

The ethics of physician-pharmaceutical company relationships

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An ethical physician will recognize that the profession demands of him integrity and dedication to its search for truth and its service to mankind . . . and will avoid advocacy of any product when he is identified as a member of the medical profession.¹

Recently two seemingly unrelated events caused me to reflect on a problem that our profession has tended to ignore. The first was the resignation of a cabinet minister for taking a \$250 000 loan that, despite the prime minister's conflict-of-interest guidelines, he failed to report. The second was a call from a pharmaceutical company representative offering me an all-expenses-paid trip to Europe to hear about a new drug that the firm plans to introduce in Canada. These events forced me to ask myself At what point does a physician's acceptance of a drug company's goodwill constitute a conflict of interest?

I do not pretend to know the answer to this question. Like most of my colleagues, I have accepted invitations to local drug-company-sponsored symposia over dinner or snacks, at which the firm had its products clearly in evidence. Occasionally — because of my expertise, I assume — I have been invited to speak at international conferences that are organized by physicians but sponsored by drug firms. Most medical meetings, in fact, rely heavily on such support. Somehow it was less easy to rationalize a fully paid trip to Europe just to hear about a new drug for the treatment of a disease for which I had no research pretensions. What is the pay-off of such a "rent-a-crowd" for the firm? Undoubtedly, those in the marketing department hope that I will develop warm feelings about the product and oblige them by prescribing

it. Also, as an academic I might set the tone for acceptance of the drug by students, residents and colleagues. Deny as I might that such a trip would influence my teaching, an implied obligation is there that has not been reciprocated by the company's use of my scientific and professional expertise. Am I to repay the firm by helping it market the drug? Therein lies the conflict of interest.

Patients complain about the high cost of drugs. Many physicians agree that drugs are over-prescribed and are concerned about the prevalence of side effects. The Ontario Drug Benefit Plan for the elderly is many times over budget, yet how many elderly people do we see who carry in a brown paper bag several bottles of pills for which the original indication is no longer clear? As doctors we must be concerned about how data from industry-funded clinical trials are used. Data that show that a drug is beneficial for one disease (e.g., peptic ulcer) are often used unjustifiably for another (e.g., nonulcer dyspepsia). Negative results of trials are seldom published; selective and spurious positive results frequently are. Such studies need to be balanced, and we risk our integrity if we do not press for full disclosure of results. We must remain free to critically assess the data.

On the other hand, the importance of pharmaceutical houses to modern medicine cannot be underestimated. Where would the treatment of peptic ulcer, congestive heart failure, hypertension and diabetes be today without the entrepreneurial spirit and expertise of international drug houses? Studies of the efficacy and safety of new drugs would be impossible without close cooperation between clinical investigators and the pharmaceutical industry. Other benefits include funding of projects not directly related to the drug study, as well as improved research methods and education programs for residents and practising physicians. Many of my colleagues go so far as to say that the drug companies are the only available sponsors of clinical research, since federal government sponsors are underfunded and seem to concentrate on

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laboratory research, and provincial programs are interested in health care delivery. Indeed, pharmaceutical houses provide the only research support for many academic physicians.

All of this brings us no closer to solving the conflict-of-interest problem. Yet it seems clear that we academic physicians need to develop guidelines to ensure that our conduct as "public figures" is beyond reproach. It must be manifestly clear that we recommend a drug to our colleagues, patients and students only because it is needed and because it is the safest, least expensive and most effective product available.

The recently announced *Code of Marketing Practices*² of the pharmaceutical industry seems a step in the right direction, but our profession needs its own guidelines. For example, clinical researchers and prescribing physicians might consider guidelines such as the following.

- Physicians participating in drug trials must insist on the right to publish the results, even if the data prove unfavourable.

- Results of drug trials should be published first in a peer-reviewed journal or book. They should not be submitted first to drug-company-sponsored publications or the "throw-away" medical press.

- Clinical researchers should insist that the

results of uncontrolled studies not be quoted as facts, that the drawbacks and benefits of a drug be discussed equally and that the results of trials not be extrapolated to include indications for use beyond those justified by the data.

- There should be an "arm's-length" relationship between the sponsoring agency and the physicians organizing and participating in continuing education activities. In other words, physicians should control content and maintain "editorial autonomy".

- When a physician's expenses are paid by a firm or a firm has provided gifts or free samples the physician should be assured that there is no real or implied obligation to promote the firm's products.

In this age, when public figures must be seen to be above reproach, physicians and pharmaceutical houses must act and be seen to act in the public interest. Otherwise, we risk censure that we are a medical-industrial complex with ulterior motives.

References

1. *Code of Ethics*, Can Med Assoc, Ottawa, 1984
2. *Code of Marketing Practices*, Pharmaceutical Manufacturers Association of Canada, Ottawa, Feb 1988

Pediazole*

erythromycin ethylsuccinate/
sulfisoxazole acetyl

antibiotic

Indications: For the treatment of children with acute otitis media caused by strains of *Hemophilus influenzae*, *Streptococcus pneumoniae*, or *Streptococcus pyogenes* susceptible to this combination.

Contraindications: PEDIAZOLE* (erythromycin ethylsuccinate and sulfisoxazole acetyl) Granules for Oral Suspension is contraindicated in:

- Patients with known hypersensitivity to either erythromycin or sulfonamides.
- Infants less than 2 months of age.
- Pregnancy at term and during the nursing period, because sulfonamides pass into the placental circulation and are excreted in human breast milk and may cause kernicterus in the infant.

Warnings: Reports of deaths have been associated with sulfonamide administration from hypersensitivity reactions, agranulocytosis, aplastic anemia, and other blood dyscrasias. The presence of clinical signs such as sore throat, fever, pallor, purpura, or jaundice may be early indications of serious blood disorders. Complete blood counts should be done frequently in patients receiving sulfonamides.

The frequency of renal complications is considerably lower in patients receiving the most soluble sulfonamides such as sulfisoxazole. Urinalysis with careful microscopic examination should be obtained frequently in patients receiving sulfonamides.

The safe use of erythromycin or sulfonamides in pregnancy has not been established (see CONTRAINDICATIONS).

Precautions: Erythromycin is principally excreted by the liver. Caution should be exercised in administering the antibiotic to patients with impaired hepatic function. There have been rare reports of transient hepatic dysfunction, with or without jaundice, occurring in patients receiving erythromycin.

Recent data from studies of erythromycin reveal that its use in patients who are receiving high doses of theophylline may be associated with an increase of serum theophylline levels and potential theophylline toxicity. In case of theophylline toxicity and/or elevated serum theophylline levels, the dose of

theophylline should be reduced while the patient is receiving concomitant erythromycin therapy.

Sulfonamide therapy should be given with caution to patients with impaired renal or hepatic function and in those patients with a history of severe allergy or bronchial asthma. In the presence of a deficiency in the enzyme glucose-6-phosphate dehydrogenase, hemolysis may occur; this reaction is frequently dose-related. Adequate fluid intake must be maintained in order to prevent crystalluria and renal stone formation.

Adverse Effects: The most frequent side effects of oral erythromycin preparations are gastrointestinal, such as abdominal cramping and discomfort, and are dose-related. Nausea, vomiting, and diarrhea occur infrequently with usual oral doses. During prolonged or repeated therapy, there is a possibility of overgrowth of non-susceptible bacteria or fungi. If such infections occur, the drug should be discontinued and appropriate therapy instituted. The overall incidence of these latter side effects reported for the combined administration of erythromycin and a sulfonamide is comparable to those observed in patients given erythromycin alone. Mild allergic reactions such as urticaria and other skin rashes have occurred. Serious allergic reactions, including anaphylaxis, have been reported with erythromycin.

The following untoward effects have been associated with the use of sulfonamides: blood dyscrasias, agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia, and methemoglobinemia.

Allergic reactions: Erythema multiforme (Stevens-Johnson syndrome), generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritis, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia, and allergic myocarditis.

Gastrointestinal reactions: Nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis, and stomatitis.

CNS reactions: Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, and insomnia.

Miscellaneous reactions: Drug fever, chills, and toxic nephrosis with oliguria or anuria. Periarteritis nodosa and L.E. phenomenon have occurred.

The sulfonamides bear certain chemical similarities to some

goitrogens, diuretics (acetazolamide and the thiazides), and oral hypoglycemic agents. Goiter production, diuresis, and hypoglycemia have occurred rarely in patients receiving sulfonamides. Cross-sensitivity may exist with these agents.

Dosage: PEDIAZOLE* Granules for Oral Suspension should not be administered to infants under 2 months of age because of contraindications of systemic sulfonamides in this age group. (See CONTRAINDICATIONS).

For acute Otitis Media in Children: The recommended dose is erythromycin 50 mg/kg/day, and sulfisoxazole 150 mg/kg/day (to a maximum of 6 g/day).

PEDIAZOLE* Granules for Oral Suspension is to be given in equally divided doses four times a day for 10 days. It may be administered without regard to meals, but is preferably given immediately after meals.

Preparation of suspension: Reconstitute PEDIAZOLE* granules by slowly adding the required amount of water to the bottle and shaking moderately until uniformly mixed. When reconstituted, the granules form a white, strawberry-banana suspension.

Once reconstituted, keep tightly closed, store in refrigerator and use within 14 days. Unused portion should be discarded after 14 days.

Supplied: PEDIAZOLE* (erythromycin ethylsuccinate and sulfisoxazole acetyl) Granules for Oral Suspension is available for teaspoon dosage in 100-mL, 150-mL and 200-mL bottles in the form of granules to be reconstituted with water. The suspension provides erythromycin ethylsuccinate equivalent to 200 mg erythromycin activity, and sulfisoxazole acetyl equivalent to 600 mg sulfisoxazole per teaspoonful (5 mL). Product monograph available on request.

1. Bergeron MG. CMAJ 1988;138:35-42.
2. Bluestone CD. Special Report, Postgraduate Medicine 1984; Aug/Sept: III-120.
3. Bergeron MG et al. Ped Infect Dis J 1987;6(7):654-660.
4. Rodriguez WJ et al. ADJC 1985;139:766-770.
5. Based on manufacturers' published price lists, July 1988.

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