METRONIDAZOLE (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

Two epidemiological studies[1,2] of women treated with metronidazole showed some excesses of cancers of the uterine cervix, a neoplasm that has risk factors in common with vaginal trichomoniasis, the main indication in women for treatment with this drug. In one study[1], a greater excess of cervical cancer was observed in women with trichomoniasis who were not exposed to metronidazole than in those who were (relative risk, 2.1 *versus* 1.7). An excess of lung cancer (4 observed, 0.6 expected) seen in one of these studies[1] was not found in the other (2 observed, 2.6 expected)[3]. In the former, the excess was mainly of adenocarcinoma (3/4 cases) and was concentrated after at least ten years from first use of metronidazole (3 observed, 0.3 expected)[4]. Further follow-up and analysis of these data have suggested that the excess could be explained entirely by confounding with smoking[5].

Another study in which 12 280 users of metronidazole were followed up for two and one-half years gave a relative risk of 0.9 (95% confidence interval, 0.5-1.9) for all cancers[6].

B. Evidence for carcinogenicity to animals (*sufficient*)

Metronidazole has been tested for carcinogenicity by oral administration to mice and rats. It significantly increased the incidences of lung tumours in mice of each sex, of lymphomas in female mice[7,8] and of mammary, pituitary, testicular and liver tumours in rats[7,9,10]. It increased the incidence of colonic tumours induced in rats by subcutaneous administration of 1,2-dimethylhydrazine[11,12].

C. Other relevant data

Studies on bone-marrow cells and lymphocytes from a series of patients treated with metronidazole showed no increase in the incidence of chromosomal damage. Metronidazole was active in body fluid assays using sweat, faeces and urine from humans exposed *in vivo* and urine from rodents exposed *in vivo*[13].

Metronidazole did not induce micronuclei in bone-marrow cells of mice or rats, sister chromatid exchanges in bone-marrow cells of Chinese hamsters or unscheduled DNA synthesis in germ cells of male rabbits treated *in vivo*. Human cells exposed to metronidazole *in vitro* did not show increased incidences of chromosomal aberrations, whereas results with respect to sister chromatid exchanges were inconclusive. Metronidazole did not induce sister chromatid exchanges in cultured hamster cells; conflicting results were reported for the induction of mutation and DNA damage in rodent cells *in vitro*. It did not induce sex-linked recessive lethal mutations in *Drosophila* or recombination in yeast. It induced mutation in fungi and bacteria and induced prophage in bacteria[13].

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