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CLINICAL TRIALS OF A NEW AMINOPHYLLINE PREPARATION

BY

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Treatment with oral bronchodilator drugs is often of value in supplementing other measures in the management of patients with asthma and bronchitis, where airway obstruction is reversible or partially reversible. Oral preparations of theophylline derivatives are widely used in this way, and several clinical trials (Simon, 1956; Pengelly and Brockbank, 1959; Turner-Warwick, 1957; Gandevia *et al.*, 1957) have shown that, of the preparations tested, aminophylline and choline theophyllinate are the most effective. Both give a plasma theophylline level adequate to produce improvement in airway obstruction (Turner-Warwick, 1957), but they are prone to cause troublesome gastric side-effects; Gagliani *et al.* (1954) found that 24% of a series of patients taking aminophylline and 5% of those taking choline theophyllinate complained of nausea or abdominal pain, and Brown and Clancy (1955) reported an incidence of 14% in a series of 35 patients taking the latter drug.

The new preparation "delaminoph" was produced in an attempt to reduce the frequency of these side-effects, by coating aminophylline with an inert lacquer so that disintegration of the tablet is delayed beyond the stomach. The present study was designed to find out whether this drug produced an adequate blood level and symptomatic response, and whether there was any difference between it and choline theophyllinate in the incidence of side-effects.

Effect of a Single Dose

In a small series of patients in hospital the effect of a single dose of 250 mg. of "delaminoph" on the plasma levels of theophylline and on tests of ventilatory function was obtained. The nine patients were all being treated for an exacerbation of chronic lung disease associated with severe airway obstruction, the average forced expiratory volume in one second (F.E.V.₁) being 860 ml., and vital capacity 2,170 ml. Drugs and food-stuffs known to affect the plasma theophylline level were stopped 16 to 24 hours before the dose of delaminoph. The test was begun at 9 or 10 in the morning to avoid the possibility of a false improvement in the degree of airway obstruction due to diurnal variation in tests of ventilatory function reported by Lewinsohn *et al.* (1960). Heparinized samples of venous blood were taken just before and two, four, and six hours after the dose, and the plasma theophylline levels were estimated by the method of Schack and Waxler (1949); in two cases a final sample was taken after 24 hours. The degree of airway obstruction was assessed at the same intervals by measurements of peak flow rate measured by the Wright peak flow meter (Wright and McKerrrow, 1959) and by measurement of the F.E.V.₁ and vital capacity, using a modified Gaensler spirometer (McKerrrow *et al.*, 1960).

The results of these investigations are shown in Figs. 1 and 2. A rise in plasma theophylline level was observed at four and six hours after the dose, a mean level of over 1 mg./100 ml. being obtained at these times. This level has been suggested by Turner-Warwick (1957) to be that at which a therapeutic result may be expected, and this has been confirmed by the studies of the F.E.V.₁; the mean improvement was 20% of the initial

FIG. 1.—Plasma theophylline following a single dose of 250 mg. of delaminoph. (Mean values and 2 S.D. shown.)

FIG. 2.—F.E.V.₁ readings following a single dose of delaminoph.

reading at four hours and 30% at six hours. Similar improvement in peak flow measurement (15% at four hours and 25% at six hours) was also obtained, and in general the subjective improvement reported by the patients paralleled these objective measurements. The plasma level recorded is less than that found by Turner-Warwick after oral doses of 790 mg. of choline

theophyllinate and 600 mg. of aminophylline : these doses are higher than those commonly used for maintenance therapy, and contain the equivalent of 470 mg. of theophylline. The test dose of delaminoph (250 mg.) was that normally used in practice, and had a content of 198 mg. of theophylline, accounting for the lower blood level. The maximum blood level and effect occur later than with choline theophyllinate, which has its peak action two to three hours after an oral dose, the blood level falling after five hours (Turner-Warwick, 1957). The delayed peak blood level is due to the special covering of the tablet causing delayed absorption of theophylline ; some scatter in the blood levels may indicate variability of absorption in different patients. It was concluded that a single dose of 250 mg. of delaminoph produces an adequate therapeutic response and given at intervals of six to eight hours should maintain an effective blood level.

Controlled Comparison with Choline Theophyllinate

This comparison took the form of a double-blind sequential trial, in which each subject was his own control in a comparison between four tablets. The trial was designed to compare the effectiveness of delaminoph and choline theophyllinate ; as all the subjects had taken the latter previously, it was essential that comparison with placebo treatment be included. A statistically valid comparison between the two drugs was impossible, as the two active tablets could not be made identical without changing their action, and thus placebo tablets identical to both were included in the trial. For the same reason the difference in theophylline content (delaminoph 100 mg., choline theophyllinate 120 mg.) was also accepted.

The patients entering the trial were aged 45 to 71 and were taken at random from those attending an out-patient clinic ; all suffered from chronic bronchitis and showed evidence of severe airway obstruction. The mean F.E.V.₁ was 770 ml. and the mean vital capacity 2,290 ml.; these figures were improved by the inhalation of isoprenaline in all patients, the mean values following this being 1,035 and 2,920 ml. respectively. As they depended on oral bronchodilators to ease respiratory difficulty, the period of treatment with each of the four tablets was limited for ethical reasons to three days each ; this kept the trial period short and reduced the likelihood of variation in symptoms due to infective exacerbations. The patients received four boxes of tablets, each containing a three-day course of delaminoph 125 mg., choline theophyllinate 200 mg.,

the inert delaminoph placebo, or the choline theophyllinate placebo ; these were taken in a prescribed order, which was randomly varied by the hospital pharmacist, the identity of the tablets being unknown until after the trial. The patients were asked to record on a special diary form at the end of each day whether their breathing had been better than usual, the same as usual, or worse than usual, and whether they had any indigestion or sickness.

It was not feasible to make repeated ventilatory function tests during the trial, and as Gandevia *et al.* (1957) showed that patients' opinions were significantly related to objective methods of assessment, the recording of symptoms was thought to be sufficient. At the end of the two weeks the patients were seen again, and by allocating points for the recorded symptoms each day (+1 for breathing better ; 0 for same as usual ; -1 for worse than usual) a comparison between each of the tablets was obtained. After this "blind" assessment the identity of the tablets and the order in which they were taken was ascertained from the pharmacist and the results were then plotted graphically in a sequential analysis, the boundaries being fixed so that the probability of detecting a significant difference between treatments was 95% ($P=0.95$, $\theta=0.8$) (Armitage, 1954). Only preferences for one or other treatment in each comparison was plotted : where the "score" was the same for both tablets no preference for that particular comparison was provided, and it was not plotted.

Each preference was plotted serially, as shown in Figs. 3-5, in either a north-east or south-east direction, according to the preference. The boundary in the comparison between delaminoph and choline theophyllinate was reached after 12 patients had entered the trial (Fig. 3) ; as it had been found impossible to make these two drugs identical and all the patients had had the latter previously, this could well have been a false preference for delaminoph. The trial was continued until the limit of confidence was reached in the comparison between delaminoph and its placebo (Fig. 4). Twenty patients had entered the trial up to this time ; one patient was excluded from the trial because he failed to take more than one of the tablets. At this stage the limits of confidence in the comparison between choline theophyllinate and its placebo had not been reached (Fig. 5). As a further precaution the mean score recorded for each drug was calculated ; for each patient the maximum score possible was +3, indicating that the breathing was better than usual for all three days on the drug, and the minimum -3, when the breathing was worse than usual

FIG. 3

FIG. 4

FIG. 5

FIG. 3.—Result of sequential trial: comparison between delaminoph and choline theophyllinate. FIG. 4.—Result of sequential trial: comparison between delaminoph and an identical placebo. FIG. 5.—Result of sequential trial: comparison between choline theophyllinate and an identical placebo.

on all three days. The mean score for delaminoph was +1.26, and for its placebo -0.36, this difference being statistically significant ($0.01 > P > 0.001$). The mean score for choline theophyllinate was -0.31, and for its placebo -0.10; this difference is not significant ($0.4 > P > 0.3$).

Gastric side-effects were reported with all four tablets, being more frequent with choline theophyllinate than with delaminoph. Using a similar method of scoring for the side-effects as used for beneficial effects (+1 for sickness and/or indigestion, 0 for none) the mean score for delaminoph was 0.70, being identical to that of its placebo; the mean score for choline theophyllinate was 1.3, and for its placebo 0.55, this difference being significant ($P > 0.001$). The conclusion was drawn that in a dose of 25 mg. three times daily delaminoph was of benefit to these patients and caused no more side-effects than a placebo. The lack of significant response to the dose of choline theophyllinate (in spite of having a higher theophylline content than the dose of delaminoph) is unexplained, but may be related to the fact that the patients in the trial had all been treated with it previously; it was more prone to cause side-effects than its placebo.

Use in Patients Intolerant of Choline Theophyllinate

Turner-Warwick (1957) found choline theophyllinate to be as effective as aminophylline, both being more effective than a group of other theophylline compounds; and Gandevia *et al.* (1957) confirmed its effectiveness. Although it is less apt to cause gastric side-effects than aminophylline (Gagliani *et al.*, 1954) an appreciable incidence of these symptoms arises in patients taking it (Brown and Clancy, 1955). A group of 14 patients who complained of such symptoms—epigastric pain, flatulence, anorexia, nausea, or vomiting—while taking choline theophyllinate 200 mg. four times daily were assessed by simple tests of ventilatory function. The choline theophyllinate was then replaced by delaminoph 250 mg. three times daily before meals, and the patients were reassessed after one month. Eleven patients reported complete clearing of the gastric symptoms; in the three others they had become less, and on a dose of 125 mg. three times daily these also cleared. The tests of ventilatory function did not show any significant change, except for one patient who developed an infective exacerbation of chronic bronchitis with resulting increase in airway obstruction. Nine of these patients have continued to take the drug for an average of five and a half months without a recurrence of side-effects. These observations are uncontrolled, and wider use of delaminoph has shown that it is not entirely free from similar side-effects, but there seems no doubt that its use is of value in patients intolerant of choline theophyllinate.

Discussion

Several studies have demonstrated that oral bronchodilators are capable of relieving the airway obstruction of asthma and chronic bronchitis. The trials of Turner-Warwick (1957) and Gandevia *et al.* (1957) suggested that choline theophyllinate was the most effective of the drugs available at the time. However, Turner-Warwick found similar blood levels with aminophylline, and if this did not cause gastric irritation so frequently it would doubtless be used more often.

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The present trial of the new aminophylline preparation delaminoph has shown that adequate theophylline blood levels can be obtained with it; the peak blood level and maximum effect occur six hours after an oral dose, and this delayed action may be an advantage in long-term therapy.

The double-blind trial revealed delaminoph to be more effective than a placebo in relieving the symptoms of a series of patients with chronic bronchitis; it also appeared to be more effective than choline theophyllinate, though this observation is of doubtful significance. Although it is not entirely free from side-effects, it appears to be less likely to cause gastric irritation than choline theophyllinate, and patients who are intolerant of the latter appear to be able to tolerate delaminoph in a therapeutic dose taken before meals. It is doubtful if any potent theophylline derivative will ever be free from the production of nausea and anorexia in certain subjects, these side-effects occurring after rectal and parenteral aminophylline, as well as with oral administration.

Summary

A clinical trial of the new aminophylline preparation delaminoph showed that:

1. An oral dose of 250 mg. gave adequate theophylline blood levels and improved airway obstruction in a group of chronic bronchitics. The peak blood level and maximum effect occurred six hours after the dose.
2. In a double-blind controlled sequential trial in a group of 19 patients a dose of 125 mg. three times daily was significantly more effective than a placebo in producing symptomatic relief. It appeared more effective than choline theophyllinate, 200 mg. three times daily, in this respect.
3. A group of 14 patients suffering from the gastric side-effects of choline theophyllinate were improved when delaminoph was substituted, this observation being uncontrolled.

The drug appears to be effective in a dose of 125–250 mg. given six- to eight-hourly before meals; it is not entirely free from gastric side-effects, but these are infrequent.

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