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THERAPEUTIC NOTE

A Double-Blind Clinical Trial on Diphenhydramine in Pertussis

Whooping cough is a severe disease among young infants. Clinically, most complications seem related to the coughing spells. A trial was undertaken to determine whether diphenhydramine could reduce the frequency of cough paroxysms in young children afflicted by pertussis.

Patients were prospectively included in the study if they were younger than 12 months of age, if nurses noted characteristic whooping spells, and if the cases were not treated with steroids. Randomization and allocation of treatment followed a double-blind pattern, according to a list determined by the Parke-Davis Company from a table of random numbers. The hospital pharmacy was responsible for the assignment of patients to the treatment groups.

The following baseline data were measured: age at entry, previous vaccination for pertussis, interval between the first paroxysm and hospitalization, concomitant administration of erythromycin, and presence of an opacity on chest radiography. Since patients were included in the trial at different stages of their disease, the number of fits during the 24 hours preceding the introduction of drug or placebo was measured as an indicator of the severity of disease at time zero. Systematic laboratory tests included white blood cell count, lymphocyte count, glycemia, chest radiography, viral serology, and three nasopharyngeal cultures for *B. pertussis*. Paired serum specimen, obtained at least two-weeks apart, were tested for complement fixing antibody to adenovirus, influenza, parainfluenza and respiratory syncitial virus. Appearance, smell, and taste of active and placebo syrups were similar. Patients in the experimental group received 5 mg/kg/day of the active drug in three doses.

The outcome was the frequency of paroxysms between the 25th and the 48th hour after initiation of treatment. Monitoring was similar for all patients. Coughs were monitored around the clock with a system of microphones set up in each room. All patients were fed with frequent small meals. None received sedatives or humidity. The average number of fits per day was compared with a Student's *t*-test. A dummy regression analysis was used to test the hypothesis that the slopes for the compared groups were parallel (no interaction between prognostic factors and treatment). Having accepted that the slopes were parallel, the mean number of fits per day was compared in the two groups, adjusting for baseline data and the number of fits during the 24 hours preceding entry into the trial. Results were considered as significant for $p<0.05$. The smallest detectable difference between the two groups, given the sample size, was estimated using a formula suggested by Lachin (1). Informed consent was obtained from a parent or a guardian for each patient. The study was approved by the Ethics Committee of Sainte-Justine Hospital.

Twelve patients (7 in the experimental group and 5 controls) were withdrawn because no lymphocytosis (>8 000/mm^3) was found and *B. pertussis* did not grow on medium. Forty-nine patients were included in the final analysis. Cultures were positive for *B. pertussis* in four cases belonging to the experimental group (20%) and in seven controls (29%). Viral serology was negative in all 49 patients. Diphenhydramine was administered to 25 patients, and a placebo to 24 patients. The average number of fits between the 25th and the 48th hour after initiation of therapy was 22.6±13.1 fits per day in the experimental group, and 20.7±10.2 fits per day in the placebo group ($p=0.57$). A 95% confidence interval for the difference of the means ranged from −8.5 to 4.7.

No statistically significant interaction between prognostic variables and treatment was found. On the other hand, the number of fits in the previous 24 hours and the patients' age were found to be confounders in the data. After adjusting for the confounders, the means were 21.5 fits per day in the experimental group and 21.8 fits per day in the control group ($t=0.1$; $p=0.92$). The 95% confidence interval for the difference between the adjusted

means ranged from −3.3 to 3. The minimum detectable difference in this study was 9.32 f per day (alpha error = 0.05, beta error = 0.2).

Most patients were monitored for side effects for more than a week. None could be at buted to the active drug or the excipient. However, nurses noted that giving syrup orally duced cough paroxysms in at least four patients of the experimental group (16%) and in least two patients of the control group (8.3%).

There is an histaminic sensitization during the paroxysmal phase of pertussis. Th diphenhydramine, a potent antihistaminic, might have been helpful in alleviating the clini manifestations of pertussis. We found no decrease in the frequency of paroxysms in patic receiving medication for more than 24 hours. Since diphenhydramine must be effective af four half-lives of elimination of 3.5 hours (2), benefit should be apparent if present after hours of therapy. The minimum decrease in the number of fits that this study could det was 9.32 per day; therefore, we conclude that diphenhydramine is not clinically useful in p tussis. On the other hand, the administration of syrups (placebo or active drug) induc paroxysms in 12% of cases, and this number was probably underestimated since we did n systematically check for this complication. So cough syrup could be detrimental in pertussi

Whooping cough is a severe disease among toddlers. Vaccines presently available about 80% effective, and the incidence of the disease is not expected to decline even in w vaccinated countries (3). Clearly, an effective treatment is warranted in pertussis. Clini trials with salbutamol (4–7) or steroids (8) gave conflicting results, and from this study conclude that an antihistaminic such as diphenhydramine does not reduce cough paroxysi Other clinical trials are required to find an effective treatment for pertussis.

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