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ARTICLES

THE USE TRANQUALIZING AGENTS IN THE TREATMENT OF PERTUSSIS*

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Pertussis is one of the most severe of the childhood diseases, causing more deaths in all pediatric age groups than measles, diphtheria and scarlet fever combined. Particularly during the first year of life, for instance, pertussis causes nearly seven times as many deaths as all three of these diseases.

Various methods of therapy have been tried in the past to treat pertussis, including high altitude flights, garlic phytoncides, snail extracts, fresh air and prolonged sleep, vitamins K and C, succinic acid, trypsin, vaccines, hyperimmune sera, intradermal procaine blocking and pharyngeal aspirations. Sulfa drugs, hormones, isoniazid, aerosols and gamma globulin are some of the many new therapeutic agents that have been used. Each new antibiotic has been tried in this disease, and penicillin, streptomycin, chloramphenicol, chlortetracycline and oxytetracycline have all had their advocates. However, none has proved completely satisfactory.

Although the fatality rate declined and the prognosis improved after the introduction of the broad-spectrum antibitiotics, pertussis has remained a problem because our present-day treatment continues to be inadequate in preventing complications during and after the

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disease. After-effects (for the most part, interstitial processes of atelectasis and bronchiectasis) continue to be seen relatively often in these children. The duration of the illness remains unchanged, even with modern therapy. It is well accepted that these antibiotics should not be used over extended periods of time because of the possibility of complications attributable to the drugs themselves or of the development of resistant strains of *Hemophilus pertusis.*

As many other investigators have found, chloromycetin is the most effective agent yet developed for the treatment of pertussis [1,5]. However, used by itself chloromycetin leaves much to be desired in providing an effective treatment that is free of the complications associated with the disease.

Thus, one of the chief problems in treating pertussis has been to find effective therapeutic measures that will improve the prognosis. Our knowledge of the pharmacological effects of chlorpromazine and prochlorperazine—the antiemetic, antispasmodic, antihistaminic and tranquilizing actions and the effects of these drugs on pain centers and on the cough mechanism— led me to believe that these drugs would be of value in the treatment of pertussis.

Method

Sixty infants and young children were selected for this study. These 40 females and 20 males ranged in age from 1-1/2 months to 7 years; one-half of the group were under six months of age. Only 3 had received a complete course of prophylactic inoculations against *Hemophilus pertussis*; the remaining 57 children had not been inoculated.

The 60 patients were divided equally into three groups. Group A received chloromycetin and prochlorperazine*. Group B received chloromycetin and chlorpromazine**. Group C, used as a control, was treated with chloromycetin alone.

All patients in Groups A and B were severely ill and in the paroxysmal stage of the disease. Twelve children in Group C had mild cases of pertussis; 7 other cases were of medium severity and in only 1 instance was the disease classified as severe. Table 1 shows the frequency of occurrence of presenting signs and symptoms of the disease.

In Group A the initial dose of prochlorperazine was administered rectally to 16 children, the dosage being calculated on the basis of 2.5 mg/kg of body weight. Depending on age and weight, succeeding

* Compazine, Smith, Kline & French Laboratories, Philadelphia.

** Thorazine, Smith, Kline & Franch Laboratories, Philadelphia.

TABLE: 1

FREQUENCY OF SINGS AND SYMPTOMS ON ADMISSION

Signs and symptoms	Group A* Number of patients	Group B** Number of patients	Group C*** Number of patients
Paroxsymal cough	20	20	20
Vomiting	20	20	16
Cyanosis	20	18	15
Whoop	18	16	12
Convulsive episodes	6	4	2
Anorexia	4	2	2

doses were 20 to 40 drops (1 to 2 mg.) of the syrup given orally every 4 to 8 hours for four to ten days. The remaining 4 severely ill patients in Group A were given an initial intramuscular dose of 2.5 mg. of prochlorperazine, followed by 20 drops (1 mg.) of the syrup every 6 to 8 hours for five to seven days. In Group B initial rectal doses of chlorpromazine were calculated on the basis of 5 mg/kg of body weight; thereafter the syrup was used in doses of 2-4 mg/kg, given every 6 to 8 hours for five to ten days.

Chloromycetin was administered orally to all patients in Groups A and B as the palmitate syrup and was given five to ten minutes after the administration of either proclorperazine or chlorpromazine. Antibiotic therapy was continued for five to seven days after prochlorperazine or chlorpromazine was withdrawn. The daily dosage of chloromycetin was calculated on the basis of 100 mg/kg of body weight for the majority of infants less than 6 months of age. The average initial dose of the antibiotic was 250 mg.; thereafter 125 mg. was usually given every 8 hours. Children between the ages of 1 and 3 years were given an initial dose of 250 mg., followed by dose of 250 mg. every 8 hours. Children older than 3 years were given an initial 250-500 mg. dose, followed by doses of 250-300 mg. every 6 to 8 hours.

In Group C chloromycetin palmitate was administered alone according to the following dosage schedule: Children under 1 year of age were given an initial dose of 100 mg/kg of body weight, followed by a dose of 60 mg/kg every 3 hours. Those whose ages ranged from 1 to 3 years were given an initial dose of 100 mg/kg, followed by doses 125 mg/kg every 3 hours. For children over 3 years of age the initial dose of 100 mg/kg was followed by doses of 250 mg/kg, given every 3 hours. The course of chloromycetin therapy for patients in Group C was continued for ten to fourteen days.

* Group A treated with combination of chloromycetin and prochlorpromazine

** Group B treated with combination of chloromycetin and chlorpromazine

*** Group C treated with chloromycetin alone.

Laboratory tests were usually limited to complete blood counts; in all cases bacterial cultures were taken by means of Bordet-Gengou cough plates and nasopharyngeal swabs. Chest X-rays, taken in all cases before treatment began, were repeated two or three months after completion of treatment.

Results

Group A (chloromycetin and prochlorperazine) and Group B (chloromycetin and chloropromazine)

In patients in Group A, vomiting was controlled very rapidly during the first twenty-four hours of administration of prochlorperazine. These patients were much more alert than they had been before treatment and took food and oral medication much more readily; they obviously felt better. Most sympotoms diminished considerably during this first twenty-four hour period (Table 2).

TABLE : 2

FREQUENCY OF SIGNS AND SYMPTOMS 14 HOURS AFTER TREATMENT

Signs and symptoms	Group A Number of patients	Group B Number of patients	Group C Number of patients
Paroxysmal cough	15	13	19
Vomiting	6	10	17
Cyanosis	10	9	15
Whoop	12	8	11
Convulsive seizures	4	3	2
Anorexia	2	1	2

In the Group B patients given chloromycetin with chlorpromazine somnolence was observed within the first twenty-four hours, and paroxysmal coughing spells diminished in intensity and frequency of occurrence. These patients were able to retain food, fluids and vitamins given by mouth. Improvement was steady and after five to ten days of treatment all patients were completely asymptomatic. There were no sequelae or complications of therapy.

In both Groups A and B elevated temperatures decreased to normal levels within twenty-four to forty-eight hours in those cases in which there was fever on admission. Symptoms of nausea and vomiting were controlled within twenty-four hours in most cases. Control of nausea and vomiting was established more rapidly and more completely with prochlorperazine than with chlorprmazine. Paroxysmal coughing spells and cyanosis were reduced markedly after twenty-four to forty-eight hours and were eliminated completely in both groups within seven to ten days. In both groups anxiety and apprehension were

eliminated, and patients showed very marked improvement in behavior and emotional response to treatment. Because vomiting was controlled rapidly, it was relatively easy to maintain fluid and electrolyte balance and to administer oral medications, including the antibiotic and vitamins, with the assurance that they would be retained. In no case (other than the initial doses of prochlorperazine given to 4 severely ill patients in Group A) was it necessary to use parenteral medication, which, in children, often induces crying and coughing spells, cyanosis and psychogenic vomiting.

The serious complications often associated with pertussis did not appear in Groups A and B. Comparison of chest X-rays taken in all cases before treatment with those taken two or three months after treatment showed no evidence of pulmonic disease in these thwo groups. Tables, 3, 4 and 5 show that convulsions and anorexia were eliminated completely within seven to ten days. Tachycardia and facial puffiness also disappeared.

TABLE : 3

FREQUENCY OF SIGNS AND SYMPTOMS ON FOURTH DAY OF TREATMENT

Signs and symptoms	Group A Number of patients	Group B Number of patients	Group C Number of patients
Paroxysmal cough	10	8	17
Vomiting	3	6	16
Cyanosis	6	5	14
Whoop	10	7	10
Convulsive seizures	3	2	1
Anorexia	1	1	2

TABLE : 4

FREQUENCY OF SIGNS AND SYMPTOMS ON SEVENTH DAY OF TREATMENT

Signs and symptoms	Group A Number of patients	Group B Number of patients	Group C Number of patients
Proxysmal cough	3	4	14
Vomiting	0	3	14
Cyanosis	4	3	12
Whoop	3	2	8
Convulsive seizures	1	0	1
Anorexia	0	1	1

TABLE : 5

FREQUENCY OF SIGNS SYMPTOMS ON TENTH DAY OF TREATMENT

Signs and symptoms	Group A Number of patients	Group B Number of patients	Group C Number of patients
Paroxysmal cough	0	0	12
Vomiting	0	0	12
Cyanosis	0	0	10
Whoop	0	0	7
Convulsive seizures	0	0	0
Anorexia	0	0	1

The course of the disease, usually running from one to three months, was shortened to a period of five to ten days. There were no complications of any type and no sequelae among patients in Groups A and B.

Group C (chloromycetin alone)

The patients in Group C, treated with chloromycetin alone, experienced frequent episodes of vomiting, severe coughing spells and cyanosis during the course of the disease. Irritability, conjunctival hemorrhages, marked edema of the eyelids, facial puffiness, tachycardia, anorexia and nutritional disturbances were also seen. In many instances the chloromycetin could not be retained because of vomiting. Thirty per cent of the patients in Group C developed complications: inguinal hernia occurred in 2 cases and pulmonary collapse, anorexia and malnutrition occurred in 4 patients. In the latter 4 patients re-expansion of the lungs was spontaneous and complete within two (3 cases) or three (1 case) months. The latter child developed an iron deficiency anemia during the third week of treatment with chloromycetin. In 7 other cases severe hypochromic anemia occurred after the disease resolveed. In 2 cases tachycardia was observed, and 1 child developed bilateral suppurative otitis media (Table 6).

TABLE: 6

COMPLICATIONS OCCURRING AFTER THE DISEASE

Complications	Group A Number of patients	Group B Number of patients	Group C Number of patients
Pulmonary collapse	0	0	4
Anorexia	0	0	4
Malnutrition	0	0	8
Anemia	0	0	8
Tachycardia	0	0	2
Otitis media	0	0	1
Inguinal hernia	0	0	2

In all three groups elevated leucocyte counts returned to normal levels within four to seven days. The degree of lymphocytosis varied between 45 and 90 per cent, and about 70 per cent of the smears showed 60 to 80 per cent lymphocytes. Bordet-Gengou cough plates were positive for *Hemophilus pertussis* in 7 patients (3 from Group A, 2 from Group B and 2 from Group C) and were negative in 53 cases. Cultures of nasopharyngeal swabs were positive in 8 cases (2 from Group A, 2 from Group B and 4 from Group C) and were negative in 52 cases. All cough plate and nasopharyngeal swab cultures were negative after three to five days of therapy.

Discussion

The most frequent complications of pertussis are those associated with the respiratory tract, and involvement of the lower respiratory tract with resulting bronchopneumonia or diffuse pneumonitis is most frequent in young infants. Vomiting typically accompanies the paroxysms of coughing, except during the early catarrhal stage and the late stages of resolution. Weight loss is common, and weak children and infants may develop malnutrition. In older children the exertion imposed by severe paroxysmal cough may cause massive hemorrhage.

In the most unpredictable complication, that of central nervous system involvement, there seems to be no correlation between the severity of the illness and the sudden appearance of neurological symptoms and signs. A sudden convulsive seizure occurring late in the catarrhal stage or, most commonly, after the paroxysmal stage has become established is usually the first indication of brain involvement. The child may recover from a single convulsion or a series of convulsions, or he may become comatose and exhibit signs and symptoms of irreversible encephalitis. Reports of less well-defined neurloogical sequelae even when the course of the active disease has been uncomplicated have appeared in the literature. Investigators have reported instances of mental retardation following postpertussis encephalitis and of mental retardation caused by pertussis [6,7].

Chajes-Rosenbund [8] found that roentgenographic evidence of an increase in the size of the heart frequently could be correlated with severe pertussis. Congestive heart failure has been known to develop during the course of the disease [9], and patients develop a wide range of manifestations of myocardial insufficiency [10]. Excessive tachycardia may also appear in severe cases of pertussis [11].

Prompt diagnosis and institution of adequate therapy are the only ways to prevent the complications that invariably influence the

prognosis of the disease most unfavorably. It is necessary that children who have recovered recently from pertussis be checked systematically and periodically.

This study of the efficacy of a combination of chloromycetin and the tranquilizers, chlorpromazine and prochlorperazine, in treating pertussis suggests that, while such therapy does not eliminate completely the possible development of complications, it does shorten the course of the disease. Furthermore, the treatment of patients in Group C with chloromycetin alone showed that the comparatively poor results obtained with this group might be due to the fact that vomiting often prevented patients from retaining the oral antibiotic. The addition of chlorpromazine or prochlorperazine made patients in Groups A and B more susceptible to antibiotic therapy. Since patients in Groups A and B were more severely afflicted, the efficacy of the antibiotic-tranquilizer regimens is even more striking. In general prochlorperazine is probably a safer drug for pediatric use than chlorpromazine.

The result of this study indicates that the following routine may provide the most successful treatment of pertussis. In combination with chloromycetin administered according to the dosage schedule outlined for Group A, prochlorperazine should be given in the recommended dosage for the first three days to establish rapid control of nausea, vomiting and chest pain. Chlorporomazine can be substituted for the next three to seven days of therapy and chloromycetin continued until bacterial cultures are negative and the danger of complications is past.

Summary

Sixty pediatric patients with pertussis were divided into three therapeutic groups, the first (Group A) receiving chloromycetin and prochlorperazine; the second (Group B), chloromycetin and chlorpromazine; and the third (Group C), chloromycetin alone. The addition of the tranquilizing drugs in Groups A and B provided rapid control of vomiting, and in these patients most symptoms (vomiting, paroxysmal cough, cyanosis, whoop, convulsive episodes and anorexia) diminished considerably during the first twenty-four hour period. After five to ten days of treatment all patients in Groups A and B were asymptomatic, and there were no sequelae or complications of therapy. Patients in Group C, treated with chloromycetin alone, experienced frequent episodes of vomiting, severe coughing spells and cyanosis during the course of the disease. The antibiotic often could not be retained because of vomiting. Thirty per cent of the patients in Group C developed complications, inculuding pulmonary collapse, inguinal

hernia, anorexia, anemia and malnutrition. In combination with chloromycetin, prochlorperazine and chlorpromazine appear to provide a successful method of treating pertussis.

REFERENCES

1. Rudino, C. R.: Tretemiento de la tos ferina con el largactil y cloromicetina, Acta pediat. espan., **13** (150): 424, 1955.
2. Morini, A.: L'impiego della chlorpromazina nella terapia sintomatica della tosse, Riforma med., **70** (36): 1015, 1956.
3. Perović, S.: Upotreba largactila u terapiji teških stanja pertusisa, Liječ vijes., **78**: 139, 1956.
4. Sedallian, P., Gaillard, L., and Garin, J. P.: Résultats du traitement curatif moderne de la coqueluche, J. Med. Lyon, **35** (837): 885, 1954.
5. Caussade, L., Neimann, N., Stehlin, S., and Pierson, M.: L'action de la chlorpromazine en médecine des enfants, Rev. Med. Nancy, **79**: 73, 1954.
6. Schnute, L. E., and Mallroy, E. W.: The sequelae of post-infection encephalitis, with special reference to mental retardation, Univ. Hosp. Bull. (Ann Arbor), **53**: 3, 1939.
7. Levy, S., and Perry, H. A.: Pertussis as a cause of mental deficiency, Am. J. Ment. Deficiency, **52**: 217, 1948.
8. Chajes-Rosenbund, F.: Increase in the size of the heart of children with pertussis. Ztschr. f. Kinderh., **46**: 55, 1928.
9. Thomson, A. R.: Congestive heart failure in pertussis, Brit. J. Child. Dis., **34**: 273, 1917.
10. Walker, S. H.: Cardiac complications of pertussis, J. Pediat., **40**: 200, 1952.
11. Fanconi, G., and Frischknecht, W.: Tachycardia in pertussis, Helvet. padediat. acta, **5**: 2, 1950.