Randomised controlled trial of aminophylline for severe acute asthma

Michael Yung, Mike South

Abstract

Objectives—To determine whether children with severe acute asthma treated with large doses of inhaled salbutamol, inhaled ipratropium, and intravenous steroids are referred any further benefits by the addition of aminophylline given intravenously.

Study design—Randomised, double blind, placebo controlled trial of 163 children admitted to hospital with asthma who were unresponsive to nebulised salbutamol.

Results—The placebo and treatment groups of children were similar at baseline. The 48 children in the aminophylline group had a greater improvement in spirometry at six hours and a higher oxygen saturation in the first 30 hours. Five subjects in the placebo group were intubated and ventilated after enrolment compared with none in the aminophylline group.

Conclusions—Aminophylline continues to have a place in the management of severe acute asthma in children unresponsive to initial treatment.

Keywords: asthma; aminophylline; randomised controlled trial

Most children admitted to hospital with acute asthma will improve with nebulised β2 agonists, such as salbutamol, and systemic corticosteroids, with or without nebulised ipratropium. A few with severe acute asthma will not, however, respond to these drugs and require additional treatment to avoid respiratory muscle fatigue and respiratory failure.

Despite conflicting evidence about its effectiveness, aminophylline is still recommended by the National Heart, Lung and Blood Institute of the USA and the British Thoracic Society for the treatment of children with severe acute asthma unresponsive to frequent doses of β2 agonists and corticosteroids.

Controlled trials of aminophylline in adults have had conflicting results. Early studies used currently outmoded sympathomimetic drugs, so that their relevance to current clinical practice is questionable. Patient selection and methodological problems make more recent trials showing no benefit from aminophylline difficult to interpret. Some studies have excluded patients with severe asthma, whereas others have not selected patients unresponsive to nebulised sympathomimetic drugs. Methodological problems such as the inclusion of patients already taking theophylline by mouth, a lack of blinding, and low power are also problem areas. Two studies in adults have found a benefit. One used infrequent doses of salbutamol and excluded severely ill patients, and the other showed a reduction in the rate of admission to hospital. Five controlled trials, the largest of which studied 42 subjects, have been performed in children. One showed that aminophylline improved the forced expiratory volume in one second (FEV1), but used currently outmoded sympathomimetic drugs. Four showed no benefit, but all excluded severely ill patients. Methodological problems included low power and withdrawals for a lack of response.

We performed a randomised, double blind, placebo controlled trial to answer the question: Do children with severe acute asthma unresponsive to frequent doses of β2 agonists, ipratropium, and steroids benefit from the addition of aminophylline given intravenously? We aimed to study the most severely ill children with severe acute asthma, including those too sick to perform pulmonary function tests, those admitted to the intensive care unit, and those requiring mechanical ventilation.

Methods

Eligible subjects were children (aged 1–19 years) with severe acute asthma who were unresponsive to three nebulised doses of 5 mg salbutamol. Subjects had to have an asthma severity score (ASS; see later) of > 6, spirometry (where possible) of < 50% predicted, or be obviously very sick and being admitted to the intensive care unit. Unresponsive to nebulised salbutamol meant no improvement in an ASS of > 1, or spirometry of > 15%. Exclusion criteria were: pregnancy, other chronic respiratory disease (for example, bronchopulmonary dysplasia or cystic fibrosis), significant disease of other organ systems, a known adverse reaction to theophylline, previous enrolment, and administration of theophylline (by mouth or intravenously) in the previous 24 hours.

The parents of participating children gave written informed consent. The study was approved by the institutional human ethics committee.

All subjects were given standard care for our institution. Frequent nebulised salbutamol, 5 mg/dose in a volume of 4 ml, was given through a jet nebuliser driven by 8–10 litres/min of oxygen. The dosing frequency of nebulised salbutamol and the use of salbutamol given intravenously were determined by the medical
staff carrying out the treatment and were not
dictated by the study protocol. Also given were
nebulised ipratropium bromide 250 µg every
four to six hours and intravenous methylpred-
nisolone 1 mg/kg every six hours, followed by
oral prednisolone 1 mg/kg twice daily during
convalescence.

Subjects were randomised to receive either
aminophylline or a sterile water placebo (both
clear, colourless, odourless fluids) from glass
ampoules which were identical in appearance.
Aminophylline infusions were given as a
loading dose of 10 mg/kg infused over one
hour, followed by a continuous infusion of 1.1
or 0.7 mg/kg/hour for subjects younger than 10
years and 10 years of age or older, respectively.
Placebo infusions were given in the same fluid
at the same volumes and rates. The duration of
the infusion was determined by the medical
staff giving the treatment and not by the inves-
tigators.

Sequentially numbered boxes were ran-
domly assigned to contain either aminophylline
or placebo using a computer generated code
with randomly permuted blocks of different
sizes (two, four, and six subjects) such that the
balance between the treatment arms was main-
tained every 12 subjects. Subjects were strati-
ﬁed by age as older and younger than 6 years.

Theophylline concentrations were measured
within one hour of the completion of the loading
dose, and again 12–18 hours later if the subject
was still receiving the infusion. The results were
conveyed to the second investiga-
tor (MS), who issued instructions to the medical
staff carrying out the treatment, who then
adjusted the infusions according to a protocol
determined at the beginning of the study aimed
at achieving concentrations in the high ther-
apeutic range (80–110 mmol/l). Instructions
consistent with the protocol used for amino-
phylline in infants were issued for patients
receiving the placebo.

The principal investigator, the medical and
nursing staff carrying out the treatment, and
the subject and his or her family were blind to
the treatment group. Blinding was maintained
throughout the period of hospital admission
and to the end of the study. Only the
statistician, the pharmacist, and the second
investigator (MS) were aware of the assign-
ment and flow rate of supplemental oxygen, the
number of doses, and the dose in milligrams of
salbutamol given were all recorded.

Adverse effects, including nausea, vomiting,
headaches, irritability, tremor, and seizures, were
recorded every six hours by the nurse caring for
the subject. Nursing staff were asked to enquire
speciﬁcally about each symptom and to record it
as present if it had occurred at any time in the
previous six hour period. The development of
adverse effects which were not present at enrol-
ment were deﬁned as “new” for the purpose of
analysis. Headaches and nausea in the absence
of vomiting could not be recorded if the child
was too young or sick to answer.

For mechanically ventilated subjects, the
duration of mechanical ventilation, and the
area under the peak pressure–time curve were
analysed.

Sample size calculations were performed
using PC Size,21 based on length of stay and
spirometry as the primary outcome measures.
From the most recent ﬁgures available for our
institution for patients with severe acute
asthma, the mean length of stay was 2.3 days,
with an SD of 1.0 days. A reduction in length of
stay of 12 hours or more was considered the
smallest clinically important difference which
might be produced by aminophylline. To
detect a 0.5 day reduction in length of stay with
90% power, and a value of 0.05, we aimed to
study 172 subjects, 86 in each group. We knew
that only a proportion of the subjects would be
able to perform spirometry, the others being
too young or too sick. We aimed to study 22 in
each group to detect a difference in FEV1 of
10% points at six hours, with 90% power and a
value of 0.05.

Results are expressed as means and SDs for
normally distributed data and as medians and
ranges for non-normal data. Treatment groups
were compared by the unpaired Student’s t test
for normally distributed data and the Mann–
Whitney U test for non-normally distributed
data. Logarithmic transformations of skewed
data were performed to make the data normally
distributed where possible. Spirometric data
were analysed by the change from baseline in
percentage predicted values at different time
points, but the change from baseline at six
hours was the principal spirometric outcome,
speciﬁed in advance. Analysis of covariance

Percutaneous oxygen saturation, after
breathing air for 10 minutes, was measured
every six hours via a ﬁnger probe with a pulse
oximeter. The measurement was recorded
when the signal was stable, without movement
artefact, and when the oximeter gave an accu-
rate pulse rate. If the Sao2 fell below 80% dur-
ing the 10 minutes of air breathing, it was
recorded as “< 80”, and supplemental oxygen
was reinstated.

The ASS,22 the sum of scores for wheeze,
accessory muscle use, and heart rate, was
recorded by the nurse caring for the subject
every six hours throughout the time the subject
was receiving the study drug infusion and for 24
hours thereafter. The ASS was not recorded for
the subjects receiving mechanical ventilation.

Heart rate, respiratory rate, the total dura-
tion and ﬂow rate of supplemental oxygen,
the number of doses, and the dose in milligrams of
salbutamol given were all recorded.

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points, but the change from baseline at six
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speciﬁed in advance. Analysis of covariance
Aminophylline in severe acute asthma

Table 1  Baseline characteristics of both groups

<table>
<thead>
<tr>
<th></th>
<th>Aminophylline (n = 81)</th>
<th>Placebo (n = 82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>43 (53%)</td>
<td>46 (56%)</td>
</tr>
<tr>
<td>Pulmonary function tests</td>
<td>(n = 27)</td>
<td>(n = 21)</td>
</tr>
<tr>
<td>Mean (SD) FVC%</td>
<td>51.4 (19.0)</td>
<td>51.8 (19.7)</td>
</tr>
<tr>
<td>Mean (SD) FEV1%</td>
<td>35.7 (13.5)</td>
<td>43.9 (14.6)</td>
</tr>
<tr>
<td>Mean (SD) MMEEF%</td>
<td>14.0 (6.3–87.5)</td>
<td>19.4 (12.1–47.4)</td>
</tr>
<tr>
<td>Mean (SD) PEFR%</td>
<td>38.7 (13.5)</td>
<td>88.9% (75–100%)</td>
</tr>
<tr>
<td>Median (range) SPO2</td>
<td>8 (4–9)</td>
<td>8 (4–9)</td>
</tr>
<tr>
<td>Mean (SD) heart rate</td>
<td>166 (23.3)</td>
<td>166 (22.0)</td>
</tr>
<tr>
<td>Median (range) rate</td>
<td>42 (14–84)</td>
<td>40 (12–91)</td>
</tr>
</tbody>
</table>

FVC, forced vital capacity; FEV1, forced expiratory volume in one minute; MMEEF, maximum mid-expiratory flow; PEFR, peak expiratory flow rate.

Table 2  Change in pulmonary function tests (% predicted) over first day

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>n</th>
<th>P</th>
<th>A – P</th>
<th>95% CI for difference</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forced expiratory volume in one minute (FEV1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 h</td>
<td>14.1</td>
<td>25</td>
<td>3.7</td>
<td>17</td>
<td>10.4</td>
<td>(4.2 to 16.6)</td>
</tr>
<tr>
<td>12–18 h</td>
<td>17.1</td>
<td>19</td>
<td>7.6</td>
<td>16</td>
<td>9.5</td>
<td>(2.6 to 16.3)</td>
</tr>
<tr>
<td>24 h</td>
<td>22.5</td>
<td>22</td>
<td>13.1</td>
<td>17</td>
<td>9.4</td>
<td>(1.0 to 17.9)</td>
</tr>
<tr>
<td>Maximum mid-expiratory volume (MMEEF)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 h</td>
<td>13.3</td>
<td>25</td>
<td>−0.4</td>
<td>17</td>
<td>9.3</td>
<td>(4.3 to 15.7)</td>
</tr>
<tr>
<td>12–18 h</td>
<td>13.2</td>
<td>19</td>
<td>6.9</td>
<td>16</td>
<td>6.3</td>
<td>(0.3 to 12.3)</td>
</tr>
<tr>
<td>24 h</td>
<td>17.1</td>
<td>22</td>
<td>11.6</td>
<td>17</td>
<td>5.5</td>
<td>(&gt;3.0 to 14.1)</td>
</tr>
<tr>
<td>Peak expiratory flow rate (PEFR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 h</td>
<td>14.8</td>
<td>25</td>
<td>−0.3</td>
<td>17</td>
<td>15.1</td>
<td>(6.5 to 23.7)</td>
</tr>
<tr>
<td>12–18 h</td>
<td>16.6</td>
<td>19</td>
<td>6.3</td>
<td>16</td>
<td>10.3</td>
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<td>17</td>
<td>10.2</td>
<td>(0.3 to 19.9)</td>
</tr>
</tbody>
</table>

Group means for FEV1, and PEFR are compared using a t test. For change in MMEEF as percentage predicted over first three days, group medians are compared using a Mann-Whitney test, and the difference (A – P) is the point estimate for the difference between medians. A; aminophylline, P; placebo, n; number of subjects.

was used to compare pulmonary function tests between groups after adjusting for baseline. A change in ASS from baseline at six hours was the principal outcome for ASS, but a repeated measures analysis of variance was also used to compare treatment groups at multiple points. Differences in proportions were compared using Fisher’s exact test and by calculating the odds ratio (OR) and 95% confidence intervals. A p value of < 0.05 was taken as significant.

Results

Subjects were enrolled from March 1994 to November 1995. During this period there were 1300 admissions to our institution with severe acute asthma, most of whom were not eligible for the study because they were not ill enough. One hundred ninety one families were approached for consent to enter the study, of which 163 consented. Table 1 gives the baseline characteristics of the 163 study subjects. The trial profile is shown in fig 1.

For the aminophylline group, 79 subjects had a first level (post-loading dose) and 42 had a second level (after 12–18 hours of receiving continuous infusion). The first theophylline concentration was < 55 µmol/l in four subjects (5%), 55–79 in 26 (33%), 80–110 in 42 (53%), and > 110 in seven (9%). For the second level, the numbers of subjects were three (7%), 15 (35%), 11 (26%), and 13 (31%), respectively. The geometric mean length of stay for the placebo group was 2.87 days and for the aminophylline group 2.69 days. The ratio aminophylline length of stay to placebo length of stay was 0.94 (95% confidence interval (CI) 0.77 to 1.14, p = 0.53). Thus aminophylline could have reduced the length of stay by as much as 23%, or increased it by as much as 14%.

There were 83 subjects older than 6 years (41 aminophylline, 42 placebo), of whom 48 (58%) were able to perform pulmonary function tests at baseline. Table 2 shows the change in pulmonary function tests at 6, 12–18, and 24 hours for the 42 subjects able to perform tests at both baseline and six hours. Adjustment of the mean change at six hours for baseline values using analysis of covariance made no difference to the results.

Table 1 gives the baseline SPO2 for each group. Twenty six subjects had an SPO2 < 80% (11 placebo, 15 aminophylline). The overall median SPO2 was 88%. Figure 2 shows the SPO2 over the first 48 hours, after which time the number of subjects was small. Aminophylline was associated with a significantly higher SPO2 up to 30 hours. Sixty two subjects in each group completed all five measurements.

Supplemental oxygen, other than that used to drive the nebulisers, was used at baseline in 24 (35%), 11 (26%), and 13 (31%) respectively. The geometric mean length of stay for the placebo group was 2.87 days and for the aminophylline group 2.69 days. The ratio aminophylline length of stay to placebo length of stay was 0.94 (95% confidence interval (CI) 0.77 to 1.14, p = 0.53). Thus aminophylline could have reduced the length of stay by as much as 23%, or increased it by as much as 14%.

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A significant difference in the decrease in ASS occurred at six hours, favouring aminophylline (2.04 v 1.32, difference 0.72, 95% CI 0.22 to 1.22, p = 0.005), but no significant differences existed at any other time.

Table 1 gives the baseline heart and respiratory rates. No difference occurred between groups at any time. There was no difference between groups in the geometric mean number or dose (mg) of salbutamol nebulisations given.

Seventy one subjects, 43% of the study sample, were admitted to the intensive care unit. Thirty (42%) were in the aminophylline group and 41 (58%) were in the placebo group. There was no difference in the geometric mean length of stay in the intensive care unit.

Forty one subjects, 15 in the aminophylline group and 26 in the placebo group (18 v 32%, OR = 0.49, 95% CI 0.23 to 0.99, p = 0.03), received intravenous salbutamol in the intensive care unit. The placebo group had a significantly longer duration (16.0 v 8.8 h, OR 1.82, 95% CI 1.10 to 3.25, p = 0.045) and higher pulmonary oxygenation rates. No difference occurred between groups after enrolment. Two subjects had seizures during the study period, one in each group.

Discussion

The addition of aminophylline to frequent inhaled \( \beta \)-sympathomimetic drugs, ipratropium, and intravenous corticosteroids made no difference to the length of stay in children admitted to hospital with severe acute asthma. Aminophylline conferred clinically and statistically significant early benefits on airway function and oxygenation, sustained to 24 hours for oxygenation, but not for airway function, and reduced the risk of endotracheal intubation. At the dose used, however, it was associated with a significant risk of nausea and vomiting.

To ensure that most subjects had aminophylline concentrations above the lower limit of the therapeutic range, in contrast with some previous studies, we tried to achieve concentrations in the high part of the therapeutic range, in contrast with some previous studies, we tried to achieve concentrations in the high part of the therapeutic range. This may explain the high incidence of side effects.

Pulmonary function tests could be performed by only half the subjects older than 6 years, the others being too ill. This was a reflection of the severity of illness in our sample, in contrast with the study of Carter et al.,20 in which ability to perform pulmonary function testing was a requirement. Other aminophylline studies in children did not document pulmonary function tests,16 18 19 apart from that of Pierson et al.,17 who found an improvement of 6 and 16% at 1 and 24 hours respectively with aminophylline. The improvement in pulmonary function tests with aminophylline in this study can be compared with that seen with other drugs used in addition entering the study as this was an exclusion criterion. Only five subjects were intubated after randomisation and study drug administration. All five were in the placebo group (p = 0.027).

There was no significant difference, but there was an apparent trend to reduction in the duration of intubation between groups (aminophylline 8.25 hours, placebo 34.0 hours, p = 0.087) and in the median area under the curve of peak inspiratory pressure \( v \) time (aminophylline 123 h-cmH\(_2\)O, placebo 867.5 h-cmH\(_2\)O, p = 0.087).

Table 3 shows the number and percentage of subjects with new adverse effects (those not present at enrolment). Subjects in the aminophylline group were significantly more likely to have their infusions stopped because of adverse effects than placebo subjects (32 v 5%, \( \text{OR} = 8.7, 95\% \ CI \ 2.9 \ to \ 28.4, p < 0.0001 \). Two subjects had seizures during the study period, one in each group.

### Table 3 Frequency of new adverse effects in both groups after enrolment

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Aminophylline</th>
<th>Placebo</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>New</td>
<td>Absent at baseline</td>
<td>%</td>
</tr>
<tr>
<td>Nausea</td>
<td>29</td>
<td>66</td>
<td>7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>35</td>
<td>67</td>
<td>8</td>
</tr>
<tr>
<td>Headache</td>
<td>15</td>
<td>62</td>
<td>15</td>
</tr>
<tr>
<td>Irritability</td>
<td>23</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Tremor</td>
<td>27</td>
<td>68</td>
<td>20</td>
</tr>
<tr>
<td>Seizures</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Any new</td>
<td>11</td>
<td>100</td>
<td>4</td>
</tr>
</tbody>
</table>

Percentages are rounded to the nearest whole number.

*p value by Fisher’s exact test, two tailed.
A, aminophylline; P, placebo.
to nebulised salbutamol for severe acute asthma in children. It was similar in magnitude to that for FEV₁, found in a study of ipratropium bromide (10.3 ± 4.0% in the present study), and for peak flow in a study of prednisolone (11.8 ± 15.1%).

The interpretation of the SaO₂ data may be limited by the 10 minute washout period, which may have been insufficient to reduce alveolar PaO₂ to atmospheric levels, as evidenced by the child with an SaO₂ of 100% on entry. Despite this limitation, however, the median SaO₂ in the aminophylline group was significantly higher than in the placebo group (93% ± 91%), even though the aminophylline group had started with a lower median SaO₂ (85 ± 89.5%). This difference is small, but was sustained to 30 hours. Furthermore, there was a significant difference in the median duration of supplemental oxygen treatment of 6 ± 18 hours (p = 0.015), favouring aminophylline. It is not possible to say whether this improvement in oxygenation with aminophylline represents an improvement in alveolar ventilation, ventilation-perfusion mismatch, or both.

At six hours there was a significantly greater improvement in ASS in the aminophylline group than in the placebo group. The mean difference in decrease in ASS at six hours was 0.72, favouring aminophylline. There was no difference in heart rate between the two groups. We suggest that the expected decrease in heart rate with a faster recovery in the aminophylline group was masked by the pharmacological effects of the drug on the heart (tachycardia).

Five subjects in the placebo group, 7%, compared with none in the aminophylline group (p = 0.027) were intubated and mechanically ventilated. This may have important implications for clinical practice.

The sample (163 subjects) was the largest of any published study of aminophylline in children with severe acute asthma and was sufficient to exclude a reduction in length of stay in hospital by more than 23% or an increase by more than 14%.

We aimed to study the effect of aminophylline in addition to maximum treatment with other drugs: frequent nebulised salbutamol, systemic corticosteroids, and nebulised ipratropium. We used ipratropium every four to six hours, as was the usual practice at our institution. Ipratropium given every 20 minutes has, however, been shown to be superior to less frequent doses. Ideally, the study should be repeated using frequent ipratropium as well as frequent salbutamol.

The study raises questions for further research. The finding that aminophylline reduces the risk of endotracheal intubation and mechanical ventilation.

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At six hours there was a significantly greater improvement in ASS in the aminophylline group than in the placebo group. The mean difference in decrease in ASS at six hours was 0.72, favouring aminophylline. There was no difference in heart rate between the two groups. We suggest that the expected decrease in heart rate with a faster recovery in the aminophylline group was masked by the pharmacological effects of the drug on the heart (tachycardia).

Five subjects in the placebo group, 7%, compared with none in the aminophylline group (p = 0.027) were intubated and mechanically ventilated. This may have important implications for clinical practice.

The sample (163 subjects) was the largest of any published study of aminophylline in children with severe acute asthma and was sufficient to exclude a reduction in length of stay in hospital by more than 23% or an increase by more than 14%.

We aimed to study the effect of aminophylline in addition to maximum treatment with other drugs: frequent nebulised salbutamol, systemic corticosteroids, and nebulised ipratropium. We used ipratropium every four to six hours, as was the usual practice at our institution. Ipratropium given every 20 minutes has, however, been shown to be superior to less frequent doses. Ideally, the study should be repeated using frequent ipratropium as well as frequent salbutamol.

The study raises questions for further research. The finding that aminophylline reduces the risk of endotracheal intubation and mechanical ventilation requires confirmation. It would be best to study a population with a higher prior probability of intubation, such as those with a history of previous intubation admitted to an intensive care unit with severe acute asthma, because this group stands to benefit most from such an effect.

The role of aminophylline in children already mechanically ventilated has not been addressed adequately by this study because the number of subjects involved (14) was small and the methods of measurement not ideal. Future research in this area would include more accurate measurements of respiratory mechanics, such as compliance and resistance. Future research into the role of aminophylline should include a comparison with salbutamol given intravenously.

In conclusion, in children with severe acute asthma unresponsive to maximum treatment with β₂ sympathomimetic drugs and systemic corticosteroids, aminophylline confers an additional early benefit on airway function and a more sustained benefit on oxygenation, but at the cost of a high frequency of adverse effects. The improvement in airway function is comparable in magnitude with that produced by corticosteroids and frequent ipratropium. Aminophylline reduces the risk of endotracheal intubation and mechanical ventilation.

On the basis of these findings, the clinician faced with an ill child with severe acute asthma unresponsive to salbutamol and corticosteroids should use treatments with a lower risk of adverse effects, such as frequent ipratropium, in preference to aminophylline, but aminophylline should maintain its place as an emergency treatment for severe acute asthma in critically ill children when other treatments have been unsuccessful.
The first randomised controlled trial

The Dutch trials of paludrine in malaria and the MRC’s first trial of streptomycin in pulmonary tuberculosis are usually cited as the first publications of the results of randomised controlled trials (RCT). They were both published in the late 1940s. They indeed are probably the first reports of RCTs with a positive outcome. However, negative trials are equally important and results of trials of patulin as a treatment for the common cold were published as a letter in 1943 and a full paper in 1944 by Stansfeld and colleagues. Jim Stansfeld who died in 1998 was later to become the first paediatrician in the City of Durham from 1950–82. In his self written obituary he wrote “Later posted to Bovington Camp, Dorset, in order to investigate a supposed cure for common colds—which proved useless.” With this he dismissed, or did not recognise, his major contribution to medical science.

Patulin was isolated in 1941 as part of a search for antibacterial substances produced by molds. It was sent to Dr W E Gye who was investigating anticancer agents. He had a severe cold at the time and tested patulin on himself with encouraging results. Further tests on other staff members were equally positive. A supply was made available to the army in March 1943 and over the next six months 100 soldiers with severe colds were given either patulin or a placebo on an alternate basis. The subjects improved equally quickly and they concluded that patulin had no demonstrable effect on the course of the disease.

Patulin was useless, but this first randomised trial probably saved a huge number of people the indignity of a useless treatment.


A W CRAFT

We encourage the submission of short pieces of historical interest to be published as fillers.

THE EDITORS