of some preparations may be causal factor in the aetiology of fibrosing colonopathy.[20] This hypothesis would explain the association with high strength preparations, and the difference in association between different high strength products. Indirect evidence in support of the second hypothesis has come from two further observations. The first is that two, histologically confirmed, cases of fibrosing colonopathy have been described in young children treated with the low strength preparation Nutrizym GR (Merck).[20 21] Nutrizym GR is one of the few low strength preparations that contains the methylacrylic acid copolymer.[20] The second observation was reported recently by Croft *et al*, who used the technique of whole gut lavage to study gut inflammation in patients with cystic fibrosis receiving high strength pancreatic enzyme preparations.[22] They found that two patients, who were both taking Nutrizym 22, had strikingly abnormal results indicative of severe mucosal inflammation.

Clearly there is still uncertainty about the aetiology of fibrosing colonopathy and further work is needed to investigate both of the hypotheses described above. The Committee on Safety of Medicines has considered the results of the case-control study and has recommended that Pancrease HL and Nutrizym 22 are not used in children under the age of 15 years. They have also suggested that it would be prudent to avoid total daily doses of enzyme supplementation above 10 000 units of lipase/kilogram/day.[23] In the USA, a recent consensus committee has made similar recommendations, advocating a maximum dose of 2500 units of lipase/kilogram/meal.[24]

Conclusion

The introduction of enteric coated pancreatic enzyme supplements in the early 1980s was undoubtedly one of the major advances in the care of children with cystic fibrosis. Further refinements in the presentation of these preparations inevitably followed, to improve patient acceptability and compliance. The emergence of fibrosing colonopathy took clinicians dealing with cystic fibrosis completely by surprise, and in the last two years there has been a gradual appreciation that as far as pancreatic enzyme products are concerned 'More is not necessarily better'.[16] However, it is encouraging that, in the UK, there have been no histologically confirmed cases in children receiving high strength pancreatic enzyme preparations since July 1994. Hopefully this trend will continue and the causal factors will be defined, ensuring that this serious complication can be effectively prevented in the future.

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Commentary

Implications of the Committee on Safety of Medicines 10 000 IU lipase/kg/day recommendation for use of pancreatic enzymes in cystic fibrosis

The latest recommendation of the Committee on Safety of Medicines that 'it would be prudent to avoid doses of pancreatic enzyme supplements in excess of 10 000 units of lipase/kg/day, irrespective of the preparation' has caused a problem for paediatricians who have cystic fibrosis patients, many of whom are taking considerably more enzymes than recommended. Most patients have reached their present dose by increasing the number of enzymes to a level sufficient to control their gastrointestinal symptoms and signs. In some patients the symptoms may not have been caused by their intestinal malabsorption and the increase in dose is inappropriate and results in their taking an excessive dose of enzymes. However, there are many others who certainly do require more than the recommended 10 000 units of lipase/kg/day to control both their symptoms and their fat malabsorption. Unfortunately both must be monitored, as symptoms can occur with normal fat absorption, and severe malabsorption may occur without any symptoms.

The aims of pancreatic enzyme treatment are to abolish unpleasant gastrointestinal symptoms, particularly pain and distension, and to achieve a normal bowel habit and stools. The nutritional state and growth should be normal and over 85% of the fat ingested should be absorbed. These aims are achievable in 90% of cystic fibrosis patients using standard enzyme preparations.[1]

In many clinics, although the symptoms and growth are monitored at every attendance, it is unusual for there to be any regular measurements of intestinal absorption, either by semi-quantitative methods, for example faecal microscopy for fat,[2] or more quantitative measurement of timed faecal fat output.[3 4] *As a result it is relatively common for the dose of pancreatic enzyme to be increased in response to symptoms when these are due to some cause other than malabsorption.* Thus a proportion of cystic fibrosis patients who are taking in excess of 10 000 units of lipase/kg/day do not require such high doses.

A suggested regimen for use of pancreatic enzyme treatment is as follows – *For infants* start with one third to one half capsule per feed of standard Creon or Pancrease, which is equivalent to 1500–2500 units lipase (Pancrease) or 2600–4000 units lipase (Creon) per feed. *For children* we used standard preparations of Creon or Pancrease (some paediatric units use Creon 25000 as the Committee on Safety of Medicines advised avoiding only Pancrease HL and Nutryzim 22 in children aged 15 years and under with cystic fibrosis). Start with 1–2 capsules per meal and vary dose with fat content. Enzymes should also be given with fat containing snacks. Gradually increase the dose to control the symptoms, using ideally not more than 10 000 units of lipase/kg/day. Larger doses may be necessary but should only be used after investigation including some estimate of fat excretion to measure the presence and severity of the intestinal malabsorption. It is important to consider other gastrointestinal disorders as a cause of the persisting symptoms which must always be thoroughly investigated.[1–5] If significant malabsorption persists (<80% absorption of ingested fat) when receiving correctly administered enzymes in doses of 10 000 units lipase/kg/day consideration should be given to changing to the other recommended standard enzyme preparation, which surprisingly sometimes causes a quite dramatic improvement in symptoms. Also there has been renewed interest in the reduction of gastric acid by adding either an H_2-blocker[6] or omeprazole,[7] both of which improve absorption and have an enzyme sparing effect. This treatment should be tried in patients requiring more than the recommended dose of enzyme to control their symptoms.

The US Cystic Fibrosis Foundation's recommendations have been reported in detail[8] and are similar to those described above.

In patients who are well, asymptomatic and growing normally, yet on higher than the recommended dose of enzymes, an attempt should be made to reduce the dose. Intestinal absorption should be checked either by a timed faecal fat estimation or, as a minimum, by faecal fat microscopy. If absorption is satisfactory (fat absorption over 85% or no neutral fat and little split fat on microscopy), the dose of enzymes should be reduced gradually by 10% every few weeks. If symptoms occur or weight gain is adversely affected the previous dose should be resumed. Absorption is again checked. If the dose is still substantially over 10 000 units of lipase/kg/day a drug to reduce gastric acid should be added. Further enzyme reduction can then be attempted while taking regular ranitidine or omeprazole.

By employing the regimen suggested above, 66 (47%) of 139 pancreatic insufficient children attending our cystic fibrosis clinic are taking more enzymes than the recent dose recommendations of 10 000 units of lipase/kg/day but only 18 (13% of the clinic) take more than 15 000 units and only four (3%) more than 20 000 of lipase/kg/day. Thus although the Committee on Safety of Medicines recommended dose is exceeded by a substantial number of children the excess is modest, and rarely exceeds 20 000 units/kg/day; only one child just exceeded the 25 000 units, above which the risk of fibrosing colonopathy seems to increase.

Some regular gastrointestinal surveillance of all patients taking pancreatic supplements should now become routine practice in all clinics where people with cystic fibrosis are treated. Patients unwilling to collect timed faecal specimens for their annual review should be offered the alternative of faecal microscopy and chymotrypsin estimation, which is more acceptable to older patients. Clinicians must convince laboratories of the importance of monitoring faecal fat and chymotrypsin and impress on their patients and their families the importance of providing occasional faecal specimens. Repeated faecal microscopy for fat using a very small (pea sized) faecal specimen collected at home is invaluable during this type of enzyme dose adjustment. Faecal chymotrypsin can be performed on the same specimen[9]; high values suggest a substantial dose of enzyme is being taken and low values confirm an inadequate enzyme dose or non-compliance with taking the enzymes.

It is encouraging that no further cases of fibrosing colonopathy have occurred since 1994 but important that the occurrence of this totally unexpected and very serious complication results in the introduction of as careful regular monitoring of the gastrointestinal tract as already occurs of the chest.

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Cholera in Peru

The world is experiencing its seventh known cholera pandemic. It began in Indonesia in 1961 and reached South America in 1991. The disease spread rapidly through Peru and adjacent countries and by the end of 1992 more than 500 000 cases and 4000 deaths had been counted.

During February and March 1991 over 1500 children with diarrhoea presented to a hospital north of Lima and 626 of these were studied (Juan M Fukuda and colleagues, *Journal of Pediatrics* 1995; **126:** 882–6). *Vibrio cholerae* was isolated from the stools of 310 of these 626. About 25% of the children under 2 years old and some 60 to 70% of those over 2 years had cholera.

In young children (<2 years) severe dehydration was the main feature distinguishing cholera from other diarrhoea. In older children sudden onset of watery diarrhoea, abdominal pain, muscle cramps, vomiting, and severe dehydration were characteristics of cholera. Severe dehydration increased in frequency with age, being seen in 16% of the under 2s, 32% at ages 2 to 5, and 49% over 5 years. Only one child died and the authors attribute the low fatality rate to rapid correction of shock and early and liberal use of oral rehydration solution. Lack of suitable drinking water and eating uncooked food, especially raw fish, were the main community risk factors.

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