A Case of Cardiac Arrest Following Orel 250mg. Mefenamic Acid

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Introduction

ANAPHYLACTIC or anaphylactoid reactions can occur with any drug, whether given orally, by intravenous, intramuscular, subcutaneous or intradermal injection, or by local instillation to the mouth, nose or eyes, and in the case of a hypersensitive patient, even local application to the skin. A case of cardiac arrest, successfully resuscitated with external cardiac massage and insertion of a pharyngeal airway, is reported. A search of the literature and of the reports of clinical trials with mefenamic acid, has shown that no anaphylactic or anaphylactoid reactions have ever been reported following oral mefenamic acid (ref.1,5,6,9 & 10), and it is believed that this is the first case of its kind in the world.

Case History

L.N., a 66-year-old Chinese male, living in Ipoh but working in Kuala Lumpur, presented at about 9.50 in the morning on the 24th. March 1975, with a history of epigastric pain and pain in both shoulder joints and legs of one week's duration. On examination, his blood pressure was 140/90 mm Hg., his abdomen was soft with no liver or spleen palpable, but his epigastrium was slightly tender. There were no rhonchi or crepitations in his chest, although he said he had a slight cough. His temperature was normal and his urine was free of albumin and sugar. There was no inflammation in his shoulder and knee joints, although crepitus was present in his knee joints. When asked whether he was allergic to any drugs, he produced a note from his previous doctor dated the 20th. March 1975, which stated that he was sensitive to "PHENSEDYL" May and Baker (Promethazine 3.6 mg., Codeine phosphate 9 mg. and Ephedrine 7.2 mg. per 3.6 mls.), "NOVAPYRIN" T. W. Wu (Sulpyrin J.P., Metamizole, Sodium Methylaminoantipyrine methane sulphonate), and "BUTAZOLIDIN" Geigy (Phenylbutazone). He also said that he was suffering from "gastric" before. A provisional diagnosis of arthritis of the shoulder and knee joints and gastritis was made and the patient was prescribed "TITRALAC" Riker (Calcium carbonate 420 mg., Glycine 180 mg. per tablet), "STROCAIN" Eisai (Oxethazaine 5 mg., Polymigel 244 mg. per tablet), and "PONSTAN" Parke Davis (Mefenamic acid 250 mg. per capsule), one each orally four hourly, four times a day. He took the tablets and capsule at approximately 10 a.m., and was told to lie on a couch for one hour. At 11.15 a.m., he was re-examined and as he had no complaints and no itchiness, he was allowed to go home. On reaching the bus station, he developed itchiness in both hands and he returned at 11.30 a.m., complaining of itchiness in both hands and was scratching them. Within two minutes after examining him, he was given orally one tablet "INCIDAL" Bayer (Mebhydrolin napadisylate 50 mg.), one tablet "PIRITON" Glaxo (Chlorpheniramine maleate 4 mg.), and four tablets of "DELCORLON" Synco (Prednisolone 5 mg. per tablet), and was told to stay back for two hours. He was lying on a couch and was reviewed every five minutes. At 11.45 a.m., he complained of severe itch all over his head with uncontrollable scratching and also started to cough. At his wife's insistence for injections, he was called to the injection room and corticosteroid and antihistamine injections were prepared. Before he could come to the injection room and before he could be given the injections, his wife called out that her husband was not responding to her calls. He

was examined and found to be clinically dead with no heart beat, no pulse, no respiration and he was cold and cyanosed. Immediate external cardiac massage was done and an adult size pharyngeal airway ("LIFE-SAVER" Lepetit) was inserted, after the left index finger was put into his mouth and his tongue pulled forward and some phlegm removed. After approximately one minute, he gave a groan and after a further two minutes, he was able to cough and his heart beat and respiration returned. This was kept up for a further five minutes. At 12.10 p.m., he was able to get up assisted by two persons and was able to hold on to his pharyngeal airway, and at 12.20 p.m., he was able to walk to a chair and remove his pharyngeal airway. Investigations later showed that his electrocardiogram, which was done at 1.30 p.m., to be normal with no evidence of ischaemia or myocardial infarct. A chest X-Ray was not done. His urine was clear. His Hb. was 8.6 G.%, and his WCC was 12,200/cumm., with polymorphs 83% and Lymphocytes 17%. Over the next 48 hours, he was kept under observation and complete rest in bed. He was given orally "Piriton" 4 mg. three times a day, Magnesium Trisilicate half an ounce three times a day, and "Actal" Winthrop (Sodium polyhydroxy aluminium monocarbonate hexitol complex 360 mg. per tablet), two tablets as required. No analgesics were given even for his arthritic pains. He was seen in town a week later and he said he had no complaints except that he nearly lost his life.

It was later learnt from his previous doctor, that on the 20th. March 1975, he was given IMI "BUTAZOLIDIN" Geigy, 600 mg. phenylbutazone or 3 cc., and he had collapsed in a restaurant less than 15 minutes later. When examined, he was unconscious and soon after a rash appeared all over his face and body. He was given IMI Adrenalin 1/1000 w/v (1 mg./cc.), 0.5 cc. at first and another 0.5 cc. slowly later, and also IMI "Kenacort A" Squibb (Triamcinolone acetonide) 40 mg. or 1 cc. Besides "Phensedyl", "Novapyrin", and "Butazolidin", he was also sensitive to chloramphenicol, as he was the previous doctor's patient for some time.

Classification of Analgesic, Antipyretic and Anti-inflammatory Agents

A broad classification is given below. Not all drugs have the above properties. There are some that are mainly anti-inflammatory, e.g. the anti-inflammatory enzymes, corticosteroids and indomethacin. Others are mainly analgesic, e.g. morphine and some of its derivatives, glafenine, or have anti-inflammatory and analgesic but little antipyretic properties. Still others, e.g. the antimalarials of the chloroquine (4-aminoquinolines) group, D-penicillamine, gold salts and the immunosuppressive drugs, in rheumatoid arthritis, and the alkaloids from the autumn crocus, viz. colchicine and demecolcine, in gout, do not themselves have analgesic and antipyretic properties. Their mode of action is still debatable. Gold does have a definite action on collagen and synovial membrane, immunological reactions and enzymatic systems. Chloroquine has anti-inflammatory effects (ref. 4, pg. 12.35), while colchicine and demecolcine probably act by interrupting the inflammatory cycle (ref. 4, pg. 12.38). If rheumatoid arthritis is considered as an inflammatory process resulting from an immune reaction, there is a possibility that immunosuppressive agents could have a role in its management, as "they can inhibit the function of immunologically committed cells as well as inhibit cells with a rapid proliferative rate, but they have no definite immunological commitment. The same applies to D-penicillamine. and the response is better in cases where the serum copper level is high" (ref. Professor J. F. Silva:- The General Management of Rheumatoid Arthritis. Medical Progress, May 1975, Vol. 2, No. 5, pg. 12).

There are two main groups of analgesic, antipyretic and anti-inflammatory agents, viz.

(I) the steroidal hormonal group, e.g.

(a) the corticosteroids, e.g.

(i) Betamethasone ("Betnelan" Glaxo, "Celestone" Schering U.S.A.),

(ii) Cortisone ("Cortone" Merck Sharp and Dohme),

(iii) Dexamethasone ("Decadron" Merck Sharp and Dohme, "Deltafluorene" Lepetit, "Oradexon" Organon),

(iv) Fludrocortisone,

(v) Fluocortolone ("Ultralanum" Schering AG),

(vi) Hydrocortisone (cortisol, "Solu-Cortef" Upjohn),

(vii) Methyl prednisolone ("Medrol" Upjohn, "Urbason" Hoechst),

(viii) Paramethasone ("Metilar" Syntex),

(ix) Prednisolone ("Deltacortril" Pfizer, "Juvasolon" Dolder, "Nisolone" Lepetit, "Precortisyl" Roussel, "Scherisolone" Schering AG),

(x) Prednisone, and

(xi) Triamcinolone ("Kenacort" Squibb, "Ledercort" Lederle).

(b) the corticotrophins, e.g.

(i) Adrenocorticotrophic Hormone (ACTH, corticotrophin, "Acthar Gel" Armour, "Cortrophin-Zn" Organon),

(ii) Tetracosactrin, and

(iii) Tetracosactrin Zinc (tetracosactide adsorbed on zinc phosphate, "Synacthen Depot" Ciba-Geigy).

(II) the non-steroidal group. This is divided into two sub-groups, viz.

(1) the opiate and opioid group, viz. the opium alkaloids and their synthetic derivatives. They belong chemically to two separate groups (ref. 3, pg. 122),

(a) PHENANTHRENE derivatives and other related drugs, e.g.

(i) Dextropropoxyphene ("Doloxene" Eli Lilly),

(ii) Diamorphine (Heroin),

(iii) Dihydrocodeine ("DF 118" Glaxo-Allenburys),

(iv) Fentanyl ("Fentanyl" Janssen),

(v) Levallorphan ("Lorfan"),

(vi) Meperidine ("Pethidine" Burroughs Wellcome),

(vii) Methadone ("Physeptone" Burroughs Wellcome),

(viii) Methylmorphine (Codeine),

(ix) Morphine,

(x) Nalorphine ("Lethidrone" Burroughs Wellcome),

(xi) Pentazocine ("Fortral" Winthrop, Australia, "Talwin" Winthrop/Sterling Drug),

(xii) Phenazocine ("Narphen"), and

(xiii) Thebaine.

Some of these, e.g. dextropropoxyphene and pentazocine, are said to have less dependence potential.

(b) ISOQUINOLINE derivatives, e.g.

(i) Papaverine, and

(ii) Narcotine (Noscapine).

These derivatives exert no analgesic or narcotic action.

(11) the non-opiate and non-opioid group. This includes:–

(a) Aniline derivatives, e.g.

(i) Acetyl derivative of aniline (acetanilide, "Antifebrin"),

(ii) N-acetyl-p-aminophenol (acetaminophen, paracetamol, "Calpol" Calmic, "Datril' Bristol-Myers, "Dumin" Dumex, "Milidon" Malayan Pharmaceutical Factory, "Panadol" Winthrop, "Tabalgin" Berk Pharmaceuticals Ltd.),

(iii) p-ethyl derivative of acetanilide (acetophenetidin, phenacetin).

(b) Anthranilic acid derivatives or the fenamates, e.g.

(i) Aluminium N-(3'-trifluoromethylphenyl) anthranilate ((Aluminium flufenamate, "Opyrin" Taisho Pharmaceutical Co., Ltd., Tokyo, Japan)),

(ii) Meclofenamic acid (Parke Davis),

(iii) N-(alpha, alpha, alpha-trifluoro-m-tolyl) anthranilic acid (Flufenamic acid, "Arlef" Parke Davis)), and

(iv) N-(2,3-xylyl) anthranilic acid ((Mefenamic acid, "Ponstan" Parke Davis)).

(c) Anti-inflammatory enzymes, e.g.

(i) Chymotrypsin ("Chymar" Armour, "Deanase D.C." Consolidated Chemicals Ltd., "Kimopsin" Eisai),

(ii) Chymotrypsin and trypsin ("Chymoral" Armour),

(iii) Lysozyme chloride ("Neuzym" Eisai),

(iv) Prolase ("Papase" Warner-Lambert),

(v) Proctase and pancreatin ("Proctase P" Meiji Seika),

(vi) Seaprose S ("Jeoase" Suzuken, "Kyorinase" Kyorin), and

(vii) Serratio-peptidase ("Danzen" Takeda).

(d) 1,2,4-Benzotriazine derivative, e.g. 3-dimethylamino-7-methyl-1,2-(n-propylmalonyl)-1,2-dihydro-1,2,4-benzotriazine dihydrate (Azapropazone, "Prolixan 300" Siegfried Ltd., Switzerland).

(e) Carboxylic acid derivatives, e.g.

(i) Diacetylpyrocatechol carboxylic acid ("Movirene" Union Chemique Belge), and

(ii) 2-Phenylquinoline-4-carboxylic acid (Phenylcinchoninic acid, Cinchophen, Quinophan).

(f) 7-chloroquinoline derivative, e.g. Glycerylaminophenaquine (Glafenine, "Glifanan" Roussel). Exclusively an analgesic, without antipyretic, anti-inflammatory or hypnotic properties, though concomitant anti-inflammatory and antipyretic activity is observed with very high doses, well above therapeutic levels (ref. "Glifanan" brochure pg. 3 and 6, 184-69 EXA).

(g) Indole derivative, e.g. 1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid (Indomethacin, "Confortid" Dumex, "Indocid" Merck Sharp and Dohme).

(h) Nicotinic acid derivative, e.g. Trifluoromethyl-3-phenylamino-2-nicotinic acid (Niflumic acid, "Niflucid" Squibb).

(i) Phenothiazine derivative with dimethylaminopropyl side-chain, e.g. Methotrimeprazine ("Veractil"). It is a potent analgesic and sedative (ref. 4, pg. 12.32; 14.9).

(j) Phenylacetic acid derivatives, e.g.

(i) 4-allyloxy-3-chlorophenylacetic acid (Alclofenac, "Prinalgin" Berk), and

(ii) Sodium-[0-[(2,6-dichlorophenyl)-amino]-phenyl]-acetate (Diclofenac Sodium, "Voltaren" Geigy).

(k) Propionic acid derivatives, e.g.

(i) DL-2-(3-phenoxyphenyl)-propionic acid (Fenoprofen, "Fenopron" Dista Products Ltd.),

(ii) 2-(2-fluro-4-biphenyl)-propionic acid (Flurbiprofen, "Froben" Boots Company Ltd.). It is 10 to 15 times more potent than ibuprofen.

(iii) 2-(4-isobutylphenyl)-propionic acid (Ibuprofen, "Brufen" Boots Company Ltd.),

(iv) 2-(3-benzoylphenyl)-propionic acid (Ketoprofen, "Orudis" May and Baker Ltd.), and

(v) D-2-(6'-methoxy-2'-naphthyl)-propionic acid (Naproxen, "Naprosyn" Syntex Pharmaceuticals Ltd.).

(l) Pyrazolone derivatives, e.g.

(i) Antipyrine and its derivatives, e.g.

(a) Amidopyrine (Aminophenazone, aminopyrine, dimethylamino-antipyrine, dimethylaminophenazone, pyramidon),

(b) Antipyrine (Phenazone),

(c) Antipyrine salicylate (Phenazone salicylate, salipyrin),

(d) Isopropylantipyrine (Isopropylphenazone, isopyrin, propyphenazone) and

(e) Methylaminoantipyrine-methane sodium sulfonate (Analgin, dipyrone, metamizol, metamizole, noramidopyrine methane sodium sulfonate, novamine sulfone, phenyldimethyl-pyrazolone-methylamino-methane-sodium sulphonate, "Bonpyrin" Takeda, "Conmel" Winthrop, "Himapyrine" Himalaya Medical Hall, "Novalgin" Hoechst, "Novapyrin" T. W. Wu, "Pyralgin" Siegfried, "Sulpyrin" Chugai, Grace Pharmaceutical Co., "Tanapiron" Tanabe Seiyaku). The magnesium salt of dipyrone is "Magnopyrol" Siegfried.

(ii) Pyrazolidine derivatives, e.g.

(a) Butylmalonic acid mono-(1,2-diphenylhydrazide) calcium semihydrate ((Bumadizone, "Eumotol" Byk Gulden)),

(b) 4-Butyl-1,2-diphenyl-ketopyrazolidine-3,5-dione ((Ketophenylbutazone, "Ketazon" Kyowa Hakko Kogya Co.)),

(c) 4-Butyl-1-phenyl-pyrazolidine-3,5-dione ((Monophenylbutazone, "Mobutazon" Benzon, Denmark)),

(d) 2,3-Dimethyl-4-nicotinamido-1-phenyl-5-pyrazolone ((Nifenazone, "Thylin" West-Silten Pharmaceuticals)),

(e) 1-Phenyl-2-(p-hydroxyphenyl)-3,5-di-oxo-4-n-butylpyrazolidine monohydrate ((Oxyphenbutazone, "Tanderil" Geigy)), and

(f) 4-Butyl-1,2-diphenylpyrazolidine-3,5-dione ((Diphenylbutazone, phenylbutazone, "Butazolidin" Geigy)).

(m) Pyrimidine derivative, e.g. 5-n-butyl-1-cyclohexyl-2,4,6-trioxoperhydropyrimidine (Bucolome, "Butymidin" Takeda).

(n) Salicylic acid derivatives, e.g.

(i) Acetylsalicylic acid ("Aspirin" Bayer, "Aspro" Nicholas, "Levius" Farmitalia, "Palaprin Forte" – aloxiprin – Nicholas, "Paynocil" Bencard),

(ii) Salicylamide ("Salamide" Hamilton Laboratories, Adelaide, "Salimed" Medo-Chemicals), and

(iii) Sodium salicylate.

(o) Thienopyridine derivative, e.g. 2-amino-3-ethoxycarbonyl-6-benzyl-4,5,6,7-tetrahydrothieno (2,3-c) pyridine hydrochloride (Tinoridine hydrochloride, "Nonflamin" Takeda).

(p) Others, e.g.

(i) 4-aminoquinolines (amodiaquine "Camoquin" Parke Davis, chloroquine, hydroxychloroquine "Plaquenil" Winthrop),

(ii) D-penicillamine,

(iii) Gold salts (Sodium aurothiomalate), and

(iv) Immunosuppressive drugs, e.g.
(a) Azathioprine ("Imuran" Burroughs Wellcome),

(b) Chlorambucil ("Leukeran" Burroughs Wellcome),

(c) Cyclophosphamide ("Endoxan" Asta-Werke AG), and others.

Combinations of the two main groups are also available, e.g.

(i) "Delta-Butazolidin" Geigy (Phenylbutazone 50 mg. and Prednisolone 1.25 mg.), and

(ii) "Realin" Geigy (Oxyphen-butazone 100 mg. and Prednisolone 2.5 mg.),

so also are combinations of the two subgroups of the main group II, e.g.

(i) "Algaphan" Boehringer Mannheim (D-propoxyphene 25 mg. and aminophenazone 300 mg.),

(ii) "Codopar-118" Glaxo-Allenburys (Dihydrocodeine tartrate 10 mg. and paracetamol 500 mg.),

(iii) "Dologesic-32" Eli Lilly (D-propoxyphene 32.5 mg. and paracetamol 325 mg.),

(iv) "Doloxene Compound" Eli Lilly (D-propoxyphene 32 mg. or 65 mg., aspirin 227 mg., phenacetin 162 mg., and caffeine 32.4 mg.),

(v) "Safapryn-Co" Pfizer (enteric-coated core aspirin with paracetamol and codeine phosphate), and

(vi) "Veganin" Warner-Lambert (Acetylsalicylic acid 250 mg., phenacetin 250 mg. and codeine phosphate 10 mg.),

or of combinations of members of subgroup 11, of main group II, sometimes with caffeine, e.g.

(i) A.P.C. (Acetylsalicylic acid 225 mg., phenacetin 150 mg., and caffeine 30 mg.),

(ii) "Irgapyrin" Geigy (Phenylbutazone 125 mg. and amidopyrine 125 mg.),

(iii) "Mopyrine" Malayan Pharmaceutical Factory (Amidopyrine 125 mg. and monophenylbutazone 125 mg.),

(iv) "Safapryn" Pfizer (enteric-coated core acetylsalicylic acid 300 mg. and paracetamol 250 mg.),

(v) "Tomanil" Byk Gulden (Isopyrin hydrochloride 200 mg. and phenylbutazone 100 mg.),

and others.

Discussion

The antacids, "Titralac" and "Strocain", are extremely unlikely to cause anaphylactic or anaphylactoid reactions as very few side-effects to calcium carbonate, glycine and polymigel (Al_2O_3. $2CaCO_3$. $MgCO_3$. XH_2O), have ever been reported (ref. 2, 11). Glycine is an amino acid and as such is a constituent of the normal diet, and calcium carbonate is also a very unreactive substance. Besides, the patient did not react to sodium polyhydroxy aluminium monocarbonate hexitol complex ("Actal" Winthrop) and magnesium trisilicate, when he took these orally over the next 48 hours. As to the local mucosal surface anaesthetic agent, oxethazaine, N,N-bis-(N-methyl-omega-phenyl-tertiary-butyl-acetamido)-beta-hydroxyethylamine, the amount 5 mg. in one tablet of "Strocain" would be too little to be absorbed enough into the blood stream to produce the cardiac arrest in this patient. In combination with polymigel, a co-precipitate of aluminium, calcium and magnesium present in "Strocain", its absorption rate is prolonged.

Oxethazaine is an amide anaesthetic and is insoluble in water but soluble in dilute acids. It is unique in that as a weak base it is relatively non-ionised in acid solutions. The potency of a local anaesthetic appears to depend on the availability of the un-ionised free base (ref. 15, F 8143, pg. 2 and 3). Oxethazaine antagonizes the action of acetylcholine (slight antiacetylcholine action), histamine (potent antihistaminic action), physostigmine, serotonin, and barium sulfate on smooth muscle (ref. 2, 15), and these anticholinergic, antihistaminic and anti-serotonin actions can be shown in vitro but not in vivo. No effects on the central nervous system or on respiration have been observed. In studies for acute toxic effect, 32 mg. oxethazaine administered to normal volunteers at four-hourly intervals, four times in the day, produced no significant changes in blood pressure or pulse taken at hourly intervals for twelve hours, and comparison of the initial and final electrocardiograms showed no change (ref. 15, F 8143, pg. 3 and 5). It therefore has a wide safety margin because of its low toxicity and its least absorption rate. When administered orally, oxethazaine produces a peak blood level approximately

four hours after administration and then declines. Its oral LD 50 in mice is approximately 400 mg. of base per kg., and when suspended in alumina gel as a vehicle, the oral LD 50 in mice is 1012 mg. of base per kg. When oxethazaine is suspended in acacia, the oral LD 50 in mice is 1800 mg. of base per kg., while the intraperitoneal LD 50 in mice is 118 mg. of base per kg. A dose of 10 or 20 mg. of oxethazaine respectively in a human weighing 50 kg. is only 0.2 or 0.4 mg. per kg. of body weight (ref. 15, P. 441705). Oxethazaine as present in "Strocain", is therefore only 0.0833 mg. per kg. body weight in this patient as his weight was approximately 60 kg. It is generally believed that oxethazaine permeates the lipid of peripheral nerves and that it anaesthetizes the vagus nerve ending, when present in the stomach (ref. 16, pg. 11), and it is scarcely absorbed through the digestive system as only 1% of oxethazaine in aqueous solution is absorbed from the gastro-intestinal tract, and if oxethazaine is given with an alumina gel, an insignificant 0.4% is absorbed. The very little oxethazaine that is absorbed, is so rapidly and thoroughly decomposed and detoxicated that it is hardly detected in the blood or urine. Side-effects of oxethazaine are usually mild and transient, and include dryness of the mouth, nausea, soreness of the tongue, and one case of glossitis of the hypersensitive type and one observed case of skin eruption. Dizziness, drowsiness, and faintness have been reported following more than 120 mg. of oxethazaine per day (ref. 15, P. 441705). Side-effects following "Strocain" are rarely reported and include anorexia, constipation, and diarrhoea.

Mefenamic acid, which is N-(2,3-xylyl) anthranilic acid (Figure 4), is slowly absorbed from the small intestine following oral medication. Peak blood levels are attained two to three hours after dosage. Blood levels resulting from oral administration of mefenamic acid are not necessarily proportional to the size of the dose beyond a certain range. Single dose of one Gm. each of mefenamic acid (four capsules of 250 mg. each) produces peak plasma levels of 7 to 10 micrograms per millilitre within two to three hours following oral administration. The levels decline sharply to values between one and two micrograms at six hours following dosage and then gradually taper off to mere traces of drug at 24 hours. Plasma levels for free and total drug are nearly identical, indicating that mefenamic acid occurs mainly in the unconjugated form (ref. 6, pg. 24, 25 and 27). Side-effects of mefenamic acid that have been reported include brisk diarrhoea (occurring in some 10 to 20 per cent of patients on long-term continuous dosage of 2,000 mg. or more daily), constipation, depression (ref. 1), dizziness, dyspepsia, gastric irritation, gastric upset, haemolytic anaemia (ref. 5), leucopenia, and maculopapular rash leading to mild exfoliative dermatitis if medication is continued (ref. 6, pg. 2).

Though mefenamic acid is not related to other analgesic and anti-inflammatory agents, e.g. acetylsalicylic acid, ibuprofen, indomethacin, metamizol, paracetamol, pentazocine and phenylbutazone, outside the group of fenamates, it contains the basic benzol ring structure (Figure 1), in its composition, like the other analgesic and anti-inflammatory agents. It is of interest that this patient is also sensitive to chloramphenicol (Figure 2), which is D-threo-(-)-1-p-nitrophenyl-2-dichloro-acetamido-1,3-propanediol, and to codeine (Figure 3), the methyl derivative of morphine, as they both have this benzol ring structure.

From the above, it could be said that the cardiac arrest in this patient was due to mefenamic acid, probably to the benzol ring structure. Thus a patient who is sensitive to certain analgesic and anti-inflammatory agents, might develop severe reactions to a different and unrelated analgesic and anti-inflammatory agent, whose basic structure is essentially the same.

Pros and Cons of Immediate Injections in the Treatment of Drug Reactions

It might be argued why adrenalin, corticosteroid, anti-histamine, calcium gluconate or even an intravenous drip, were not given when this patient returned with itchiness one and a half hours after oral medication.

The cons are viz.

1. the bias and prejudices of patients regarding injections in private medical practice especially among the Chinese population, and the previous adverse reaction to an injection in this patient, although to an unrelated drug.

2. the side-effects of adrenalin viz. increased heart rate, the much increased excitability and conductivity of the heart, the rise of systolic and fall of diastolic blood pressure, and the stimulation of the central nervous system with feelings of fear and anxiety, increased respiration and tremor (ref. 4, pg. 17.4), considering the age of the patient and his questionable blood pressure.

3. the patient was given oral medication and he did not react to it until one and a half hours later and he did not present with urticaria or collapse, but with itchiness, and it was considered that he should be given orally anti-histamines and corticosteroid and watched over a period of two hours. Supposedly, if the patient had been given adrenalin,

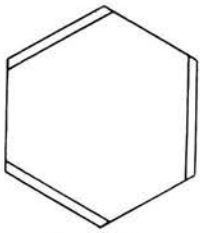

Figure 1.
Benzol Ring

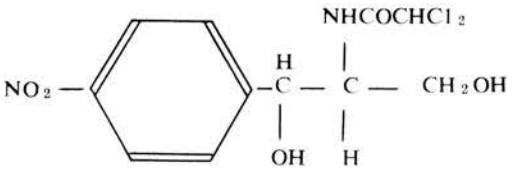

Figure 2.
Chloramphenicol

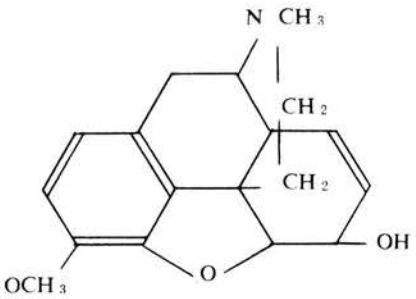

Figure 3.
Codeine

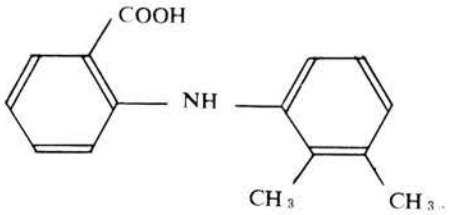

Figure 4.
Mefenamic Acid ("Ponstan")

corticosteroid and anti-histamines and then suffered a cardiac arrest and could not be resuscitated, only a doctor who had such an unfortunate experience would know the severe repercussions on his practice and good name, and it would "be remembered for a long time that Dr. X killed a patient with an injection. Sad but true." (ref. 13, Donal R. O'Holohan:– Collapse as a medical emergency pg. 237).

The pros are viz.

1. that immediate adrenalin, corticosteroid and anti-histamine injections given as soon as he presented with the itch, would have prevented the cardiac arrest approximately twenty minutes later.

2. that medico-legally, a doctor would be able to argue that he had given the necessary injections, even if the patient failed to be resuscitated.

No doubt, immediate injections and even an intravenous drip to counteract the allergy and shock should be given if there is immediate or delayed anaphylactoid reactions following injection or oral medication of any drug, but it is not considered necessary if there is only itchiness as the presenting symptom, and scratching as the presenting sign. There can certainly be a spirited debate regarding the relative merits of alternate courses of management in this patient. "Even if such an alternative course was established to have been preferable, this does not of itself indicate that a doctor would be liable medico-legally because the law does not require a doctor to be correct, all that is required is that a doctor acts reasonably according to his qualifications and experience." (ref. 8)

Summary and Conclusion

A case of cardiac arrest, successfully resuscitated with external cardiac massage and insertion of a pharyngeal airway, following one capsule orally of 250 mg. mefenamic acid is recorded. This case also served to remind doctors that even well-proven and well-tried drugs might produce anaphylactoid reactions, even though such reactions had never been reported before. "No drug is entirely harmless or non-toxic to the partaker and treatment is essentially a balance between its baneful and useful effects..... It is certainly essential to be vigilant in the surveillance of drug reactions and to document the yet unknown side-effects of drugs" (ref. 12, Dr. Leong Vie Chung:– Hospital Monitoring of Adverse Drug Reactions, pg. XXXIV). It is also to inform doctors, especially private medical practitioners, that in the case of a medical emergency, they are all alone in their resuscitative efforts, as usually onlookers are too spell-bound to be able to

do much, as was in this case where there were nearly twenty onlookers who would not even help to lift up the patient's chin when requested. It is also intended to help doctors, especially private medical practitioners, who are faced with such a dilemma, to make a decision in their choice of treatment, and not to be implicated medico-legally later.

A plea is made to those who have sensitivities to join the Medic Alert Foundation, West Malaysia, and to wear the Medic Alert "Warning" emblems, and to doctors who have patients with sensitivities, to give to them the full list of drugs they are sensitive to and to warn them that should they consult another medical practitioner, they must produce the warning note.

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