Response to Atropine in Down's Syndrome

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Mir, G. H., and Cumming, G. R. (1971). Archives of Disease in Childhood, 46, 61. Response to atropine in Down's syndrome. A previous report indicated abnormally rapid heart rates in patients with Down's syndrome given atropine, and the possibility of a potentially dangerous idiosyncrasy to atropine in these patients has been raised. The heart rate response to atropine in doses of 30 to 60 μg/kg was studied in 14 children and 11 adults with Down's syndrome, using for control subjects 7 children and 9 adults with mental retardation not due to Down's syndrome. The heart rate response to atropine was similar in the patients with and without Down's syndrome. Peak heart rates occurred at 25 μg/kg of atropine after an initial slowing with 5 to 7 μg/kg. The heart rates of the subjects with Down's syndrome tended to be lower than those of the controls after propranolol was given in addition to the atropine, but the significance of this was not known. Ophthalmic atropine produced a more rapid mydriasis in the Down's syndrome patients, but the degree and duration of the pupillary dilatation was the same as in the control subjects.

Adults with Down's syndrome are said to be abnormally sensitive to the mydriatic (Berg, Brandon, and Kirman, 1959; O'Brien, Haake, and Braid, 1960; Priest, 1960) and cardio-acceleratory (Harris and Goodman, 1968) effects of atropine. Our initial purpose was to study the effects of atropine in mentally retarded children with and without Down's syndrome. When no increased cardio-acceleration was found in the children with Down's syndrome, a group of adult subjects was added to the study. After the heart rate response to atropine was assessed, the 'intrinsic heart rates' (Jose, 1966) of these patients were determined by producing β-adrenergic blockade with propranolol.

Paediatric Subjects

Seven male and seven female children, 2 to 10 years of age with proven Down's syndrome, were selected from the wards of a hospital for retarded children. Five boys and two girls (aged 3 to 10 years) with chronic brain damage served as controls. Parental permission was secured for each patient to enter the study. All patients were active and physically well and not on medication. Resting 13-lead electrocardiograms were normal in all subjects. One patient with Down's syndrome had a small ventricular septal defect.

Adult Subjects

Six male and five female patients, 20 to 29 years of age with Down's syndrome were selected from an institution for the mentally retarded. Five men and four women, aged 22 to 32 years, with mental retardation of unknown cause, served as controls. Family permission for the patients' participation was obtained. All patients were ambulatory and were not receiving drugs. Cardiac examinations including 13-lead electrocardiograms were normal.

Chromosome studies indicated one child and one adult with Down's syndrome had 21/15 translocations, the other Down's syndrome patients had 21 trisomy. Control subjects had normal karyotypes.

Methods

The subjects were studied sitting comfortably watching television. Heart rate was monitored from lead II of the electrocardiogram. A scalp vein needle was inserted into a left arm vein and kept open with a slow infusion of 5% glucose/water. After starting the intravenous infusion and connecting the electrocardiograph leads, the subject was allowed to rest undisturbed for 10 minutes before the control heart rate was taken. As a further control 1 ml saline was injected into the side arm...
of the intravenous tubing and heart rate was obtained 3 minutes later. Atropine sulphate was given intravenously in doses of 5 to 7 μg/kg every 3 minutes to a total dose of 30 to 40 μg/kg. Heart rate was determined before each dose by measuring the interval between 5 consecutive beats of the electrocardiogram. Three minutes after the last dose of atropine, propranolol 0.2 mg/kg was given and heart rate was followed for an additional 10 minutes.

The pupillary response to atropine was studied in 6 of the children with Down's syndrome and in 6 control subjects, and in 10 adults with Down's syndrome and 10 matched controls. One drop of 1% atropine sulphate was placed in the left conjunctival sac of each subject. Pupillary size was estimated by holding a standard card near the eye. Measurements of the pupil of each eye were obtained before atropine and after every 5 minutes for 1 hour, and then at 1, 3, and 7 days. For the eye study in the children, the patients and controls were of the same mean age (8 years), and in each group 4 patients had brown and 2 had blue eyes. For the adult study there were 6 patients with brown and 4 with blue eyes in each group. A windowless room with constant ambient light was used.

Significance of differences between the Down's syndrome and control groups was determined with the t test.

Results

Children. The mean values for age, height, and weight were slightly greater for the control children, but the differences were not significant (Table I).

The means and standard deviations of the heart rates in response to the cumulative atropine doses are given in Table II. Because of the reported sensitivity to atropine, only 3 patients with Down's syndrome were given 40 μg/kg; 9 received a total dose of 35 μg/kg; while 5 of the 7 controls received 40 μg/kg.

The mean resting heart rate was greater for the control subjects. The heart rate decreased below control values in both groups after the initial 7 μg/kg of atropine, then increased to a mean maximum rate of 153 beats/min in the control and 143 beats/min in the children with Down's syndrome. There were no significant differences between control and Down's syndrome patients when the pulse rates were presented as absolute values or as differences from the control value (taking the value after the saline as the control) at each dose level.

β-adrenergic inhibition with propranolol produced a prompt reduction in mean heart rate of 18 and 19 beats/min in the control and Down's syndrome patients, and after 10 minutes further

TABLE II
Heart Rates of Children

<table>
<thead>
<tr>
<th>Mean Heart Rates</th>
<th>Mean Change from Rest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=7)</td>
<td>Down's Syndrome (n=14)</td>
</tr>
<tr>
<td>Control—start</td>
<td>108 ± 26</td>
</tr>
<tr>
<td>Control—10 min</td>
<td>106 ± 23</td>
</tr>
<tr>
<td>3 min after saline</td>
<td>106 ± 23</td>
</tr>
<tr>
<td>Atropine (μg/kg)</td>
<td>95 ± 20</td>
</tr>
<tr>
<td>7</td>
<td>115 ± 25</td>
</tr>
<tr>
<td>14</td>
<td>136 ± 21</td>
</tr>
<tr>
<td>21</td>
<td>149 ± 17</td>
</tr>
<tr>
<td>28</td>
<td>153 ± 17 (7)†</td>
</tr>
<tr>
<td>35</td>
<td>151 ± 12 (5)†</td>
</tr>
<tr>
<td>40</td>
<td>133 ± 12</td>
</tr>
<tr>
<td>1</td>
<td>130 ± 11</td>
</tr>
<tr>
<td>5</td>
<td>129 ± 13</td>
</tr>
<tr>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

± = standard deviation. * = p<0.05 compared to control. † = number of subjects.
reductions of 4 and 5 beats/min. At this point, the difference in heart rate between the groups reached statistical significance and was 10 beats/min greater in the control subjects.

Table III shows the mean differences in pupillary size between the control eye and the eye receiving the atropine. There was a more rapid mydriatic response in the Down's syndrome patients. The difference between control and Down's syndrome subjects reached statistical significance 10 and 15 minutes after the atropine administration. After this, the differences in pupillary size tended to be greater in the control subjects, but the differences between the groups were not statistically significant.

There were no untoward side effects from the intravenous or ophthalmic atropine. Subjects with Down's syndrome exhibited more flushing and drowsiness than the controls, but this was not quantitated.

**Adults.** The patients with Down's syndrome were shorter and heavier (Table I). The mean heart rate data for the adult subjects are given in Table IV. The patients with Down's syndrome had slower resting heart rates, and slower heart rates in response to atropine compared to the control subjects. The mean maximum change in rate was 43 beats/min for the control subjects, and 44 beats/min for the patients with Down's syndrome. The mean maximum change occurred at an atropine dose of 30 μg/kg in the control subjects and 25 μg/kg in the patients with Down's syndrome. There was no significant difference between the absolute heart rates or the changes in rate of the Down's syndrome and control groups at any dose level of atropine.

Two patients with Down's syndrome had peak heart rates of 108 and 114 beats/min after 40 μg/kg of atropine, and these subjects were given additional atropine to a total dose of 60 μg/kg. The heart rates failed to increase any further, and there were no side effects from this high dose of atropine other than dry mouth and flushed face.

After propranolol, the heart rates slowed abruptly, and 10 minutes after propranolol the mean rate of the control subjects was 18 beats/min above the control, and for the patients with Down's syndrome 15 beats/min above. The mean intrinsic heart rate was 15 beats/min lower in the Down's syndrome patients compared to the control (p < 0.05).

The mean heart rates for all control and Down's syndrome patients with separation of children and adults is shown in Fig. 1. The mean heart rates for the adult patients with division into male and female are shown in Fig. 2. Male and female control and Down's syndrome patients were
Fig. 1.—The mean heart rates for control and Down's syndrome patients plotted against the atropine dose per kg body weight on a logarithmic scale. Two control rates (C) and one rate after placebo (P) were obtained 3 minutes apart. The mean heart rates fell after the initial small dose of atropine, and then increased to reach plateau values at 25 to 30 μg/kg. C = control patients. D = Down's syndrome patients.

Fig. 2.—Sex comparison of mean heart rate response to atropine. There was no significant sex difference in the heart rate response to atropine. C = control patients, D = Down’s syndrome patients, P = placebo injection.

patients of Harris and Goodman (1968), about 10 beats/min at 10 μg/kg, 30 beats/min at 20 μg/kg, and 40 beats/min at 30 μg/kg. Harris and Goodman found a mean increase in heart rate of about 35 beats/min with 10 μg/kg in 12 adult patients with Down’s syndrome, while in our 11 adult patients with Down’s syndrome the mean increase was only 11 beats/min at a similar atropine dose, and in our 14 children with Down’s syndrome the mean increase was only 10 beats/min with 14 μg/kg of atropine. There were no significant differences between the heart rate responses to atropine in our patients with and without Down’s syndrome. We have no explanation for our results being different than those reported by Harris and Goodman. The diagnosis of Down’s syndrome in our patients was confirmed by chromosome studies; the patients studied were not on any additional medication. Our patients were studied in a sitting position (which causes less anxiety in the retarded patient) and at 2.00 p.m. (two hours after eating), while Harris and Goodman studied their patients in a supine position in the post-absorptive state. All their patients were male while half of our patients were female, but we found no difference between male and female Down’s syndrome patients in their response to atropine. The total dose of atropine given to our adult patients with Down’s syndrome ranged from 1.4 to 3.0 mg (mean of 2.33 mg), and there were no disorders of cardiac rhythm, no systemic side effects, other than dry mouth and facial erythema. We were unable to confirm McKusick’s contention that the patient with Down’s syndrome is abnormally

compared using the t test and no significant differences were found.

The eye data for the adult subjects are given in Table V. As in the children, the pupillary response to atropine was accelerated in the patients with Down’s syndrome and significant differences were noted at 10 and 15 minutes after the instillation of the atropine. No significant differences between control and Down’s syndrome subjects were noted in the mean change beyond 15 minutes.

Discussion

Our control patients showed about the same increase in heart rate after atropine as the control
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sensitive to atropine (McKusick, 1957). Both Priest (1960) and Berg et al. (1959) comment on the lack of side effects to atropine used for preanaesthetic medication in patients with Down's syndrome.

In the majority of subjects, the initial 5–7 μg/kg dose of atropine reduced heart rate below the control value, while a second 5–7 μg/kg increased the rate above the control value. Heart rates reached the plateau with an atropine dose of 25–30 μg/kg.

Our eye studies confirmed previous studies showing a more rapid onset of mydriasis after topical atropine in the patient with Down's syndrome. Priest (1960) recorded greater pupillary dilatation in subjects with Down's syndrome up to 12 days after administration, while O'Brien et al. (1960) found a difference from controls at 15 minutes but not at 30 minutes when it was assumed that the eyes of both the Down's syndrome and control subjects were fully dilated. Priest (1960) also found a similar greater pupillary response to hydroxyamphetamine hydrobromide (a sympathomimetic pupillary dilator) in Down's syndrome patients, suggesting that the increased dilatation in these patients was not specific for atropine but possibly due to some of the structural anomalies of the iris known to be present in patients with Down's syndrome.

Children with Down's syndrome are reported to have depressed blood levels of serotonin (Keele et al., 1969; Rosner et al., 1965), low urinary epinephrine excretion, but normal plasma catecholamine values. Knowledge of an abnormal response to atropine might provide leads for further investigations of biochemical abnormalities in this common cause of mental retardation. However, we have been unable to confirm that the patient with Down's syndrome responds abnormally to intravenous atropine. As the accelerated pupillary dilatation may be due to anatomical peculiarities rather than biochemical, an abnormal pharmacological response to atropine in patients with Down's syndrome remains to be proven. In addition, there does not appear to be any contraindication to giving atropine to Down's syndrome patients for preoperative medication.

The intrinsic heart rate is the term applied by Jose (1966) to the heart rate after partial pharmacological isolation of the heart from neurohumoral control by atropine and propranolol. In normal subjects aged 20–30, this rate is reported to be 107 beats/min (range 87–127) (Sutton et al., 1967). A similar rate was found in our adult control subjects. In both our children and adult groups, the intrinsic heart rate was slower in the subjects with Down's syndrome (P < 0.05). This finding is in contrast to the report of Harris and Goodman (1967) who found high intrinsic heart rate in their patients with Down's syndrome. Intrinsic heart rate is known to be slower in patients with heart disease and hypometabolic states (Jose, 1966), and in more physically fit subjects (Sutton et al., 1967). The significance of the slower intrinsic heart rate in our mongol subjects is not known.

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REFERENCES


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