IN VIVO CYTOGENETIC EFFECTS OF HALOPERIDOL IN MICE

DWARKANATH K. MURTHY and
S. SUBRAMANYAM*
Department of Genetics, Nizam College, Hyderabad 500 001, India.
** Department of Genetics, Osmania University, Hyderabad 500 007, India.*

HALOPERIDOL belonging to butyrophenone group is a potent anti-psychotic and anxiolytic agent used extensively as an alternative to phenothiazines. Mutagenic effects of haloperidol have been reported in *Drosophila melanogaster*[1,2]. Reports available on its cytogenetic effects both under the *in vivo* and *in vitro* conditions are scanty and conflicting [3–5]. Reddy *et al*[6] demonstrated mitodepressive, strong C-mitotic and chromosome damaging property of the drug by employing the *Allium* test. The present note reports a systematic analysis to assess the *in vivo* effects of haloperidol on mitotic chromosomes of male mice.

Haloperidol was fed orally to Swiss albino, 8–10 week old male mice, at doses of 0.312, 0.624 and 1.248 μg in 0.5 ml of sterile double distilled water. Single and cumulative dose series were employed, animals in the latter group received the same doses of the drug consecutively for 15 days at 24 hr intervals. Doses of the drug computed on body weight basis lie within the therapeutic range. Animals were sacrificed 24, 48 and 72 hr after single dose administration and at the same periods following the last day of drug feeding in cumulative series. For each treatment period in either series a control animal fed with equal volume of distilled water, was maintained and processed simultaneously. Somatic chromosome from bone marrow was prepared by standard air drying technique and stained with buffered Giemsa. One hundred well spread metaphases per dose per period were scored for structural and numerical chromosome aberrations and the results obtained were statistically analysed.

Quantitative details on various types of chromosomal aberrations recorded following different periods of treatment for each dose in the single and cumulative series are given in table 1. Chromatid and isochromatid gaps, chromatid breaks, unidentifiable fragments and centric fusions constituted the structural anomalies. As seen in the table, their values are negligible and statistically insignificant when individual values are considered. The total percentages of structural aberrations showed significant increase only for two doses in the single dose series. Numerical anomalies like hypo- or hyperploid cells were totally absent in any of the treatments. Premature chromatid separations were recorded and statistically significant increase is seen only for some treatments in either series. Since these are visualised in controls the process may only be accentuated under the influence of the drug. In the above instances as no broken fragments are realised and only chromatids are precociously separated, it resembles a fission in the middle of the chromosome. The present observations confirm those from mitotic cells of the plant test system reported earlier[6], where higher concentrations of the drug were shown to induce breaks selectively at the centromeric region. The overall rate of aberrations is also provided for both the series and does not show significant variation for any specific type of structural anomaly. Between the two series only a marginal variation is noted with respect to the overall percentage of aberrations. The results suggest that the drug is non-clastogenic and is therefore not hazardous to the genome at the doses attempted. A nonmitoclasic nature of haloperidol can be emphasised in view of the total absence of polyploids. The present results agree with those of van Den Berghe[7]. Though the drug has been reported to induce chromosome damage in *Allium*[6] it need not be necessarily the same for mammalian test system[8]. The observations reported here are considered important in view of the emphasis laid by the World Health Organization that all therapeutic agents should be screened for their cytogenetic effects[9] and publish the results even if they are negative[10].

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Table 1. *Chromosomal aberrations induced by Haloperidol in mitotic cells of male mice.*

Period and Dose (μg)	Structural aberrations: Percentage of cells with Gaps	Breaks	Fragments	Centric fusions	Total	Premature chromatid separations
Single dose series (S.D.)						
24 hr						
Control	0	0	0	0	0	1
0.312	0	0	0	1	1	6
0.624	1	2	0	1	4*	12*
1.248	0	1	0	1	2	5
48 hr						
Control	0	0	0	0	0	1
0.312	2	0	0	0	2	4
0.624	2	1	0	1	4*	9*
1.248	1	0	0	0	1	8*
72 hr						
Control	0	0	0	0	0	2
0.312	0	0	0	2	2	4
0.624	0	0	0	1	1	9*
1.248	0	0	0	1	1	5
Cumulative dose series (C.D.)						
24 hr						
Control	0	0	0	0	0	1
0.312	0	0	0	0	0	3
0.624	2	1	0	0	3	6
1.248	0	1	0	1	2	7*
48 hr						
Control	0	0	0	0	0	3
0.312	1	0	0	0	1	8
0.624	0	1	1	1	3	9
1.248	1	0	0	1	2	13*
72 hr						
Control	0	0	0	0	0	5
0.312	2	0	0	0	2	4
0.624	2	1	0	0	3	7
1.248	1	1	1	0	3	6
Overall percentages:						
Control(SD)	0	0	0	0	0	1.33
Treated(SD)	*0.67*	*0.44*	0	0.89	2.00	6.89
Control(CD)	0	0	0	0	0	3.00
Treated(CD)	1.00	0.56	0.22	0.33	2.11	7.00

* *Significant at 5% level.*

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