

Self-medication – encourage only when it is informed

Drugs are powerful chemicals having the potential to interact with and modify bodily functions. Used intelligently they can do wonders – prolong life, improve the quality of life, keep diseases and discomfort at bay. However, injudicious use of drugs poses serious hazards and may even threaten life. Drugs are not like other commodities for which the consumer decides the quantity and mode of consumption. One usually seeks the help of doctors – experts in the health care field – who decide whether, why and how one should use medicines. Nevertheless, it is well known that a considerable proportion of all medical consultations is redundant, burdensomely expensive and sometimes counter-productive. Many minor ailments and symptoms do not really require the attention of doctors. With little awareness, anyone can take care of these quite successfully.

Self-medication refers to consumption of medicinal products for addressing common health problems by the lay public, that does not follow consultation, advice or prescription by a registered medical practitioner or an informed member of a health care delivery team authorized to prescribe medicines. The consumer himself uses his general knowledge and wisdom to decide such interventions. Further, compliance with advice relating to medicine use, given by a family member, friend or acquaintance, who does not have formal training in medicine or pharmacy, is also considered as self-medication.

In India, the practice of self-medication is extremely common in any locality. To procure any medicine, be it a couple of aspirin tablets or a carton of antibiotic injections, just step into a retail pharmacy outlet and you would usually be readily obliged. You really don't need a doctor's prescription except perhaps for some sedatives and a handful of controlled drugs. Although it may be argued that by law many medicinal items [the 'Schedule H' drugs] are meant to be dispensed only against prescription by a registered medical practitioner, in effect this is often flouted. Indeed, most prescribers themselves are unaware of such categorization of medicines. The situation therefore is always confusing. For instance, while paracetamol 500 mg tablets are often consumed off the shelf, the recent introduction of a brand of Paracetamol 1000 mg tablets for pain relief in arthritis and its vigorous promotion by the manufacturer, creates a dangerous situation where an ill-informed consumer will consume it like conventional paracetamol tablets and will run the risk of toxicity. A clear-cut distinction, appreciated by the prescribers as well as the consumers, between prescription-only medicines [PoM] and over-the-counter [OTC] medication is yet to be implemented in India. Unscrupulous retailers take full advantage of the situation.

While self-medication behavior as it exists in our country today, carries formidable inherent risk, informed and disciplined self-medication, restricted to common and simple ailments and contraindicated for select drug groups, makes great sense not only from a logistical and economic standpoint but also for issues of great public importance like population control.

The problem demands appropriate attention by the drug regulatory authority with promulgation of relevant law or act. Needless to say that such regulations must be adequately enforced in order to ensure rationalization of self-medication practice in the country. And most importantly, public education on rational self-medication must be emphasized as this is the key to success in such an endeavor.

Santanu K. Tripathi

RATIONAL DRUG BULLETIN

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Emergency contraception with emphasis on emergency contraceptive pills

Joydev Mukherji

Emergency contraception [EC] refers to a particular type of contraception that is used as an emergency procedure to prevent pregnancy following unprotected, possibly fertile, intercourse.

Interruption is unacceptable as a family planning method and access to reliable contraception is often unavailable even in today's world. It is estimated that the annual maternal death toll due to unsafe abortion, which is a direct consequence of unwanted pregnancy, is approximately 200,000 – most of it in developing countries. Even in a highly developed country like the USA, approximately 50% of pregnancies are unplanned, and half of them occur due to contraceptive failure or misuse of the contraceptive device. Where contraceptives have not been used or have been used improperly, EC provides a well established benefit – the prevention of unwanted pregnancy with a consequent decreased rate of induced abortion. It is surprising therefore that so little endeavor has been made to promote ready availability and more extensive use of EC.

EC should fulfil the following criteria

- It aims to prevent pregnancy.
- It should be applicable after coitus.
- It includes procedures employed before pregnancy has become definite and before implantation & certainly prior to the onset of menses.
- It should not be a regularly use system, but an exceptional one time intervention.

Indications for EC use include

- unplanned sex
- forced sex / rape
- contraceptive failure e.g. condom broke or slipped / missed three or more pills.

Modern postcoital contraception using high dose estrogen was first applied in human practice for rape victims in the 1960s. Following the successful use of estrogens, the combined regimen of estrogen plus progestin was introduced in the early 1970s and become popular as the Yuzpe method. The Intra Uterine Device [IUD] was administered as emergency contraception in 1976. The aim of decreasing the side effects of estrogen-progestin combination led to pills containing levonorgestrel alone in the early 1980s. Research has continued with other drugs including danazol, mifepristone, centchroman and gonadotropin releasing hormone antagonists [GnRH-a]. At present the most

effective EC is still the insertion copper-containing IUD: it can be inserted upto 5 days after the earliest predicted dated of ovulation, regardless of how many times unprotected intercourse has occurred. In future mifepristone holds great potential. Recent studies investigating the use of 600 mcg mifepristone as a single dose given within 72 hours of unprotected intercourse reported no pregnancies. A recent World Health Organization [WHO] study suggests that delayed menstruation, a problem with 600 mcg dose, may be overcome without loss of efficacy if the dose of mifepristone is lowered to as little as 10 mcg.

Emergency Contraception Pill [ECP]

Both combined estrogen-progestin and progestin only formulations are effective. ECPs can prevent ovulation, fertilization or implantation, depending on the time of administration relative to the appropriate part of the menstrual cycle. However, they will not disrupt an established pregnancy. There is no evidence that ECPs adversely affect the fetus after failed EC.

The woman should take pills totaling at least 100 mcg ethinyl estradiol [EE] plus 500 mcg levonorgestrel [LNG] (or 1 mg norgestrel) within 72 hours of the unprotected intercourse, and repeat the same dose later 12 hours later. This regimen [Yuzpe regimen] can be fulfilled by:

- 2 conventional combined oral contraceptive pills each containing 50 mcg EE + 250 mcg LNG (or 500 mcg norgestrel) [e.g. OVRAL brand in India] and then two more of these same pills 12 hours later.
- 4 'low dose' combined oral contraceptive pills, each containing less than 50 mcg of EE + 150 mcg LNG (or 300 mcg norgestrel) [e.g. OVRAL-L or MALA-N in India] and then 4 more of these same pills 12 hours later.

Alternatively, to use progestin only pills, a woman must take a total of 750 mcg of LNG within 72 hours of unprotected intercourse and then take a second dose of 750 mcg 12 hours later.

In some countries combined and progesterone only oral contraceptive pills are packaged specifically as ECPs [dedicated products]. However, these are yet to be available in India.

Effectiveness: It is predicted that approximately 8 of 100 healthy women will become pregnant following unprotected sexual intercourse in the pre-ovulatory period and the 3rd week of the cycle. Following ECP, the estimated number would drop to 2 of 100 women for combined ECP, and 1 of 100 women for progestin only ECP. This compares to a pregnancy rate of almost zero with mifepristone or with IUDs for emergency contraception.

Adverse drug reactions: Some women experience nausea and vomiting – 20% with Yuzpe regimen and 5% with progestin only regimen. Antinausea medications may be used e.g. meclizine hydrochloride 30 minutes to 1 hour before the first dose of ECP. The other common side effect is menstrual disturbance which may occur early or late. Spotting frequently appears. Pregnancy should be suspected if the woman has not menstruated within 3 weeks of treatment or her period is unusually light. As it has less side effects and is more effective, the progestin-only formulation is now being preferred over the Yuzpe method.

What the woman should know.

- The first dose of ECPs should be taken as soon as possible after the intercourse – the sooner they are started the more effective they will be.
- ECPs do not protect against other acts of unprotected coitus later in the menstrual cycle. The woman should start an ongoing method of contraception e.g. if a woman chooses oral contraceptive pill [OCP], she should take the first pill the next day after she finishes the ECPs. She should also ensure that her partner uses condoms for the next 7 days. IUDs for EC can be a good ongoing contraception.
- ECPs do not protect against STDs
- The common side effects of ECPs include nausea and menstrual disturbances. If she vomits within 2 hours, the dose needs repetition either orally or vaginally.
- There are no known contraindications to ECP use. The medical conditions that rule out OCPs do not apply to one time ECP use.
- ECPs are not 100% successful.

Disseminating knowledge of and promoting access to ECPs

Leaving aside the question of morality, it is an undisputed fact that ECPs fulfill a vital health need of women. More women and more providers need to know about ECPs and their availability needs to be increased. Information can come from a pharmacist, a community

based healthcare provider, a doctor, a nurse, or form mass media – radio, television, newspapers, magazines, etc. Women should be able to get them easily from chemist shops, as well as at clinics, emergency rooms, shelters and private healthcare providers' offices. Women may be encouraged to keep an extra packet of pills on hand specifically for emergency use if needed. ECPs should not require a prescription and should be offered over the counter with appropriate counseling.

In December 1995, WHO added Yuzpe regimen of combined oral contraceptive pills for EC to the WHO model list of essential drugs. Yet EC is grossly underused in developing countries including India. A study conducted by the Population Council in India found strong support for over-the-counter provision of ECPs among women themselves. Giving women reproductive autonomy through precise and up-to-date information about all methods, improving access to ECPs and supportive counseling where required, will address an important unmet need of large sections of women in their reproductive years, namely the prevention of unwanted pregnancies from unprotected coitus and the consequent detrimental health and socioeconomic consequences.

References

1. Henshaw S. Unintended pregnancy in the United States. *Fam Plann Prespect* 1998; 30: 24-9.
2. Van Look PFA, von Hertzen H. Emergency contraception. *Br Med Bull* 1993; 49: 158-70.
3. Yuzpe AA, Thurlow HJ, Ramzyl I, Leyshon JJ. Post-coital contraception: a pilot study. *J Reprod Med* 1974; 13: 53-61.
4. Glasier A. Emergency post-coital contraception. *N Engl J Med* 1997; 337: 1058-64.
5. WHO Taskforce on Postovulatory Methods of Fertility Regulation. A randomized clinical trial of levonorgestrel versus the Yuzpe regimen of combined oral contraceptives for emergency contraception. *Lancet* 1998; 352: 428-433.
6. WHO Taskforce on Postovulatory Methods of Fertility Regulation. Comparison of three single doses of mifepristone as emergency contraception: a randomized trial. *Lancet* 1999; 353: 697-702.
7. Cardy GC. Outcome of pregnancies after failed hormonal post-coital contraception: An interim report. *Br J of Fam Plann* 1995; 21: 112-15.
8. Wells E, Crook B, Muller N. Emergency contraception: A resource manual for providers. Seattle: Program for appropriate Technology in Health, 1997.

Selective COX-2 inhibitors in India

Amitava Sen & Avijit Hazra

Nonsteroidal anti-inflammatory drugs [NSAIDs] are used to control pain and inflammation and are among the most widely used medications. Aspirin, the prototype of the NSAIDs is a household name and has been in use for more than 100 years. Although widely used, the long-term or high dose use of these agents is fraught with the risk of adverse drug reactions, particularly gastrointestinal and renal adverse effects. Life threatening complications and even deaths due to gastrointestinal ulceration caused by NSAIDs are regularly reported. In 1971 it was first proposed that both the therapeutic and toxic effects of NSAIDs are mediated by inhibition of cyclooxygenase [COX]. This is a key enzyme in the biochemical pathway for synthesis of prostaglandins which are among the most important chemical mediators of pain and inflammation.

Two decades later it became evident that the enzyme cyclooxygenase exists in two isoforms – COX-1 and COX-2. The COX-1 enzyme is present in essentially every organ of the body and performs a variety of day-to-day physiological functions, the so-called house keeping functions. It is less involved in inflammation. The expression of the COX-2 enzyme is restricted under basal conditions, but it can be induced substantially during the processes of inflammation, repair and tumor growth. It is normally present in a few organs, like the small intestine, kidney and brain, but is expressed predominantly at inflammatory and neoplastic sites. It transpires that selective inhibition of the COX-2 enzyme subdues the process of inflammation while leaving the house keeping functions of COX-1 intact. Clinically, this should translate to control of pain and inflammation with less of gastrointestinal and renal adverse drug reactions.

Over the past decade research has led to the development of several compounds that show selectivity for inhibition of the COX-2 enzyme in preference to the COX-1 enzyme. The exact extent of selectivity remains a confusing issue because the results vary with the type of biological assay being employed and from laboratory to laboratory. There is also no general agreement on the optimum ratio for COX-2 selectivity. Keeping these limitations in view, NSAIDs can now be categorized as:

- Non-selective COX inhibitors e.g. aspirin, diclofenac, ibuprofen, indomethacin, piroxicam, etc.
- Preferential COX-2 inhibitors e.g. etodolac, meloxicam, nimesulide, etc.
- Selective COX-2 inhibitors e.g. celecoxib, rofecoxib, etc.

The last group shows the maximum ratio of COX-2 to COX-1 inhibition. Celecoxib and rofecoxib have been recently approved by the United States Food and Drug Administration. These drugs have also been launched in the Indian market and are being vigorously promoted. Table 1 lists several brands of these drugs now available.

Unfortunately, promotional literature often makes extravagant claims conveying the impression that these drugs are much more powerful than conventional NSAIDs and offer the final solution to the problems of NSAID gastropathy and nephropathy. These claims are not true and in this article we emphasize the evidence that while these drugs are possibly safer, they do not represent revolutionary therapeutic progress over their conventional counterparts.

Efficacy and safety of celecoxib

In comparative clinical trials celecoxib was better than placebo in osteoarthritis [OA] and rheumatoid arthritis [RA], comparable to naproxen in OA and RA and comparable to diclofenac sustained release preparation in RA. It is noteworthy that there is still dearth of clinical trial data published in peer-reviewed journals. Data from some trials are available only in abstract form. In no study reported so far, celecoxib has shown significantly better efficacy than conventional NSAIDs in standard doses.

In clinical studies so far celecoxib has been administered to more than 13,000 subjects in dose is ranging from 50 mg to 400 mg twice daily. Pooled data reveals that the most common adverse drug reactions to celecoxib pertain to the gastrointestinal tract and headache. The incidence of adverse events in celecoxib groups were generally similar to those in the placebo groups except for higher incidences of dyspepsia, abdominal discomfort, flatulence and diarrhoea. However, compared with other NSAIDs tested, a lower incidence of these adverse events have been reported for celecoxib. In controlled trials both gastroduodenal erosions and gastroduodenal ulceration, confirmed endoscopically, have been reported with celecoxib in upto 6% cases which was lower than that of comparator drugs like ibuprofen, diclofenac and naproxen. The withdrawal rates for celecoxib at 3 to 8% were also comparable to placebo. Interestingly, unlike aspirin celecoxib does not appear to inhibit platelet aggregation. Celecoxib causes more peripheral edema than placebo but does not appear to induce significant renal dysfunction in recommended doses.

Table 1. Selective COX-2 inhibitors brands being marketed in India

Celecoxib brand	Company	Rofecoxib brand	Company
CELECT	Sun	ACROBAT	Merck
CELEDOL	Ipca	MCROFY	Dr. Reddy's
CELFAST	Indchemie	ROFACT	Solares
CELIB	Unichem	ROFADAY	Lupin
COLCIBRA	Croslands	ROFEGESIC	Megacare
COXIB	Brown & Burk	ROFF	Unichem
ICEL	Recon	ROFIBAX	Ranbaxy
REVIBRA	Dr. Reddy's	ROFICA	Micro Labs
SIONARA	Alembic	ROFIXX	Cipla
ZYCEL	Cadila	ROFLAM	Micronova
		TOROXX / TOROXX MT	Torrent

- In India, these celecoxib brands are available as 100 & 200 mg capsules and the rofecoxib brands are available as 12.5 mg and 25 mg tablets.
- *Recommended dose of celecoxib:* 100 mg twice daily or 200 mg once daily in osteoarthritis; 100 to 200 mg twice daily in rheumatoid arthritis; not generally used for acute pain relief. The drug should be given after food (absorption increases with fatty meals). Reduced doses are recommended in mild to moderate hepatic insufficiency. It is contraindicated in subjects with severe hepatic insufficiency, severe renal insufficiency, acute peptic ulcer disease, and history of urticaria, bronchospasm or angioedema or acute sensitivity to NSAIDs. Some drug interactions are possible.
- *Recommended dose of rofecoxib:* 12.5 to 25 mg once daily in arthritis; similar dose for short-term management of acute pain and primary dysmenorrhea. Up to 50 mg has been given short-term without significant problems. The drug is given after food like other NSAIDs. Food has no significant effect on absorption. Caution is required in renal insufficiency and in patients with a history of cardiac failure, left ventricular dysfunction, hypertension and edema for any reason. Contraindications are similar to celecoxib. Potential for drug interactions is perhaps less than celecoxib but not absent.
- Safety of use during pregnancy or lactation has not been established for either of these 2 drugs. As with conventional NSAIDs, use during 3rd trimester of pregnancy may lead to premature closure of the patent ductus arteriosus in the newborn

Efficacy and safety of rofecoxib

Short-term studies have shown that rofecoxib 25 or 50 mg once daily is better than placebo and comparable to naproxen in relieving the pain of primary dysmenorrhea and to ibuprofen in relieving the pain following dental surgery. There is one study which has reported that rofecoxib 12.5 or 25 mg is better than placebo and equivalent to ibuprofen 400 mg as an antipyretic. In trials in OA rofecoxib has not been found to be significantly more effective than diclofenac or ibuprofen in giving pain relief. It is also not clear from the reports whether these trials had sufficient statistical power to conclude that the two compared NSAIDs had equivalent efficacy.

Regarding gastrointestinal adverse events, a meta-analysis of 8 comparative trials of rofecoxib [12.5 mg/day], involving about 5,435 patients, with a placebo or another NSAID [ibuprofen, diclofenac or nabumetone] at the maximal recommended daily dose, has been conducted. It was seen that annual incidence of major gastrointestinal complications [perforation or symptomatic ulcer or hematemesis] was 1.3% on rofecoxib and 1.8% on other NSAIDs, a

statistically significant but clinically small difference. Similarly, the cumulative 6-month incidence of symptomatic dyspeptic disorder was 23.5% on rofecoxib and 25.5% on other NSAIDs, once again a statistically significant but small difference.

Two studies have been conducted specifically to look at the gastrointestinal safety of rofecoxib. A long-term randomized safety study compared rofecoxib [25 or 50 mg once daily] with placebo and high dose ibuprofen [800 mg thrice daily], in 742 patients with OA, and concluded that rofecoxib is safer for the gastroduodenal mucosa at 24 weeks follow-up. The cumulative incidence of gastric ulcers at 12 weeks was 4.1% with rofecoxib 25 mg, 7.3% with rofecoxib 50 mg, and 27.7% with ibuprofen. At 24 weeks, the corresponding rates were 9.6%, 14.7% and 45.8%. In a 7-day study in healthy volunteers, a very high dose of rofecoxib [250 mg once daily] caused less mucosa damage than aspirin 650 mg thrice daily or ibuprofen 800 mg thrice daily.

The question of renal safety of rofecoxib is also important. In a study involving elderly patients with moderate renal failure, rofecoxib reduced the glomerular filtration rate by 12% versus 10%

on indomethacin. No other studies specifically focus on changes in renal function. There has been a noteworthy report of a major aggravation of previously moderate renal failure, warranting hemodialysis; however the outcome was favorable. Another case of reversible renal failure occurred in a German patient with previously normal renal function. These reports necessitate caution when treating patients with advanced kidney failure.

In September 2000, the British National Pharmacovigilance system published a review of 1120 spontaneously notified adverse events linked to rofecoxib between June 1999 and July 2000. Gastrointestinal disorder accounted for nearly half the notification [554 cases], including 68 cases of perforation of ulceration or upper gastrointestinal hemorrhage, 5 of which were fatal. Cardiovascular disorders accounted for 177 notifications. The most frequent were edema [101 cases], hypertension [31 cases] and palpitations [19 cases]. Fifteen cases of new or aggravated heart failure were reported [3 deaths], together with 9 cases of myocardial infarction [3 deaths]. The other notified adverse effects were psychiatric disorders [including depression in 28 cases, confusion in 14 and hallucinations in 11], angioedema [35 cases], bronchospasm or exacerbation of asthma [25 cases].

Conclusion

The selective COX-2 inhibitors are being marketed in India with lot of hype. The reality is that the evidence from clinical trials so far, involving several hundreds of patients, indicate that these drugs are comparable in efficacy to more conventional NSAIDs like ibuprofen, diclofenac and naproxen, and not dramatically

better than them. They are also subject to the same precautions as older NSAIDs. However, studies do favor these drugs in terms of a moderately lower incidence of gastrointestinal adverse events and dyspeptic disorders. This, coupled with a simple dosing schedule that helps patient compliance, are advantages of these drugs but this does not represent major therapeutic advance. Exploration of the safety aspect in certain special situations, like in patients with renal insufficiency, history of peptic ulceration, or those with inflammatory bowel disease, is warranted. Postoperative pain relief in anesthesia and pain management in intensive care units are other issues that must be assessed because of concerns regarding the role of COX-2 in wound healing, and use of COX-2 inhibitors in patients at risk of stress ulceration, renal dysfunction, hepatic dysfunction and compromised cardiopulmonary status. If these drugs turn out to be safer than conventional NSAIDs in these indications, only then can they be hailed as major new analgesics.

References

1. Buttar NS, Wang KK. The 'aspirin' of the new millennium: Cyclooxygenase-2 inhibitors. *Mayo Clinic Proceedings* 2000; 75: 1027-38.
2. Boyce EG, Breen GA. Celecoxib: A COX-2 inhibitor for the treatment of osteoarthritis and rheumatoid arthritis. *Formulary* 1999; 34: 405-6, 411-17.
3. Rofecoxib: A disappointing NSAID analgesic. *Prescrire International* 2000; 9(50): 166-7.
4. Non-steroidal anti-inflammatory drugs. *British National Formulary* 2001; (41): 462-71.
5. *CIMS* 2001; 24(2): 203, 226.

Recent additions to our library

- **Estimating Drug Requirements: A Practical Manual. Geneva: World Health Organization: Action Programme on Essential Drugs, 1988 [1990 reprint].**
- **Quality Assurance of Pharmaceuticals: A compendium of Guidelines and Related Materials. Vol 1. Geneva: World Health Organization, 1997.**
- **Essential Drugs: Practical Guidelines. 2nd ed. Paris: Medecins Sans Frontieres, 2000.**
- **Bellamy C. The State of the World's Children 2001. New York: United Nation's Children's Fund, 2001.**
- **Newbrander W, Collins D, Gilson L. User Fees for Health Services: Guidelines for Protecting the Poor. Boston: Management Sciences for Health, 2001.**

Knowledge is proud that he has learned so much. Wisdom is humble that he knows no more.

William Cooper

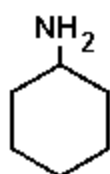
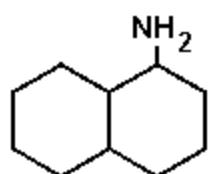
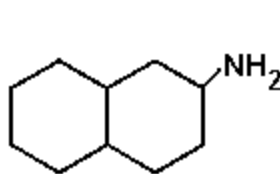
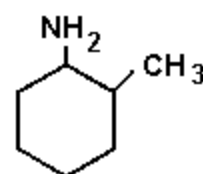
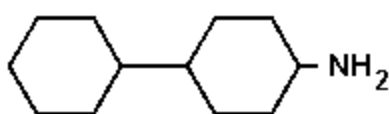
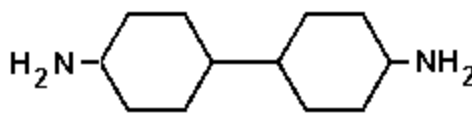
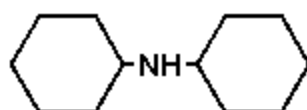
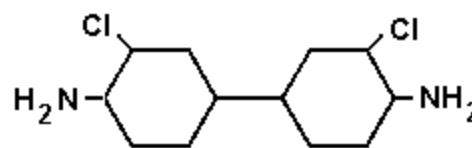
Are dyestuffs cancer causing?

We recently received a query from the relative of a middle-aged woman suffering from urinary bladder cancer, as to whether dyes are carcinogenic. The woman used to work in a saree printing concern many years back. Well, it is an established fact that some dyes and pigments, but not all, may cause cancer of the urinary tract (more specifically of the urothelium i.e. the epithelial lining of the urinary tract) and the effect may appear long after direct exposure has ceased. Indeed, the first suspicion of a chemical cause for bladder cancer was raised as early as 1894 when Rehn recorded a series of tumors in workers in aniline dye factories. Subsequent animal experiments confirmed the suspicion. Clinicians confronted with patients having urothelial tumors should suspect a possible association with certain dyestuffs, industrial chemicals, and even, drugs. The following agents have been incriminated as bladder carcinogens:

- Aniline
- Alfa- and beta-naphthylamine
- Diphenyls substituted by one nitro or primary amine group
- Substances as above, further substituted by halogen, methyl or methoxy groups
- Salts of substances listed above
- Auramine and magenta (the risk pertains to their manufacture but not use)
- Cigarette smoking possibly
- Certain drugs e.g. cyclophosphamide, phenacetin

In practice, individuals engaged in the following occupations are at particular risk:

- Aromatic amine (aniline) and azo dyes / pigments manufacture
- Textile printing
- Rubber tyre / electrical cables manufacture
- Leather work / shoe manufacture
- Petrol workers
- Laboratory chemicals manufacture
- Laboratory workers who use above chemical types
- Retort house of glass works
- Rodent pest control and sewage work

**Aniline****α-naphthylamine****β-naphthylamine****Orthotoluidine****4-Aminodiphenyl****Benzidine****Diphenylamine****Dichlorobenzidine****Some potent urothelial carcinogens**

Patients presenting with painless passage of blood in urine should be questioned carefully regarding the above associations. Bladder cancers usually appear between 50 to 70 years age and both sexes may be affected. Investigations become specially urgent if any of the above associations are revealed. In the absence of symptoms, urothelial tumors are suspected when abnormal cells are discovered during urine analysis.

We reproduce below some important gazette notifications issued by the Government of India recently banning some irrational fixed dose combinations in the Indian market. CDMU whole-heartedly appreciates the government's effort and hopes that it will extend to several other irrational formulations that deserve banning.

THE GAZETTE OF INDIA: EXTRAORDINARY
MINISTRY OF FAMILY WELFARE (Department of Health) NOTIFICATION
New Delhi, the 12th March 2001

G.S.R. 169 (E). - Whereas the Central Government is satisfied that the use of the fixed dose combination of Diazepam and Diphenhydramine hydrochloride is likely to involve risk to human beings and that in the public interest it is necessary and expedient to prohibit the manufacture, sale and distribution of the said combination of Diazepam and Diphenhydramine hydrochloride.

Now, therefore, in exercise of the powers conferred by section 26A of the Drugs and Cosmetics Act, 1940 (23 of 1940), the Central Government hereby makes the following further amendment in the notification of the Government of India in the Ministry of Health & Family Welfare No. GSR 578(E) dated 23rd July 1983, namely:

In the Table appended to the said notification after serial No. 58 and the entries claim thereto, the following shall be added namely: Fixed dose combination of Diazepam and Diphenhydramine hydrochloride.

[F. No. X-11014/1/2001-DMS & PFA]

DEEPAK GUPTA, Jt. Secy.

Foot Note: The Principal Notification was published in the Gazette of India vide G.S.R No. 578(E) dated 23-7-1983 and last amended vide G.S.R No.499(E) dated 14-8-1999.

G.S.R. 170 (E). - Whereas the Central Government is satisfied that the use of the drugs specified below do not have the therapeutic value claimed or purported to be claimed for them or the said drugs contain ingredients and in such quantity for which there is no therapeutic justification and that in the public interest it is necessary and expedient to prohibit the manufacture, sale and distribution of the said drugs.

Now, therefore, in exercise of the powers conferred by section 26A of the Drugs and Cosmetics Act, 1940 (23 of 1940), the Central Government hereby prohibits the manufacture, sale and distribution on the said drugs for human use with effect from 1st January, 2002.

1. Fixed dose combination (FDC) of Nitrofurantoin and Trimethoprim.
2. FDC of Phenobarbitone with any anti-asthmatics drug.
3. FDC of Phenobarbitone with Hyoscin and/or Hyoscyamine.
4. FDC of Phenobarbitone with Ertamine and/or Belladonna.
5. FDC of Haloperidol with any anti-cholinergic agent including Propantheline bromide.
6. FDC of Nalidixic acid with any antiameobics including Metronidazole.
7. FDC of Loperamide hydrochloride with Furazolidone.
8. FDC of Cyproheptadine with Lysine or Peptone.

[F. No. X-11014/2000/DMS & PFA]

DEEPAK GUPTA, Jt. Secy.

Foot Note: Principal Notification was published vide G.S.R. 578(E) dated 23-7-1983 and last amended vide G.S.R No. 40(E).



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