A Clinical Trial of a Quaternary Ammonium Antiseptic Lozenge in the Treatment of the Common Cold

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THE present study was stimulated by the reports of Ritchie[1, 2] on the efficacy, in the treatment of the common cold, of short-term administration of antibiotic lozenges containing 15 mg. of chlortetracycline, oxytetracyline or tetracyline. His premise was that the full-blown symptoms of the common cold are the result of the relatively enhanced virulence of the patient's normal nasopharyngeal flora following depression of his resistance by the initial viral infection. Very recently, McKerrow, Oldham and Thomson[3] reported that they found a significantly higher three-day cure rate in a group of patients treated with lozenges containing one of the tetracylines than in a placebo group, thus confirming Ritchie's work.

It occurred to us that a quaternary ammonium antiseptic with a range of antibacterial activity comparable to that of the tetracycline compounds should prove equally useful in the treatment of the common cold. The use of such a compound would avoid some of the disadvantages of antibiotic therapy, especially the danger of widespread dissemination of antibiotic-resistant organisms through the repeated use of small doses in a condition as prevalent as the common cold. Zelmanowits[4] claimed, in a letter to the editor of *Lancet*, that he had successfully used dequalinium chloride in a few cases of the common cold.

The compound chosen for this trial was beta-phenoxy-ethyl-dimethyl dodecyl ammonium bromide, known as domiphen ("Bradosol"—Ciba). This is a non-sensitizing and relatively non-toxic substance[5, 10] with proved antibacterial and antifungal activity.[7, 8, 11-13] Although domiphen was not claimed to be useful in the common cold, the Ciba Company (Canada) agreed to provide us with Bradosol lozenges which contain 1.5 mg. domiphen in a flavoured candy base and to prepare placebo lozenges of identical appearance and taste.

METHOD OF STUDY

Volunteer subjects for the trial were from ground-crew personnel of R.C.A.F. Stations at North Bay, Clinton, Camp Borden, St. Jean and Aylmer and army personnel from the 2nd Battalion, Royal Canadian Regiment, at Wolseley Barracks, London.

Subjects were urged to report to the medical officer as soon as possible after the onset of a cold. Upon reporting they were given a supply of either domiphen or placebo lozenges to be taken over the next 48 hours. The men were instructed to place the lozenge in the side of the mouth and to avoid chewing or active sucking. In the first part of the series 10 lozenges were supplied to each subject; later this was increased to 16. Allocation to the two treatments was randomized in sequences of 12, so that fluctuations with time in type and severity of colds should impinge equally on the treated and placebo groups. Neither the volunteers nor the medical officers knew the identity of the individual boxes of lozenges. The treated subjects were examined by the medical officer at the first visit and again on the second, fifth and seventh days. At each visit, the presence and severity of the following symptoms were recorded on a standard form: (1) nasal discharge or congestion, (2) sore throat, (3) cough, (4) fever and (5) other symptoms. No subject was used in the trial more than once.

RESULTS

The trial began in the winter of 1959 at R.C.A.F. Station, North Bay, and was terminated in the spring of 1961, by which time 180 subjects had been treated. A subject was considered eligible for inclusion in the analysis if he reported 24 hours or less after the onset of a cold, took at least six lozenges, and reported for subsequent examination on at least one of the three specified occasions. A total of 138 subjects met these criteria, 69 of whom had received the domiphen and 69 the placebo lozenges. Thirty-five (19.4%) of the 180 were ineligible because they reported too late, six (3.3%) because they did not return even once, and one because he took only five lozenges.

TABLE I.—PRESENTING SYMPTOMS

	No. of cases	
	Domiphen group	*Placebo group*
Coryza only	13	14
Coryza and sore throat	15	19
Coryza and cough	10	9
Coryza, sore throat and cough	19	17
Coryza, fever, sore throat and cough	1	2
Sore throat only	2	2
Sore throat and cough	9	6
Total	69	69

A comparison of the domiphen and placebo groups in terms of presenting symptoms is given in Table I. Clearly, similar types of upper respiratory illness appear to have been included in the two series.

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TABLE II.—PERCENTAGE OF SUBJECTS FREE OF ALL COLD SYMPTOMS

	Domiphen group	*Placebo group*
At two days	7.9	12.1
N*	63	66
At five days	22.7	26.7
N*	66	60
At seven days	33.9	40.0
N*	56	60

*The number of cases (N) varies within each group because some subjects did not report on all three occasions.

Table II depicts the proportion of subjects who were free of all signs and symptoms of respiratory illness at each of the three time periods after the beginning of treatment. If anything, the outcome in the placebo group was slightly superior to that in the domiphen group.

It is apparent that the frequency of non-reporting differs somewhat in the two groups, particularly at five and seven days. One can test the potential bias produced by this discrepancy by assuming various frequencies of "cure" among the non-reporters and recalculating the results accordingly. The most extreme reversal of the results is produced by assuming that at seven days all of the domiphen and none of the placebo non-reporters were free of symptoms, which would give "cure rates" of 46% and 35% in the domiphen and placebo groups, respectively. Even in such an unlikely situation, the superiority of domiphen would not be great, or statistically significant.

TABLE III (A).—PERCENTAGE OF SUBJECTS FREE OF NASAL DISCHARGE

	Domiphen group	*Placebo group*
At two days	17.5	27.3
N*	63	66
At five days	39.4	38.3
N	66	60
At seven days	50.0	58.3
N	56	60

TABLE III (B).—PERCENTAGE OF SUBJECTS FREE OF SORE THROAT

	Domiphen group	*Placebo group*
At two days	68.3	69.7
N	63	66
At five days	83.3	68.3
N	66	60
At seven days	82.1	81.7
N	56	60

TABLE III (C).—PERCENTAGE OF SUBJECTS FREE OF COUGH

	Domiphen group	*Placebo group*
At two days	38.1	37.9
N	63	66
At five days	34.8	35.0
N	66	60
At seven days	42.9	46.7
N	56	60

*N = number of cases.

In Table III the outcome of treatment is considered separately for each of the three main symptoms: nasal discharge, sore throat and cough. In only one instance, the frequency of sore throat at five days, did the domiphen group show a better outcome than the placebo group. The difference is not, however, significant at the 5% level.

Since it was possible that domiphen might have had an effect only if given very early in the course of the cold, a separate analysis was made for subjects who had been treated within 12 hours of onset. The results, shown in Table IV, provide no evidence in favour of domiphen.

TABLE IV.—PERCENTAGE OF SUBJECTS FREE OF ALL SYMPTOMS AMONG THOSE TREATED WITHIN 12 HOURS OF ONSET

	Domiphen group	*Placebo group*
At two days	12.5	14.7
N*	32	34
At five days	24.2	34.4
N	33	32
At seven days	33.3	46.9
N	30	32

*N = number of cases.

Another possibility which seemed worthy of consideration was that the antibacterial effect of domiphen lozenges would be of value only in colds which initially were of the simple coryzal type. This possibility was examined by making a separate analysis for the 13 members of the domiphen group and the 14 members of the placebo group who presented with coryza as the only initial symptom.

TABLE V.—PERCENTAGE OF SUBJECTS FREE OF ALL SYMPTOMS AMONG THOSE PRESENTING WITH CORYZA ONLY

	Domiphen group	*Placebo group*
At two days	16.7	21.4
N*	12	14
At five days	46.2	41.7
N	13	12
At seven days	58.3	50.0
N	12	12

*N = number of cases.

The results are shown in Table V. The outcome was similar in the domiphen and placebo groups. By comparing Tables II and V it may be seen that the outcome for subjects presenting with coryza only was somewhat better at each time period than that for all subjects.

The analyses described so far deal only with the presence or absence of symptoms, but take no account of their severity. For this reason, further analyses were made in which each of the main symptoms was scored for severity. Mean symptom scores calculated for the domiphen and placebo groups did not suggest any advantage in the domiphen-treated group.

CONCLUSIONS

In this trial early treatment with a potent and broad-spectrum quaternary ammonium antiseptic lozenge had no effect upon the course of the common cold. This finding is in conflict with expectations based upon the results of controlled trials using antibiotic lozenges of comparable antibacterial activity.

The methods used in this and the other trials have been similar except that in the present trial the outcome was evaluated by asking the patient specifically about each symptom rather than asking merely whether his cold was gone, improved, or about the same. It is difficult to see why such a difference in evaluation should produce appreciably different results among controlled trials which were all conducted on a double-blind basis. In fact, the placebo cure rate in our trial was closely comparable to that of McKerrow although far below that of Ritchie.

Another conceivable cause of the difference between the results of this and the antibiotic trials is that in the latter some systemic effect may have been obtained. With the dosage of the tetracycline used (15 mg. two to three times a day for two to three days) such a possibility seems most unlikely in the light of what is known about the oral doses required to achieve therapeutic blood levels.[14]

Our results in a restricted group of healthy young adults lend no support to the view that early bacterial invasion of the oropharynx or enhanced virulence of commensal parasites in the pharynx is responsible for the full symptom-complex of the common cold. It should be emphasized, however, that these conclusions might not be applicable to colds in children or in subjects with chronic respiratory disease.

SUMMARY

A controlled, double-blind trial of a quaternary ammonium antiseptic lozenge in the early treatment of the common cold was evaluated in 138 volunteer subjects from the Canadian Armed Forces. The proportion of subjects free of all respiratory symptoms and of the three common symptoms, taken separately, was comparable in the actively treated and placebo groups at two, five and seven days after the beginning of treatment. This comparability was maintained when separate analyses were carried out for subjects treated within 12 hours of onset and for subjects whose colds began with simple coryza as the only symptom.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

THE INSURANCE ACT

In a recent number we took occasion to discuss the effect which the Insurance Act in England would have upon the practice of medicine and upon the status of the poor. Fear was expressed that, if the public paid by compulsion for the treatment of the poor, charitable persons would be disposed to allow the support of hospitals to come from the public funds. The Insurance Act extends practice by contract to some nine million persons, with the effect that a part of the profession is to be badly paid for doing what all have hitherto done cheerfully for charity.

These fears are being realized, although payments under the Act do not come into force until July. Mr. Sidney Holland, the president of the London Hospital, has drawn attention to the effect which the new provisions are having on that great charity. At the moment, he says that people, alarmed at or indignant with the Insurance Act, are withdrawing and threatening to withdraw their subscriptions. Mr. Holland points out several contingencies that may arise. It may be that the Act will relieve hospitals of some of their patients; but it may be, on the other hand, that the numbers to be treated will increase, because attention to health and sickness will be further concentrated.

As a matter of fact, the new regulations will have no value to the poor who are suffering from serious illness, with the single exception of tuberculosis. The Act guarantees to the insured, skilled medical attendance at their homes only for minor illnesses which require no skilled nursing and no specialized medical treatment. The Chancellor endeavoured to console the hospital authorities by saying that they could refuse help to the poor. But Mr. Holland quite properly points out that they can now refuse to help the poor if they choose to do so, but that hospitals exist for the sake of helping and not of refusing to help.

In the meantime, the campaign by the profession against the Act still goes on. . . . The socialist doctors were also taking a hand, and they have passed resolutions that opinion in the medical profession and amongst the general public is not yet ripe for a nationalized medical service.—Editorial: *Canad. Med. Ass. J.*, 2: 228, 1912.