Quarterly

ISSN 1022-257X March 1996, Vol. 5, No. 1

The Network's NEWSLETTER Rx

Association for Rational Use of Medication in Pakistan

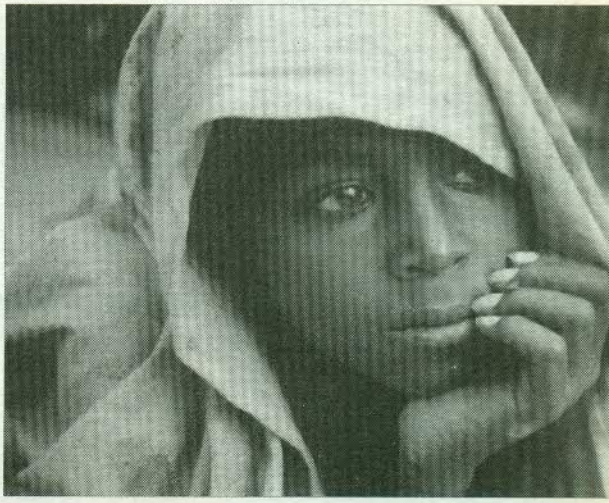
The Network s mission is to promote rational use of medication and essential drugs concept in Pakistan in order to optimize the usefulness of drugs and help bring equity in their access.

A policy paradox

The chances that a child will die before seeing his/her fifth birthday in Pakistan are seven times more than a child in a neighboring South Asian country, Sri Lanka. About half of these deaths are due to diarrheal diseases and acute respiratory infections.

These killer diseases are avoidable and can be successfully managed in earlier stages with very simple and effective measures. National Programs for Control for Diarrheal Disease (CDD) and Acute Respiratory Infections (ARIs) have clear protocols based on WHO guidelines for the management of children with these disorders. Both the programs recognize that the most important impeding factor in the "correct case management" of these disorders is unnecessary and incorrect use of drugs and the programs categorically condemn, as a policy, the use of anti-diarrheals and cough syrups.

It is ironical that in complete disregard to the policies of two most important Programs, the Drug Registration Board (DRB) of the Ministry of Health (MoH) keeps on allowing ever increasing number of anti-diarrheals and cough syrups to be available in the market. According to the results of our recent study (see page 10 for the preliminary report), currently more than 275 cough syrups and 65 anti-diarrheals are registered by the DRB. Majority of the cough syrups are combinations of up to seven active ingredients and some include chemicals like chloroform. Likewise, most of the anti-diarrheals are available in combinations and in pediatric formulations though adult formulations are also freely prescribed and given to children.



Both the programs and the DRB are run by the Federal MoH! This disturbing situation on the one hand clearly indicates obvious inconsistencies and gaps at policy levels of CDD - ARI and DRB and on the other hand provides evidence about the superficialness of government's efforts for "child survival".

We have initiated a process of dialogue at different levels involving all the stakeholders and sincerely hope that this clear demonstration of facts will lead to deregistration of unwanted drugs for diarrhea and ARIs and would also provide an opportunity to policy makers and members of the DRB to look into problems in registration procedures in general. These steps will strengthen our national programs and complement the efforts for child survival in the country.

NOTE

Due to shortage of space we cannot print details of references with each article. However, interested readers can get these references by sending a request to The Network. Please, mention the title of the article for which you need references and your complete postal address with the request.

Editor

▼Eclampsia: magnesium sulfate favored in anticonvulsant therapy

At least 500,000 women, overwhelmingly from developing countries, still die each year from causes related to pregnancy[1]. Eclampsia which now complicates only about 1 in 2,000 pregnancies in developed countries, but which is associated with a high mortality[2] is estimated to be a factor in about one in ten of these deaths[3,4].

The pre-eclamptic syndrome of increasing blood pressure and proteinuria and its association with a risk of potentially fatal eclamptic convulsions during or immediately after pregnancy has been recognized by generations of clinicians. However, the cause of these remains obscure. Symptomatic anticonvulsant management of eclampsia with diazepam or phenytoin has been essentially empirical and based on the assumption that "eclampsia is a seizure like any other seizure"[5].

Parenteral administration of magnesium sulfate offers an alternative approach which has been widely practiced in the United States for the best part of a century[6,7]. Suggestions have been offered that it may exert a vasodilator or other effect that attenuates ischaemic brain damage[8-10]. However, lack of a proven, physiological-based therapeutic rationale for its action, and of any comparative assessment of its efficacy, has apparently frustrated its acceptance elsewhere[11]. Choice of treatment has been claimed to be more a matter of faith than of objectivity[12]. Clinicians have had to rely largely on experience conveyed in uncontrolled case series[6, 13-15], and on the outcome of a few small randomized trials[16-19], one of which decisively favored magnesium sulfate in a comparison with phenytoin[17].

Eclampsia now complicates few pregnancies in developed countries. However, it has proved possible to organize a multicenter randomized comparative trial of these two approaches to treatment on a scale required to provide statistically secure results in hospital centers in Africa, Asia and South America[20]. In these countries, eclampsia is still estimated to complicate as many as 1% of all deliveries[21-23].

The trial comprised two separate arms:

— diazepam was compared with magnesium sulfate in a sample of 910 women admitted to centers in Argentina, Brazil, Colombo, Ghana, India, Uganda, Venezuela and Zimbabwe; and

— phenytoin (administered after an initial loading dose of diazepam) was compared with magnesium sulfate in a sample 777 women admitted to four centers in India and South Africa.

Magnesium sulfate was administered as a slow intravenous loading injection of 4g (5g in South American centers) followed over the next 24 hours either by an intravenous infusion providing 1g/hour, or by an immediate intramuscular dose of 10g in divided dosage with a further 5g every 4 hours (as long as respiratory rate, knee jerks and urinary output raised no suspicion of over dosage). Whenever a further convulsion occurred, an additional 2-4g was given intravenously over 5 minutes.

Diazepam was administered as an intravenous loading dose of 10mg over 2 minutes, followed by two consecutive 24-hour intravenous infusions delivering 40 mg and 20 mg respectively.

Since phenytoin is recommended only for prevention of convulsions, patients allocated to this drug were pretreated with the intravenous loading dose of diazepam. This was followed by a loading dose of phenytoin, 1 g intravenously over 20 minutes (with continuous cardiac monitoring) followed by 100 mg every 6 hours for 24 hours.

The results obtained are interpreted by the collaborators as "providing compelling evidence in favor of magnesium sulfate, rather than diazepam or phenytoin, for the treatment of eclampsia." In both settings maternal mortality was lower among women allocated magnesium sulfate, but these differences did not attain significance. The case for favoring magnesium sulfate is based essentially on the finding that this intervention approximately halved the risk of recurrent convulsions when compared with diazepam, and reduced it by a somewhat greater margin when compared with diazepam/phenytoin.

Magnesium sulfate held no statistically demonstrable advantage over diazepam in

Fueling the fire

The Drug Registration Board of the Ministry of Health has refused to budge. It has uptil now stuffed the chaotic Pakistani medicine market with 19,157 drugs. The registeration spree is touching new heights. Total number of working days from May 1, 1994 to March 20, 1996 comes out to be 466. During this period the Board (DRB) has registered 3,969 new drugs. That means over 8.5 drugs per working day or a new drug every hour.

During the last reported Board meeting held on March 20, 1996 alone 412 drugs were registered. It is humanly impossible to even read out the namesand composition of 412 drugs in the usual 2-3 hour Board meeting. We fail to get any information about the supposedly super natural methodology that the Board has adopted to clear such huge jobs in so short a time.

any other measure of serious maternal morbidity. However, it was less likely than phenytoin/diazepam to depress breathing or to be associated with pneumonia and the need for intensive care.

Most women convulsed after delivery. Some 250 infants were born to mothers treated before delivery and, among these, the overall mortality was 27%. Non-significant perinatal deaths occurred more among those exposed to phenytoin/diazepam than those allocated to magnesium sulfate (31% v. 26%). Live-born babies of women allocated magnesium sulfate were less likely than those in other treatment groups to have signs of respiratory depression, as reflected in Apgar scores, need for intubation and admission to special care nurseries.

These results, it is claimed, establish the superiority of magnesium sulfate in the routine anticonvulsant management of women with eclampsia beyond all reasonable doubt. The authors urge clinicians everywhere to align their practice with these results, and they call for WHO to accommodate parenteral magnesium sulfate within its list of essential drugs. Notwithstanding the failure of their study to demonstrate an advantage in survival of statistical significance, they estimate that several million women have died unnecessarily since magnesium sulfate was first proposed for the treatment of eclampsia.

In presenting their results the authors emphasize that "the only unbiased comparison in this trial are of magnesium sulphate versus diazepam and of magnesium sulphate versus phenytoin". Other comparisons, they claim are potentially misleading. This principle, however, does not absolve trialists from examining and accounting for evident bias whenever it emerges. The incidence of recurrent convulsions in women allocated to magnesium sulfate in one limb of the trial was 13.2%, yet in the other, it was only 5.7%. Such a large difference merits consideration and discussion. A search for possible factors contributing to this bias is unlikely to overturn the general conclusions of the study, but it might provide important insights into other determinants of eclampsia and, perhaps, into their management.

Reprinted from WHO Drug Information, Vol. 9, No. 3, 1995

References available on request. See note on page 2.

Contents

▼Hepatitis B vaccination in infancy: evidence of long term efficacy

Hepatitis B virus infection in infancy commonly results in chronic carriage of the virus[1] and, eventually, in a high risk of chronic hepatitis, cirrhosis, and primary hepatocellular carcinoma[2]. Infection is hyper endemic in large areas of Sub-Saharan Africa and Southeast Asia. Most infections in Africa are spread from sibling to sibling within the first few years of life[3], while, in Asia, perinatal infections predominate that are acquired from mothers who are carrying the HBVe antigen[4].

These patterns of transmission suggest that, in Africa, infection might be effectively controlled by mass vaccination during infancy, whereas, in Asia, very early vaccination and, ideally passive immunization would be required. Even short term immunity would be of considerable value since it seems that the chronic carrier state rarely develops in children older than 4 years[5]. Results already obtained among pre-school children in the African Sahel with hepatitis B vaccine have been highly promising. Protective efficacy over a six-year period has been estimated to be between 80% and 90%[6], while regimens involving 2 or 3 booster doses given over a period of several months have been highly efficient in protecting children against persistent infection[7].

The only long-sustained program of vaccination against hepatitis B infection in West Africa was started in Gambia in 1986[8]. At that time, all non-immune children under the age of 5 years in two Gambian villages were vaccinated. Since then, all children born in these villages have been vaccinated in infancy. After 4 years, the efficacy of vaccination in protecting children against chronic carriage of the virus was 97.3%, and the choice of different schedules of vaccination involving different timings, doses, and routes of administration (intradermal or intramuscular) was found to have little influence on this outcome[7].

As breakthrough infections continue to occur, overall vaccine efficiency must be expected to fall. By 1993 it had dropped among children vaccinated between 1984 and 1989 to 89.8% (95% confidence interval: 86.0-92.9), and antibody concentrations had fallen to a geometric mean of 4.8% (3.6-6.4) of the peak value[8]. However, examination of the temporal pattern of infection within a cohort of children drawn from this group indicates that the incidence of breakthrough infection (when adjusted for duration of exposure and antibody concentrations) is falling to a highly significant extent: in the second of two successive 4-years periods there were fewer than half the expected number of infections.

This is a most encouraging finding. It suggests that not only has the vaccination program had an immediate impact on transmission by reducing the prevalence of acutely-infected and highly-infectious children; it has also greatly reduced the risk of children becoming chronic carriers of the disease. Meanwhile, in accordance with expectation[9], existing carriers, formerly the principle source of infection within families are becoming less infectious with the passage of time.

References available on request. *See note on page 2.*

Indian court deprives doctors of their halo

In a land mark judgement the Indian Supreme Court has put medical service under the Consumer Protection Act 1986. The Court ruled that doctors were like any other providers of services under contract and thus are under the same obligation to compensate the purchaser for any deficiency in the quality of their services.

Doctors are already liable under civil and criminal laws for acts of negligence. But the judgement has brought these kinds of suits in the purview of consumer courts which are speedy and economical. Consumer courts in India are special courts which take up cases of consumer grievances and there is no stamp duty or court fee for filing a case in these courts.

The medical profession and consumer groups are engaged in a heated debate over whether the judgement will help improve the quality of health care in a system which is fast becoming commercial. Some say that easy access to courts awarded to patients will force doctors to become 'defensive prescribers'. Others fear that to avoid risks doctors will start using heavily diagnostic tests and the cost of treatment will rise. But everybody is sure that the greater possibilities and fears of litigation will give rise to health insurance business.

Tips on
Evaluating new drugs

Dr Arshad Mehmood
offers tips to sift truth from the tall claims about new drugs

It would be evident to any doctor who has critically evaluated new drugs brought to the market in recent times that the pharmaceutical industry is spending more on promotion than on research. And also that most of this research is producing "me-too" drugs, add-ons to existing preparations, rather than innovative products which are expensive and risky to develop.

A seven year survey of new drugs completed recently by the US Food and Drug Administration (FDA) found that: only 3 percent of them made an important potential contribution to existing therapies; 13 percent made a modest potential contribution and 84 percent made little or no potential contribution. World Development Report 1993, a World Bank publication, says that less than four percent of research money goes to finding treatments for diseases prevalent in the majority world where three-quarters of the worlds population lives and dies.

Pharmaceutical industry, like any other industry, is driven by a quest for profits. This has resulted in a situation where 70% of the drugs on the market today are non-essential, unnecessary or downright harmful. There is fierce competition amongst a large number of powerful companies to increase their market shares. This situation has the following dire consequences for public health:

1. Treatment failures, including death from the use of the wrong therapy.
2. Patients suffering from unnecessary adverse effects.
3. Increase in antibiotic-resistant micro-organism strains.
4. Waste of patients money and scarce national health resources.

A doctor can play his/her role more effectively in this challenging situation by finding answers to the following key questions and clearly define the therapeutic place of every new drug in his/her practice. This will minimize inappropriate prescribing, ensure proper use of resources and is in the interest of good patient care.

Ask yourself

♦ Is it a truly novel medicine or a "me-too" product?

♦ What are the licensed indications? Can the claims for it be substantiated?

♦ Has it been compared with standard existing drugs in controlled, randomized trials published in authentic journals? How does it compare?

♦ Are there any comparative safety data?

♦ Has it been registered and used in other countries where effective regulatory controls and post marketing surveillance exist, for example: USA, UK, Norway, Sweden?

♦ Are there any contraindications or precautions in the data sheet relating to particular groups of patients?

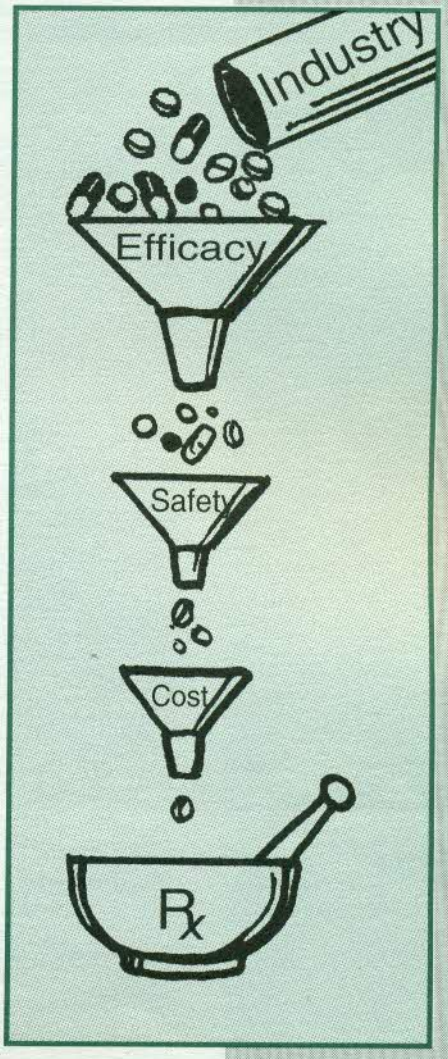
♦ Are there some patients for whom it might be particularly suitable?

♦ Have you only heard of the drug from the manufacturer? Have you read any independent information on it?

♦ How does its price compare with existing therapies? Is there any evidence that it is more cost-effective?

♦ Is there a problem with existing therapies?

♦ Should it replace an existing drug, or does it fill a gap in your practice formulary?



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Availability and accessibility of drugs in a market economy

Dr Azra Talat Sayeed argues that a market economy cannot cater to the health needs of a vast majority of our people

Medicines, although not the primary tool needed for maintaining a healthy population, are a critical intervention for controlling and eradicating diseased states. The current global and national environment is much in favor of a market economy growth model. Medicines, in such an environment are treated as commodities to be regulated and governed by the market forces.

What does a market economy demand? The first crucial emphasis is on making profits without which no venture is either successful or sustainable. How are profits possible? I believe competition is the key. Another critical element of a market economy is deregulation.

The pharmaceutical market needs examination in light of the three prongs of the market economy. The common person's Pakistan is indeed not the lucrative market being sought by any business enterprise including the pharmaceutical industry. Hence it is logical to assume that the focus of attention will be the financially well off consumers. Therefore now we have a division of consumers. Those who are in the position of being able to bear the cost of medicines will also be the ones to access the needed medicines. Those who are unable to afford medicines are not the problem of the profit-seeking market. The government with its 2% spending on total health care has the responsibility of looking after the pharmaceutical needs of the poor. It is important to point out that a market economy model frowns on subsidy; according to laws of competition, subsidies distort markets.

Therefore, logically subsidized medication to the poor would undermine the overall thrust of a market economy initiative. The answer is then to stop providing subsidized medicine.

The next important bastion of a market-oriented economic model is competition. The foundation stone of competition is research and development which allows new products/medicines to be marketed. It needs to be pointed out for the pharmaceutical industry, its main markets are in the industrialized countries. About 80% of the world's medicines are consumed in the industrialized world. Hence, the focal market for the pharmaceutical industry is not the Third World. Pakistan is categorized a low-income Third World country. It needs no reminding that the health/pharmaceutical needs of populations living in the industrialized world are very different from the average Pakistani. Malaria, typhoid, cholera are unknown in the industrialized world.

That the pharmaceutical industry is earmarking very little research money for the diseases of the Third World needs no reiteration. But maybe it does. When we talk about a market economy model, we no doubt give the pharmaceutical industry the right to market whatever medicines it wants. But it should be remembered that products being sold in the Pakistani market are those demanded by consumers in the industrialized world. Therefore, competition which is supposed to be hinged to the needs, and wants of consumers does not necessarily come into play with respect to pharmaceutical needs of Pakistanis.

Finally deregulation. A market economy stresses deregulation. The logic is that the market is self-governing. What consumers do not need/want will be automatically rejected by the market, hence a legal system of regulation will not be needed. If that is the case, then it is difficult to understand why more than 19,000 drugs are registered in Pakistan. As has been stressed above, very few of the basic needs (including health) of Pakistanis have been met. The World Health Organization (WHO) suggests less than 500 drugs essential for the pharmaceutical needs of Third World populations. It would be difficult for any health professional to justify the presence of 19,000 drugs as a needed medical service in

Pakistan s per capita income is US$ 420 per annum, or roughly Rs 1200 per month per person. About about 26 million Pakistanis have an income less than Rs 280 per month. While the government spending on health and education comes to less than 2.5% of the GNP.

any part of the world, let alone a poor Third World country. It seems that market forces regulating the pharmaceutical market in Pakistan are non-existent.

If one examines the pricing of medicines in Pakistan, there is further evidence of the failure of the market's self-governing principle. For instance, the Indian pharmaceutical market, a market which has a history of being highly regulated is able to provide medicines far more cheaply than the Pakistani market.

What is causing these extreme anomalies in the system? An examination of the competitive market model and its application to medicines may provide some answers. For a competitive market model to succeed a number of parameters need to be satisfied. The first being that a product must have many sellers and many buyers. Due to high cost of research and development firms within the pharmaceutical industry work in specific therapeutic groups (for example; cardiovascular drugs). The result is that there are a limited number of drugs marketed by a handful of firms for a particular disease. This phenomenon limits the number of sellers of drugs for different disease states.

The second parameter of a competitive market is that producers should have no barriers in entering or exiting the market. The pharmaceutical industry is primarily driven by research and development. The exorbitant costs of research and development, and then of marketing medicines, allows only capital intensive investors. Hence the pharmaceutical market does not allow free entry into the market place. It is also worthwhile to remember that the patient/consumer does not have free entry or exit into the market. S/he takes medication based on the advice of a health professional; and is not free to stop medication based on self-defined pharmaceutical need.

The third parameter of a competitive market is knowledgeable consumer. Drug therapy is a highly specialized field. Even an educated consumer is unable to prescribe medication for herself/himself and is dependent on the advice of a physician. Therefore, even in the first world, where literacy rates reach near maximum, consumers cannot take responsibility for self-prescribing. In Pakistan, with official literacy rates at 35%, one cannot say that consumers have even a basic understanding of the complexities of drug therapy.

▼ *Abundance does not mean easy availability and equitable access.*

The last parameter of a market model dictates that products should be substitutable. For example, if one wants a black pair of shoes, s/he has the freedom to go to any number of shoe shops and choose any pair based on personal choice; if the consumer ends up buying a brown pair instead of black it is not a life-threatening situation. That is not the case with medicines. If one is suffering from malaria, one cannot substitute anti-malarial drugs with vitamins. The choice of drugs for a single disease is limited as at a time any particular disease may have only 3-4 drugs available; if the market is further constrained by patented brand name products than it is possible that only one medicine may be available in the market.

It seems that even a very cursory analysis of the pharmaceutical market does not construct a good case for allowing medicines to be governed by the rules of a market economy. In this era of competition, governments should not forget that an educated highly skilled work force is critical to economic development. Some of the basic inputs needed by such a work force is excellent educational system and health. Allowing the market to dump its anomalies on an undernourished, non-privileged society may well lead to further deterioration of our people and economy.

Prof Tariq Iqbal Bhutta builds a strong case in favor of universal immunization against Hepatitis B

A pediatric perspective

Control of Hepatitis B: Need for universal immunization

A large number of childhood diseases causing morbidity and mortality can now be controlled effectively by immunization. small pox has been eradicated from the globe and no case has been reported since 1978. WHO's target for eradication of polio has been achieved in a large number of countries. Hopefully tetanus will also be totally eliminated by the year 2000. These infections were responsible for high morbidity and mortality and mass immunization has proved to be a cost effective method of controlling these infections.

Hepatitis B virus (HBV) infection is on the increase in all those countries where immunization is not being effectively provided. In spite of a vaccine being available for more than 12 years, about 200,000 to 300,000 new cases of Hepatitis B occurred annually in the USA alone[1]. In Italy about 400,000 new cases used to occur each year, and because of this high rate of HBV infection; vaccination of Hepatitis B was made compulsory in Italy in 1991.[2] The vaccine is administered to neonates and 12 years old adolescents. In 12 years time, all Italians under the age of 24 will be immune to HBV.

We do not have community based figures of HBV infection showing the extent of disease or the prevalence rate in Pakistan. A few small scale surveys[3] have been carried out in different parts of the country by various workers to find out the carrier rate of Hepatitis B surface antigens (HBsAg), which have shown the HBsAg carrier rate being about 10-15% in adults. In children up to the age of 5 years, it is reported to be 5%[4].

If the HBV infection occurs during the perinatal period, the carrier rate is extremely high (70-90%), while the symptoms of acute viral hepatitis occur in only 5-10% of noenates[5]. This high risk of developing chronic carrier state in neonates, makes the vaccination a high priority because of the threat of developing serious complications like cirrhosis and hepatocellular carcinoma in them after many years. Hepatitis B vaccine should, therefore, be offered to all babies at birth, if possible.

Gambia, the country with very high infection rate of HBV infection introduced Hepatitis B vaccine in 1986. By 1990, 124,577 children had been carefully identified and recruited into the 35 year longitudinal cohort study; 59,803 of them have received the vaccine. Rest of them (65,774 unvaccinated children) will serve as control. The preliminary studies have demonstrated that the rate of HBV infection has fallen to less than 5% in children who received all 4 doses of Hepatitis B vaccine[6,7]. In other words 95% of the children had achieved protective antibody levels against HBV.

The chronic HBV infection may lead to hepatocellular carcinoma. Therefore, vaccination against HBV may prevent not only HBV infection and the development of chronic carrier state but will also prevent the development of hepatocellular carcinoma.

In the USA and some other countries, Hepatitis B vaccine was initially given to high risk groups like health care personnel and patients who required frequent blood transfusions. After 10 years, it was seen that the infection rate did not drop significantly.

Although, a number of risk factors are known for HBV infection e.g. inoculation with blood of HBV carriers, reuse of infected needles and sharp instruments without sterilization. However, no risk factor could be identified in 30-40%, of cases of acute viral hepatitis with HBV[8,9]. Hence, if Hepatitis B vaccine is to be given on a selective basis, then many persons will remain unprotected, and may acquire HBV infection (asymptomatic or symptomatic) with possibility of some becoming carriers of HBsAg.

Many types of Hepatitis B vaccines are available in Pakistan e.g. Engerix B by Smith Kline and Beecham and Hevac B by Meriux

Current estimated cost of Rs 2.4 billion per year of immunizing all the 4.5 million new borns against Hepatitis B could be brought down to as little as Rs 100 million. But for that we need to conduct studies at local level.

(France) and recently the vaccine prepared by MSD has also been marketed. Currently, the cost of these vaccines is very high. A course of three 10 mcg doses for children currently costs about Rs 600. If we recommend it for universal immunization of all neonates (4.5 million babies born annually) and make it a part of EPI program, the total cost of the vaccine alone would be Rs 2.4 billion (240 crores). This is not feasible because of the scarcity of available financial resources. But if the immunization is not offered to all the babies there is a real chance that the fresh infections with HBV will continue to occur and disastrous outcomes will appear with the passage of time.

There are two ways by which the objective of providing universal vaccination can be achieved at a lower cost. The first one is to get vaccine at a lower cost by floating world-wide tenders for the vaccine. In Gambia, the vaccine used is of Korean origin costing less than one dollar per dose. One pharmaceutical company in Pakistan claims that the vaccine can be supplied at the rate of 25 rupees per dose provided the Government of Pakistan orders a supply of vaccine in bulk.

This would bring down the cost of immunization to all neonates born annually to less than Rs 400 million (40 crore) per year from the total estimated cost of Rs 240 crores, if all newborns are given the vaccine. Secondly, in Singapore, a study was published in 1992[10]. They used four different dosages which were compared for the immunogenicity. It was shown that the reduced dosage of 2.5 micro gram and even 0.6 microgram given intramuscular was as effective as the standard dosage of 5 microgram.

This is very promising observation. If we can also prove that the small dose of 0.6 microgram is as effective as 5 microgram, we can bring down the cost of the vaccine required to immunize all our neonates to about 100 million (10 crore) rupees, which is very much within the resources of the government for universal immunization of our neonates.

Before integrating Hepatitis B vaccine in our EPI program, we need to conduct more studies to know about the prevalence rate of HBV in the community. It may help us to evolve proper strategy for prevention of the disease. We also need to look into effectiveness of low dose intra-dermal immunization, which can in turn, lead to significant financial savings. The possibility of having single multiple vaccines injections is another long term strategy proposed for providing vaccination against multiple diseases.

All these aspects need further studies in our country so that we could evolve the most feasible and cost effective method for controlling Hepatitis B in Pakistan by universal immunization against HBV

References available on request. See note on page 2.

▼ *Hepatitis B vaccine should be offered to all babies at birth.*

The Network presents interim report of its research project on Availability of Harmful/Irrational/Non-Essential Drugs For Treatment of Acute Respiratory Infections and Diarrheal Diseases

Rationalizing CDD, ARI programs

The Government's efforts to reduce the infant mortality rate over the years through its different "child survival" initiatives (ARI, CDD programs etc) have not been very successful. The main factor limiting the success of these programs has been irrational drug use. Ironically, while the WHO's standard case management guidelines for the ARI and CDD programs explicitly reject cough syrups and anti-diarrheals, the Drug Registration Board (DRB) of the government continues unabatedly to register more of these drugs for manufacture and sale in the country.

The Network undertook a survey, with UNICEF funding, to quantify the extent of the availability of these drugs, which are not recommended by the ARI and CDD programs yet are freely available and being continuously registered by the DRB. The objective was to use the findings as an advocacy tool to campaign for a rational registration policy.

The broader aim of this research was to improve the management of children with diarrheas and ARIs by helping minimize one of the important impediments in the way of correct case management that is irrational use of drugs.

A brief summary of the main findings of this survey is presented here. The survey has been limited by the non-availability of latest reliable registration data from the Ministry of Health. The main source of data was a 1994 publication of the ministry which contained information until April 1994. Commercial drug compendiums have been used to fill in the information gaps after that.

Cough syrups

There are 275 cough syrups registered with the Drug Registration Board, marketed by 140 companies.

None of the active ingredients used either alone or in combination are present in the National Essential Drug List, May '95. prepared by the Ministry of Health, Government of Pakistan.

Most of the preparations available are in the form of combination drugs (163 - 61%). The combinations are not consistent with those recommended by the WHO in the policy document of the ARI case management protocol.

The combinations generally combine either an antitussive and an expectorant or an antitussive and an antihistaminic.

Single ingredient preparations either have ammonium chloride (13.6%) or pholcodine (8.1%) while dextromethorphen is present in 7.0% of preparations.

All the preparations indicate a pediatric dosage regimen on their label.

Anti-diarrheals

A total of 64 antidiarrheals are available in the market, marketed by 48 companies.

Combination drugs are common (56% , 34 of 64) while an antibiotic combined with an antidiarrheal is present in 11 (17%) of the preparations. The antibiotics are streptomycin and neomycin.

Furazolidone is present in 40.6% of preparations while kaolin pectin are present in 26% of preparations.

Drugs containing furazolidone as single ingredient also indicate them for treatment of simple diarrhea. Furoxone (furazolidone, SKB) is indicated as "the reliable antidiarrheal".

All suspensions/liquid dosage forms are labeled with pediatric dosage and most of them are indicated in under one year age group.

Infant mortality rate in Pakistan is estimated at 95 per 1000 live births and the country ranking is 10th out of a total of 11 in the region.

Which anti-hypertensive first and why?

Lt Gen (R) Mahmud Ahmad Akhtar offers advice on treatment of hypertension and says doctors should not succumb to promotional pressures.

These days many new expensive drugs are being promoted as first line anti-hypertensives and it is very unfortunate that a few leading professionals of our country have chosen to toe the promotional line provided by the manufacturers instead of following the scientific principles enunciated in authentic books of medicine. Those who advocate their use as first line drugs are not doing their professional duty to the patient. They should follow the scientific literature and not succumb to unethical promotional activities of the vested interest.

JAMA August 1992 has discussed this problem and concluded that none of the new drugs has proven its superiority over the first line drugs, ie beta-blockers and thiazides. In fact beta-blockers are proven to have cardioprotective properties. It is also beyond any doubt now that thiazides in low doses prevent cerebrovascular accidents. In young hypertensives, beta-blockers should be used as first line drug and thiazides in low dose added if blood pressure is not stabilised. In older people thiazides are to be used as first line drug and betablockers added later if and when needed.

These group of drugs are recommended in every authentic book of medicine, therapeutics, pharmacology and cardiology. Recently, the National Advisory Committee of New Zealand has also recommended beta-blockers and low dose thiazides as first line drugs (unless, of course, there are contraindications or there are special situations). Similarly, European Congress of Cardiology and British Medical Research Council has given the same guidelines.

Patents for betablockers like propranolol and atenolol have expired and these are now available in cheap brands or generics and are relatively much less expensive.

Beta-blockers in low doses do not cause any significant biochemical changes and whatever changes occur are soon stabilized.

Alpha-blocker prazosin is another inexpensive and good choice anti-hypertensive known to improve lipid profile as well. Prazosin may be added as a third drug if the BP is not controlled with betablockers and thiazides. It may cause first dose hypotension which could be avoided if precautions are taken. In fact alpha-blockers have no contraindications and they can be used for hypertension with any other accompanying disorder. Methyldopa is an inexpensive anti-hypertensive but has some side effects. It has proven its worth nevertheless and it could be useful for many patients particularly the poor ones. It is safe in pregnancy while many new drugs including ACE inhibitors are not safe.

The newer anti-hypertensives including the calcium channel blockers and the ACE inhibitors may be used under special circumstances contraindicating use of betablockers like bronchial asthma, severe bradycardia and congestive heart failure etc. Similarly thiazides may be contraindicated if there is accompanying gout and hypokalemia etc. Thiazides in low dose usually do not cause hypokalemia in uncomplicated hypertension. However, after two months' use serum 'K' should be evaluated.

It should be realized that these newer drugs are not only expensive but also not free of side effects. It is aptly said that the old drugs earn publicity for side effects and the new ones from promotion. Already a lot of toxic side effects have been reported on new drugs. Even depression has been reported with ACE inhibitors recently. For this, one has to consult the literature and even the pamphlets accompanying these drugs.

MarketScan

▼ Relaunching niclosamide top priority with new Bayer chief

Disappearance of niclosamide (Yomesan) tablets from the Pakistan market a few years ago left doctors with no drug for the treatment of tape worm disease leading to a lot of hardship for the patients. The Network has been campaigning Bayer, the only company producing nilcosamide, to make it available in the market. Bayer's new Pharma Division Manager, Alfred Bonatz, appointed last year, responded to our campaign by assuring that the relaunch of Yomesan would be his top priority. He promised in his letter of 19 February, 1996 addressed to Chairman Network Council, Lt Gen (Retd) Mahmud Ahmad Akhtar, that the relaunch would take place "no later than 01.06.1996 but as soon as possible", and that, "we will inform you about further progress in the month of April". While The Network welcomes the change in Bayer's stance on Yomesan to relaunch it, the promised date of relaunch has come and gone close and there is no visible activity in this regard. We are however optimistic about Bayer's intentions and hope earnestly that the promise is kept.

▼ Nabumetone: a breakthrough or a me-too

Nabumetone (Relifex) has been claimed in the promotional campaign by the manufacturers SmithKline Beecham to be a "breakthrough" in the treatment of arthritis. Many symposia have been held through out the country over the last almost two years of its launch in Pakistan where "distinguished" speakers sung praises of this product. Astonishingly what has dawned to these leading men and women of medicine in this country is still unknown to world authorities of clinical pharmacology!

British National Formulary (BNF) states that nabumetone is comparable to naproxen in efficacy and to ibuprofen in side effects but long term data are awaited. Surely long term studies will show higher adverse reactions as has been shown with other NSAIDs. At present, treatment with this new drug costs Rs 20, a month's treatment costs Rs 608, and a years cost Rs 7,303. Ibuprofen in comparison costs 1/10th of this.

▼ Servier s promotion of Arcalion and Duxil

The French independent drug bulletin Prescrire has reviewed the scientific dossier of Arcalion provided by the Servier's subsidiary "Therval" which is marketing it in France, the home country of these companies. The company could not provide even one clinical trial. Prescrire located only one comparative clinical trial without any scientific value. Their conclusion was: "A hazy official indication (certain states of inhibition) supported by a clinical evaluation file empty of serious publications and laboratories which refuse to do their duty to inform prescribers rigorously. All of this deserve severe reprobation".

Servier recognized in a recent letter to MaLAM (see MaLAM introduction on page 16) its advertisements of Duxil in Philippines lacked the information about serious side effects including peripheral neurological disorders. The company seems to have woken up to MaLAM's pointing out to them although reports of almitrine (one of the two components of Duxil) causing peripheral neuropathy are as old as 11 years. However, Servier has thanked MaLAM for "having drawn its attention to this flaw in its quality control procedures."

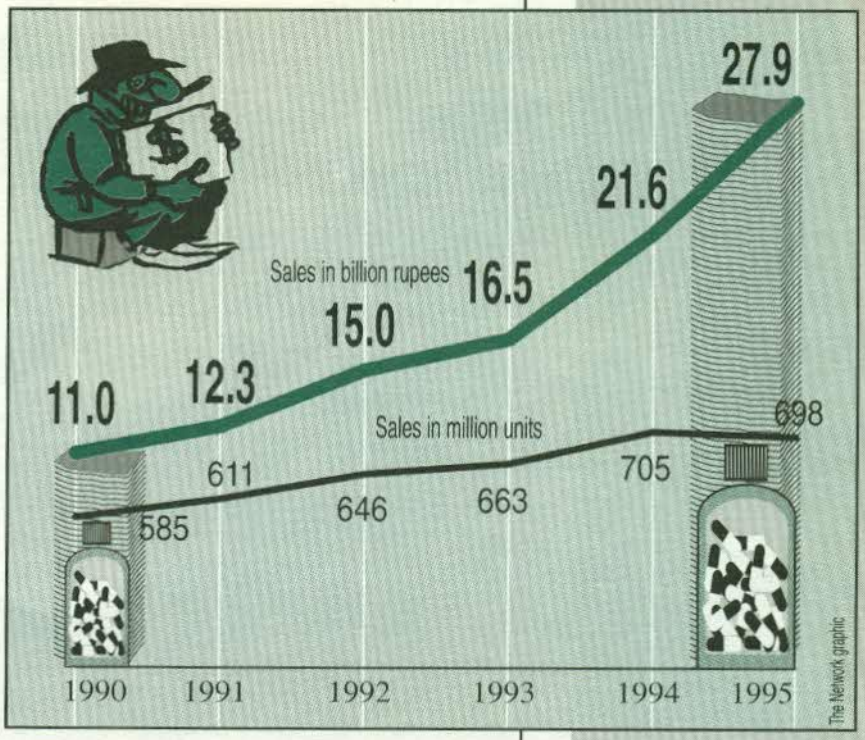
MaLAM has asked Sevier to cease the promotion of these products totally in developing countries. It is high time in countries like Pakistan that those who care stand up against such dubious and harmful drugs and tell the profit hungry companies that they have had enough!

▼ Market grows, people languish

Pharmaceutical market in Pakistan is growing at a phenomenal rate of over 29%. The total turn over of the industry in 1994 was Rs 21.59 billion while for 1995 it is reported to be Rs 27.93 billion. But surprisingly, the figures do not reflect any increase in the people's access to medicines as the industry's sales in volume or number of units of medicines sold has in fact decreased. According to the statistics provided in the book "The Pakistan Pharmaceutical Industry" published by the multinational companies' union Pharma Bureau, unit sales in 1995 have actually decreased by 1% compared with the unit sales in 1994. This simply means that the industry is fattening its profits by unduly increasing prices of medicines and not by selling medicines to more and more patients.

This trend is not new as over the years the pharmaceutical industry has grown with a far high rate in terms of turn over in rupees than in terms of units sold. See graphic. For every 100 units (tablets, capsules, ampules etc) of medicines that the industry sold in 1990, it sold 119 units in 1995 or an increase of 19% in volume sales in six years. While for each 100 rupees that the industry earned in 1990, it is earning 251 rupees in 1995 or an increase of 151%.

This contradiction had sharpened after the Ministry of Health surrendered its authority to control prices in 1993 and allowed the industry to raise prices according to their wishes. The industry has been since then raising prices on one pretext or the other. But what has made the situation grave is that the authorities are taking a defensive stand in this war between profits and people. The Ministry of Health's officials do not shy saying that they can't do much in a free market economy.



▼ *Lifting of controls on prices is adversely affecting the direct relationship between sales in volume and the turn over in rupees in the pharmaceutical sector.*

▼ Baby milk boom

Pakistan's import bill of milk powder and baby milk food has doubled during the first 10 months of 1995-96 compared with the previous year. Pakistan imported 17,296 tonnes of powder milk and baby food worth $43.5 million from July 95 to April 96 against 9,550 tonnes at a cost of $20.6 million a year ago.

This sudden upsurge in milk coincides with the new aggressive marketing of baby food by Nestlé. The company which is among the top 20 multinationals of the world is now ranked 25th biggest 'pharmaceutical' company in Pakistan with a Rs 279 million turn over in 1995.

Nestlé which is violating all the international norms and the WHO code for baby food manufacturers earned Rs 84 million from its product Cerelac alone in 1995.

The company is 'donating' free samples of baby food to hospitals, advertising its products to common consumers directly. The company's ads are even offering readers free samples if they fill up and post a coupon. It is also sponsoring a TV talk show on NTM about baby care. Nestlé's marketing teams are also making rounds to schools to entice kids.

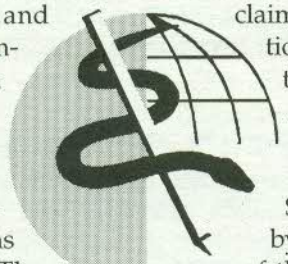
An introduction

MaLAM and pharmaceutical promotion

By Robyn Clothier

The Medical Lobby for Appropriate Marketing (MaLAM) is an international non profit organization for health professionals who want pharmaceutical promotion to be trustworthy.

Most countries lack reliable up to date data on the prevalence of misleading drug promotion but it would appear to be common[1]. A 1992 study reviewed advertisements in medical journals and judged 25% in Brazil, 50% in Finland, 30% in Italy and 38% in Pakistan to be misleading[2]. Frequently, the information provided to Third World doctors is far different and much less accurate than that given to physicians in industrialized countries. The range of indications for use of the drugs is expanded and fewer side effects, warnings and contraindications are mentioned[3].



Although many doctors deny it, promotion works. Controlled trials have shown that advertising techniques are more effective than the methods used in medical education[4]. Avorn et al (1982) found that 63% of a sample of US doctors believed that advertising was of "minimal importance" in influencing their prescribing. However, 49% revealed a misunderstanding about the drug dextropropoxyphene that could only have come from the advertising[5].In countries such as Pakistan, the problems caused by the effectiveness of such advertising are further compounded by very limited access to reliable independent drug information and fewer of the controls that well resourced regulators are able to provide. Ahmad and Bhutta's 1988 survey of Pakistani doctors found that 41% were prescribing Lomotil to children with diarrhea, despite the well recognized dangers of this drug, and 14% prescribed Durabolin, the anabolic steroid, to children as an appetite stimulant. Ninety five percent of these doctors cited detailers and promotional materials as their main sources of prescribing information[6].

MaLAM seeks to improve this situation by addressing concerns directly to pharmaceutical manufacturers. Every month a topic is chosen from the most serious of complaints received from health professionals around the world and a MaLAM letter addressed to the company is prepared. However, MaLAM letters are designed as requests for information rather than complaints. Most of the letters quote a questionable promotional claim, provide a summary of the scientific literature for comparison and ask the manufacturer to provide evidence to support the claim or reconsider their promotion. Copies of the MaLAM letter and MaLAM News (in English or French) are sent to over a thousand subscribers in more than thirty countries. Subscribers support the letter by requesting a personal copy of the answer from the manufacturer. The ensuing dialogue is reported in MaLAM News and other medical journals. These reports assist health professionals to determine for themselves whether the manufacturer's claims are reliable and what place the drug under scrutiny should have in their clinical practice.

MaLAM is very pleased to be associated with The Network of Association for Rational Use of Medicines in Pakistan. With The Network's assistance, MaLAM has recently challenged Parke Davis about the promotion of Ponstan (mefenamic acid) in Pakistan and negotiated with Sandoz for a "Dear Doctor" letter to Pakistani doctors indicating regrets about its promotion of Parlodel (bromocriptine) for lactation suppression.

Participation in the MaLAM process provides the subscriber with both a good source of independent drug information and skills in critical analysis. Enquiries about subscription and concerns about particular promotions can be addressed to MaLAM via The Network, who act as MaLAM's distributor in Pakistan.

The Network s Newsletter is a member of the International Society of Drug Bulletins.

The Network is funded by OXFAM, UNICEF, CRS and StJF.

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