

The place of antibiotics in the treatment of acute gastroenteritis in general practice: a controlled clinical trial

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ANTIBIOTICS are still widely used in general practice for the treatment of diarrhoea occurring in acute gastroenteritis, despite evidence that their use is unnecessary and may be harmful.

The general practitioner understandably has to start treatment before the bacterial nature of the diarrhoea is known, and this 'immediate-treatment' role is acknowledged by Anderson (1971) of Australia. In advocating antibiotic treatment he states that many cases of *Salmonella* gastroenteritis have high fever, toxæmia and prostration; that differentiation of the invasive case is difficult on clinical grounds, and that antibiotics may prevent subclinical bacteraemia. This view, possibly also held by some practitioners in this country, amounts to the use of antibiotics as an insurance—an insurance against what?

In general practice most patients presenting with acute gastroenteritis have no intestinal bacterial pathogen, and the incidence of bacterial diarrhoea in the more selected hospital patient is only slightly higher.

Tuckman *et al.* (1962) in a large and detailed general-practice survey of gastroenteritis occurring in all ages showed a 0.5 per cent incidence of *Salmonella*, and in children under two, a three per cent incidence of enteropathic *E. coli*. Their figure of 18 per cent for *Shigella* included an epidemic. More recently, Randall and Tuckman (1970) re-emphasised the low incidence of bacterial diarrhoea in general practice by reporting that of 335 stool specimens sent to the laboratory at Orpington Hospital, only 11 were positive (*Salmonella typhimurium* five; *Shigella* one; enteropathic *E. coli* five). Hospital figures for infants show a two or three per cent incidence of *Salmonella* and *Shigella*, and a 12–16 per cent incidence of enteropathic *E. coli* (Moffet *et al.*, 1968; Mann, 1969; Ironside *et al.*, 1970).

A viral aetiology accounted for 22–23 per cent of hospitalised infants (Sommerville, 1958; Moffet *et al.*, 1968), although in general practice Tuckman *et al.* (1962) isolated only one ECHO virus from 49 children under five.

It is illogical to use antibiotics in either viral or non-bacterial diarrhoea, and any controversy about their use is confined to the small minority, or the epidemic cases, with bacterial cause.

Dixon (1965) in comparing two separate but similar outbreaks of *Salmonella typhimurium* food poisoning, suggested that antibiotic treatment prolonged excretion of the organism. This concept was confirmed by Aserkoff and Bennett (1969) in a large outbreak of *Salmonella typhimurium*, when antibiotic treatment increased both the proportion and duration of the carrier state.

The joint project by members of the association for the study of infectious disease (1970) similarly found a higher proportion of carriers in non-invasive *Salmonella* infection after treatment with neomycin, although the clearance rate was not prolonged.

They also reported no difference in the duration of symptoms between those treated with, and those without, neomycin. Similar conclusions were reached by Smith and Young (1966) in *Shigella sonnei* infection in children; the rate of clearance was the same in those treated with and without streptomycin.

Infections caused by enteropathic *E. coli* form a separate clinical entity owing to the young age-group and dangers of dehydration, but antibiotic controversy here seems to rest not so much with the treatment of the hospitalised infant *per se*, but rather with prevention of cross-infection. Severe gastroenteritis *per se* is not considered an indication for antibiotic treatment (Ironside *et al.*, 1970) and Lindquist and Meeuwisse (1971) emphasise the attendant risk of antibiotic use in infants. While Mann (1969) argues that first-class barrier nursing precludes the need for antibiotics, Valman and Wilmers (1969) advise their use where conditions for barrier nursing are not ideal.

Emond *et al.* (1969) embrace the whole field in their belief that excluding typhoid and blood-stream infection, intestinal infections due to *Salmonella*, *Shigella*, and enteropathic *E. coli* all behave in a similar way, and that acute symptoms are not relieved and clearance of organisms is not expedited by antibiotics.

It is against this background that antibiotics are still widely used in general practice. The present situation is perhaps best summed-up by Howie (1971) who suggests that prescribing habits will remain unaltered until the point is proven one way or the other by trial in a general-practice setting.

Method

Consecutive patients in a Plymouth general practice presenting with diarrhoea alone, or with diarrhoea and vomiting, were included in the trial if aged 12 months or over. I did not like submitting infants to a trial of this kind. Patients with recent exposure to an antibiotic or with responsible organic disease were excluded.

So 132 episodes of gastroenteritis occurring in 128 patients were admitted to the trial during the two-year period mid-May 1970 to mid-May 1972, and these were divided by random selection into two groups, A and B. Group A patients were treated by dietary means and a neomycin-kaolin mixture; those in Group B by dietary means and kaolin alone.

The same dietary measures were employed in both groups. Solid food was excluded and fluids of any kind freely allowed provided that milk was diluted. Solids in some form were invariably taken again after 24 hours.

A common proprietary mixture was used in group A cases, containing 350mgm of neomycin and 4.0 grams of kaolin in each 20ml adult dose. Mist.Kaolin B.P.C. was given to group B cases, also containing four grams of kaolin in each 20ml adult dose. Kaolin doses were therefore the same in each group, and neomycin the only variant. Patients aged 12 years and over were given 20ml of the respective medicine four times a day. The 5-12 and 1-5 year age groups were given 10ml and 5ml respectively four times daily.

In accordance with the manufacturer's suggestion and to avoid an open invitation to antibiotic side-effects, the neomycin-kaolin mixture was stopped after three days in group A cases and kaolin alone substituted if diarrhoea persisted. The kaolin was then continued, as in group B cases, until the diarrhoea ceased.

Patients were assessed by measuring the duration of diarrhoea after initial consultation. In order to avoid the use of hours or half-days in this measurement, I thought that diarrhoea lasting until, and ceasing on, the day after initial consultation should be classed as lasting one day. Diarrhoea of longer duration was classified in a similar way in whole days. Instances of diarrhoea which ceased earlier were recorded separately.

Bacteriology

At the initial consultation each patient was asked to collect a single specimen of stool. Delay in reaching the Public Health Laboratory was avoided by its proximity. Specimens were examined for organisms of the *Salmonella* and *Shigella* groups by direct plating onto Wilson and Blair's medium and deoxycholate-citrate agar, and by enrichment through selenite-F medium. Examination for enteropathic *E. coli* was also undertaken in patients under two years of age.

Results

The patients who failed to satisfy the criteria of the trial formed a minority group. Infants under 12 months with gastroenteritis were treated with non-sweetened, half-strength, half-cream milk, exclusion of solids, and no drug of any kind. The hospital admission rate for rehydration was very low.

The rest comprised several patients with antibiotic-induced diarrhoea, a few with acute diverticulitis, and one instance each of ill-defined colitis, ulcerative colitis, ulcerative proctitis, post-radiation diarrhoea, and abdominal aortic aneurysm. The few patients with large-bowel carcinoma seen during the two-year period did not present with diarrhoea as a specific entity, and no instances of Crohn's disease or malabsorption syndrome were encountered. Diarrhoea in association with bacterial infection such as otitis media was not seen at all.

Seven patients who were otherwise suitable for admission to the trial were not included. Four had severe abdominal colic and were given immediate antispasmodics for the relief of pain. Social reasons prevented the other three from completing the follow-up arrangements.

Of the 132 examples of gastroenteritis admitted to the trial (66 group A, 66 group B), 45 occurred in patients under the age of five, 75 were fairly evenly distributed in the 5-40 age group, and the remaining 12 scattered among those aged 40-80 years. Sex distribution was: 73 male and 59 females. The month of presentation was variable, but each month was represented and an epidemic was not encountered. On 69 occasions diarrhoea occurred alone, while associated vomiting was present on 63.

Thirty-one instances (20 group A, 11 group B) were unsuitable for final comparison. In 22 follow-up was inadequate. A further four were given antispasmodics for prolonged diarrhoea (three) and colic (one). Of the remaining five, one had taken prior kaolin, one stopped the neomycin-kaolin mixture owing to vomiting, and one showed carbohydrate intolerance to the syrup in the neomycin-kaolin mixture. The other two, and the only two, were sent to hospital. Both had prolonged diarrhoea; a 26-year-old woman queried as colitis who attended outpatients, and a five-year-old boy admitted at parental request who "settled quickly without (further) treatment". Bacterial data were obtained for 15 of these 31.

A further 18 instances (seven group A, 11 group B) were also unsuitable. Their diarrhoea ceased spontaneously after the initial consultation, and the treatment advocated clearly did not influence the outcome. Three provided bacterial data. In two, specimens were collected before attending surgery, and the third (normal stool) collected two days after.

In a further six instances (three group A, three group B), the influence of prescribed treatment was questionable, as the diarrhoea, while occurring after the initial consultation, ceased on the same day. Bacterial data were obtained in five.

The remaining 77 (36 group A, 41 group B) were valid for comparison. Bacterial data were obtained in 73. The 36 instances in group A and the 41 in group B are shown to be evenly matched for age, sex, time of year, and incidence of diarrhoea occurring

alone or with vomiting. These two groups are also shown to be representative of the whole series (132 instances) in the same parameters (Tables 1 and 2).

TABLE 1

AGE, SEX, AND INCIDENCE OF ASSOCIATED VOMITING IN THE WHOLE SERIES, AND IN THE 77 FINALLY COMPARED

| <i>Number of instances of gastroenteritis</i> | <i>Age in years</i> | | | <i>Sex</i> | | <i>Associated vomiting</i> | |
|---|---------------------|-------------|----------------|-------------|---------------|----------------------------|----------------|
| | <i>Under 5</i> | <i>5-40</i> | <i>Over 40</i> | <i>Male</i> | <i>Female</i> | <i>Absent</i> | <i>Present</i> |
| Total (132) | 45 | 75 | 12 | 73 | 59 | 69 | 63 |
| Group A (36) | 13 | 20 | 3 | 22 | 14 | 20 | 16 |
| Group B (41) | 15 | 23 | 3 | 22 | 19 | 24 | 17 |

TABLE 2

THE MONTHLY INCIDENCE OF GASTROENTERITIS IN THE WHOLE SERIES, AND IN THE 77 INSTANCES FINALLY COMPARED

| | <i>1970</i> | | | <i>1971</i> | | | <i>1972</i> | | |
|-----------|--------------------|---------------------|---------------------|--------------------|---------------------|---------------------|--------------------|---------------------|---------------------|
| | <i>Total (132)</i> | <i>Group A (36)</i> | <i>Group B (41)</i> | <i>Total (132)</i> | <i>Group A (36)</i> | <i>Group B (41)</i> | <i>Total (132)</i> | <i>Group A (36)</i> | <i>Group B (41)</i> |
| January | | | | 9 | 4 | 1 | 3 | 1 | 0 |
| February | | | | 9 | 1 | 6 | 5 | 1 | 3 |
| March | | | | 4 | 2 | 0 | 6 | 1 | 2 |
| April | | | | 6 | 1 | 1 | 3 | 1 | 1 |
| May | 4 | 1 | 2 | 8 | 2 | 3 | 1 | 0 | 1 |
| June | 6 | 1 | 2 | 6 | 3 | 1 | | | |
| July | 2 | 0 | 1 | 2 | 0 | 0 | | | |
| August | 3 | 2 | 0 | 2 | 1 | 0 | | | |
| September | 14 | 3 | 5 | 7 | 3 | 1 | | | |
| October | 7 | 4 | 2 | 10 | 3 | 3 | | | |
| November | 2 | 0 | 0 | 6 | 0 | 4 | | | |
| December | 4 | 0 | 2 | 3 | 1 | 0 | | | |

Although associated bacterial infection was sought and excluded in all cases, a record of associated symptoms and virus infection was kept in the latter 16 months of the trial only. These results are tabulated, as they also serve to show similarity between the 36 in group A and the 41 in group B (Table 3).

The duration of diarrhoea in these two groups is shown in Table 4. Although statistical analysis showed no significant difference between the effects of treatment in the two groups, an observed difference exists with a mean duration of 3.36 days in group A cases and 2.46 days in group B.

TABLE 3
ASSOCIATED SYMPTOMS AND VIRUS INFECTIONS OCCURRING IN THE WHOLE
SERIES, AND IN THE FINAL 77 CASES OF GASTROENTERITIS

| | <i>Number of cases of gastroenteritis</i> | | |
|-------------------------------------|---|-------------------------|-------------------------|
| | <i>Total (132)</i> | <i>Group A (36)</i> | <i>Group B (41)</i> |
| No record | 44 | 12 | 14 |
| No other symptom or virus infection | 55 | 14 | 19 |
| Influenzal illness | 10 | 4 | 3 |
| Common cold | 9 | 2 | 1 |
| Temperature with no other cause | 7 | 2 | 3 |
| Headache | 2 | 1 | 1 |
| Cough | 3 | 0 | 0 |
| Reaction to measles vaccine | 1 | 1 | 0 |
| Non-specific rash | 1 | 0 | 0 |

TABLE 4
THE DURATION OF DIARRHOEA IN THE FINAL CASES OF GASTROENTERITIS

| <i>Number of cases of gastroenteritis</i> | <i>Duration of diarrhoea (days)</i> | | | | | | | | | | | | | <i>Mean duration (days)</i> |
|---|-------------------------------------|----|---|---|---|---|---|---|---|----|----|----|----|-------------------------------------|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | |
| Group A (36) | 9 | 10 | 6 | 3 | 3 | 1 | 0 | 2 | 0 | 0 | 0 | 1 | 1 | 3.36 |
| Group B (41) | 18 | 10 | 4 | 2 | 2 | 2 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 2.46 |

Separate assessment of the 45 children under five revealed a similar pattern. Here, diarrhoea occurred 28 times with vomiting, included six of those without adequate follow-up, the single case of carbohydrate intolerance, nine when diarrhoea ceased spontaneously, and one which ceased on the same day. The remaining 28 were valid for comparison (13 group A, 15 group B). Group A comprised three children aged 12–14 months and ten in the two to five-year age group. In group B, the numbers were seven and eight respectively. The mean duration in group A cases was 3.34 days, and 2.53 days in group B.

Bacteriology

A total of 96 stool specimens was obtained; 23 from those unsuitable for comparison, and 73 from the 77 finally compared. Organisms of the *Shigella* group were found in none, and *Salmonella typhimurium* once only; a seven-year-old girl excluded from the final comparison owing to prior kaolin. Twenty-four of the specimens were also examined for enteropathic *E. coli*, but none was isolated. The 24 examined comprised ten of 12 specimens from the 14 children aged 12–24 months, and 14 of 20 specimens from the 31 aged two to five years.

Forty-eight of the 96 stool specimens had been collected on the same day as initial

consultation, and 40 on the first day after. Five were collected on the second day after, and the remaining three on the third or fourth day.

Complications

There were no apparent complications attributable to the antibiotic treatment. The clinical picture of enterocolitis was not seen, and it was not possible to implicate the antibiotic as a cause of prolonged diarrhoea. Twelve instances (seven in final comparison, three given antispasmodics, and two sent to hospital) produced diarrhoea lasting seven days or more, but six of these were in group B.

Complications of gastroenteritis *per se* were also absent. The five patients (four excluded from trial and one included but not compared) given antispasmodics for severe abdominal colic responded quickly and recovered without other drug treatment.

Discussion

The patients treated with antibiotic in the form of neomycin derived no benefit; possibly the reverse. This result is hardly surprising in view of the almost totally negative bacteriological findings. On these grounds alone, there would seem to be no justification for the general use of antibiotics to 'cover' the rare bacterial instance indistinguishable clinically from the non-bacterial occurrences.

While the results of this trial cannot contribute to the question of treatment of bacterial infections, evidence against the value of antibiotics in bacterial diarrhoea comes from a wide body of informed opinion as outlined above, and is supported by the attendant risks of antibiotic use. In addition to the better known and possibly disastrous staphylococcal or monilial enterocolitis, transferable drug resistance is recognised (Anderson, 1968; Moorhouse and McKay, 1968). The incidence of resistance may be high; in *Shigella sonnei* infections, Davies *et al.* (1970) reported 70 per cent of strains resistant to three or more antibacterial drugs.

The apparent freedom from antibiotic side-effects in this trial is no argument in favour of their use. With reference to enterocolitis, the general-practice patient particularly runs the risk of taking any drug for longer than may have been intended, and restriction in the quantity prescribed coupled with exact instructions are necessary to avert possible disaster in this sphere of antibiotic use.

The suggestion by Gorbach (1970) that toxins from 'normal' bacterial flora may cause non-specific gastroenteritis is of relevance to this trial, in that he goes on inevitably to suggest that antimicrobial therapy may therefore have a place in treatment. This trial shows quite clearly that neomycin was of no therapeutic value in non-specific gastroenteritis.

A re-orientation in traditional thinking is required in gastroenteritis where both non-bacterial *and* bacterial instances fare as well and probably better without antibiotic treatment. Having found a positive culture one then has to do nothing about it. Some would question the point of culturing the stool at all. It is suggested that stool culture is still of value in providing a more exact diagnosis, in determining which patient *might* need antibiotic treatment (invasive case), and to show whom to follow-up and where to implement hygienic measures.

While it is claimed that antibiotics have no place in the treatment of gastroenteritis except in typhoid and invasive infection, it is not claimed that kaolin is necessarily the best treatment. Antispasmodics have a place, but unintentionally prolonged use can result in profound constipation causing greater distress than the original diarrhoea.

In general practice it is suggested that the most valuable treatment is restriction of solids, free fluids, dilution of milk and attention to fluid balance; that a modest response

may be expected from kaolin; that antispasmodics in restricted duration are of value in adults with colic or profound diarrhoea, and that antibiotics will rarely if ever be required.

Summary

The effect of a neomycin-kaolin mixture was compared with kaolin alone in the treatment of acute gastroenteritis in general practice. The trial covered a two-year period and included patients over the age of 12 months. Of the 96 instances in which bacterial data were obtained, a bacterial intestinal pathogen was isolated once only.

Although there was no significant difference between the effects of the two treatment methods, the observed difference suggested that those treated with kaolin alone fared slightly better.

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DIARRHOEA IN GENERAL PRACTICE

Effective assessment of diarrhoea as a symptom encountered in general practice entails knowledge of the patient as a person, and of his family setting. It also involves a working knowledge of probabilities based on general-practice epidemiology. A decision to investigate diarrhoea in a general-practice patient entails exercising judgement of factors which are less relevant in hospital patients, but all doctors should be increasingly concerned to use antibiotics judiciously in the management of diarrhoeal diseases. The prevention and effective control of the dehydration which occurs in infantile diarrhoea is extremely important.

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