Interaction between cyclosporin A and phenobarbitone

The immunosuppressive agent cyclosporin A (CSA) has been well documented as a preventer or modifier of graft-versus-host disease (GVHD) following bone marrow transplantation (BMT). CSA is extensively metabolised by the liver before being excreted in the bile (Kahan *et al.*, 1983). It has been suggested that the biodegradation of CSA is mainly mediated through the mono-oxygenase multiple forms of cytochrome P-450 in the hepatic microsomal enzyme system (Maurer, 1985). Drugs known to be inhibitors of this enzyme system, e.g. ketoconazole (Ferguson *et al.*, 1982) and cimetidine (Wood *et al.*, 1983), increase CSA serum levels, while rifampicin (Langhof & Madsen, 1983) and phenytoin (Freeman *et al.*, 1984), both known to activate hepatic microsomal cytochrome P-450 (Herman *et al.*, 1983; Pirttiaho *et al.*, 1982), have been reported to reduce serum levels of CSA in humans. We suggest that such an interaction was responsible for the enhancement of elimination of CSA observed in the following case, in which phenobarbitone was given simultaneously, and which to our knowledge only has been reported briefly in the previous literature (Burckart *et al.*, 1984; Wideman, 1983).

A 4-year-old girl was admitted with severe aplastic anaemia of unknown aetiology. Twenty-three days before BMT she had had a generalized seizure due to a minor subarachnoid haemorrhage, and treatment with phenobarbitone was started, 50 mg twice daily. Prior to the transplantation (= Day 0) she received cyclophosphamide 200 mg kg^{-1} as immunosuppressive therapy. On days +1–+2, viable donor buffy coat cells were given intravenously to facilitate grafting. The post-transplantation course was uneventful. A rapid engraftment was observed and no evidence of acute GVHD occurred. CSA 25 mg kg^{-1} was administered orally from the day before BMT, and reduced to 12.5 mg kg^{-1} daily on day +4.

Trough serum concentration of CSA, as measured by radioimmunoassay, have been within or above a range of 100–400 ng ml^{-1} in 45 other patients treated with similar doses in this centre. However, in this patient, who had a serum level of phenobarbitone of about 120 μmol l^{-1} before BMT, no CSA could be detected in the serum (detection limit 60 ng ml^{-1}), even after increasing the dose to 18 mg kg^{-1} day^{-1} on day +10. Phenobarbitone was reduced on day +36 to 50 mg per day and further to 25 mg on day +44, after which there was a rise in trough serum CSA values (Table 1). No vomiting occurred during therapy, and renal and hepatic function remained normal. The patient did not receive any other drug known to cause metabolic interactions with CSA.

Phenobarbitone is known to induce the hepatic microsomal enzyme system and thereby accelerate the biotransformation and elimination of other drugs metabolised in the liver (Goodman & Gilman, 1980). The present suggestion of an interaction between CSA and phenobarbitone is supported by studies in rats, in which enhancement of the metabolism of CSA during simul-

Table 1 Cyclosporin A/phenobarbitone interaction

Days after BMT (= Day 0)	*Serum concentration* Trough cyclosporin A (ng ml^{-1})	*Serum concentration* Phenobarbitone (μmol l^{-1})
+5	<60	
+11	<60	
+30	<60	163
+36	<60	79
+40	60	54
+44	205	50
+50	180	34
+60	62	25
+78	140	18
+92	125	3

taneous administration of phenobarbitone has been demonstrated by Cunningham *et al.* (1984).

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