Perception of differences between pairs of tablets

As an exercise with students in clinical pharmacology, we did visual comparisons of pairs of tablets to detect differences. The objective was to demonstrate the necessity of manufacturing exactly similar placebo tablets for clinical trials. One hundred and nineteen students (86 physicians and 33 pharmacists) took part. They were asked to compare pairs of tablets in small boxes seen during a limited time. Students were divided in groups of six (plus one group of five). Each group received a randomized block of six numbered boxes containing pairs of tablets of three types (a) white, round, flat; (b) yellow, round, convex; (c) pink, oblong, convex. Each type of tablets had been prepared in two forms differing only by the pressure rate and therefore having a slightly different rough surface. Pairs of tablets exactly similar or slightly different were stuck at the bottom of small plastic boxes bearing numbered codes. Three times at signals, each student opened and closed one box and then exchanged it with the student next to him in the group. The three boxes were examined for 1s, 5s and 30s, respectively (there were therefore $119 \times 3 = 357$ answers). The only questions asked were: 'different or similar tablets' and corresponding number of box.

Results were tested with chi-square and G tests. Blindness was broken at the end of the session by distributing the code to all groups. The test detected no difference between physicians and pharmacists ($\chi^2 = 0.28$; $P = 0.87$); between students with correct (102) or unsatisfactory (17) vision ($\chi^2 = 0.18$; $P = 0.9$); there were no differences on the total number of errors according to time: 36, 37 and 39 with 1, 5 and 30 s examination respectively, but great difference as to the type of error: respectively 37, 24 and 15 'different pairs perceived as similar', and 12, 13 and 24 'similar pairs perceived as different' ($\chi^2 = 24$; $P = 0.0005$). The response was influenced by the type of tablets: 31, 49 and 45 errors respectively for white, yellow and pink tablets ($\chi^2 = 7.3$; $P = 0.03$). Irrespectively of true answer, white tablets were found more often similar (78 times) than yellow (71) or pink (49): $\chi^2 = 13.6$; $P = 0.001$.

This 'class-room' experiment was welcomed by the students as it provided interesting opportunities to discuss double-blindness, and matching placebo. Increased perception of differences with time of examination looked interesting although foreseeable.

Finally, the fact that slight differences due to compression force were less apparent in white flat tablets than coloured and convex ones seems to give an interesting indication for double-blind trials.

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Received June 15, 1983,
accepted December 12, 1983

Impaired enzyme induction by rifampicin in the elderly

The pharmacokinetic factors contributing to the high incidence of adverse drug effects in the elderly include reduced hepatic biotransformation by microsomal mixed function oxidase enzymes in this age group (O'Malley *et al.*, 1971; Crooks *et al.*, 1976; Greenblatt *et al.*, 1982).

Animal studies have demonstrated an age-dependent decrease in the activity of microsomal oxidative enzymes and the extent to which they can be induced (Kato *et al.*, 1964; Kato & Takanaka, 1968; Adelman, 1975). Salem and his colleagues (1978) found no evidence of enzyme induction in six elderly patients who had been treated with dichloralphenazone, yet enzyme induction assessed by enhanced clearance of quinine and antipyrine was evident in a group of six younger subjects following exposure to identical doses of dichloralphenazone for the same period of 2 weeks.

Our observations in an elderly man whose quinidine clearance was enhanced by the antituberculous drug, rifampicin (Ahmad *et al.*, 1979), has led us to question this conclusion. A study by Cusack and his colleagues (1980) suggests that theophylline clearance is increased by cigarette smoking in older patients as well as younger subjects. Other investigators have reported enhancement of the metabolism of quinidine and theophylline by phenytoin in patients aged 65 years (Urbano, 1983; Kroboth *et al.*, 1983). Since phenytoin and rifampicin appear to be more powerful enzyme inducing

agents than dichloralphenazone (Gelehrter, 1976; Marshall, 1978), it seemed possible that differences in the enzyme inducing drugs might explain the apparent discrepancy.

We have, therefore, studied the influence of rifampicin on antipyrine pharmacokinetics in six elderly male subjects age 69 to 79 years and compared them with our observations in a group of younger subjects aged 22 to 28 years (Twum-Barima & Carruthers, 1981). All subjects were apparently healthy, did not smoke or abuse alcohol and were not on any medications. They provided written informed consent. Each subject received two separate oral doses of antipyrine 10 mg/kg before and after rifampicin 600 mg daily for 8 days. Plasma concentrations of antipyrine were measured by h.p.l.c. (Eichelbaum & Spannbrucker, 1977) and pharmacokinetic measurements were determined using standard techniques.

Individual observations of antipyrine half-lives ($t_{½}$) and area under the concentration-time curves (AUC) before and after rifampicin administration in the eight younger subjects and the six elderly subjects are presented in Figure 1. In the younger subjects mean elimination $t_{½}$ (± s.d.) was reduced from 8.8 ± 3.2 to 1.7 ± 0.5 h ($P < 0.01$) and AUC was reduced from 92.9 ± 61.1 to 13.7 ± 8.7 μg ml^{-1} h ($P < 0.05$). In the elderly subjects, $t_{½}$ was 9.5 ± 1.5 h before and 8.8 ± 2.5 h after rifampicin and corresponding AUC were 99.9 ± 8.0 and 88.4 ± 8.7 μg ml^{-1} h respectively (NS).

In only one elderly subject out of six was the half-life of antipyrine reduced by 30% or more. In the study by Salem *et al.* (1978), three older subjects had a modest reduction in antipyrine half-life but, as in our study, the half-life was actually prolonged slightly in two subjects, thereby removing any chance of a statistically significant difference in the relatively small groups we have studied.

Although these results support the conclusions of Salem *et al.* (1978), clinically important drug interactions resulting from enzyme induction have been described in individual older patients. Since drug interactions resulting from enzyme induction might occur less frequently, develop more slowly or simply reflect the greater heterogeneity of pharmacological responsiveness of older patients,

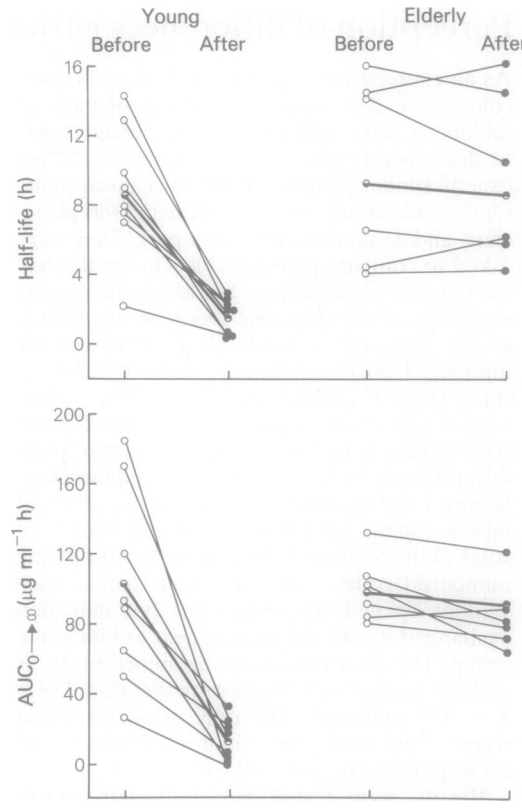

Figure 1 Comparison of antipyrine half-lives and AUC in young (n = 8) and elderly subjects (n = 6), before and after rifampicin administration. The heavy lines represent mean data.

studies involving larger populations of elderly patients are clearly necessary to evaluate more fully these aspects of enzyme induction in the elderly.

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Received August 10, 1983,
accepted January 3, 1984

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Phenytoin intoxication as the first symptom of fatal liver damage induced by sodium valproate

Sodium valproate is a valuable drug with increasing usage for the treatment of many types of epilepsy. Fatal hepatic failure has been reported during therapy with valproate (Suchy *et al.*, 1979; Ware & Millward-Sadler, 1980; Höjer & Rane, 1982) as has reversible hepatotoxicity (Thygesen & Boesen, 1982). We report a case of fatal hepatic failure in a woman on combined therapy with valproate and phenytoin, where phenytoin intoxication was the first sign of the liver damage.

Case report

A 30 year old woman with epilepsy of partial type with secondary generalisation had been treated with phenytoin for two and a half years. She slowly deteriorated, developing balance problems and mental disturbances. Because of poor seizure control, with repeated episodes of status epilepticus, treatment with valproate, 900 mg/day (19 mg/kg body weight and day), was added to her phenytoin dose of 300 mg/day. Before valproate was instituted, her serum phenytoin concentration was within the recommended range (40–80 μmol/l, conversion factor for μg/ml is 0.25) and liver function tests were normal. Three weeks after the addition of valproate, she had a new episode of status epilepticus. At this time, her serum level of valproate was 310 μmol/l (recommended range 300–600 μmol/l, conversion factor for μg/ml is 0.14) and phenytoin was 39 μmol/l. The routine liver tests were still normal. Valproate dosage was then increased to 1200 mg/day. One month later the patient became unable to stand and exhibited increasing choreoathetoid movements involving the face, neck and arms. She also had myoclonus of the diaphragm and difficulty speaking. A new serum sample, 7 weeks after beginning valproate, showed a valproate level of 210 μmol/l and a phenytoin level of 80 μmol/l. The valproate dose was then increased to 1800 mg/day because of presumed poor seizure control. Her neurological condition rapidly deteriorated with increasing somnolence and choreoathetoid movements. Ten weeks after the start of valproate, she had increased bilirubin, aspartate- and alanine-aminotransferase concentrations. Her simplastin A, which measures coagulation factors II, VII and X, was low. Albumin concentration in serum was 25 g/l. A considerably increased serum phenytoin concentration, 184 μmol/l, was noted, while her serum valproate was 340 μmol/l. Analysis of protein binding of phenytoin by equilibrium dialysis at room temperature showed that 40% of the drug in serum was unbound. The binding assay as presented by Barth *et al.* (1976) is available in the laboratory on special request. All drug administration was stopped. However, eventually the patient developed fulminant liver failure with ascites, icterus and a haemorrhagic diathesis. She died 12 weeks after the start of valproate administration.

Sections from the liver showed extensive cell