

## Carcinogenicity of Lipid-lowering Drugs

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### BACKGROUND INFORMATION:

#### **Fibrates:**

Bezafibrate (e.g. Bezalip)

Ciprofibrate (e.g. Modalim)

Gemfibrozil (e.g. Lopid)

Fenofibrate (e.g. TriCor)

<b>Statin</b>	<b>Brand name</b>	<b>Derivation</b>
Atorvastatin	Lipitor, Torvast	Synthetic
Fluvastatin	Lescol	Synthetic
Lovastatin	Mevacor, Altacor, Altoprev	Fermentation-derived
Mevastatin		Naturally-occurring, found in red yeast rice
Pitavastatin	Livalo, Pitava	Synthetic
Pravastatin	Pravachol, Selektine, Lipostat	Fermentation-derived
Rosuvastatin	Crestor	Synthetic
Simvastatin	Zocor, Lipex	Fermentation-derived
Simvastatin+Ezetimibe	Vytorin	Combination therapy
Lovastatin+Niacin	Advicor	Combination therapy
Simvastatin+Niacin	Simcor	Combination therapy

### OBJECTIVE

To review the findings and implications of studies of rodent carcinogenicity of lipid-lowering drugs.

### DATA SOURCES

Summaries of carcinogenicity studies published in the 1992 and 1994 Physicians' Desk Reference (PDR), additional information obtained from the US Food and Drug Administration, and published articles identified by computer searching, bibliographies, and consultation with experts.

### STUDY SAMPLE

We tabulated rodent carcinogenicity data from the 1994 PDR for all drugs listed as "hypolipidemics." For comparison, we selected a stratified random sample of antihypertensive drugs. We also reviewed methods and interpretation of carcinogenicity studies in rodents and results of clinical trials in humans.

## DATA SYNTHESIS

All members of the two most popular classes of lipid-lowering drugs (the fibrates and the statins) cause cancer in rodents, in some cases at levels of animal exposure close to those prescribed to humans.

In contrast, few of the antihypertensive drugs have been found to be carcinogenic in rodents.

Evidence of carcinogenicity of lipid-lowering drugs from clinical trials in humans is inconclusive because of inconsistent results and insufficient duration of follow-up.

## CONCLUSIONS

Extrapolation of this evidence of carcinogenesis from rodents to humans is an uncertain process. Longer-term clinical trials and careful post-marketing surveillance during the next several decades are needed to determine whether cholesterol-lowering drugs cause cancer in humans.

In the meantime, the results of experiments in animals and humans suggest that lipid-lowering drug treatment, especially with the fibrates and statins, should be avoided except in patients at high short-term risk of coronary heart disease.

## THESE AUTHORS ALSO NOTE:

In the past decade (1985 – 1995) there has been a greater than 10-fold increase in the prescription of lipid-lowering drugs because they are being aggressively promoted by their manufacturers.

Lipid-lowering drugs may be taken for 30 years or more, yet the FDA approved these drugs based upon clinical trial that lasted only a fraction of this time.

“Thus, millions of asymptomatic people are being treated with medications, the ultimate effects of which are not yet known.”

“Meta-analyses of randomized clinical trials have suggested that cholesterol-lowering drugs may increase noncardiovascular mortality.”

“Drug companies are required to submit data from rodent carcinogenicity studies to the FDA. These studies are not generally published in scientific journals but are summarized in the *Physicians' Desk Reference* (PDR).” These authors evaluated the results of these carcinogenicity rodent studies in the PDR and compared them to other classes of drugs.

## RESULTS

“The product information for lipid-lowering drugs indicates that all the fibric acid derivatives and statins caused cancer in rodents.”

"In most cases the rodent exposure at which carcinogenicity was observed was of the same order of magnitude as that observed with the maximum dose recommended for humans."

"Unlike the lipid-lowering drugs, most drugs for lowering blood pressure do not cause cancer."

"Almost all known human carcinogens have been found to be carcinogenic in mice and rats."

### **"Why Were These Drugs Approved?"**

These authors reviewed the minutes of the approval committee meeting, and found that representatives of the makers of these drugs downplayed the importance of the rodent carcinogenicity studies. Additionally, for gemfibrozil, "only three of the nine members of the advisory committee believed that the potential benefit of using gemfibrozil, for the prevention of coronary heart disease outweighed the potential risks associated with such use."

Sadly, such votes are only advisory, and the FDA approved gemfibrozil, when all of the following criteria are met:

- 1) Low high-density lipoprotein cholesterol.
- 2) Elevated low-density lipoprotein cholesterol.
- 3) Elevated triglycerides.
- 4) Inadequate response to weight loss, diet, and exercise.

"Unfortunately, the subsequent popularity of gemfibrozil suggests that its use has not been restricted to this small group."

"For patients not at high short-term risk of CHD death, especially patients with life expectancies of more than 10 to 20 years, pharmacologic treatment probably should be avoided."

It is possible that these drugs are not carcinogenic, but rather that it is the lower cholesterol levels they cause being responsible for the adverse effects. "Persons with low cholesterol levels have higher cancer death rates in cohort studies."

"It seems prudent to reserve the statins for people at high short-term risk of heart disease and to be wary about their long-term use."

### **CONCLUSION**

"Most cholesterol-lowering drugs cause or promote cancer."

"Patients to whom these drugs are prescribed are exposed throughout many years to doses approaching those shown to be carcinogenic in animals."

Use of cholesterol-lowering drugs should be restricted to those at high risk of short-term CHD death, such as those with prior CHD, in whom the short-term benefits of treatment are most likely to justify the long-term risks.

#### KEY POINTS FROM DAN MURPHY

- 1) "Drug companies are required to submit data from rodent carcinogenicity studies to the FDA. These studies are not generally published in scientific journals but are summarized in the *Physicians' Desk Reference* (PDR)." These authors evaluated the results of these carcinogenicity rodent studies in the PDR and compared them to other classes of drugs.
- 2) "The results of experiments in animals and humans suggest that lipid-lowering drug treatment, especially with the fibrates and statins, should be avoided except in patients at high short-term risk of coronary heart disease."
- 3) Lipid-lowering drugs may be taken for 30 years or more, yet the FDA approved these drugs based upon clinical trials that lasted only a fraction of this time.
- 4) "Millions of asymptomatic people are being treated with medications [lipid-lowering drugs], the ultimate effects of which are not yet known."
- 5) "Meta-analyses of randomized clinical trials have suggested that cholesterol-lowering drugs may increase noncardiovascular mortality."
- 6) "The product information for lipid-lowering drugs indicates that all the fibric acid derivatives and statins caused cancer in rodents."
- 7) "In most cases the rodent exposure at which carcinogenicity was observed was of the same order of magnitude as that observed with the maximum dose recommended for humans."
- 8) "Almost all known human carcinogens have been found to be carcinogenic in mice and rats."
- 9) "For patients not at high short-term risk of CHD death, especially patients with life expectancies of more than 10 to 20 years, pharmacologic treatment [with lipid-lowering drugs] probably should be avoided."
- 10) It is possible that these drugs are not carcinogenic, but rather that it is the lower cholesterol levels they cause being responsible for the adverse effects. "Persons with low cholesterol levels have higher cancer death rates in cohort studies."

- 11) "It seems prudent to reserve the statins for people at high short-term risk of heart disease and to be wary about their long-term use."
- 12) "Most cholesterol-lowering drugs cause or promote cancer."
- 13) "All members of the two most popular classes of lipid-lowering drugs (the fibrates and the statins) cause cancer in rodents, in some cases at levels of animal exposure close to those prescribed to humans."
- 14) "Patients to whom these drugs are prescribed are exposed throughout many years to doses approaching those shown to be carcinogenic in animals."
- 15) Use of cholesterol-lowering drugs should be restricted to those at high risk of short-term CHD death, such as those with prior CHD, in whom the short-term benefits of treatment are most likely to justify the long-term risks.