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without diarrhoea at the time of testing (table III). Negative results were obtained in all control tests (those without addition of mucosa), in 1 of the 8 patients with diarrhoea, and 5 of the 7 patients without diarrhoea. Of the 7 positive fluorescence results 2 were obtained against mucosal bacteria only, 2 against bacteria from the juice, and in 3 there was positive fluorescence with bacteria from both juice and mucosa (table III). In the group without diarrhoea the only positive fluorescence was seen on mucosal bacteria.

DISCUSSION

Like earlier observers, we found bacteria on culture of small-intestinal mucosal homogenates. These organisms resembled the luminal flora. Our mucosal flora consisted of predominantly coccal forms but there were also some rod-shaped forms—a finding which accords with the findings of Nelson and Mata.¹⁰ We cultured organisms from all mucosal homogenates, whereas Nelson and Mata took cultures from only 4 of 7 patients studied.

Despite the normal morphology of the small-intestinal mucosa by light microscopy, mucosal antibody against luminal and mucosal antigen was demonstrated. Furthermore the findings of such antibody was associated with persistent diarrhoea at the time of testing. The 2 children who had mucosal antibody but no diarrhoea had previously had an abnormal small-intestinal mucosa.

For the first time mucosal antibody was detected against "non-pathogenic" bacteria of both coccal and rod-shaped forms, grown not only from the mucosa itself but also from the luminal juice. The importance of the mucosal antibody in the pathogenesis of diarrhoea is unclear. We have no evidence of any structural damage caused by antigen/antibody reaction; indeed the mucosa was normal or near normal in all patients. Possibly, in persistent diarrhoeal states adherent and also non-adherent bacteria which are regarded as being non-pathogenic acquire toxins which are absorbed by the mucosa, and this leads to antibody production either locally by the mucosal plasma-cells or through the systemic immune system. It is also possible that there is, or had been, an increase in mucosal permeability to bacterial antigen which had allowed sensitisation to occur—a similar mechanism as has been postulated for food antigens as a complication of gastroenteritis. Further work is necessary to characterise the positively fluorescing bacteria and their adhering properties, as well as the nature of the antigens. Classification of the antibody will also be necessary and may give insight into pathogenesis.

If the antibody is class IgA, antibody production may represent a protective mechanism and be a marker of bacterial colonisation and adherence to the mucosa. If the class is IgM, antibody production may be involved directly in pathogenesis of diarrhoea by activation of complement. IgG antibody is more likely to be derived from the serum since IgG plasma-cells in the jejunal mucosa are normally few in number. Immunohistochemical techniques on the mucosal-biopsy specimens are currently used to correlate plasma-cell numbers and class with anti-bacterial antibody production.

Phillips et al.¹¹ have demonstrated by scanning electron microscopy rod-shaped bacteria adhering to the surface of a lymphoid follicle in patient 7. The duodenal mucosa was obtained at the same time as our specimens.

Absorption of bacterial antigens may have occurred here through the epithelium overlying the lymphoid nodules.¹² The consequent "priming" of the lymphocytes within the nodules may thus stimulate antibody production. There is now good evidence that antigen entry normally occurs via this epithelium in the gut and that immunoblasts are primed at lymphoid follicles before they migrate to the lamina propria elsewhere in the gastrointestinal tract. The mucosal antibody in this child may be the consequence of sensitisation to the bacteria shown to be adhering to the epithelium overlying the lymphoid follicles.

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ALTERED THEOPHYLLINE PHARMACOKINETICS DURING ACUTE RESPIRATORY VIRAL ILLNESS

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Summary The plasma half-life of theophylline was determined during and 1 month after serologically confirmed upper-respiratory-tract viral illness in six children with chronic asthma. In this group the plasma-theophylline half-life (mean=419.8 min) was significantly longer during the acute stage of their illness than 1 month later (mean 249.9 min). There was no appreciable change in half-life in 4 patients who were febrile but in whom seroconversion did not occur. These preliminary results suggest that certain upper-respiratory-tract viral infections may affect theophylline metabolism.

INTRODUCTION

THE effect of acute viral infections, with the exception of acute hepatitis, on the distribution of drugs is largely unknown. Plasma-theophylline is often raised during acute upper-respiratory-tract viral illness in our asthmatic patients receiving round-the-clock theophylline

PLASMA-THEOPHYLLINE HALF-LIFE IN SIX ASTHMATIC CHILDREN DURING AND AFTER INFLUENZA AND ADENOVIRUS
UPPER-RESPIRATORY-TRACT INFECTION

Subject	Age	Sex	Seroconversion	Plasma-theophylline half-life (min)		Symptoms†	Medication changes
				Acute	1 month		
1	15	M	Influenza A	279.6	125.5	ABCF	None
2	14	F	"	352.8	82.1	BCDF	Prednisone added
3	13	F	"	204.8	167.1	BCDF	Prednisone reduced, terbutaline added
4	12	M	"	558.5	381.4	BCDF	None
5	9	M	Adenovirus	686.1	303.2	BDF	None
6	13	M	Influenza B	436.8	439.8	BCDF	None
Mean±s.d.				419.8±179.3	249.9±146.1		

†A=coryza, B=cough, C=increased asthma, D=sore throat, F=body temperature of 38° C or greater.

therapy. We have investigated the effect of viral infection on the metabolism of theophylline in such patients.

METHODS

Ten asthmatic children (aged 9 to 15 years) were studied during and after febrile infections. Serological studies performed during the acute and convalescent (14–21 days) phases of the illness included complement-fixation tests for respiratory syncytial virus, influenza viruses A and B, adenovirus, *Mycoplasma pneumoniae*, and corona viruses (OC43, 229E), and haemagglutination-inhibition tests for influenza viruses A and B and parainfluenza viruses 1, 2, and 3. Fourfold or greater increases in titre were regarded as indicating infection.

Theophylline half-life was determined during the acute illness and 1 month later. All patients received round-the-clock aminophylline (theophylline ethylenediamine) before the study, but this therapy was suspended at least 6 h before the half-life was determined. The half-life was measured after a 10-min intravenous dose of aminophylline equivalent to the patient's regular oral dose which had been adjusted to maintain plasma-theophylline between 10 and 20 µg/ml. Plasma samples were collected after 1, 1½, 2, 3, 4, and 5 hours. Theophylline concentrations were measured by a modification of the Schack and Waxler procedure.¹ Inter-assay variation between duplicate control theophylline measurements in our laboratory does not exceed 3.7%.² The equation for the regression line of the log of plasma-theophylline concentration against time was obtained by the least-squares method. The half-life was determined by dividing the log of 2 by the slope of the last half of regression line. Statistical analysis was performed by means of a 1-tailed Student's *t* test. Two subjects (3 and 4) had positive throat culture for group-A β-haemolytic streptococcus and received therapy for 10 days with oral penicillin. 3 of the 4 subjects in whom seroconversion, as judged by a respiratory-virus panel, was lacking had gastrointestinal symptoms and signs, rather than indications of respiratory illness.

During their acute illness serum-transaminases in these children were within the normal range (7–29 units/ml). Urinary specific gravity ranged from 1.007 to 1.023. There was no statistically significant change in urinary creatinine clearance in these subjects.

RESULTS

The plasma-theophylline half-life was significantly longer during serologically proven upper-respiratory-tract infection in five of six asthmatic children than 1 month after the illness (see accompanying table). Four additional subjects having febrile illness without seroconversion had no change in half-life; their mean half-life was 317 (±66) during the illness and 332 (±64) min

1 month afterwards ($P>0.1$). Subject 1 experienced acute theophylline toxicity during the febrile illness (plasma-theophylline 43.3 µg/ml).

DISCUSSION

Our data suggest that patients with influenza A and adenovirus infection may have longer theophylline plasma half-lives during acute infection than 1 month afterwards. This could be the result of viral infection-induced acute-phase prolongation or convalescent-phase shortening of half-life. We have insufficient data to determine the exact mechanism. Future confirmation of our data, by means of steady-state clearance determinations, may help us to understand this phenomenon. Since subjects' liver transaminases remained normal, and there was no evidence of dehydration or important alteration of renal function, it is quite possible that influenza and adenovirus infection specifically affected the enzymatic mechanism for theophylline metabolism.

The fever accompanying infection is unlikely to have induced this change since febrile patients in whom there was no serological conversion showed no change in plasma-theophylline half-life.

While in other subjects changes were striking, the magnitude of change in plasma-theophylline half-life in subject 6 was less than 1%. This result is compatible with the hypothesis that certain, but not all, viral infections may affect theophylline metabolism.

Since theophylline concentrations may increase to toxic levels during certain acute viral infections or, alternatively, may fall afterwards, concentrations should be monitored both when symptoms of theophylline toxicity, such as nausea, vomiting, or seizures, accompany acute viral infection and when asthma is poorly controlled with an unchanged theophylline dose after viral infection.

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