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IN VIVO MUTAGENICITY EVALUATION OF DOMPERIDONE IN *DROSOPHILA* GERM CELLS AND RAT BONE MARROW CELLS

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SUMMARY

Possible induction of chromosome aberrations and gene mutations by domperidone was studied in vivo respectively by a micronucleus test on female rats and a sex-linked recessive lethal test on Drosophila. In accordance with previous results all these studies revealed negative findings for domperidone so that it can be concluded that domperidone has no potential to induce chromosome aberrations and/or gene mutations.

Key words: Mutagenicity tests; Recessive lethal test; Micronucleus test; Domperidone; Cyclophosphamide

INTRODUCTION

Domperidone (Janssen Pharmaceutica N.V., 2340 Beerse, Belgium) (5-chloro-1-{1-[3-(2,3-dihydro-2-oxo-1*H*-benzimidazole-1-yl) proppyl]-4-piperidinyl}-1,3-dihydro-2H-benzimidazole-2-one) is a new potent gastrokinetic drug with antiemetic activity [1—2].

In a previous study, using the micronucleus test we found that domperidone has no chromosome damaging potential on bone marrow cells of male mice [3]. As in toxicology testing the choice of species takes a key-position in determining a reliable conclusion on mutagenic potential [4—7], a supplementary micronucleus test was performed on female rats. For the assessment of gene mutations on eukaryotes, a sex-linked recessive lethal test was performed on *Drosophila.*

MATERIALS AND METHODS

The micronucleus test was carried out on Wistar-derived young female rats weighing about 100 g. The female rats were treated once orally with 20, 40,

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80 and 160 mg/kg domperidone or 40 mg/kg cyclophosphamide as positive control. Domperidone was administered as a suspension containing tween 80 and distilled water. The rats were killed 30 h after treatment and smears were made according to Schmid [8]. The slides were blind coded and a total of 1000 polychromatic erythrocytes (PCE) were examined for the presence of micronuclei.

The sex-linked recessive lethal test was performed on *Drosophila* using Oregon-K wild type males and Muller-5 (Basc) females. Domperidone (Motilium R: 5 mg/ml ampullae) was added at concentrations of 100, 500 and 1000 μg/ml to the nutritive medium. Flies of the Oregon-K strain were transferred to this medium and allowed to lay eggs. Larvae were fed with this medium during their whole life cycle. The toxic effects were scored at the treated generation. Treated wild-type males of the Oregon-K strain were mated individually to virgin females of the Basc genotype. The fertility and the mutagenic effects were analysed respectively at the first and the second generation.

Statistical analysis was performed using the Mann-Whitney U-test for the micronucleus test and the Kastenbaum-Bowman tables [9] for the *Drosophila* test.

RESULTS

The incidence of micronucleated PCE found in the 20, 40, 80 and 160 mg/kg domperidone treated female rats was found to be comparable to the control values (Table I). As expected, the administration of 40 mg/kg cyclophosphamide produced a high incidence of micronucleated PCE [10].

Results on the *Drosophila* test are summarized in Table II. Although a slight delay in hatchability was observed, no significant decrease in the viability could be evidenced at the treated Oregon-K generation. The fertility of the domperidone treated Oregon-K males was found to be higher when compared to the control group indicating the absence of any toxic effect.

TABLE I

RESULTS OF THE MICRONUCLEUS TEST IN RATS

Dosage group	No. of animals	PCE analysed	PCE with MN	
			Number	%
Negative control	6	6000	4	0.07
Cyclophosphamide (40 mg/kg)	6	6000	139[a]	2.32
Domperidone (20 mg/kg)	6	6000	2	0.03
Domperidone (40 mg/kg)	6	6000	6	0.10
Domperidone (80 mg/kg)	6	6000	4	0.07
Domperidone (160 mg/kg)	6	6000	7	0.12

Abbreviations: PCE, polychromatic erythrocytes and MN, micronuclei.
[a]Mann-Whitney U-test: $P \leq 0.01$.

TABLE II

RESULTS ON THE VIABILITY OF THE TREATED OREGON-K GENERATION, THE FERTILITY OF DOMPERIDONE TREATED OREGON-K MALES AND THE FREQUENCY OF SEX-LINKED RECESSIVE LETHAL MUTATIONS AT THE SECOND GENERATION AFTER TREATMENT

Concentrations (μg/ml food)	Viability[a]	Fertility[a]	No. of chromosomes analyzed	Lethals	
				Number	%
Control	56.6	36.0	601	2	0.33
100	50.9	40.5	618	2	0.32
500	44.5	39.7	621	3	0.48
1000	50.3	45.7	604	2	0.33
Total for 3 concentrations			1843	7	0.38

[a] Mean number of flies/couple.
Statistics: Kastenbaum and Bowman tables [9].

The frequency of sex-linked recessive lethals in the 3 domperidone dosage groups was found to be normal and comparable to the control group. The cumulated results of the 3 domperidone dosage groups also revealed no significant increase in the frequency of recessive lethals.

DISCUSSION

Some benzimidazole analogues are known to possess mutagenic activity [11]. The mutational mechanisms are base substitutions, chromosome aberrations and mitotic arrest of which the latter has the most pronounced effect. The base substitution type point mutations arise by incorporation of benzimidazole into nucleic acids. In the *Salmonella*/microsomal activation test (unpublished results) domperidone was not found to be mutagenic either with or without a rat metabolic activation system. The negative findings of the present sex-linked recessive lethal test confirmed that domperidone has no potential to interact with nucleic acids.

In previous studies, domperidone failed to demonstrate any chromosome damaging potential and/or mitotic arrest in vitro in human lymphocytes and in vivo in mice germ cells and bone marrow cells [3].

However, within the chemical family of benzimidazoles, difference in response according to the animal species have already been reported. Methyl-2-benzimidazole carbamate administered orally increased the frequency of chromosome aberrations in the rat [12] but failed to induce chromosome aberrations in the Chinese hamster [13]. These differences in sensitivity are probably related to differences in pharmacokinetic behaviour and metabolism.

The absence of clastogenic activity found in this micronucleus test on rats confirmed the results found in previous studies [3] indicating that domperi-

done has no chromosome damaging or spindle poisoning potential. Furthermore no differences in sensitivity to domperidone could be evidenced between the different species and sexes.

Studies carried out by Seiler and Limacher [14] revealed that mutagenicity of 2-substituted benzimidazoles was depressed by the increasing size of the 2-substituents, because of an increasingly difficult incorporation into nucleic acids. The absence of any mutagenic effect of domperidone observed in the performed tests is most likely related to the occurrence of a large sized molecule preventing incorporation into the nucleic acids.

It can be concluded from this study that domperidone did not induce an increase of gene mutations in *Drosophila* and chromosome aberrations in rat. As no differences in genetic response were found between earlier results [3] and the recent findings using different test systems, it is unlikely that domperidone will show any genotoxic activity in vivo in man.

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