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Metabolism of Antiestrogens

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Since the first description of the metabolism of tamoxifen by Fromson and coworkers in 1973 (1,2), there has been an increasing interest in the pharmacology of antiestrogens that has paralleled their expanding clinical applications.

This chapter is a guide to the fundamental advances that have occurred during the past 25 years as a result of increasing knowledge about the metabolism of tamoxifen. Detailed reviews of studies have been published in earlier articles (3–8). Tamoxifen has become the gold standard for the endocrine treatment of all stages of breast cancer (9). The success of tamoxifen, however, has resulted in an intense reexamination of its toxicology because of the proposals to test the drug in the prevention of breast cancer and its current evaluation in clinical trials (10). The finding that tamoxifen produces cancer in the rat liver (11–13), despite there being no evidence of hepatocellular carcinoma after 20 years of clinical use, has caused an urgent reexamination of the metabolism of tamoxifen in animals and humans. Additionally, as a result of the commercial success of tamoxifen, new antiestrogens, based on tamoxifen and its metabolites, are entering clinical trials for a variety of uses from breast cancer treatment to the treatment of osteoporosis (14).

There are, therefore, two major areas of current research interest that are discussed in this review. A close examination of the metabolites of tamoxifen has resulted in (1) the development of new antiestrogens with broad clinical applications and (2) an understanding of rat liver carcinogenesis.

METABOLIC ACTIVATION AND ANTIESTROGEN ACTION

Extensive examination of tamoxifen has identified two principal routes of metabolism: (1) 4-hydroxylation and (2) the progressive degradation of the dimethyaminoethane side chain (Fig. 1).

Tamoxifen is hydroxylated in the 4-position to produce 4-hydroxytamoxifen, a minor metabolite with a high binding affinity for the estrogen receptor (15). The metabolite has been observed as a minor metabolite in rats and humans, but it is a major metabolite in the mouse (16). Metabolic activation seems to be a general principle for most antiestrogens based on triphenylethylene. Antiestrogens that have a methoxy group in an equivalent position, for example, U-23,469 (an analogue of the antiestrogen nafoxidine) (see Chapter 2) (17) or nitromifene (18,19) (Fig. 2), can be demethylated to the hydroxylated metabolite with a high binding affinity for the receptor.

In contrast, the progressive demethylation of the tamoxifen side chain, first to N-desmethyltamoxifen, the principal metabolite in humans (20), and then to didesmethyltamoxifen (21), does not affect the biological actions of the triphenylethylene. However, deamination of didesmethyltamoxifen, first to