

# Selections from Drug & Therapeutics Letter\*

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## Unsafe use of Pesticides in Nepal

### Dangerous substances

Although pesticides are useful in agriculture, public health programmes and livestock production, their improper use can pose great health and environmental hazard. They are widely used all over the world and are a cause of much morbidity and mortality, particularly in developing countries.

Harmful environmental effects of pesticides include:

- destruction of wildlife, live-stock, pets and useful insects
- contamination of water
- resurgence of resistant pest population and secondary pest outbreaks
- genetic damage and loss of biodiversity
- reduction of crop yield in the long-run.

Harmful health effects may be acute or chronic. Acute poisoning with highly toxic poisons can lead to quick death, if unattended. Chronic low-level exposure may lead to damage of liver, kidney, lungs, brain or the reproductive organs. Even cancer may develop.

### Problem in Nepal

Pesticide use has been increasing in Nepal over the past decades. It is believed that their improper use is widespread. Many different types of pesticides are available in the market (see Sep-Oct 1996 issue of this bulletin). They are one of the commonest causes of poisoning in this country. Parathion-methyl ("Metacid"), dichlorvos ("Nuvan"), aluminium phosphide ("Celphos"), and zinc phosphide are the agents that have been commonly encountered in poisoning.

Reported misuse and unsafe use of pesticides in Nepal include:

- overuse
- wrong selection, e.g. fungicides for insects
- using in wrong concentrations
- spraying without wearing protective clothing
- using broom for spraying
- entering too soon into the area where pesticides has been sprayed
- harvesting and marketing vegetables too soon after spraying insecticides

- storing pesticides improperly and carelessly
- storing water, oil and food in empty pesticide containers
- disposing pesticide containers improperly after use
- using pesticides for fishing.

The Pesticide Act was announced in BS 2048. The Pesticide Regulation was announced in BS 2050 & the Pesticide Board in BS 2051. The implementation of these Rules and Regulations is, however, still weak. There is inadequate provision of information to the people on safe storage and use of pesticides. There is also lack of adequate information on alternatives to chemical control such as integrated pest management.

Recently there have been some encouraging activities such as registration of pesticides, orientation and registration of importers/retailers, & provision of inspectors.

Pesticide storage and use:  
some do's and don'ts

- Do not store pesticides in water, food or medicine containers. Always keep them in their original containers. Avoid storing them in bedroom or kitchen.
- Always keep pesticides under lock and key and well out of reach of children.
- Never use pesticides unnecessarily. Always consider if safer alternatives can be utilised.
- Always try to remember the brand as well as generic names of the pesticide being used.
- Before using any pesticide, carefully follow the instructions given on the label or the package insert.
- Do not allow children to play near the place where pesticide is being used. Never allow children to handle or spray pesticides.
- Always use gloves for spraying pesticides. Never use them with naked hands. Wear mask and full-sleeved clothes.
- Do not eat or drink while spraying pesticides.
- Check the pesticide container for any leakage. Do not use mouth to suck or blow the pipe of a blocked sprayer.
- If a pesticide is accidentally spilled on your body, wash the affected part immediately. Also change clothes if they have been soiled.
- Do not spray pesticides against the wind. Doing so incurs the risk of contaminating your breath and body.
- Take great care to avoid contamination of well, pond or any other water reservoir if it is near the spray area.
- Remember to bury empty pesticide containers out of reach of children.
- Wash your body properly with soap and water after spraying pesticides.

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## TU Teaching Hospital Formulary 1997

### Emergency Drugs

Drug Dosage form(s) and strength(s)

*Acetazolamide Tablet, 250 mg.*

*Activated charcoal Powder.*

*Adrenaline (epinephrine) Injection, 1 mg in 1-ml ampoule (1:1000).*

*Aminophylline Injection, 25 mg/ml in 10-ml ampoule.*

*Antacid Suspension.*

*Aspirin (dispersible) Tablet, 100 mg, 325 mg.*

*Atropine sulphate Injection, 0.6 mg in 1-ml ampoule.*

*Bismuth iodoform paraffin paste (BIPP) Paste.*

*Calcium gluconate Injection, 10%.*

*Chlorpromazine Injection, 25 mg/ml in 2-ml ampoule.*

*Dexamethasone Injection, 4 mg/ml in 2-ml vial.*

*25% Dextrose Injection in 25-ml ampoule.*

*50% Dextrose Injection in 25-ml ampoule.*

*Diazepam Injection, 5 mg/ml in 2-ml ampoule.*

*Diclofenac sodium Injection, 25 mg/ml in 3-ml ampoule.*

*Digoxin Injection, 0.25 mg/ml in 2-ml ampoule.*

*Dobutamine Injection, 12.5 mg/ml in 20-ml vial.*

*Dopamine Injection, 40 mg/ml in 5-ml ampoule.*

*Doxapram Injection, 20 mg/ml in 5-ml vial.*

*Ethyl chloride Spray.*

*Frusemide Injection, 10 mg/ml in 2-ml ampoule.*

*Glyceryl trinitrate (nitroglycerine) Sublingual tablet, 0.5 mg.*

*Injection, 5 mg/ml in 10-ml ampoule.*

*Haloperidol Injection, 5 mg/ml in 1-ml ampoule.*

*Heparin Injection, 5000 units/vial.*

*Hydrocortisone Powder for Injection, 100 mg.*

*Hyoscine-n-butylbromide ("Buscopan") Injection, 20 mg/ml in 1-ml ampoule.*

*Insulin (soluble) Injection, 40 IU/ml in 10-ml vial.*

*Intravenous fluids (IV fluids)*

*5% Dextrose 540 ml.*

*10% Dextrose 540 ml.*

*5% Dextrose with sodium chloride 540 ml.*

*Ringer-lactate 540 ml.*

*0.9% Sodium chloride 540 ml.*

*3.0% Sodium chloride 540 ml.*

*Ipecacuanha Syrup.*

*Isoprenaline Injection, 2 mg/ml.*

*Isosorbide dinitrate Sublingual tablet, 5 mg.*

*Ketamine Injection, 10 mg/ml, 50 mg/ml in 10-ml vial.*

*Lignocaine Injection, 1%, 2% in 30-ml vial.*

*Gel, 2%.*

*Topical solution, 4%.*

*Lignocaine ("Xylocard") Injection, 21.3 mg/ml in 50-ml vial.*

*Lignocaine with epinephrine Injection, lignocaine 2% and epinephrine.*

*Mannitol Injection, 20% in 300-ml bottle.*

*Methylergometrine ("Methergin") Injection, 0.2 mg/ml in 1-ml ampoule.*

*Metoclopramide Injection, 5 mg/ml in 2-ml ampoule.*

*Morphine Injection, 10 mg/ml in 1-ml ampoule.*

*Naloxone Injection, 0.4 mg/ml in 1-ml ampoule.*

*Nifedipine Capsule, 5 mg, 10 mg.*

*Noradrenaline (norepinephrine) Injection, 1 mg/ml in 1-ml ampoule.*

*Oxytocin Injection, 5 units/ml in 1-ml ampoule.*

*Paracetamol Tablet, 500 mg.*

*Injection, 150 mg/ml in 2-ml ampoule.*

*Pentazocine Injection, 30 mg/ml in 1-ml ampoule.*

*Pethidine Injection, 50 mg/ml in 1- and 2-ml ampoule.*

*Pheniramine maleate ("Avil") Injection, 22.75 mg/ml in 2-ml ampoule.*

*Phenobarbitone Injection, 200 mg/ml in 1-ml ampoule.*

*Phenytoin sodium Injection, 50 mg/ml in 5-ml ampoule.*

*Pilocarpine Eye drop, 2%, 4%.*

*Polygeline ("Haemaccel") IV solution, 3.5%.*

*Polyvenum antsnake venom Injection.*

*Potassium chloride Injection, 150 mg/ml in 10-ml ampoule.*

*Povidone-iodine Solution, 5%.*

*Pralidoxime (PAM) Injection, 25 mg/ml in 20-ml ampoule.*

*Promethazine HCl ("Phenergan") Injection, 25 mg/ml in 2-ml ampoule.*

*Propranolol Injection, 1 mg/ml in 1-ml ampoule.*

*Protamine sulphate Injection, 10 mg/ml in 10-ml ampoule.*

*Ranitidine Injection, 25 mg/ml in 2-ml ampoule.*

*Salbutamol Respirator solution, 5 mg/ml in 15-ml vial.*

*Silver sulphadiazine Cream, 1%.*

*Sodium bicarbonate Injection, 75 mg/ml in 10-ml ampoule.*

*Sodium nitroprusside Injection, 10 mg/ml in 5-ml ampoule.*

*Streptokinase Injection, 1.5 million IU.*

*Terbutaline Injection, 0.5 mg/ml in 1-ml ampoule.*

*Tetanus toxoid Injection, 0.5 ml.*

*Thiopentone Injection, 0.5 gm, 1 gm per ampoule.*

*Verapamil ("Isoptin") Injection, 2.5 mg/ml in 2-ml ampoule.*

## Source

TU Teaching Hospital Formulary, Institute of Medicine, Maharajgunj, Kathmandu, 1997.

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## Argemone oil & epidemic dropsy

Contributed by **Balmukunda Regmi**, MPharm, Incharge, Hospital Pharmacy, TU Teaching Hospital, Institute of Medicine, Kathmandu.

Argemone oil-contaminated edible oil (especially mustard oil) has been seen in the Indian market from the beginning of this year. Till now the contaminated oil has claimed dozens of lives and caused about two thousand hospitalizations. Such outcomes are due to epidemic dropsy caused by the contamination. In Nepal also many samples of contaminated edible oils have been reported, terrifying the consumers. In this connection, the Central Food Research Laboratory of the Government has called on the concerned industrialists, businessmen and consumers to have proper checking of mustard seeds and oils before production, sale and consumption. If adulteration and import of contaminated mustard seeds or oil is strictly controlled, the problem of epidemic dropsy can be avoided in Nepal.

Argemone oil is obtained from *Argemone mexicana*, commonly called prickly poppy (*phakal* in Nepali). The herb grows as a weed. It can grow at 32-38°C but needs 39-41°C or higher temperatures to mature. It needs little water. It may grow in Western Terai and other hot climatic regions of Nepal. Argemone seed is very similar to mustard seed, the only difference being that the former has comparatively rough surface. Argemone oil is orange in colour with an acrid odour. The presence of argemone oil can be easily detected by adding nitric acid to a sample of oil in a test tube and shaking, which gives rise to brown to yellow colouration if the content has at least about 0.25% of argemone oil. Paper chromatography test can detect argemone oil up to 0.0001% in all edible oils and fats.

*Argemone mexicana* is quite a toxic plant. In one study, roof rats were fed the argemone seeds at 100% of the diet up to the death or for a maximum of 10 days. Reported signs of poisoning were sedation, passiveness, sluggishness, feeble or no muscular jerks, abdominal contractions and increased defecation. Also black secretions from the eyes, corneal opacity, erection

of hairs, and oedema of the hind legs

and submandibular space were reported. Fourteen of 16 rats died. Significant reduction in the weights of the rats, and significant increases in blood glucose, BUN and SGOT were reported. In another study in rats, histopathological changes in the liver showed increased fibrosis, hyperplasia of the bile ducts and congestion in a few portal tracts. Lungs of argemone oil-fed animals indicated congestion and thickening of interalveolar septa. Alveolar spaces were disorganized and irregular. Kidney showed vascular and glomerular congestion and patchy tubular lesions. At 30 days only mild congestion was noted in the myocardium. Cardiac muscle fibers showed degenerative changes at 60 days which were more marked in the auricular wall. Haematological examination showed appearance of anaemia in experimental animals. Hepatic alkaline phosphatase, alanine transaminase and aspartic transaminase activities were inhibited by 30, 29, and 29% after 30 days of argemone intake along with concomitant enhancement in serum by 27, 29 and 66% respectively. Liver showed decrease in glutathione (32-63%) content along with significant stimulation of lipid peroxidation (49-105%) in argemone-intoxicated animals. These results suggest that liver, lungs, heart and kidneys are the target tissues of argemone oil toxicity and membrane destruction may be a possible mode of action. Another study in rats suggested that the hepatic microsomal as well as the mitochondrial membrane is vulnerable to the peroxidative attack of argemone oil and may be instrumental in leading to the hepatotoxicity symptoms noted in argemone poisoning victims. Argemone seeds when fed at 1% and 3% of a basal ration to day-old, layer strain, cockerel chickens produced growth depression, oedema and death. The mortality rate was increased by raising the sodium chloride content of the basal ration from 0.18% to 1.68%.

In man argemone poisoning symptoms appear when argemone-contaminated oil has been used for 1-2 weeks. The symptoms of epidemic dropsy consist of sudden, non-inflammatory, bilateral swelling of legs, often associated with diarrhoea. Dyspnoea, cardiac failure and death may follow. Some patients may develop glaucoma. The disease may occur at all ages except breast-fed infants. The mortality rate varies from 5 to 50%.

The alkaloid sanguinarine in argemone oil reported to be responsible for epidemic dropsy has been examined for hepatotoxic potential in rats. It is reported that a single intraperitoneal dose (10 mg/kg) of sanguinarine not only increased the activity of SGPT and SGOT substantially but also caused a significant loss of microsomal cytochrome P-450 and benzphetamine N-demethylase activity. The toxic alkaloid has long been proved to interfere with the oxidation of pyruvic acid which accumulates in the blood.

The observed toxicity in humans due to argemone includes venous dilatation and tortuosity, haemorrhages and disc oedema. Fluorescein angiographic findings include dilated and tortuous retinal veins, prominent vascular straining, blocked fluorescence, microaneurysms, disc oedema and peripapillary dye spillage. Presence of positive angiographic findings correlate well with the severity of the systemic disease; glaucoma, however, reveals no correlation. Papillophlebitis has also been reported.

Body massage with argemone-contaminated oil also causes argemone poisoning. Four cases manifesting features characteristic of epidemic dropsy following body massage with contaminated mustard oil are reported. Diagnosis of the disease was confirmed by establishing the presence of sanguinarine in the urine and serum of all four cases. Thus a transcutaneous route of absorption for the sanguinarine has been established, and massage with argemone-contaminated oil should be avoided.

The epidemic dropsy has no specific treatment. Steroids, diuretics and vitamins may help in some cases. Protein-rich diet and rest are helpful. Sodium chloride intake should be reduced. The patients recover after a long time. In case of glaucoma, surgical operation may be necessary.

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## Is azithromycin different from erythromycin ?

Azithromycin is a newer macrolide antibiotic. Compared to erythromycin, it has slightly less activity against staphylococci and streptococci but enhanced activity against *Haemophilus Influenzae*, *Moraxella (Branha-nella) catarrhalis*, *Neisseria gonorrhoeae*, and *Haemophilus ducreyi*.

In terms of pharmacokinetics, the main difference between erythromycin and azithromycin is that the latter has a much longer half-life permitting *once-daily dosing*. Azithromycin is also relatively free of drug interactions seen with erythromycin because it does not inactivate cytochrome P450 enzymes. The drug is also reported to cause fewer gastro-intestinal side-effects than erythromycin.

Azithromycin is *indicated* in respiratory tract infections, otitis media, skin and soft-tissue infections and genital chlamydial infec-tions. The generally recommended *dose* for adults is 500 mg as a single dose on day 1, then 250 mg

single daily dose for the next 4 days. But for chlamydial cervicitis and urethritis, a single 1-g dose is generally adequate. Because food decreases absorption of azithromycin, it should be given at least *1 hour before or 2 hours after food*.

The box below shows the current cost of therapy with azithromycin and erythromycin.

Dosing schedule	Approximate cost (in Nepalese Rupees)*
<u>Azithromycin</u>  <u>500 mg day 1;</u>  <u>then 250 mg day 2 through 5.</u>	228.00
<u>Erythromycin</u>  <u>250 mg 6-hourly for 5 days.</u>	100.00

\* Cost in Kathmandu in July '98.

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## Substandard Ethambutol

Contributed by **Balkrishna Khakurel**, MPharm, MSc, National Operations Officer, HMG/WHO Collaborative Essential Drugs Programme, Department of Drug Administration, Buzuli Bazaar, Kathmandu.

As per the bilateral agreement reached between the Ministry of Health of His Majesty's Government (MoH/HMG) of Nepal & Japan International Cooperation Agency (JICA) for the supply of anti-tuberculosis drugs to Nepal Tuberculosis Centre for a period of 1994 to 1999, JICA negotiated on 1 February 1996 with one of the local agents - Mrigendra International Trading Concern (MITC) - for the procurement of 9 million tablets of "Ethambutol 400 mg" manufactured by Themis Chemicals, India. MITC delivered the consignment to the National Tuberculosis Control Programme through Logistic Management Division, Department of Health Services, MoH. Within the first 5 months from the date of manufacture (February 1996), the product in the tablet was found to be physically deteriorated (melted), even though a 5 year's expiry (January 2001) was claimed on the label.

Following necessary investigation by a Committee of Health Ministry Officials, including the quality control report by the Royal Drug Research Laboratory, it was decided that the quality of the supplied batches was substandard. Subsequently, an order to recall the drug (in quantity of 6-7 million tablets) from the distribution network was passed. Meanwhile, action to contact the manufacturers for explanation and also withdrawal and replacement of substandard supplies with standard quality products was initiated both at the consignee's level as well as at drug regulatory level. The manufacturers concerned did not respond promptly to such calls and a decision to cancel the company's registration was made by the Department of Drug Administration. Later on, the concerned manufacturer offered to replace the substandard lot(s) by another lot but HMG denied this deal due to reliability concern. Taking into account the possible adverse effect of the incident on the Tuberculosis Control Programme, HMG arranged an alternative supply measure while the dispute continues even now.

The government's decision to cancel registration of the product and the manufacturer in Nepal and the subsequent stand not to revoke this decision were commendable. However, this case raises issues regarding the lack of quality examination of imported drugs before custom clearance and lack of adequate expert supervision on the drugs procured in large quantities by the government for public health programmes.

## Sources

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Reproduced from:

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## Caveats for prescribing topical steroids

- Topical corticosteroids should be used for symptom relief, never prophylactically. Whenever in doubt about prescribing these agents, it is best to consult a dermatologist to avoid unsafe use.
- It is not necessary to apply them more than once or twice a day.
- The preparations should be applied sparingly in thin layers, not heavily.
- Since topical corticosteroids with various potencies are available in the market, it is important to select an appropriate preparation based on the site and type of lesion. Generally, low efficacy agent at the lowest concentration should be tried first. In resistant cases, a high efficacy agent can be used. In chronic eczema-tous and lichenified lesions, high potency steroids may be tried right from the outset. But it should be substituted by a low potency agent once the condition is under control. Potent agents should be avoided on the face because they may cause skin atrophy, rosacea-like disorder, acne, hair growth, striae and wrinkles.

High potency topical steroids are contra-indicated in infants and should generally be avoided in children.

Examples of *low efficacy* agents are hydrocortisone 1%, betamethasone 0.2%, fluocinolone acetonide 0.01%, & triamcinolone acetonide 0.025%. *Intermediate efficacy* agents include clobetasone butyrate 0.05%, betamethasone valerate 0.1%, mometasone furoate 0.1%, fluticasone propionate 0.05%, halcinonide 0.025%, triamcinolone acetonide 0.1%, fluocinolone acetonide 0.025% and hydrocortisone butyrate 0.1%. *High efficacy* preparations include betamethasone dipropionate 0.05%, triamcinolone acetonide 0.5%, fluocinolone acetonide 0.2%, and halcinonide 0.1%. Examples of *highest efficacy* topical steroids are clobetasol propionate 0.05% and halobetasol propionate 0.05%.

- Choice of formulation depends on the type of lesion. *Ointments* are usually suitable for dry, scaly or lichenified conditions. Water-miscible *creams* are generally chosen for weeping lesions. *Lotions* are suitable for exudative lesions; they are also suitable where treatment of a large area with minimum application is intended.

- There is significant anatomic variation in the penetration of topical steroids. Penetration is high through areas like scrotum, vulvar skin, forehead and scalp whereas it is relatively low through thick skin areas such as the planter foot and the palm.

- Occlusive dressing enhances local penetration but also increases the risk of systemic absorption.

- Topical corticosteroids are used to suppress inflammatory diseases of the skin. They should never be used alone in infectious conditions. But the routine use of topical steroids as compound preparations with antibacterials or antifungals is also unjustified. Such combination preparations should be used only if there is associated infection.

- The area of the body treated and the duration of treatment should be borne in mind. Long-term treatment with potent agents on large area may lead to pituitary-adrenal suppression and even Cushing's Syndrome. Systemic absorption of topical steroid is greatest from raw areas, intertriginous areas and the areas with thin skin.

- Generally, topical cortico-steroids should be prescribed in small amounts, for example in weekly quantities.

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## Ocular uses of Cyclosporine

Contributed by **Jeevan K. Shrestha**, MBBS, FRCS, FRCOph, Lecturer, BP Lions Centre for Ophthalmic studies, Institute of Medicine, Kathmandu.

Cyclosporine was first isolated in the early 1970s as a product of the fungus *Tolypocladium inflatum*. Oral cyclosporine was soon used as a key drug in the prevention of transplant rejection and also to treat autoimmune diseases.

The uses of systemic cyclosporine has begun in various ocular conditions such as endogenous posterior uveitis, corneal graft rejection, Mooren ulcer, vernal keratoconjunctivitis, ligneous conjunctivitis, peripheral rheumatoid ulceration and other ocular surface inflammatory diseases.

Topical cyclosporine was first used experimentally in humans to prevent corneal graft rejection in the early 1980s. Soon after, such experimental uses were extended to various other sight-threatening inflammatory ocular conditions. The ameliorative effects of topical cyclosporine in the inflammatory ocular surface disorders are readily explicable through direct effects on lymphocyte action. Cyclosporine has beneficial effects in some of these diseases but not in all.

Cyclosporine 0.2% ointment is now licensed in the veterinary field for use in keratoconjunctivitis sicca and other ocular surface inflammatory diseases for domestic animals, but such a preparation has yet to reach the human pharmacy.

Why then, it must be asked, has a commercial topical cyclosporine preparation not been marketed for human use ? Regulations regarding development of novel human medication are more stringent and thus more restrictive than for veterinary products. The successful use of cyclosporine formulated in olive oil in the veterinary market as a "home made" product presumably eased the drug passage to the market as a licensed veterinary preparation.

Hopefully in the near future topical cyclosporine with reduced risk of systemic adverse effects will also be available for human use. Such a preparation will be an important addition in the field of ocular pharmacology.

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