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Prescription of fixed dose combination drugs for diarrhoea

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Abstract

Fixed-dose combinations (FDCs) of an antiprotozoal and an antibacterial, for treatment of diarrhoea, have been available in the Indian pharmaceutical market for about a decade. There is little evidence to substantiate this combination therapy. We evaluated 2,163 physician prescriptions for diarrhoea and found that 59 per cent of prescriptions were for FDCs. This is unethical because prescribing such combinations exposes a patient to higher risks of adverse drug reactions and also increases the chances of drug resistance. Physicians' prescribing practices in India are influenced by socioeconomic factors and the pharmaceutical industry's marketing techniques that include giving incentives to physicians to prescribe certain drugs.

As in other developing countries, many Indians suffer from attacks of amoebiasis, giardiasis and other infective diarrhoeas that are attributable to socioeconomic and environmental conditions such as poor sanitation and contaminated drinking water. In most cases these diarrhoeas are self-limiting and the standard treatment protocol is correction of fluid and electrolyte imbalance as a primary measure. If anti-diarrhoeal drugs are required, their prescription should be organism-specific and preceded by a diagnostic stool examination. It is rare to find infection by both protozoa and bacteria as causative agents of diarrhoea on a single occasion. In this context, prescription of a combination of an anti-protozoal and an anti-bacterial as a blanket cover for both protozoa and bacteria in a single episode of diarrhoea, without any diagnostic test, is not only unnecessary but also unethical. It is unethical because prescribing such combinations exposes a patient to higher risks of adverse drug reactions and also increases the chances of drug resistance.

Around 1995-1996 fixed-dose combinations (FDCs) of an antiprotozoal and an antibacterial (such as combinations of norfloxacin and tinidazole or ciprofloxacin and tinidazole) were introduced in the Indian pharmaceutical market. Manufacturers argued that this was logical because a significant percentage of patients have mixed infections of protozoa and diarrhoea-causing bacteria. Clinicians could play safe while treating mild to moderate amoebiasis and related infective diarrhoeas.

A scrutiny of the relevant product communications indicates that there is little or no clinical evidence to substantiate this claim. Despite this, FDCs have gained acceptance among physicians, as is evident by the growing number of such prescriptions. This study is aimed at a critical evaluation of the consequences of such prescription practices.

Methods

Observations are based on data collected between November 1998 and February 1999 by C-Marc, a Kolkata-based market research group working on prescription audit using a randomised and anonymised database of practising doctors in India. The doctors in this database belonged to different medical specialities. They included physicians with at least a MD in internal medicine, engaged in private practice and prescribing on an out-patient basis. They were distributed uniformly throughout India. These doctors provided C-Marc with copies of their prescriptions which were analysed for prescription details.

A total of 2,163 prescriptions were obtained for analysis between November 1998 and January 1999. Prescriptions containing oral antimicrobials for treatment of amoebiasis-like diarrhoea in adults were included in the audit. The audit also generated information about the total number of prescriptions of a particular brand in a particular period, diagnosis-specific prescription of a particular brand, the doctor's speciality, specific prescription of a particular brand, the gains and losses of various prescriptions relative to each other, and other areas of interest for pharmaceutical marketing. Prescriptions were included irrespective of inclusion of diagnostic tests for identification of the causative organism of diarrhoea. The prescription share of anti-diarrhoeal formulations containing antibacterial drugs alone has been excluded. However, prescription indicators of both single and multi-ingredient anti-diarrhoeals containing at least one anti-protozoal were included in the study to highlight the prescribing trends of these medicines. These prescriptions were made for clinical cure from diarrhoea.

Observations

On analysing the data it was found that 59 per cent of prescriptions were for FDCs (33 per cent ciprofloxacin and tinidazole and 26 per cent norfloxacin and tinidazole). The remaining 41 per cent were single drug antimicrobial prescriptions (14 per cent metronidazole, 14 per cent secnidazole and 13 per cent tinidazole).

The second important finding was that the most frequently prescribed regimen (FDC of ciprofloxacin and tinidazole) was also the most expensive – Rs 98 for a five-day course

in 1998. The second most frequently prescribed regimen (FDC norfloxacin and tinidazole) was also the second most expensive at Rs 67 for a five-day course. This pattern also applied to the single dose regimens, with a course of metronidazole, secnidazole and tinidazole costing Rs 35, 26 and 20 respectively.

Discussion

The data in this analysis were collected between November 1998 and February 1999, and it is possible that prescribing trends will have changed in the time since then. However, it is more likely that the practices observed in this study are even more entrenched today and the findings from this analysis are relevant today; in fact FDCs are probably more prescribed today than they were eight years ago.

Rational therapy calls for the prescription of less-costly single ingredient drugs more often than costlier combination agents. However, this audit of a sample of prescriptions generated from physicians during their outpatient practice indicates that actual practice is contrary to rational therapy.

The audit excluded physicians working in hospitals, both government and private. Because the sample studied did not contain prescriptions generated in private hospitals it is not possible to comment on the type of prescriptions given to patients with a higher paying capacity.

The study highlights two important findings: the frequency of irrational prescription of FDCs to treat common diarrhoea and the resulting higher cost to the consumer of FDCs when compared to the recommended treatment. Therapy with a single ingredient drug is less expensive than therapy with available FDCs even if the former includes the cost of one diagnostic stool examination before starting therapy. In fact, a correctly diagnosed infection can guarantee microbiological cure, something that may take place but cannot be assured with blanket therapy using a FDC as the infective organism may be resistant to the antibiotic used.

In spite of these facts we find that FDCs have a larger prescription share than do single ingredient amoebicidals (59 per cent vs 41 per cent of prescriptions audited). Why do Indian physicians prescribe costlier medicines rather than equally effective and cheaper alternatives?

The suggested explanation is that such physicians' prescribing practices are influenced by socioeconomic factors in India and the pharmaceutical industry's marketing techniques that include giving incentives to physicians to prescribe certain drugs.

To the average middle or lower middle class Indian, an early recovery from a diarrhoeal illness means an earlier return to work. A loss of working days is a significant source of financial loss to the patient. This issue becomes more important because the overall inadequacy of community health benefits (lack of proper drinking water, food safety, sanitation and other hygienic measures) make diarrhoeal diseases a constant accompaniment for many Indians. The patient's objective is to get well early and get back to work. Indian physicians are aware of their patients' psychology. Therefore, instead of spending the time needed to first do a diagnostic test and then administer the appropriate medicine, they opt for blanket coverage with an amoebicidal and an antibacterial. In this background administering FDCs is perceived as a benefit in terms of gain of workdays for the consumer.

Indeed, if one looks at the costs and benefits of single ingredient regimens when compared to FDCs, treatment with a single ingredient regimen is cheaper but requires a diagnostic test and two visits to the physician, one before the test and the second after the text. The need to wait for the test results and return to the physician before starting on treatment will result in a longer time to cure, and therefore a greater number of working days lost. An FDC is more expensive but since it requires only one visit to the physician, no test, and an immediate start to treatment resulting in a faster cure, it may be less expensive for the patient. However, this assumes that the antibiotic in the FDC will work with the particular infection; if it does not, then treatment will take longer than with a single ingredient regimen preceded by a diagnostic test. In sum, a single-ingredient regimen may be cheaper than an FDC – even when one factors in the cost of the diagnostic test – but it is generally more expensive to the patient in terms of the working days lost.

One story, possibly from the pharmaceutical industry itself, gives an explanation for the introduction of these FDCs for treatment of diarrhoea. Pharmaceutical representatives observed that many practising physicians prescribed an amoebicidal and an antibacterial together for faster symptomatic relief from diarrhoea. The industry took this cue and FDCs came into the market. In other words, the market demand was created by both patients and physicians. The pharmaceutical industry only took advantage of this demand. The pharmaceutical industry is a unique supplier because it caters to two consumers – doctors, the intermediate consumers, and patients, the ultimate consumers. The combined demand created by these two groups is reflected in industry behaviour and practices.

However, if one looks at the non-economic, long-term costs of the use of FDCs rather than single-ingredient drugs, one finds that FDCs cause more harm than good in the long run. Adverse drug reactions and drug interactions are more frequent with FDCs. These reactions and interactions are potentially debilitating and can increase the duration of illness as well as the cost of therapy with FDCs. A more alarming concern is the emergence of drug resistance to norfloxacin and ciprofloxacin from indiscriminate prescription.

Norfloxacin is still the most cost-effective choice for bacterial diarrhoea and urinary tract infections in adults. Ciprofloxacin is the most cost-effective and sometimes life-saving choice for enteric fever. By misusing either norfloxacin or ciprofloxacin in a FDC as an empirical therapy for amoebiasis-like diarrhoea, we are losing effective drugs required for the management of other important communicable and non-communicable

diseases. Both norfloxacin and ciprofloxacin are showing trends of increasing resistance. This could be a consequence of using these molecules in FDCs. As this resistance grows, the next generation of antimicrobials will be replace the existing ones in FDCs. This already seen with the introduction of an FDC of ofloxacin and tinidazole.

The ethical dilemmas may be presented as follows:

What is in the patient's best interest? How should one weigh the immediate economic benefits to the patient – shorter time to recovery and fewer working days lost – in comparison to the possible risks to the patient such as drug interactions and adverse reactions? What importance should one give to the best interest of society? After all, growing antibiotic resistance affects other people needing such drugs for lifesaving purposes. Finally, how are the patient's – and society's – best interests being determined? Are they in turn being determined by industry and the medical profession?

When industry interests and consumer demand give rise to a situation which will have long-term detrimental effects on public health, drug regulatory authorities have a greater role to play, by refusing to license irrational drug combinations and coming down heavily against unethical pharmaceutical marketing practices. There is also a need to promote rational prescribing practices; it is interesting to note the positive correlation between price and frequency of prescription of single-ingredient regimens: the market shares of metronidazole, secnidazole and tinidazole costing Rs 35, 26 and 20 respectively were 14 per cent, 14 per cent and 13 per cent respectively. While this article does not examine questionable marketing techniques, it may be safe to suppose that such practices have played a role in influencing prescribing practices.

Mass awareness and education are critical to arrest this trend. Non-governmental organisations can play a role in this. The pharmaceutical industry in India is not expected to take a lead here. Doctors prescribing FDCs without diagnostic tests are indulging in a significant violation of treatment ethics because they are ignoring the possibilities of harm to the patient from unnecessary medication as well as the long-term public health consequences of such prescriptions.

Conflict of interest: *The author worked as a consultant medical advisor for Emcee Pharmaceuticals, Kolkata, in 1998-1999. Emcee Pharmaceuticals were subscribers to C-Marc audit data.*