the concentrations achieved in Nies' patient were very high. The Denver group do not state their normal disopyramide concentrations but here, in a group of 19 inpatients (13 males, 6 females, mean age 54±13·3 [S.D.] years) receiving 600 mg disopyramide daily, the mean plasma drug concentration in a blood-sample collected close to the time of oral dosage was 3·09±1·28 mg/l (S.D.). Only one patient was reported to have side-effects—namely, dry mouth, blurred vision, drowsiness, nausea, vomiting, and anorexia. The disopyramide concentration was 3·9 mg/l but the plasma digoxin concentration at this time was 3·0 µg/l; none of these symptoms had been present 2 weeks earlier when the disopyramide and digoxin concentrations had been 4·3 mg/l and 1·8 µg/l, respectively. Our results are very similar to the mean plasma concentration found by C. Oshrain and others (G. D. Searle, unpublished) of 2·9 mg/l achieved in a previous study, in which patients received 150 mg disopyramide four times a day for 8 weeks.

Other factors could explain the high plasma concentrations in Nies' case, such as impaired renal clearance or the effects of other drug therapy on absorption, distribution, and metabolism of disopyramide. It is not, therefore, advisable to rely too heavily on the prescribed dose as a measure of therapeutic efficacy. Whilst it is right to urge due caution in the prescription of potent antiarrhythmic agents we would suggest that measurement of the plasma drug concentration at an earlier stage might have helped to elucidate this complex pharmacological problem.

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THEOPHYLLINE PHARMACOKINETICS DURING RESPIRATORY VIRAL INFECTION

SIR,—There has been much interest of late[1] in factors which affect theophylline pharmacokinetics, including age, body-weight, smoking, diet, and concurrent illness, particularly liver dysfunction. Fleetham et al.[2] found a doubled serum half-life of theophylline during an acute viral illness in a single subject, following an earlier report by Chang et al.[3] of reduced theophylline clearance during acute respiratory viral infection in children with chronic asthma. The implication is that patients previously well maintained on theophylline derivatives might require a modification of their drug dosage if toxic side-effects are to be avoided during an acute respiratory viral illness.

We have looked at side-effects in twelve patients receiving maintenance therapy with a sustained-release theophylline derivative ('Phyllocontin'). The patients had established uncomplicated chronic bronchitis. Four had serological evidence of acute viral infection with symptoms of respiratory-tract infection during the 6-week assessment period. The other eight patients were screened over the same period and had no clinical evidence of respiratory infection or change in viral titres. Comparison of factors affecting theophylline pharmacokinetics in these two groups provided no evidence of an increased propensity to reduced theophylline clearance in the four patients with viral infection. Moreover, they were heavier smokers than those in the non-infected group and this would tend to lower rather than raise serum-theophylline levels.[4] Of the four patients with viral infection three had side-effects (compared with four out of the other eight) and mean serum-theophylline levels were increased (11·2 µg/ml compared with 7·5 µg/ml). Estimation of theophylline levels in the post-infection period was possible in only one of the four patients because the others experiencing toxicity preferred to discontinue the theophylline preparation. This one patient had a serum-theophylline of 9·6 µg/ml compared with 13·4 µg/ml during the viral illness. These findings support Chang's comments relating to reduced theophylline clearance during acute viral respiratory infection, and we support the view of Chang and colleagues that clinicians should be aware of the increased liability to toxicity during these periods.

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LYSOSOMAL ENZYMES AND PANCREATITIS DURING RIFAMPICIN THERAPY

SIR,—Rifampicin has potent hepatic microsomal enzyme-inducing properties in man[1] and we have recently extended our studies to its effect, in combination with isoniazid, on the lysosomal enzymes β-glucuronidase and β-N-acetyl-glucosaminidase.[2] Both enzymes were significantly increased in plasma whereas neither the microsomal enzyme γ-glutamyltranspeptidase nor the cytosol enzyme alanine transaminase (monitored to exclude hepatocellular damage) were affected. Rifampicin and isoniazid thus contrast with anticonvulsants which raise both β-glucuronidase and γ-glutamyltranspeptidase.[3] This finding emphasises the variability of enzyme induction by different active drugs.

MEAN±S.D. LYSOSOMAL ENZYME ACTIVITIES (µmol/l/min) BEFORE AND DURING RIFAMPICIN/STREPTOMYCIN THERAPY*

Enzyme†	No.	Before treatment	During treatment	P
β-glucuronidase	10	0·448±0·132	0·986±0·496	<0·01
β-N-acetylglucos-aminidase	8	0·773±0·137	1·171±0·236	<0·001

*Rifampicin 450 mg + streptomycin 0·75 or 1·00 g intramuscularly daily for 3–43 days.
†Methods of Woollen and Walker.[4,5]

We have now established that this lysosomal enzyme effect is due to rifampicin alone. Individual patients were followed up before and during early treatment with rifampicin combined for the purpose of this study with streptomycin (see table). Both lysosomal enzyme activities rose significantly but subsequent substitution of streptomycin by isoniazid did not further change enzyme activity.

One patient had developed acute pancreatitis on the seventeenth day of treatment with rifampicin and streptomycin (serum-amylase 4300 I.U./l). Although subsequent investigation showed multiple gallstones, pancreatitis can occasionally complicate rifampicin therapy[6] and the question arises as to whether this is connected with the observed rise in lysosomal enzymes. Two possible mechanisms, other than antibody-mediated reactions, include concentration of rifampicin or its metabolites in lysosomes with resulting toxicity, or a deficiency of tissue inhibitors of these enzymes in susceptible patients. Drug-lysosomal interactions are well-recognised in experimental pharmacology[7] but more work needs to be done on these interactions in man.

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