

Carcinophobia in clinical research

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The introduction of a new drug into regular clinical use is, in fact, a very late stage in the development of the product, enabled by years of basic research, animal experiments, phase I and phase II trials in volunteers and then in selected patients to adjust dosage and detect untoward effects and, finally, extensive phase III trials to prove efficacy, establish the side-effect profile, and cost-effectiveness in comparison with the existing agents. After many years and thousands of patients in prospective, double-blinded, controlled trials monitored by various review and safety committees, regular, widespread use continues to reveal both new and beneficial effects of drugs as well as previously undetected untoward side effects. Therefore, the last 2 decades witnessed the establishment of organized, preplanned, postmarketing data collection both from the ongoing databases of the pharmaceutical companies as well as by active surveillance by public and government health authorities. Also, repeated prospective controlled trials reexamining the comparative efficacy and safety profile of common existing agents have become legitimate and publishable in highly rated journals.

The fierce competition, not to mention “catch as you can” fights, between the drug-manufacturing companies result in the abundance of these postmarketing trials, in which one company examines, through a hawk-eye, the agents of its competitors. Thus, collected data often forms the basis for altered recommendations or new warnings by health authorities and, not infrequently, also the withdrawal of a widely marketed drug.

Outstanding examples from the last decade are the cyclooxygenase-2 (COX-2) inhibitors. The first one, rofecoxib (Vioxx), was approved for use in 1999 and withdrawn 5 years later, after it had been used by hundreds of thousands of patients, when it became clear that the continuous use of the drug was associated with an increased risk of cardiovascular events and kidney damage. The data about the high frequency of untoward cardiac effects of rofecoxib were

published already in 2001.¹ It took 3 more years for the manufacturer to recall the drug (in 2004) after it had been accused of withholding the information about the risks associated with its continued use.^{2,3} It is difficult to justify the ruling of the U.S. Food and Drug Administration (FDA) to selectively withdraw rofecoxib when it was already clear at that time that both the therapeutic and untoward effects were common for the whole COX-2 inhibitor class.

Another outstanding example of a disfavored drug is rosiglitazone. This insulin sensitizer was prescribed to millions of patients with type 2 diabetes. It had been on the market for nearly 10 years before the evidence about the risk of not only fluid overload and congestive heart failure but also of an increased incidence of coronary events penetrated the awareness of regulatory health authorities, and the drug was completely withdrawn in Europe by the European Medicines Agency (EMA) and largely limited in the United States by the FDA.⁴ Interestingly, as was the case with several prominent agents, while rosiglitazone was blamed for cardiac damage, its close family member – pioglitazone – had been considered safe until data from recent trials have begun to point to a similar, class-characteristic side-effect profile.⁵

In recent years, a new trend has developed to look for excess incidence of malignancies in association with the use of common therapeutic agents. Since the recently published data includes drugs from diverse pharmacological classes, no common underlying mechanism may be responsible for this phenomenon. Moreover, a distinct pattern emerges for these warnings: usually, following the initial publication indicating an increased risk of cancer morbidity and mortality associated with a given drug, subsequent meta-analyses or in-deep analyses of the data render the primary conclusions much less definitive. Presently available data do not allow to confirm excess cancer morbidity in any of the drug classes in question. These publications have hitherto caused uncertainty and even panic among

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patients and physicians alike, resulting in clearly harmful effects of discontinuing widely used and effective medications.

The most outstanding drug so far accused of having a cancer-inducing effect is insulin. Fairly large population studies showed no such effect, but a meta-analysis of several trials which comprised a sufficiently large number of patients demonstrated an increase in morbidity of several malignancies.⁶ Since the analysis concerned a specific insulin (Glargin), the company manufacturing the competitor insulin (Determir) promptly promoted the publication of reviews highlighting the difference in the patterns of receptor binding of the two insulins, thus suggesting a plausible explanation for the presumably differential effects of the two preparations. In view of the well-known surplus of cancer morbidity in diabetes and the initiation of insulin therapy relatively late in the course of the disease in most patients, the presumed association between insulin and cancer must be considered with great caution. Already this warning deters many patients from the initiation of insulin. Given the difficulty of achieving adequate glucose control in many long-standing type 2 diabetics and the absolute dependence on insulin in type 1 patients, the so far inconclusive information places a substantial burden on patients and physicians alike. This issue has been addressed by several leading researchers who advised that the presently available data does not constitute evidence enough to amend the existing policies of insulin therapy in type 2 diabetes.⁷

The second large class of agents, the use of which has been recently linked to an increase in the risk of cancer morbidity, are the angiotensin-receptor blockers (ARBs). A meta-analysis published in *The Lancet*⁸ suggested an increase in the incidence of malignancies in ARB users. However, a closer look into the studies included in this meta-analysis showed that the single agent examined was telmisartan. Also the studies that together comprised the database for the meta-analysis included different patient characteristics to a degree which renders any interpretation doubtful if not irrelevant. The current position of most experts in the field is that for the whole class of these particularly efficient and safe antihypertensive agents, there is insufficient evidence to warrant any change in policy.⁹ Nevertheless, many doctors have already advised their patients to discontinue ARBs and many patients stopped using these agents on their own initiative.

Another new and effective agent recently accused of increasing the risk of cancer was ezetimibe (Ezetrol).¹⁰ This agent, which reduces the absorption of cholesterol for the intestinal mucosa by inhibiting one of the transfer proteins, is an important player in the treatment of dyslipidemia especially in patients in whom the therapeutic target is not obtained by statins alone and in whom statin use is limited by side effects. The initial change of inducing an increase

in cancer morbidity was subsequently refuted by a detailed analysis of the initial data.¹¹ In this case, the demon was quickly returned to the bottle before the damage became widespread. Many physicians, however, who heard the rumor but did not bother to read the publications hesitate to prescribe ezetimibe.

Here is another example: clopidogrel (Plavix), which blocks adenosine diphosphate-binding to the P₂Y₁₂ receptor, thus inhibiting the activation of the glycoprotein IIb/IIIa complex and platelet aggregation, was the sole reign in the field of anti-aggregants for patients after coronary bypass surgery or stenting. Recently, a new competitor agent, prasugrel, has been launched and proved more efficacious than clopidogrel. A controlled study which comprised 13,800 participants showed a 19% risk reduction in coronary events with prasugrel compared with clopidogrel.¹¹ The competition between the two agents led to a study which reported an increased incidence of cancer in patients who took prasugrel.¹² The presentation and the analysis of the data were criticized and followed by publications indicating that the excess of gastrointestinal bleeding with prasugrel may facilitate earlier detection of colon cancers which are not caused by the drug. However, studies in experimental animals showed a double incidence of hepatic, pulmonary, and colon cancer in prasugrel-treated mice compared with placebo. Patient data collected by the FDA demonstrated an overall 1% incidence of colon cancer, substantially lower than expected. However, the ratio of tumor detection was 1.5 to 1.0 in prasugrel-treated patients compared with those receiving clopidogrel. To further complicate the issue, the relatively short follow-up indicates that most of the tumors must have started long before the randomization.¹⁴ Thus, the comparative efficacy vs. the untoward effect profile of these two agents, remains an unresolved issue.

The newest case in this series is the reporting of an excess of cancer of the esophagus, stomach, and colon in long-term users of bisphosphonates. A retrospective study based on data collected by the Royal College of Family Physicians in Britain¹⁵ reviewed 6 million patient files and found 2954 cases of esophageal cancer, 2000 cases of gastric cancer, and about 10,000 cases of colon cancer. A case-control analysis showed an excess of gastrointestinal cancer incidence of 1.3 in patients who received 10 or more prescriptions for bisphosphonates.

A close look into the grant support of the various studies fails to detect a distinct pattern of involvement of interested parties. The scarce information that leaks into the professional literature allows to identify two parallel patterns: drug manufactures often tend to withhold information concerning untoward effects of their products and regulatory health authorities are notoriously slow in responding to such information, contrary to their proclaimed policy. The intervention of a competing company is often needed in order

to set off an inquiry by the responsible authorities, thus uncovering and publishing information which had been available months or even years earlier but nobody bothered to look.

The lessons from these recent conflicting publications are obvious: clinicians responsible for patient care who actually prescribe the various medications are the last and most important link in the chain of parties between the manufacturer and the end user. It is their responsibility to carefully screen the literature, listen to and observe their patients, and meticulously monitor each drug for both individual efficacy as well as side effects. The information provided by official agencies is often late and incomplete. The release of a given agent by the FDA or the EMA or national health authorities does not ascertain whether it is safe.

We prescribe potent medications, which alter basic metabolic and enzymatic mechanisms. It is reasonable to expect also undesirable and untoward effects. Our knowledge is, by definition, incomplete. Despite all safety certificates, surprising and unanticipated developments unfold with time and experience.

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