Could preventive intranasal interferon lower the morbidity in children prone to respiratory illness?

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ABSTRACT Recent studies have demonstrated that rhinovirus infections can be prevented in the family setting through use of intranasal interferon sprays which are commenced when another family member develops cold. One hundred and twenty-seven children aged 4 to 9 years who had been hospitalized during their first year of life for severe infections caused by respiratory syncytial virus were studied virologically and epidemiologically during a seven-month period which included the winter months. The hypothesis was that a significant part of their respiratory morbidity would be preventable by a contact prophylaxis approach using intranasal interferon. However, the findings suggest that a preventive approach of this kind would not significantly alter the burden of respiratory illness in these children because: the target children themselves more often introduced illness into the family than did other household members; rhinovirus infections preventable by interferon were associated with little lower respiratory morbidity; and rhinoviruses were minor contributors to the total respiratory illness burden in these respiratory illness-prone children.

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Interferon-α, has been effective in prophylaxis in the family setting in preventing acquisition of rhinovirus infections in adults. A dose of 5 million units instilled intranasally once a day for seven days after the index case in a family became ill was effective in preventing rhinovirus-associated colds but not in preventing illness associated with other respiratory viruses. Higher doses of intranasal interferon are unlikely to be tolerated generally. This approach to prevention would be clinically useful if subgroups could be identified in whom substantial illness was precipitated by rhinovirus infections. Children who experience hospitalization for respiratory syncytial virus (RSV) infection of the lower respiratory tract in the first year of life are at particularly high risk of respiratory morbidity in subsequent years. These children tend to experience bronchial hyperactivity, clinical asthma and prolonged and repeated respiratory infections. It seemed that this easily defined, high-risk group of children could benefit from a preventive approach if it could be shown that a significant proportion of their morbidity were precipitated by rhinovirus infections and if it could also be shown that they often developed their infections after colds had been brought into the family by other family members. We undertook a descriptive study of 127 children who had all been hospitalized for RSV infection of the lower respiratory tract in their first year of life, in an effort to explore the feasibility of preventing morbidity during the autumn, winter and early spring seasons. A "family episode" began when respiratory symptoms began in one or more family members and concluded either three days after the last member stopped having respiratory symptoms or three days after a seven-day hypothetical course of prophylactic medication (used as in the adult studies) would have been completed. All respiratory symptoms for the study children and days of symptoms for each family member were entered graphically on a family episode graph which was used to evaluate the potential usefulness of the contact prophylaxis model. The protocol and consent forms for these procedures were developed in conformity with ethical guidelines developed by the Australian National Health and Medical Research Council and approved by the Ethics Committee of the Adelaide Children's Hospital.

Results

Study population characteristics

The average age of the study children was 6.4 years, with a range of 4 to 9 years, and two-thirds were male. On average each child had experienced 3.5 hospital stays in their lifetime for chest illness. Eighty-seven per cent were attending school or kindergarten; 47% had missed more than 16 days of school or kindergarten due to respiratory illness in the previous 12 months. Eighty-seven per cent were attending school or kindergarten; 47% had missed more than 16 days of school or kindergarten due to respiratory illness in the previous 12 months.
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RYTHMODAN is available as 5 ml ampoules, each ampoule containing 50 mg of disopyramide (as phosphate) (10 mg/ml) in packs of five ampoules.

ELECTROPHYSIOLOGY: RYTHMODAN prolongs the effective refractory period of the atria and the ventricles. The effective refractory period of the A-V node is either slightly shortened or unchanged. The relative refractory period of the A-V system is unchanged by RYTHMODAN. Conduction through the His-Purkinje system is unchanged or slightly delayed.

INDICATIONS: Oral RYTHMODAN is indicated in:

1. Maintenance of normal rhythm following conversion by RYTHMODAN injection, other parental drugs or electroconversion.
2. Prevention of arrhythmias after myocardial infarction.
3. Persistent ventricular extrasystoles.
4. Control of arrhythmias following the use of digitals or similar glucosides.
5. Suppression of arrhythmias during surgical procedures, e.g. cardiac catheterization.
6. Prevention of supraventricular or ventricular tachycardia.
7. Wolff-Parkinson-White syndrome.
8. Conversion of supraventricular arrhythmias following myocardial infarction.
9. Conversion of atrioventricular arrhythmias following cardiac catheterization.
10. Control of ventricular arrhythmias following the use of digitalis or similar glycosides.
11. Control or facilitation of atrioventricular conduction.
12. Conversion of atrioventricular or ventricular tachycardia.

CONTRAINDICATIONS: Disopyramide should not be used in patients with uncompensated or marginally compensated congestive heart failure or hypotension unless the congestive heart failure or hypotension is secondary to cardiac arrhythmia. Patients with a history of heart failure may be managed with a diuretic, but careful attention should be given to fluid and electrolyte balance.

DOSAGE & ADMINISTRATION:

Loading Dose:

RYTHMODAN should not be administered in patients with uncompensated or marginally compensated congestive heart failure unless the patient is adequately digitized. Patients with myocardial infarction or other cardiopathies may develop significant hypotension in response to the usual dosage regimen. If severe hypotension occurs, a loading dose of disopyramide should be given. Such patients and initial and subsequent dosage adjustments should be made under close supervision. (See DOSAGE & ADMINISTRATION.)

Maintenance Dose:

In the majority of patients, a maintenance dose of disopyramide should be adequate. Once the dosage has been established, dosage should be individualized under close supervision. (See DOSAGE & ADMINISTRATION.)

CONTRAINDICATIONS: Disopyramide should not be used in patients with uncompensated or marginally compensated congestive heart failure or hypotension unless the cardiac arrhythmia is secondary to cardiac arrhythmia. Patients with a history of heart failure may be managed with a diuretic, but careful attention should be given to fluid and electrolyte balance.

PROLONGATION OF THE Q-T INTERVAL:

Disopyramide should not be used in patients with heart block of any degree, either drug-induced or congenital in origin, unless the ventricular rate is adequately controlled by a temporary or implanted ventricular pacemaker. When treating atrial fibrillation by electroconversion it is advisable to start RYTHMODAN one to two days prior to the applied electric shock. During this period of time, ventricular fibrillation may occur in patients with atrial fibrillation and should be treated as soon as possible with immediate reversion to atrial fibrillation by administering RYTHMODAN intravenously. The electrocardiogram should be carefully monitored for signs of oversedation (see OVERDOSAGE). Use of Disopyramide during Pregnancy: Disopyramide has been reported to stimulate contractions of the pregnant uterus. Therefore, use of disopyramide in women of child-bearing potential is not recommended unless the potential benefit of therapy outweighs the possible hazards to the fetus. Use in Patients with Renal Insufficiency: With severe renal insufficiency (creatinine clearance < 10 ml/min), the recommended dosage regimen is a 200 mg loading dose followed by 100 mg maintenance dose given approximately every half-life period. See table below for relationship between cardiac arrhythmia, heart rate and the maintenance dosage interval.

Stability studies have shown that RYTHMODAN remains active in these infusion fluids for a period of at least 10 days.
when they did not have a cold, 64.8% were claimed to wheeze whenever they got a cold and 27% wheezed occasionally with exercise. At birth 44.5% had experienced breathing difficulty and 28.9% had weighed less than 3000 g. All of the study children had been admitted to hospital during their first year of life, suffering from lower respiratory illness associated either with isolation of, or seroconversion to, respiratory syncytial virus. Fifteen per cent were taking regular medication for asthma. For 11 of the children the symptom diary showed a consistent pattern of symptomatology which was declared in the early months of the study by the investigators as “background” against which judgements about the categorization of other episodic symptoms were superimposed.

**Potential use of medication**

The families of the 127 children experienced a total of 683 separate family episodes of respiratory symptomatology. Each family episode was examined to ascertain whether the circumstances were such that the study child could have been treated with interferon in contact prophylaxis form, that is, was the family episode initiated by respiratory illness in some family member other than the study child and was the child eligible to use medication in prophylactic form? (As with our earlier adult study we required two clear weeks between the end of one and the beginning of another hypothetical course of medication.)

In 335 of the 683 family episodes, application of these criteria would have enabled the child to commence taking intranasal interferon. Thus, during the average surveillance period of 204 days, there would have been, on average, 2.6 courses of medication used by each child in the study. In 155 of these 335 theoretically “medicable” episodes, the study child actually developed respiratory symptomatology. That is, in 46.3% of the family episodes in which contact prophylaxis could have been used, a respiratory illness was available for “prevention” in the study child.

Five hundred and fourteen episodes of respiratory symptomatology were experienced by the study children, that is, an average of 4.0 episodes per child during the seven months of surveillance. For 313 of these episodes the child was the “index” case in a family episode, and for 201 episodes, the child was a “secondary” case. In 155 of these 201 episodes, the child could have been using interferon prophylaxis (in 46 cases, a full two weeks had not elapsed since a previous hypothetical “course”). Table 1 shows a comparison of the symptom profile of the 155 “medicable” episodes with the 359 which were “non-medicable”. The dominant symptoms in both groups were nasal and cough, with surprisingly little new wheeze developing over and above the background level. The medicable episodes did not differ substantially from those which were non-medicable.

**Viral findings**

Viral cultures were collected from study children in 354 of the 514 episodes (68.9%). The main viruses grown were rhinovirus (14.1%) with parainfluenza viruses from a further 4% of cultures. Table 2 shows a comparison of culture results in the 155 episodes which were medicable with those 359 episodes that were not. Rhinoviruses were implicated less frequently in the medicable group (10.7% of 122 cultures compared with 15.9% of 232 cultures collected from children who were experiencing “non-medicable” episodes). A comparison of the symptom profiles of episodes caused by rhinovirus with those from which parainfluenza virus was grown, showed that the parainfluenza virus episodes lasted longer (12.7 days v. 10.4 days) and were more often characterized by wheeze (3.0 days per episode v. 1.1 days per episode) than the episodes associated with rhinovirus.

**Preventive possibilities**

For the entire study, the children were observed for an average of 204 days and of these days, respiratory symptoms occurred on 45.4 days. Of these, 8.4 symptom days per child occurred outside defined respiratory episodes, that is, they were either sporadic single symptom days or part of a semicontinuous background of respiratory symptomatology against which decisions about episode onset had to be made in a small group of 11 children. There remained an average of 37.0 symptom days per child which occurred within clearly defined respiratory episodes. Of these, 23.4 symptom days on average for each child occurred within episodes in which the child was an index case for a family episode. Another 1.9 symptom days per child, although part of a secondary episode within the family episode, could not have been prevented by contact prophylaxis because the child would not have been eligible to use medication. There finally remained an average of 11.7 symptom days per child which were susceptible to prevention by the contact prophylaxis method. As discussed below we could not hope to reduce this burden by more than 20% (that is, an average of two to three days).

**Discussion**

The basis for a family contact prophylaxis approach is that considerable transmission of viral respiratory infection occurs in the family setting. In our earlier study of contact prophylaxis in adults, interferon-α2 prevented rhinovirus-associated colds in those who used contact prophylaxis during family episodes. This episodic use of intranasal spray was associated with acceptably low levels of nasal irritation. Efficacy in the prevention of “definite” episodes of illness was 86% if rhinovirus were isolated from the index case in a family. But efficacy was confined to family episodes in which rhinovirus was cultured either from the index case or from one or more of the secondary cases. The net benefit to those who used the active preparation was a 20% difference in respiratory symptom days.

The present study used identical virological laboratory procedures which were carried out by the same laboratory personnel as those used in the adult studies. Rhinovirus was grown in 10.7% of medicable episodes in the present study. The comparable percentage was 15.5% in the adult study. Thus a lesser net reduction in episodes in this population would be expected than that which we observed in the adult study because of the smaller contribution of rhinovirus. Accordingly, we do not have a basis for expecting a reduction of as much as a mean of 2.3 (20%) of the 11.7 days of respiratory symptomatology which are theoretically available for prevention. Thus, we could expect for 18.2 days of prophylactic dosing with interferon, a prevention of fewer than 2.3 days of respiratory symptoms per child during the average 204 days of surveillance to which each child was exposed.

### Table 1: Comparison of 155 “medicable” and 359 “non-medicable” episodes

| Variables                          | Medicable episodes (n = 155) | Non-medicable episodes (n = 359) |
|-----------------------------------|-----------------------------|---------------------------------|
| Mean duration (days)              | 9.3                         | 9.1                             |
| Mean days of nasal symptoms       | 6.8                         | 5.9                             |
| Mean days of throat symptoms      | 1.9                         | 2.2                             |
| Mean days of cough symptoms       | 5.2                         | 5.9                             |
| Mean days of ear symptoms         | 0.5                         | 0.4                             |
| Mean days of wheeze symptoms      | 0.9                         | 1.1                             |
| Mean days of shortness of breath  | 0.4                         | 0.3                             |
| Mean days of fever symptoms       | 0.6                         | 0.5                             |
| Mean days of antibiotic consumption | 1.8                        | 1.5                             |
| Mean number of doctor visits      | 0.34                        | 0.46                            |

### Table 2: Comparison of viral culture results in “medicable” and “non-medicable” episodes

| Viral culture                  | Medicable episodes (n = 155) | Non-medicable episodes (n = 359) |
|--------------------------------|-----------------------------|---------------------------------|
| Rhinovirus                     | 13 (10.7%)                  | 37 (15.9%)                      |
| Parainfluenza virus            | 6 (4.9%)                    | 8 (3.4%)                        |
| Respiratory syncytial virus    | 1 (0.8%)                    | 1 (0.4%)                        |
| Adenovirus                     | 2 (1.6%)                    | 3 (1.3%)                        |
| Other viruses                  | 5 (4.1%)                    | 6 (2.6%)                        |
| Negative culture results       | 95 (77.8%)                  | 177 (76.3%)                     |
| Culture not done               | 33                          | 127                             |
Study child was submitted. In this study, wheeze was observed for an average of 1.1 days of every 10.4 days of rhinovirus episodes. So, within the maximum 2.3 days available for symptom reduction, we would not expect prevention of more than 0.24 days per child of wheezing throughout the six months of the study.

Viruses were cultured in only 22.2% of medicable and 23.8% of non-medicable episodes in this study. This viral isolation rate is comparable to the viral yield in the earlier adult study. We do not know the contribution of coronaviruses to the present cases as they were not assessed serologically, but our adult studies suggested that contact prophylaxis was ineffective in preventing coronavirus infections.

We conclude that the contact prophylaxis approach in these high-risk children does not offer theoretical benefits. Our observations show that these young school-age children are more often than not the initiators of respiratory episodes within their families and therefore at these times would be unable to make use of contact prophylaxis. Further, it would seem that while they experience possibly preventable rhinovirus-associated illness, this infection is not associated with substantial lower respiratory symptomatology and that for them the cost of the intranasal medication would be relatively unlikely to be balanced by clinically appreciable benefits.

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Treatment of idiopathic spasmodic torticollis with botulinum-A toxin: a pilot study of 19 patients

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ABSTRACT Nineteen patients with spasmodic torticollis, unresponsive to standard therapy, were administered local injections of botulinum-A toxin into the affected muscles. During an average follow-up period of 11.5 months, a more than 25% improvement was noted in 14 of 19 patients. All those with purely focal dystonia and 9 of 10 patients with a disease history of less than three years benefited from treatment. Side effects were insignificant and transient. Botulinum toxin is a very effective and safe method of treatment for spasmodic torticollis. (Med J Aust 1990; 152: 529-530)

The term "dystonia" was coined by Oppenheim in 1911 in describing six patients with alterations in muscle tone, sustained posturing and involuntary movements. Since then the definition of dystonia has undergone many modifications, and is now described as "a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures". 1

Dystonia is classified according to age of onset, aetiology (symptomatic or idiopathic) and distribution. Thus, there are focal, segmental and generalized dystonias. Where a single area is involved, such as the eye (blepharospasm), face (oromandibular dystonia), neck (torticollis), or vocal cords (spasmodic dysphonia) the condition is called focal dystonia. 2 The commonest form of focal dystonia is spasmodic torticollis (ST) with a suggested prevalence of three per 10 000. 3 When two or more contiguous parts are involved in the disease process, such as the face and the neck, for example, it is called segmental dystonia, and generalized dystonia when one or both legs and the trunk are affected. Hemidystonia involving half the body usually indicates symptomatic dystonia, with abnormality in the basal ganglia.

Spasmodic torticollis was first described by François Rabelais, the French humanist, author and physician, in the 16th century. The mean age of presentation is 40 to 50 years, and the female to male ratio is 3:2. 4 Various combinations of neck posture may occur, such as laterocollis, retrocollis and antecollis. The head may be tilted onto one shoulder, and one of the shoulders may be elevated and displaced anteriorly. Intermittent or continuous tremor or spasmodic movement may occur. The severity of the abnormal postures and movements can be aggravated by stress and an activity such as walking, while improvement may be achieved by the patient touching the chin, face or the back of the head. This is the so-called geste antagonistique, quite characteristic of ST but lacking an adequate explanation at the present time. The involuntary movements cease during sleep. Pain can be very severe, intractable and disabling. The onset may be sudden or gradual, the condition usually progressing for a few years and then becoming stationary. Remissions occur in 15% of patients, usually in the first few years after the onset. Many patients are unable to work, and even such activities as driving a car, eating, reading or watching television may become difficult or impossible. The obvious neck deformity causes a constant embarrassment, and the patient's suffering is increased by the lack of understanding and the ineffective therapies available. Medical treatment and psychotherapy are usually unsuccessful. 5, 6 Surgical treatment may have adverse results, 7 a significant morbidity and even a small mortality. 8

Botulinum-A toxin, a neuromyotropic agent, has recently been used in the treatment of focal dystonias. It was pioneered for the treatment of strabismus by Dr Alan Scott 9 and has been shown to be effective for the treatment of blepharospasm, 10-12 oromandibular dystonias, 13 spasmodic torticollis, 14-16 spasmodic dysphonia 17 and focal hand dystonias. 18 Clostridium botulinum produces eight distinct neurotoxins, which cause widespread muscular paralysis, characteristic of the often fatal syndrome of botulism. When botulinum-A toxin is injected intramuscularly in minute quantities local denervation and muscle weakness occur, lasting for several weeks until the nerve endings regenerate. The toxin inhibits the release of acetylcholine, probably by interfering with calcium channels. 19

Over the past two years we have used botulinum-A toxin to treat over 75 patients suffering from ST. We report the results of a pilot study of the first 19 patients, who have been followed up for an average of 11.5 months.

Patients and methods

Nineteen patients (11 women and 8 men), aged from 30 to 76 years (average, 47.4), were entered in the study. The patients were referred to one of us (I T L) because of ST which was intractable to the usual medical and surgical measures. The duration of the torticollis before our treatment was from 9