CENTER FOR DRUG EVALUATION AND RESEARCH

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PHARMACOLOGY REVIEW

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BISOPROLOL CARCINOGENICITY STUDIES: REVIEW OF SPONSOR'S RESPONSE TO FDA

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DRUG: Bisoprolol fumarate

SPONSOR: Lederle Laboratories
Div. of Am. Cyanamid
Pearl River, NY

SUBMISSION CONTENT:

1. Sponsor's review of the effect of statistical approaches and biological criteria on interpretation of bisoprolol tumorigenicity studies. 2. Interpretations of the rodent studies by animal bioassay experts - Drs. J. Faccini, C. Frith, and B. Wagner. 3. 34 publications on spontaneous rodent neoplasia, chemical induction/detection of rodent tumors, and extrapolation of any results to humans.

SYNOPSIS: Sponsor's/experts' conclusion that bisoprolol is not a tumorigen in rodents (or a potential tumorigen in man) is based on: concurrent and/or historical spontaneous tumor incidences in mice and rats; presence only of common tumors in all 3 studies; conventions of combining certain tumors for analysis; analyzing lymphoma/leukemia by animal incidence rather than organ infiltrated; absence of usual tumorigenic spectra (e.g., hemangioma without hemangiosarcoma; pancreatic islet adenoma but no hyperplasia or carcinoma); lack of confirmation across sex, mice strains, or species (opposite sex typically displayed reverse "anti-neoplastic" trend if you care to interpret the data that way); absence of genotoxic or mutagenic (epigenetic) activities; and sponsor's contention that calculated incidence of false positives and incidence of disputed tumors are comparable, i.e., $p < 0.01$ criterion for common ($\geq 1\%$) tumors is not stringent enough given the approx. 600 statistical tests (sponsor's estimation) performed by SARB (100/sex/study).

I. Sponsor's Argument:

Sponsor argues from 4 vantage points - multiplicity of testing, statistical test characteristics, consistency of results, and biological criteria, as follows:

1. The probability of a false positive increases as the number of tests increases, and the expected number of false positives can be estimated by applying the nominal 5% (Type I) error rate to the no. of hypothesis tests performed by SARB (FDA). Sponsor notes that the latter analyzed approx. 100 findings per sex per study. Counting only the 150 tests of findings with an incidence of 2

or more gives an estimate of 7 or 8 false positives which agrees closely with the seven positive trends identified by SARB.

2. The exact permutation trend test performed by SARB is clearly much more sensitive than the Peto test, allowing for analysis of tumors with an incidence less than 5. Given the no. of hypotheses tested by SARB and the sensitivity of the trend test, they believe that even the critical $p = 0.01$ for common tumors is too high.

3. A third argument is the inconsistency and irreproducibility of findings. In no case was the significant positive trend in one sex supported by a positive trend in the other sex. With only one exception, a decreasing incidence was actually observed in the opposite sex.

4. Biologic criteria used to discount carcinogenicity include absence of genotoxicity in multiple in vivo and in vitro screens, no histopathologic evidence of an epigenetic mechanism of tumor induction, absence of unusual tumors in any study, and no acceleration of tumor onset.

Specific Issues

1. E. Merck mouse study.

MTD: Sponsor argues that enlarged hearts and hepatic steatosis/necrosis seen at 320 and 640 mg/kg daily in the 13 week pilot justifies use of 250 mg/kg/day in the 2-year study.

Regarding ovarian cyst adenomas, sponsor refers to the difficulty of distinguishing cystic papillary hyperplasia from papillary adenoma (Morgan and Alison, 1987). In this study, bisoprolol did not significantly increase the incidence of combined cyst adenomas above control level of 8% ($p < 0.01$ required). Regarding metastatic adenocarcinoma in female lung, sponsor argues that statistical analysis should be conducted only on primary tumors, as practiced by NTP, since a metastasis to an organ does not reflect that organ's response to a chemical insult. Regarding primary FDA reviewer's diagnosis of drug-induced male abdominal lymph node hemangioma, sponsor notes that such blood-filled nodes usually reflect a spontaneous common mesenteric disease in mice. Rather, the standard approach to assessing overall risk to vascular endothelium is to combine incidences of hemangioma and hemangiosarcomas in all tissues (McConnell et al., 1986); such an analysis with bisoprolol was not statistically significant. Regarding granulocytic tumors in females, sponsor notes its high natural occurrence (10% males; 2% females), fact that bisoprolol did not achieve the requisite $p < 0.01$, and the fact that overall incidence of hematopoietic neoplasm was low in the entire study.

2. Lederle mouse study:

At issue were broncho-alveolar adenomas and malignant lymphoma infiltration of salivary and thymus glands in females. Sponsor notes the high (11%) spontaneous rate of female lung tumors (adenoma plus carcinoma) and malignant lymphoma in this study and failure of bisoprolol to attain requisite $p < 0.01$ vs. combined lung tumors or widespread systemic lymphoma (since malignant lymphoma is considered to be a systemic disease, the animal rather than the organ should be, and was, the unit of analysis - 2 references cited).

3. E. Merck rat study:

Tumors of concern were adrenal cortical carcinoma (male) and pancreatic islet cell adenoma (female). When adrenocortical adenoma and carcinoma were combined (because of difficulty in differentiation: Greaves and Faccini, 1984) there was no significant exacerbation by bisoprolol. Sponsor also notes lack of similar findings in females. Regarding pancreatic islet cell adenomas in females, sponsor references 1.5% spontaneous control incidence in the E. Merck historical data base, the 4-8% in other studies (Vandenberge, 1990), and the fact that Peto and exact permutation trend tests came in at $p = 0.03$ and $p = 0.061$ and not the requisite $p \leq 0.01$.

II. Experts' Opinions

Since each of the three experts concludes that bisoprolol, as tested, is not carcinogenic in mice or rats, only the review of Dr. J. Faccini will be presented, and additional opinions of Drs. B. Wagner and C. Frith will be added where they provide supplementary insight.

Dr. J. Faccini (Prof. of Pathol., Univ. Surrey, U.K.):

A. Merck mouse study:

1. Ovarian cyst adenomas and papillary cystadenomas (10/50 HD vs. 3/50 and 5/50 in controls): These are common tumors and, furthermore, results weren't confirmed in the Lederle mouse repeat study.

2. Lung metastatic adenocarcinoma in females (2/50 HD vs. 0/50 both controls): Can be ignored as there was no increased incidence of primary adenoma and carcinoma.

3. Hemangioma of male abdominal lymph nodes (2/50 HD vs. 0/50 control): Not considered to be evidence of carcinogenesis in the absence of malignant vascular tumors (Faccini et al., 1990).

4. Granulocytic leukemia in females (3/50 HD vs. 0/50 or 2/50 in controls): Is naturally sporadic and variable in incidence across and within studies, e.g., the males showed a reverse trend - 1/49 in High Dose vs. 4/50 and 6/50 in controls. Therefore, 3/50 in HD vs. 2/50 in control group #1 is just biologic variation.

B. Lederle mouse study:

1. Female bronchio-alveolar adenoma/carcinoma (12/60 HD vs. 5/60 control): Among the commonest tumors in CD-1 mice, and combined incidence in treated groups is well within control incidence published in literature (Faccini et al., 1990), whereas incidence of 7/60 in concurrent control is low relative to historic control.

2. Malignant lymphoma in female salivary gland: Common neoplasm of the hematopoietic and mononuclear phagocytic system to be evaluated not on incidence in isolated organs but on general distribution, i.e., # of animals affected. Incidence of 11/50 females with widespread systemic lymphoma is within historic control incidence (Faccini et al., 1990) and not statistically different from concurrent control.

C. Merck rat study:

1. Male adrenal cortical carcinoma (2/50 HD vs. 0/50 control): It is appropriate to combine carcinomas with adenomas since benign and malignant adrenal cortical tumors in rats can only be distinguished if metastases are found (Greaves and Faccini, 1984); when combined, there was no real difference between control and treated (Male: 2-3/50 treated vs. 1-2/50 control; Female: 2-3/50 treated vs. 3-4/50 control).

2. Female pancreatic islet cell adenoma (3/50 HD vs. 0/50 or 1/50 in controls): He feels that the marginal increase in these tumors over a lower than usual control incidence and in the absence of any other endocrine effects suggests no more than usual biologic variability.

He feels it is important to also note that liver tumors and commonly-occurring mammary gland tumors were actually of much lower incidence in high dose than in either control.

Conclusion: No evidence of carcinogenic activity in either mouse or rat. Tumors occurred in relatively low incidence, and none were rare or unusual. All were tumors known to occur spontaneously in rodents. Furthermore, the liver (a common carcinogen target) had a lower than control tumor incidence at the high dose in all three rodent studies. Finally, repeat mouse study did not confirm "findings" of original E. Merck study.

OPINION OF DR. C. FRITH (Consultant in Path./Tox.; Toxicology Pathology Assoc., Little Rock, Arkansas):

Conclusions of non-carcinogenicity in both species, and their bases, essentially those of Dr. Faccini. Additional points were also made:

Merck mouse study - With regard to lymph node hemangioma, he notes that vascular neoplasms arise from endothelial cells and since the latter are ubiquitous, the denominator to be used in the analysis of vascular tumor data should be the number of animals and not individual organs.

Lederle mouse study - Regarding bronchiolo-alveolar neoplasms in this study, rationale for combining adenomas and carcinomas (as also advocated by Dr. Faccini) is provided: The two neoplasms cannot be distinguished from each other at the light microscopic level and, further, adenomas are believed to progress to carcinoma with time. When combined, the 27% incidence in HD females is not different from the 15% incidence in controls. He also finds noteworthy the approx. 50% lower incidence of such tumors in HD males vs. controls. Regarding malignant lymphoma, his position (again in agreement with Dr. Faccini) is that such neoplasm should be counted on an animal basis irregardless of whether they occur in either a single organ or is widely disseminated (11/60 HD female incidence of widespread lymphoma vs. 7/60 control was not significant). He also dismisses pancreatic islet cell adenoma in the Merck rat study, but on the basis of absence of any associated hyperplasia and/or carcinoma and, further, that adenoma incidence (3/50 HD females) is significantly different from one control but not the other.

He concludes that there is no evidence of rodent carcinogenicity, and that all of the disputed neoplasms can be explained or discounted.

OPINION OF DR. B. WAGNER (formerly Chief, Dept. of Pathol. and Lab. Medicine, Overlook Hospital, Summit, NJ):

His interpretation, based on biological rather than statistical significance, leads to the same conclusion as that of the first two reviewers. Additional points made:

1. E. Merck mouse study: He notes the absence of ovarian cystoadenomas in either control or treated mice in the Lederle, but not the Merck mouse study, supporting

importance of strain variability in spontaneous tumor incidence: when related ovarian tumors were combined, there was no bisoprolol effect.

2. Lederle mouse study: No new arguments.

3. Merck rat study: No new arguments.

He concludes that since bisoprolol was inactive in a variety of genotoxic assays, then, if carcinogenic, it would be acting, by several possible mechanisms, as a mitogen. However, he saw no histologic evidence of increased cell replication or pre-neoplasia in any of the organs with tumors. Rather, all tumors were common and typical of aging rodents. There was neither correspondence between sex or species nor evidence of accelerated tumor onset. He finds no reason to project a clinical risk of neoplasia.

RECOMMENDATION:

That, in spite of statistically significant increases in certain tumors, sponsor's conclusion be accepted given the context of: high spontaneous tumor rates and, accordingly, probability of false positive (Fears et al., 1977); irreproducibility of results with, rather, reverse trends in opposite sex; accepted conventions for combining tumor incidences prior to analysis; and lack of genotoxicity or mitogenic activity.

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A.F. DeFelice, Ph.D.

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