Short Communication

CIMETIDINE AND THERAPY OF RODENT TUMOURS

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A number of recent studies have shown that the growth of certain rodent tumours may be inhibited by the oral administration of the H-2 antagonist cimetidine (Gifford et al., 1981; Osband et al., 1981). Furthermore, it has been proposed that the antitumour effects of this compound are due to its ability to inhibit histamine-induced T-suppressor-cell activation (Osband et al., 1980a, 1981; Ogden & Hill, 1980; Gifford et al., 1981). In view of the potential of this approach to immunotherapy we decided to undertake studies on the effect of similar cimetidine protocols on the growth of some of the experimental rodent tumours routinely used in our laboratories. The results of these studies are summarized below.

Male syngeneic WAG/Ed (Edinburgh University Centre for Laboratory Animals strain of Wistar rats) were inoculated s.c. with $10^5$ viable cells of the asbestos-induced mesothelioma MF3 (Bolton et al., in preparation) and cimetidine (Smith, Kline and French Laboratories Ltd., Welwyn Garden City) was included in the drinking water from the day of tumour inoculation. Daily water consumption was recorded for all animals on a cage basis for several days before experiments to calculate the mean volume of water imbibed by each mouse or rat. Control animals were inoculated with tumour but received unadulterated drinking water. Each cage contained 4 to 5 animals. Tumour diameters were measured at regular intervals with vernier-scale calipers.

Spleen cells were prepared from syngeneic WAG/Ed rats, and the effect of cimetidine on the in vitro binding of histamine to spleen lymphocytes was followed as described by Osband et al. (1980b). Histamine dihydrochloride (Sigma, Poole) was coupled to fluoresceinated bovine serum albumin (B.S.A., Sigma) with 1-ethyl 3-(3-dimethylamino-propyl) carbodiimide hydrochloride (Sigma) at pH 5.6 using a method modified from Hannant et al. (1980).

The results of some of the in vivo experiments are summarized in the Table. They show that, at the concentration of cimetidine used, there was no observable effect on the incidence or size of tumour in the rat and mouse models. The dose of cimetidine used was the same as that shown by Gifford et al. (1981) to have a maximum inhibitory effect on the growth of a syngeneic MCA-induced fibrosarcoma in C3H mice and a lymphoma ascites of C57BL/6 mice. The MCA-induced fibrosarcoma used in our study was syngeneic

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to CBA mice, and whilst the use of a different mouse strain might have had some effect, the complete absence of any tumour inhibition is unlikely to be a result of sub-optimal cimetidine concentration. Other studies (results not presented) with tumour CCH1 showed that concentrations of cimetidine up to 200 mg/kg/day also had no observable effect. In contrast, Gifford et al. (1981) found that tumour growth in mice was sensitive to cimetidine concentrations ranging from 15 to 200 mg/kg/day.

The lack of effect in the rat mesothelioma experiments is not because cimetidine does not function as a H-2-receptor antagonist in this species. In vitro studies clearly demonstrated that histamine (labelled with fluorescing BSA) was able to bind specifically to 33.9±8.8% (mean ± s.d.) of normal WAG/Ed rat spleen cells. Pretreatment of these cells with 10⁻³M cimetidine for 1 h at 37°C before washing and incubation with the fluorescence reagent reduced the fluorescent staining to 12.1±2.7%. Therefore, although cimetidine failed to influence tumour growth, it did bind in vitro to H-2 receptors on rat spleen cells.

In summary, cimetidine has been shown to function as an H-2 receptor antagonist in both mice and rats, and to be an effective immunostimulator in therapy of some tumours. However, it appears that the compound may not have universal application in tumour therapy, because it can exhibit variable effects on tumours within the same species (mouse) and antitumour effects in tumour-bearing rats have yet to be demonstrated. Moreover, a recent report suggests that cimetidine has no effect on immunological parameters in man (Festen et al., 1981). In the light of these observations we would suggest that further studies with this compound are necessary before any decision can be reached on its suitability for clinical use.

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