. Once an adverse reaction is suspected, discontinuance of the drug followed by the disappearance of the reaction is presumptive evidence of a drug induced manifestation. Sometimes, patients themselves notice the re-appearance of similar reactions after taking similar drugs. This is confirmatory evidence that the particular drug is responsible for the reaction. This analysis is based purely on clinical observations of a hundred cases seen in general practice.

## MATERIAL AND METHOD

All patients were seen by the author for the period 1983 to 1984, a duration of two years. It is a retrospective analysis of all cases of adverse reactions seen for that period. Patients come from different sources:

1. Patients who have drug reactions solely due to medications prescribed and dispensed by the author.
2. Patients seen with adverse reactions to drugs given by other doctors.
3. National Servicemen with adverse reactions to drugs given by SAF doctors.
4. Patients with adverse drug reactions to medications given by Government doctors in OPDs or hospital out-patient clinics.

The patients seen with adverse drug reactions are therefore not necessarily those of the author's. This is common in general practice where the network of patients is wide and diverse. The easy availability of the night-clinics in general practice also helps the patients with adverse drug reactions to consult the nearest doctor as soon as possible. The labelling of all medications also helps the doctor in identifying the drug responsible.

This analysis is also based on the biased sampling of the author for the various reasons:

1. Penicillin is not used at all. Oral and injection penicillins are totally banned.
2. Sulphonamides are not prescribed to children below ten years old.
3. Tetracyclines are not used for children at all.
4. The most widely used anti-microbials are ampicillin and amoxicillin.

## RESULTS

1. Salicylic acid	—	21 cases
2. Methyl Salicylate	—	10 cases
3. Paracetamol	—	6 cases
4. Ampicillin	—	6 cases
5. Bactrim	—	6 cases
6. Tetracycline	—	6 cases
7. Mefenamic Acid	—	5 cases
8. Carbimazole	—	4 cases
9. Propranolol	—	4 cases
10. Teronac (Mazindol 2mg)	—	3 cases
11. Alcohol	—	3 cases
12. Bricanyl (Terbutaline sulphate)	—	3 cases
13. Gravol Injection (Dimenhydrinate)	—	3 cases
14. Phenylbutazone	—	3 cases
15. Lignocaine 1%	—	3 cases
16. Chloroquin	—	3 cases
17. Hair-dyes	—	2 cases
18. Griseofulvin 125 mg	—	2 cases
19. Eradacil (Rosoxacin)	—	2 cases
20. Indomethacin	—	2 cases
21. Ladogal (Danazol)	—	1 case
22. Ventolin (Salbutamol 4mg)	—	1 case
23. Hydrocortisone cream 1%	—	1 case

It must be noted that some patients have adverse drug reactions to more than one drug. This is excluded in this analysis.

## DISCUSSION

### 1. SALICYLATES

Salicylates are found in many house-hold products. They are also found in analgesic and cold tablets. Methyl salicylate is present in most skin liniments and salicylic acid itself is found in ointments and anti-fungal skin lotions. No wonder they form the majority of adverse drug reactions seen by the author.

The toxicity of salicylates are well-known and well-documented. In general practice, the majority present with acute manifestations. Of the 21 cases seen by the author, the majority present with acute periorbital swelling and bilateral chemosis (19 cases). One case, an adult male, presented with acute erythema multiforme. He took only 300 mg of acetylsalicylic acid. The other case was a fifteen year old school girl who pre-

sented with acute gastric erosion with haematemesis and tinnitus following one single dose of 300 mg of soluble aspirin.

Another observation of the author is the fact that like penicillin, salicylates can have a sensitising effect in subsequent doses. An eight year old child was seen by the author since he was an infant. He was given soluble aspirin without any adverse reaction. But on one last occasion when he was given 80 mg of soluble aspirin, both his eyes were covered by massive chemosis and periorbital oedema. His multi-millionaire father almost had the doctor castrated.

### 2. SULPHONAMIDES

These groups of drugs are commonly used in general practice. The adverse reactions are frightening and the author had stopped using them on children unless he is positively sure that the child had taken them before without any adverse effects.

The six cases seen ranged from generalised pruritus to a severe full-blown Steven Johnson Syndrome. Of the 6 cases seen, one presented with a classical fixed drug reaction on the outer aspect of his left thigh. He displayed no other manifestations.

The other interesting case is the National Serviceman who presented with only muco-cutaneous manifestations. He had severe itch of the lips with slight swelling and a very severe and embarrassing balanitis.

The other four cases presented with erythema multiforme and classical Steven Johnson Syndrome. Only two cases were referred to hospital. The rest were treated conservatively at home with uneventful recovery.

The six cases seen were reacting to Bactrim used by the author.

### 3. PARACETAMOL

Paracetamol is the commonest analgesic and antipyretic used in general practice. Toxicity has been reported with hepatatic parenchymal failure and renal pyelitis. Adverse reactions to the drug are relatively few despite the extensive use in general practice. Nevertheless, there are six cases in this analysis.

Five cases present with swelling of the eyes and maculo-papular rash with pruritus.

One case, an adult male, presented with extensive and severe erythema multiforme. He was very distressed and was admitted to hospital in a critical condition. Fortunately, he recovered uneventfully. This case illustrates that no drug is safe no matter how harmless and safe pharmacologically.

### 4. AMPICILLIN

Ampicillin is commonly used by the author both for children and the adults. There are six cases of adverse drug reactions. Five of them presented with a mild macula-papular rash which appeared about five days after taking the medicine.

The sixth case presented with an acute anaphylaxis one hour after taking 500 mg of Capsule Ampicillin. He was a male adult. He presented with acute respiratory distress, painful red and suffused eyes and generalised maculopapular rash. He fainted and was admitted to hospital. However, he recovered uneventfully. The patient's relatives and family nearly destroyed the doctor's clinic and threatened and harassed him for weeks.

## 5. TETRACYCLINE

There were six cases of adverse drug reactions to tetracyclines. Most of them presented with rashes and itch all over the body. None manifested with any serious reactions. No fixed drug reaction was seen in this analysis.

## 6. MEFENAMIC ACID

This commonly used analgesic is relatively free from adverse reactions. However, there were five cases of adverse drug reactions manifesting as peri-orbital swelling and generalised maculo-papular rash. No serious reaction was seen.

## 7. CARBIMAZOLE

This commonly used drug for thyrotoxicosis is widely prescribed by hospital and private doctors. The four cases seen presented with acute onset of rashes with severe itch. One case presented with an acute onset of alopecia. All four cases were young female.

## 8. PROPRANOLOL

The common feature of this drug is the production of broncho-spasm in susceptible patients. All four patients had no history of asthma or chronic lung diseases. None of them had any atopic history. They presented quite insidiously with chest tightness and breathlessness within a week. They felt easily fatigued and one case presented with frank bronchial wheezing. All four were young adults. There were no sleep disturbances and no clinical bradycardia. The dosage used was 40 mg per day.

Other cases of bronchospasm with the prolonged use of propranolol are also noted. But they have been excluded in this analysis.

## 9. TERONAC (MAZINDOL 2mg)

Three cases of adverse reactions to the drug were noted. Two of them were women who presented with an acute onset of breathlessness and chest discomfort. They felt giddy and one had an acute episode of syncope. There were no cutaneous manifestation.

The third patient presented with an interesting sexual phenomenon. This was a thirty-five year old married man who experienced an acute physical shrinkage of his penile size after taking Mazindol 2mg. When he stopped taking, his penile size became normal. He also experienced an impairment of function during the acute episode. He could not believe at first, but when he experimented again on himself with the same drug given by the author, his penis shrank. There was no need for the author to have any more confirmatory evidence. The patient now is a proud father of two children.

## 10 MISCELLANEOUS

### 10.1 ALCOHOL

Three cases of acute generalised rash with itch were seen in three young ladies who consumed beer. One lady presented with giant urticaria all over the body and uncontrollable itch.

### 10.2 TERBUTALINE SULPHATE

Three cases of palpitations and tremors were observed

in three female patients after the ingestion of one tablet of 2.5mg Bricanyl. One patient became so hysterical and breathless with gross tremors and uncontrollable body shakings that the author had to make a house-call to calm her. She was given an intravenous injection of 10 mg Valium.

Salbutamol (Ventolin) 4mg caused similar reaction in one patient, also a female patient. All three presented with gross tremors and perspiration.

### 10.3 DIMENHYDRINATE (GRAVOL)

Three cases of oculo-gyri episodes were observed in two school girls and a ten year old boy. The girls presented with classical ocular and cervical manifestations. The posturings were so frightening that the parents sent them to hospital immediately.

One of the girls presented with dysarthria as well. She could not talk and pronounce properly. Her tongue kept choking her, she claimed. She was holding onto her tongue all the way to the ward. She was afraid she might swallow her tongue.

The third case is a ten year old boy who took one dose of Gravol following a few bouts of vomiting. The child developed severe ocular and cervical signs and the father took the child in the middle of the night to a sinseh/medium. The father thought the child had a fit and possessed by a demon. The doctor was called in the early hours of the morning when the child's condition remained unchanged.

### 10.4 PHENYL BUTAZONE

This dreadful and fearful drug is known for its adverse and fatal reactions. Three cases were seen and all of them presented with severe erythema multiforme. All three were referred to the hospital. No exfoliative or bullae type of reactions were seen.

### 10.5 LIGNOCAINE

Three cases of adverse reaction to 1% lignocaine were observed in three young adults. One was a thirty-five year old Indian male who came in for circumcision. He developed a fit, a severe bradycardia and hypotension following the initial infiltration of the local anaesthetic. His breathing was shallow and he turned cyanosed. The patient was given intravenous fluids in the clinic and was immediately admitted to hospital. An ambulance was called. He recovered fully in hospital.

The other two cases presented with fit and syncope following the initial infiltration. Both were cyanosed and had respiratory distress. The author believed that pain and fear were contributory factors.

### 10.6 CHLOROQUIN

Three cases of Chloroquin-related jaundice were seen in National Servicemen. All three were initially diagnosed as having viral hepatitis. They were later found to be G6PD deficient. All three of them were army recruits doing their basic military training in Pulau Tekong. Chloroquin was routinely given as part of malaria prophylaxis.

### 10.7 HAIR-DYES

This familiar reaction to hair-dyes was seen in two middle-aged women who dyed their own hair. The manifestation is classical with scalp oedema and a weeping eczema that drenched the hair-lines and sent the patients frantically to the doctor.

### 10.8 GRISEOFULVIN

This is another dreadful drug with known toxicity. Two cases of severe erythema multiforme were noted in two female patients who were given Griseofulvin 125mg for systemic mycotic infections. The reaction was immediate. Both patients refused hospitalisation and were treated conservatively at home with an uneventful recovery.

### 10.9 ERADACIL (ROSOXACIN)

Two interesting cases of acute reactions were seen. The first was an adult male who presented with gonococcal urethritis. He was given two capsules of Eradacil as a stat dose in the clinic. Then minutes later, while paying for his bill, he complained of chest tightness and giddiness. Before the author could bring him into the consultation room, he fainted to the horror of the patients waiting outside. However, he recovered eventually without any adverse reaction. He rested in the surgery room for an hour.

The second case was also an adult married man who came in for gonococcal urethritis. He was given two capsules of Eradacil in the clinic and was asked to come back for review on the fifth day. He was wearing a topee when he returned to see the author. He told the author that his hair started to drop in clumps the day after he saw the doctor. He was almost bare-headed when the author saw him. The interesting thing was the patient recovered his full-blown luxurious hair after two months. He was given multivitamins as placebos.

### 10.10 INDOMETHACIN

Two cases of acute chest discomfort and breathlessness were noted in this analysis. Both were elderly patients who presented to the author with chronic osteoarthritis of the knees and backache.

### 10.11 HYDROCORTISONE CREAM 1%

Prednisolone is widely used in clinical private practice. The side-effects and toxicity are well known.

The author had an interesting case of acute alopecia in a twelve year old school-girl who was given 1% hydrocortisone cream for a small patch of irritant dermatitis. She developed extensive alopecia after she had applied the cream. The reaction was almost immediate. This was confirmed by her father who is a close friend of the author.

### 10.12 LADOGAL (DANAZOL)

This expensive drug was prescribed for a patient for secondary infertility. She spent about five hundred dollars for a two month supply. One day after ingestion, she developed generalised itch with petechial rash all over the body. The itch was intense. She was advised to stop the drug and her money went into the drain.

### CONCLUSIONS

1. No drug is totally devoid of any adverse effects. Even paracetamol can have a fatal reaction in susceptible and idiosyncratic patients.

2. No patient should be burdened with unnecessary medications. A drug can cause adverse reactions even after several safe ingestion. A sensitising and subsequent reaction is usually more severe and fatal.
3. Aspirin tops the list of allergies and adverse reactions. It is prudent on the part of the physician to avoid aspirin in children and in patients with an atopic history. The physician should avoid aspirin for common ailments where other analgesics are safer substitutes.
4. Anti-microbials are responsible for quite a number of adverse reactions seen in general practice. They should not be dispensed with abandon. Ampicillin should be avoided in atopic patients.
5. Expensive and potent medicines should be prescribed with discretion. Because of this idiosyncratic response of patients to drugs, it is wise and economically sound for the physician to prescribe initially a few days medications to his patient. This is to avoid unnecessary wastage and money. A full course is only prescribed when the physician is quite sure that the drug has no adverse effect on the patient. It is common for doctors to prescribe two to three months of new miracle and expensive drugs to patients. This form of prescription should be viewed with great discretion and concern for the patients.
5. What are the patients' reactions to the adverse effects of drugs given by their doctors. There are four patterns of reactions:-
  1. Wrong medications were given. They blame the doctors.
  2. Body cannot tolerate the strong medications given. They blame themselves.
  3. Doctor-patient relationship very incompatible. They blame both the doctor and themselves.
  4. Doctor not clever. They blame the doctor's inexperience and youth and they will never consult the doctor again.

Whatever the patients' reactions, the general practitioner still bears the full brunt of the responsibility. Any indiscreet and inadvertent remark made by the hospital staff can turn the table against the referring doctor. It is not uncommon for general practitioners to face hostile threats from patients and relatives when a severe adverse reaction occurs. This is made worse by indiscreet and incriminating remarks made by hospital staff. Hospital doctors should exercise extreme care, tact and professionalism in handling drug induced reactions referred by general practitioners for admissions. A harmless remark can be a disaster for the doctor in private practice.

6. Lastly general practitioners should equip themselves with emergency resuscitative trolley to avoid any unnecessary fatalities. Adverse reactions can be very quickly reversed if treated immediately. An intravenous drip set is mandatory. The doctor must be vigilant at all times. He must learn to anticipate trouble and to act swiftly and coolly without losing his head. Any drug and any injection can induce an adverse reaction and the doctor must be prepared to deal with it.