Antivirals for the common cold

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This chapter is dedicated to the memory of Dr. David Tyrrell

Abstract

Despite a 60-year history of discovery, trial and evaluation of scores of different compounds, there are no currently licensed effective antivirals for the common cold. The history of the development and abandonment of all potential compounds so far teaches us some important lessons for the continuation of our fight against colds. First, the common cold is a benign self-limiting condition, making the consumption of 'harmless' antivirals a requisite of prime importance for regulators. Second, the common cold is a syndrome caused by a myriad of known and unknown agents, which reduces the effectiveness of compounds that interfere with single specific agents or types of agents. The multifactorial nature of the genesis of colds makes it difficult for compounds showing *in vitro* efficacy to 'make the jump' to field effectiveness. Last, despite the heavy burden that the cold imposes on society, the vagueness and shortness of symptoms make it difficult for sufferers to present in time for physicians to prescribe antivirals, which are only effective if taken within a short time frame. Attention should be paid to the development of compounds with a non-virus-specific action.

Background

Modern attempts at identifying causal agents of the common cold started in the 1920s, in the aftermath of the great 1918–19 influenza pandemic [1, 2]. After Smith, Andrewes and Laidlaw identified the influenza A virus in 1936, research was conducted in specialised facilities such as the UK's Medical Research Council's Common Cold Research Unit (CCU), the Australian Department of Community Medicine at the University of Adelaide and by Gwaltney and Hayden, at the Department of Medicine, University of Virginia, Charlottesville, USA [3–5]. Eventually more than 200 different agents, types and subtypes have been associated with the common cold.

An early historical trial carried out during the Second World War by the MRC on patulin (a metabolic product of the mould *Penicillium patulum*) testifies to the interest in reducing the burden of the common cold especially among troops and munitions workers [6, 7].

Despite its ubiquitous nature, the high incidence and relatively high morbidity, several problems remain in our understanding of common cold epidemiology and, most of all, in the use of effective and simple preventive or therapeutics tools.

This chapter focuses on antiviral compounds for the prevention or early treatment of the common cold using available evidence from randomised controlled trials carried out on human volunteers or in naturally occurring colds in a community. Antiviral drugs may be defined as natural or synthetic compounds that interfere with different stages of the cycle of the agent. I have stretched this definition to include both substances that act against specific viruses and those that work by building up our immune response.

The chapter is based on an earlier Cochrane review that I co-authored with the late Dr. David Tyrrell, the last director of the MRC Common Cold Unit (CCU). Our original dataset included correspondence records about the trials between CCU staff and manufacturers and other researchers active in the field. The Cochrane review identified 129 trials of antivirals and 63 of interferons carried out in the CCU between 1949 and 1989, the year of its closure (Tab. 1). Because of the difficulty in reconciling the raw data of the trials carried out in the CCU with those published in international journals at the time, we privileged the raw records, referring to them by the prefix "CCU" followed by the original trial serial number (e.g. CCU 362). In most cases no leading investigator's name was recognisable from existing records. In addition, several trials were run in 1 year making the use of the year identifier impossible. The final number of trials from CCU and all other sources included in our Cochrane review was 89. The review has since been withdrawn because of lack of funds for its maintenance. I hope

Table 1. Number of identified MRC Common Cold Unit trials of interventions for the common cold

Intervention	Number of CCU trials
Antivirals (other than IFN)	129
Interferon (IFN)	63
Environmental	13
Zinc	11
Nedocromil	8
Vaccines	7
Vitamin C	6
Antibiotics	5
Promethazine Hydrochloride	1
GRAND TOTAL	243

this chapter will serve as a memorial to the huge amount of work carried out on antivirals for the common cold in past decades and help direct the work ahead.

I was asked to update the content of the original review for this chapter. I have done this with the help of my Trial Search Coordinator Alessandro Rivetti who conducted searches of six different databases. As of today there are no antivirals registered for the common cold anywhere in the world, so the evidence is grouped according to type of compound, rather than its commercial name. Each compound is presented firstly by its pharmaceutical manufacturer (if known) and then its route of administration but readers should be aware that some of the reports contained data from several sub-studies. The sub-studies have been subdivided using alphabetical suffixes.

Interferons

After its discovery in 1957, the interest in the use of interferon for its marked *in vitro* antiviral properties grew rapidly. Early methods of preparation of interferon were bedevilled by problems of impurity (leading to high incidence of harm to recipients) and availability. By the early 1970s, purity and availability of interferon had considerably improved and a new set of trials could be conducted [8]. As knowledge of interferon grew, several types of interferons were synthesised. These are indicated by a Greek alphabet suffix.

The early trials (from 1962) had multiple arms, only two of which were concerned with assessing interferon against a control intervention (such as tissue culture fluids) and the potential harm of its use. In these early experiments volunteers were exposed to artificial challenge with mainly rhinoviruses (RV). Quarantine periods ranged from 2 to 3 days (necessary to minimise the chances of volunteers being exposed to viruses circulating in the community) and isolation periods from 9 to 10 days. Later interferon trials were carried out between 1972 and the closure of the CCU in the summer of 1989. Some of the earliest trials are reported in Merigan 1973 [9].

With advances in biology and genetics the recombinant interferons entered the scene. For example, trials CCU 843–853 [10] are reports of a double-blind, placebo-controlled study, self-administered intranasal human interferon alpha A produced by Hoffman LaRoche Ltd and Schering Plough Ltd by recombinant DNA technology. This was administered both before and after viral challenge with respiratory coronavirus and RV9 and RV14.

Four separate comparisons can be constructed from available data.

The first comparison assessed the effects of intranasal interferon in the prevention of experimental colds caused by a variety of common cold

viral types (rhino, corona, parainfluenza, influenza and coxsackie) and subtypes. In addition, we included data on different commonly reported adverse events, ranging from nasal stuffiness to blood-tinged mucus. Data on adverse events (in all comparisons) must be read singly and not cumulatively as one participant could have reported more than one adverse event at a time. Results show that, overall, interferon is significantly more efficacious than placebo in preventing experimental colds (protective efficacy: mean 46%, range 37–54%). The effect is significant in larger trials and against RV and coronavirus. Interferon does not appear to prevent middle ear and Eustachian tube pressure dysfunction, although denominators are very small. Administration of intranasal interferon is significantly associated with nasal stuffiness [odds ratio (OR) 2.22, 1.33–3.70] and increased sneezing. Blood-tinged nasal mucus was not statistically significantly associated with exposure to interferon (OR 1.71, 1.00–2.94) but there is a clear tendency favouring the control intervention.

The second comparison assessed the effects of intranasal interferon in the prevention of naturally occurring colds. Results show that when the denominator considered are the number of participants, interferon is, overall, significantly more efficacious than placebo in all age groups in preventing naturally occurring colds (preventive efficacy 26%, 23–29%) and those caused by RV (preventive efficacy 35%, 17–49%), despite the negative outcome of the study by Douglas et al. [11]. Readers should note that age categories (adults, children and families) are not mutually exclusive and there are overlaps in years and grouping. Interferon, however, is no better than placebo when the denominator considered are the number of courses administered (preventive efficacy 11%, 4%–26%). Blood-tinged nasal mucus was observed with statistically significant increased frequency in the interferon arm of trials of naturally occurring common colds (OR 4.52, 3.78–5.41), as well as nasal erosion (OR 2.58, 1.71–3.91), sneezing and nasal irritation (OR 2.58, 1.88–3.52) and nasal stuffiness (OR 3.07, 2.09–4.51) (see Figs 1 and 2).

The third comparison assessed the effects of intranasal interferon in combination with the synthetic antiviral enviroxime in the prevention of experimental colds. The single small trial by Higgins et al. [12] shows no statistically significant difference between placebo and interferon with enviroxime (efficacy 43%, 0–78%), probably a reflection of the small denominator.

Finally, the fourth comparison assessed the effects of intranasal interferon alone or in combination with naproxen and ipatropium in the treatment of experimental colds caused by RV.

The combination appeared significantly more effective than placebo in attenuating the course of colds by reducing the amount of nasal secretion [weighted mean difference (WMD) 7.40, 2.98–11.82] and appears safe, although this observation is based on a single study [13]. Interferon alone is also significantly more effective than placebo in attenuating the course of experimental colds (WMD 15.90, 13.42–18.38) [14–16].

Review: Antivirals for the common cold (Edited)
Comparison: 02 Intranasal or oral IFN Alpha, Beta or Gamma vs control (prevention of naturally occurring colds)
Outcome: 01 Common cold (denominator is number of participants)

Study or sub-category	IFN n/N	Control n/N	Peto OR 95% CI	Weight %	Peto OR 95% CI
01 Adults & elderly					
Douglas 1985	39/203	45/205		3.31	0.85 [0.52, 1.37]
Hayden 1985	64/142	40/145		3.30	2.13 [1.31, 3.44]
Hayden 1986	32/79	52/76		1.92	0.33 [0.17, 0.61]
Sperber 1989	102/321	104/338		7.02	1.05 [0.75, 1.46]
Betts 1983	1/83	14/62		0.66	0.10 [0.03, 0.30]
Herzog 1983	8/43	5/16		0.40	0.48 [0.12, 1.91]
Herzog 1983	44/220	24/101		2.30	0.80 [0.45, 1.42]
Saito 1985	6/13	7/11		0.31	0.51 [0.11, 2.47]
Solov'ev 1969	231/2994	551/3129		33.77	0.41 [0.35, 0.48]
Tannock 1988	110/310	33/102		3.45	1.15 [0.72, 1.84]
Farr 1984	94/151	64/153		3.77	2.26 [1.44, 3.54]
Imanishi 1980	6/41	15/43		0.79	0.34 [0.13, 0.92]
Subtotal (95% CI)	4600	4381		61.00	0.61 [0.55, 0.69]
Total events: 737 (IFN), 954 (Control)					

Test for heterogeneity: Chi² = 120.84, df = 11 (P < 0.00001), I² = 90.9%
Test for overall effect: Z = 8.54 (P < 0.00001)

02 Children (aged 1-12)					
Isomura 1982	7/13	8/14		0.34	0.88 [0.20, 3.90]
Yuldashev 1988	976/1100	989/1078		9.52	0.71 [0.54, 0.94]
Solov'ev 1969	141/2380	466/2509		26.32	0.31 [0.26, 0.37]
Subtotal (95% CI)	3493	3601		36.18	0.39 [0.34, 0.45]
Total events: 1124 (IFN), 1463 (Control)					

Test for heterogeneity: Chi² = 24.94, df = 2 (P < 0.00001), I² = 92.0%
Test for overall effect: Z = 12.66 (P < 0.00001)

03 Families					
Douglas 1986	53/109	71/120		2.82	0.66 [0.39, 1.10]
Subtotal (95% CI)	109	120		2.82	0.66 [0.39, 1.10]
Total events: 53 (IFN), 71 (Control)					

Test for heterogeneity: not applicable
Test for overall effect: Z = 1.60 (P = 0.11)

Total (95% CI)	8202	8102		100.00	0.52 [0.48, 0.57]
Total events: 1914 (IFN), 2488 (Control)					

Test for heterogeneity: Chi² = 169.78, df = 15 (P < 0.00001), I² = 91.2%
Test for overall effect: Z = 14.55 (P < 0.00001)

0.1 0.2 0.5 1 2 5 10
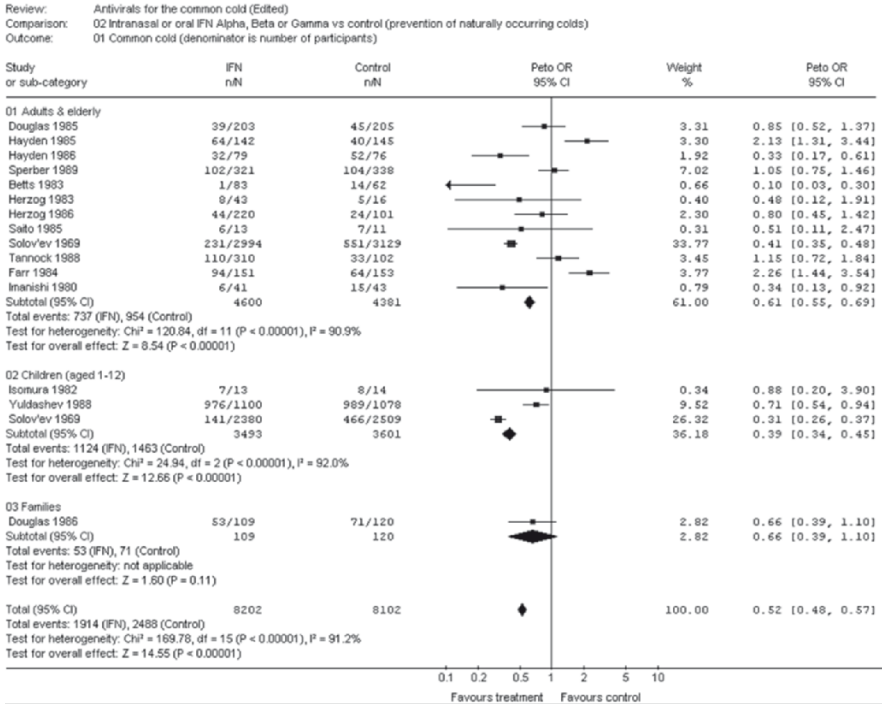Favours treatment Favours control

Figure 1. Effectiveness of intranasal interferon alpha, beta or gamma in preventing the onset of the common cold in the community by age group of participants. Comparators were a mixture of do-nothing or placebo recipients. The forest plot of the meta analysis is based on over 16000 observations.

Review: Antivirals for the common cold (Edited)
Comparison: 02 Intranasal or oral IFN Alpha, Beta or Gamma vs control (prevention of naturally occurring colds)
Outcome: 05 Blood-Tinged Nasal Mucus

Study or sub-category	IFN n/N	Control n/N	Peto OR 95% CI	Weight %	Peto OR 95% CI
Douglas 1985	94/203	15/205		16.67	7.29 [4.70, 11.30]
Hayden 1985	62/142	22/145		12.41	3.94 [2.37, 6.55]
Hayden 1986	12/79	5/76		3.17	2.40 [0.88, 6.56]
Hayden 1987/1	2/19	0/21		0.40	8.68 [0.52, 144.35]
Hayden 1987/2	6/19	2/18		1.34	3.24 [0.69, 15.18]
Hayden 1988/1	23/27	12/25		2.42	5.25 [1.66, 16.54]
Hayden 1988/2	13/148	1/72		2.41	3.44 [1.09, 10.87]
Betts 1983	95/171	7/171		14.94	11.61 [7.31, 18.44]
Douglas 1986	41/109	11/120		8.38	5.02 [2.71, 9.31]
Hayden 1983/1	5/26	1/26		1.13	4.39 [0.81, 23.65]
Monto 1986a	8/198	1/198		1.84	4.89 [1.31, 18.32]
Monto 1988	97/293	31/196		18.93	2.44 [1.62, 3.68]
Tannock 1988	81/310	9/102		10.94	2.75 [1.60, 4.72]
Monto 1986b	22/74	8/75		5.02	3.25 [1.46, 7.21]
Total (95% CI)	1818	1450		100.00	4.52 [3.78, 5.41]
Total events: 561 (IFN), 125 (Control)					

Test for heterogeneity: Chi² = 35.66, df = 13 (P = 0.0007), I² = 63.5%
Test for overall effect: Z = 16.54 (P < 0.00001)

0.1 0.2 0.5 1 2 5 10
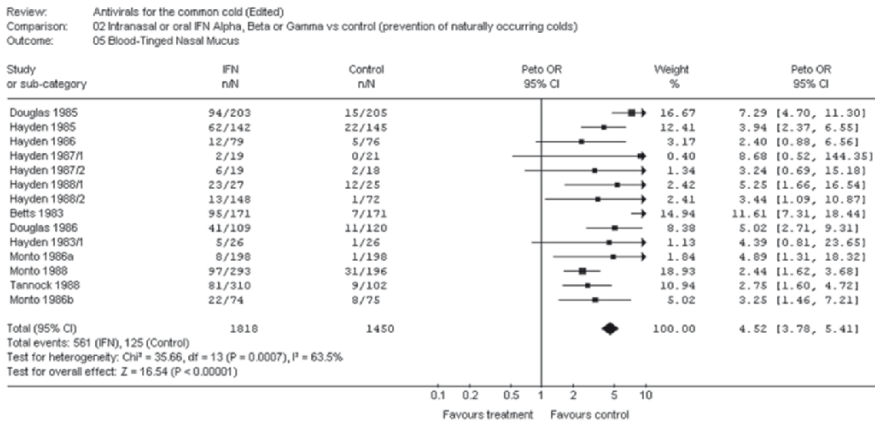Favours treatment Favours control

Figure 2. Harm (nasal discharge of blood tinged mucus) induced by the intranasal administration of interferon alpha, beta or gamma in preventing the onset of the common cold in the community by age group of participants. Comparators were a mixture of do-nothing or placebo recipients. The forest plot of the meta analysis is based on over 3200 observations.

Interferon inducers

Interferon inducers are substances that, when given orally or intranasally, stimulate the natural 'internal' (endogenous) production of interferon by white cells. There are six reports containing a total of ten randomised controlled trials of the effects of interferon inducers.

Two comparisons were constructed from the data.

In the first comparison, interferon inducers were compared to placebo in the prevention of experimental colds. No compound appeared more efficacious than placebo in preventing colds [17, 18]. The compound poly(I)·poly(C) appears more effective than placebo in reducing severity of illness (WMD 7.99, 7.45–8.53). These data are difficult to interpret, given the small denominators involved.

However, the anti-platelet aggregant dipyridamole was significantly more effective than placebo (preventive efficacy 49%, 30–62%) in preventing of naturally occurring colds in all age groups [19].

One important aspect that emerges from the data of these early aerosol interventions is that repeated and continuous intranasal application of antivirals and even of placebo aerosols causes irritation and nose blockage. In the case of interferons, these substances also induce systemic symptoms mimicking that of common colds. The combination of these side effects makes the practical use of these early intranasal antivirals problematic as, although effective, their application led to dubious benefits.

Capsid-binding compounds

Alongside assessment of interferon and its inducers, the late 1960s and early 1970s saw a growth of attention on "capsid-binding" compounds (this interest, although at a lower level, is still alive today). The name of these compounds derives from their biological action based on interference with viral capsid (envelope) metabolism and replication. At the time several experimental compounds were investigated using RV challenge: Pfizer UK 2731 (oral), Rhone-Poulenc RP 19326 (aerosol), Phillips Duphar DU 34796 (an oral compound with a chemical structure similar to that of amantadine). The target agents were a combination of RV and influenza viruses. Viral challenge studies showed that these compounds had very limited or no efficacy. For example, UK2731 had a preventive efficacy of 20% (0–51%) [10].

Most of these compounds such as the intranasal spray Rhone Poulenc RP 44081 {the synthetic compound, 2-[(1,5,10,10a-tetrahydro-3H-thiazolo[3,4b] isoquinolin-3-ylidene) amino]-4-thiazoleacetic acid (S)} (which was assessed in a small trial in 1983) inhibited the multiplication of RV in cell cultures but had no effect in preventing infection and symptoms after challenge [19].

Other compounds equally failed to live up to their *in vitro* performance promise.

The CCU carried out three trials between February and November 1973 to assess the effects of the oral antiviral M&B 15497. The target agents were a combination of influenza viruses. Quarantine was applied for 3 days and isolation for 10 days. The nasal spray and oral Eli Lilly compound Enviroxime was then assessed by five trials carried out between 1980 and 1981. The target agents were RV9. Quarantine was applied for 3 days and isolation for 10 days. Surviving CCU enviroxime records appear to contain data from a larger volunteer population than the corresponding publications [20]. RP 19326 (preventive efficacy 0%, 0–33%), Enviroxime (preventive efficacy 0%, 0%–36%), RP 44081 (preventive efficacy 31%, 0–81%), CGP 19635 (preventive efficacy 0%, 0–63%) do not appear to be more effective than placebo in preventing experimentally induced colds due to RV or influenza virus. This was another dead end for common cold antiviral research.

Other experimental molecules were developed from existing registered antivirals. Between 1983 and 1985 the oral compound ICI 130, 685 (a cyclononane compound, related to amantadine but thought to have superior preventive and therapeutic effects) was tested in 13 trials against influenza A viruses. Both the resulting publication [21] and surviving CCU records show a good preventive efficacy (58%, 35–74%) compared to placebo in preventing and providing early treatment for influenza-related common colds. However, because of concerns over side effects (mainly CNS effects, similar to those caused by the other adamantanes: amantadine and rimantadine) the compound was not developed further.

Some capsid-binding compounds were mixed with other substances, as in the case of the intranasal spray Janssen Pharmaceuticals Ltd R61837 (a pyridazine mixed with a cyclodextrin). However, R61837 was no more effective than placebo in preventing experimental colds caused by RV (0.49, 0.22–1.07) [10].

In the case of the bradykinin antagonist Nova Pharmaceuticals Ltd NPC 567 ([22] integrated with CCU data) this compound also did not work and as always with intranasally administered substances, worsened the clinical course of colds.

Testing of oral Eli Lilly LY 217896 was reported in a trial carried out in the USA [23]. The compound appeared to be no more effective than placebo in the prevention of colds due to influenza A virus (preventive efficacy 0%, 0–32%).

One unexpected finding concerned the performance of SPOFA Pharmaceutical Works oral Impulsin (*N*-2-hydroxyethyl palmitamide). Impulsin was tested in three controlled clinical trials reported in [24]. The field trials were carried out on 1864 male volunteers in Czechoslovakian army units in January 1973, 1974 and 1975. Impulsin appears to be more effective than placebo in preventing acute respiratory infections and colds from all causes (preventive efficacy 44%, 35–52%), but its therapeutic effect is less marked.

Pirodavir spray (Janssen Ltd) (formerly known as R 77975) is a synthetic antiviral (phenoxy-pyridazinamine) with potent *in vitro* activity against RV. The trials were carried out in Virginia, USA. Pirodavir appears to be no more effective than placebo in preventing RV-induced colds if used at least six times a day (preventive efficacy 85%, 0–98%), although this observation is based on a very small denominator (25 individuals). Its therapeutic effect is no better than that of placebo. Adverse effects such as nasal dryness may affect compliance [25].

The compound WIN 54954 Sterling Winthrop Inc (oral) was no more effective than placebo in the prevention of colds due to RV (preventive efficacy 7%, 0–49%) [26].

Isoquinoline derivatives

These are compounds that showed antiviral activity in cell culture and in animals. The class includes Hoffmann-La Roche oral 3, 4-dihydro-1-isoquinolineacetamide hydrochloride (DIQA) [27] and Newport Pharmaceuticals oral Inosiplex (Isoprinosine, formerly NPT 10381) [28, 29]. Of the isoquinoline derivatives, both DIQA (preventive efficacy 1%, 0–75%) and Inosiplex (preventive efficacy 38%, 0–64%) may have been assessed with insufficient denominator size, but the latter appears to have promising preventive efficacy. Few data on the safety profile of these compounds are available.

Chalcones

Hoffmann-La Roche Ltd Ro-09-0410 (liquid chalcone) inactivated RV particles in suspension. Trials CCU 875, CCU 876, CCU 920, and CCU 927–9 assessed the preventive effects of liquid Ro-09-0410, against RV2 and RV9. The trials were carried out in the winter of 1983/84. CCU 875 and CCU 876 are interruption-of-transmission trials, in which volunteers self-inoculated RV9 into the nose with fingers pre-treated with either drug or placebo. Ro 09-9415 chalcone either by oral or intranasal routes appears to be no more effective than placebo in the prevention of colds due to RV, a conclusion in agreement with that reported in the two published versions [30, 31] (preventive efficacy 9%, 0–36%).

Several other miscellaneous antivirals were assessed in the CCU. This grouping includes compounds tested in few trials or for which few CCU data are available because of lack of allocation schedules.

Lederle Guanidine (liquid), [1-phenyl-3-(4 phenyl-2-thiazolyl) guanidine (CL 88,277)], was tested in a CCU trial 369 [10] and in a trial carried out in the USA [32].

Lederle Guanidine appears to be no more effective than placebo in the prevention of colds due to RV or coxsackie A21 virus (preventive efficacy 0%, 0–58% and 20%, 0–68%, respectively).

Ciba-Geigy CGP 19635 (nasal liquid) is an immunomodulatory compound that had been shown to have anti-influenza A properties in rodents. CCU trials 955–960 assessed the prophylactic effects of CGP 19635 against influenza A/Eng/40/83 virus. The trials were carried out in the spring of 1987 and volunteers completed psychological profiles and performance tests before and after viral challenge. No description of allocation methods is made.

In the CCU archives we identified evidence of testing of other miscellaneous antivirals comprising the following compounds: CP-196J aerosol (Janssen Ltd), RO5-3369 (Roche Ltd) capsules, AH 1581 (oral) and ICI 73602. Evidence is thin, comprising either single small trials of two to three participants for which allocation codes are missing. No data are reported for these compounds.

Finally, the effects of intranasal 7-thia-8-oxoguanosine (NARI 10146), a nucleoside analogue with proven immunomodulatory activity against coronavirus 229E were tested in the summer of 1989, shortly before the closure of the CCU. It was no more effective than placebo in the prevention of colds due to coronavirus (preventive efficacy 33%, 0–64%). Possible reasons for the failure to confirm successful rodent experiments in man include an inadequate dosage, a different concentration of the viral challenge and differences in rodent and human immune systems.

Recent antivirals and a look to the future

An interesting (and ongoing) story is that of Pleconaril, an oral capsid-binding antiviral developed jointly by ViroPharma Inc. and Sanofi-Synthelabo.

Pleconaril (formally known as WIN 63843) effectively interferes with capsid function of picornaviruses, especially RV, both *in vitro* and *in vivo* by inhibiting viral docking to the intercellular adhesion receptor molecule-1 (ICAM-1) of which the respiratory epithelium is particularly rich. Pleconaril administration within 24 hours of symptoms onset shortens the duration of colds by up to 24 hours. In a preventive role Pleconaril prevented 71% (15–90%) of RV-related colds. Despite notable media hype and these promising Phase II trial results, the oral formulation of Pleconaril was refused registration by the FDA in August 2002 chiefly on the basis of side effects (menstrual irregularities and pregnancy in women already on oral contraceptives) [33–36].

In 2007, Schering-Plough, under license of ViroPharma, completed a Phase II clinical trial of an aerosol formulation of Pleconaril on common cold symptoms and asthma exacerbations but its results have not been published yet (Study P04295AM2).

At present, Pleconaril is used on a compassionate basis for serious cases of picornavirus infections (such as acute pancreatitis).

However, efforts to develop an effective antiviral against picornavirus-associated diseases are ongoing.

Rupintrivir (AG 7088), an RV protease inhibitor developed by the Pfizer subsidiary Agouron Pharmaceuticals, reached clinical trials but its development was stopped. Finally, the anti-RV drug BTA-798 developed by the Australian company Biota started Phase II prevention challenge studies trials in August 2008 [37]. The full results are expected by the end of April 2009 [38].

Other efforts have been directed at interfering with viral functions that are mediated by antigens with high level of conservation across viral serotypes (i.e. in the case of RV all or most of the 100-odd serotypes present the same antigenic structure). On the basis of advances in the understanding of viral docking and uncoating, it is possible to design potential antiviral compounds (a recent example are di-substituted and tri-substituted benzamides) that show good *in vitro* promise [39].

No other antiviral compounds appear to be under development despite perusal of eight trial registers and one meta-register of trials.

Methodological quality of studies mentioned in the chapter

Most of the published reports and surviving records from the CCU do not allow a systematic evaluation of the four key design aspects of antiviral testing in humans: randomisation schedule generation, allocation concealment, blinding and completeness of follow-up. However, it was possible to reconstruct some of the methodology by looking at existing documentation and interviewing scientists. Here is how one scientist described early CCU viral challenge studies (carried out in the 1940s and 1950s): "volunteers' names were listed and also the number of experimental groups defined. Then they were allocated usually using a table of random numbers (Yates). The group, usually indicated as A, B, C, was written on the list and was also used for the server capped bottles in which the inoculum was carried round to the flats. The list and the bottles could not easily be seen by the volunteers and the clinician and the nurse made their rounds separately and so did not see them at all. The list was kept in a laboratory drawer and rarely visited by the clinical team members. The scientist who performed the inoculum and often administered it had little contact with the volunteers in the early trials. He/she might collect nasal secretions if a cold developed. After 1960 there were influenza trials. Blood rhinovirus antibodies could be often measured, but we could not pre-screen our volunteers as they did in the USA. Antiviral treatments at this stage might have been 'wasted' on volunteers who could have been shown to be immune. Thus, two researchers would bleed volunteers on arrival, do a rapid antibody assay and arrange volunteers in groups

with similar antibody titres, usually nil or low, and the high-titre individuals might be allocated to experiments with an alternative virus or placebo (we always included volunteers with dummy inocula to motivate clinicians and volunteers – they were firmly told that some of them would be given inert drops and dummy drops and so they would be, we believe, discouraged from reporting symptoms if they fell into these placebo groups). Ordinarily, the groups would be allocated to treatments by a random method. Things became more formalised in the last phase with trials of interferons and capsid-binding drugs. Many of these trials were set up by Dr. Peter Higgins. The blinding methods remained virtually the same, though they were enhanced during the 1980s by distributing the inoculum into trials with the volunteers' names on the labels, so that the allocation information never left the lab and there was an extra safeguard against the volunteer being given the wrong material by mistake in the volunteer accommodation. It is difficult to document all these points, or to be precise about the dates on which practices were changed, but it should be possible to work out to some extent by using the date and clues supplied by the descriptions in the reports and papers. It is a generalisation that we never did open trials. Even when we were testing the effect of hot humid air we used a comparison or "control" in which the machine was adapted to generate warm but not too hot (43°C) air. In the zinc lozenge experiment we used a very strong washing flavour, and in the lab we thought the active and placebo preparations tasted the same on a direct comparison and by volunteers reorganising the active preps. I would want to be able to go back and do more experiments to contest that challenge. We did have some evidence that in the vitamin C experiments there was a fault of this sort. We had the practice of telling the volunteers at the end of the trial that they had been given active or placebo material. It then appeared that vitamin C was reducing symptoms after the end of the trial – the system then included the volunteers sending back a postcard with a report of symptoms they had after they got home. But we wondered whether this was an error, and only told the volunteers their treatment after they had sent their postcard. There were reports of apparent 'late' cures of symptoms."

One of the critical aspects that scientists had to decide on was: how do you define a cold?

Here is more evidence: "The diagnosis of colds within the unit of course included a number of the symptoms reported by volunteers. In the early days they looked for an 'objective' means of detecting a response, and concluded that the best was the 'handkerchief' count – any record of an increase of five or more used per day signified a cold. Nevertheless, a number of symptoms could be used and indeed the opinion of the volunteer that they had a cold seemed very reliable and was supported by a direct comparison organised with the MRC Epidemiology unit in Glasgow. In order to document the time course and to measure the response quantitatively, we added the handkerchief weight and found that with non-parametric statistics we could

analyse the results in more detail. However, from the very first years it was clear that the very mildest cold could occur in those given non-infectious material and, although they were summarised as for example an "abortive cold", they did not represent a significant response. When there was a recognisable excess of nasal secretions this was considered a mild cold, more severe symptoms signified a moderate cold and a systemic response meant a severe cold. When we started working with influenza viruses these criteria did not quite meet the case. It was possible to have a definite systemic response with very little in the way of respiratory symptoms, so for these trials we added a separate assessment of systemic reactions. In general I think our threshold for a significant cold is very similar to that of the Virginia group and the Australians".

Because of small numbers, the problem of volunteer susceptibility was ever present and we have received criticism from fellow researchers. Here is how two surviving CCU staff remember how they dealt with the problem: "Volunteers were divided into two groups, which were balanced for age and sex. Rapid antibody assays were done using serum collected when they arrived at the unit and the antibody assay results were available by the end of the quarantine period. So the groups were balanced for antibody levels also. On the day of the beginning of the experiment the excluded volunteers were notified, and the volunteers with highest antibody were usually allocated to receive saline placebo. The groups were then allocated to either drug or placebo as described above – there was no particular system or method in this, e.g. no particular flat was used for drug treatment and because of the construction of groups the flats were allocated differently in each trial. After the trial volunteer's questionnaires were also scored for psychological susceptibility and it usually turned out that these were allocated in a balanced way too. Drugs and virus were sent out labelled with the volunteer's name. For drug trials, volunteers were allocated to groups balanced by age, sex and antibody titre against the virus to be given. There were always a few given no virus. Volunteers were not divided by flats but by individual characteristics. No particular method was used to decide which group had which treatment. When trials against two different viruses were running, volunteers with high titres against one virus would be put into a group to be given the other one. They were very strict about ensuring that the volunteer allocation record was shut away in the laboratory and not seen by either clinical staff or volunteers (it would be passed to the clinician after the final schedule of the volunteer clinical records had been written)".

To sum up, the outcome "cold" is defined in early CCU trials as volunteers presenting with the symptom "coryza" plus one other constitutional symptom (such as malaise, sore throat or fever). From 1973 the definition of a cold relied on a clinical score based on the 9-day average of daily handkerchief counts, presence and grading from 1 to 4 of a list of signs and symptoms (nasal discharge, nasal obstruction, postnasal discharge, sinus pain, red throat, cervical adenitis, hoarseness, cough, sputum, headache,

malaise, myalgia and chills), presence of pyrexia, retirement to bed and other supplementary signs and symptoms (e.g. earache). Throughout our review of CCU data we considered volunteers as presenting with a "cold" if they suffered from a "mild", "moderate" or "severe" cold as defined in CCU records. "Very mild" and "doubtful" colds were classified by us as "no colds". Other routinely assessed outcomes, such as a rise in antibody titres and nasal shedding of viruses, were not included in the review as their clinical significance is doubtful.

It would appear that CCU trials did not have a standard method of allocating participants but were a mixture of individual randomisation, cluster randomisation (by accommodation block) and non randomised allocation depending on the compound being tested, volunteer numbers and profile and scientists involved. When reading this, one must remember that standardised methods, huge resources and clinical registries were not available at the time.

What history and evidence tell us

Interferons are effective in preventing colds caused by RV, respiratory syncytial virus, coronavirus and influenza viruses. Their ease of application is counterbalanced by their effects on the nasal mucosa. Adverse events due to the use of interferons became more evident as more potent and purer interferons became available in the 1970s and 1980s. The reversible infiltrate and inflammation caused by intranasal administration led to the symptoms and signs of the very syndrome interferon use was trying to prevent. This caused poor compliance and ultimately poor effectiveness. The effects were more marked after prolonged intranasal administration. Little can be said about interferon effectiveness in treating ongoing colds, given the small denominators of the relevant studies and the difficulty in distinguishing between prevention and early treatment. These observations confirm what is known on the effects of interferons and confirm the rationale for their failure to achieve further development and registration.

The best interferon inducer appears to by dipyridamole but for reasons which are not clear this widely used, cheap and potentially effective drug has not been further studied for this indication.

Pleconaril appears to be the most promising (or at least the best tested so far) compound. However, results of the trials of its aerosol formulation need to be available before reaching a more definite verdict.

As we have seen, the history of antiviral development is littered with promising compounds that failed to live up to expectations. Either because of their lack of *in vivo* efficacy (in viral challenge studies) or effectiveness (in field trials), or because of their side effects (which are of prime importance when dealing with a benign and self-limiting syndrome like the common cold). In addition, the apparent effectiveness of non-specific interven-

tions such as interferons and dypiridamole teaches us an important lesson. When you are dealing with what is to all effects and purposes a syndrome caused by scores of different known and unknown agents, your best bet of success lies in introducing interventions or administering compounds that have a non-specific action like erecting physical barriers (social distancing), removing agents by physical attrition (hand washing), or building up your immune defences (immunomodulators). Until we understand more of the aetiopathogenesis of the common cold this is where our efforts should lie.

Acknowledgements

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