CHLOROQUINE INTOXICATION

Chronic chloroquine treatment is associated with several side effects. During the treatment of rheumatoid diseases most side effects are reversible but occur frequently and are related to the blood concentration of the drug (Frisk-Holmberg *et al.*, 1979). Irreversible side effects occur when higher total doses are given. The most commonly encountered side effects are symptoms from the central nervous system, gastrointestinal tract and myo- and neuropathies. Several acute intoxications with chloroquine have been reported of which some have resulted in death (Good & Shader, 1982). In addition to the side effects encountered during chronic treatment shock, convulsions, respiratory and cardiac arrest are seen. The lethal dose is reported to be 50 mg chloroquine base/kg (Bochner *et al.*, 1978; Nir, 1981; Good & Shader, 1982).

Case report

A previously healthy 18 year old girl took 7.5 g (136.4 mg/kg) of chloroquine phosphate corresponding to 82 mg chloroquine base in a suicidal attempt. One and a half hours after intake the patient experienced nausea and diplopia, shortly thereafter respiratory distress and was brought to hospital. At the first clinical investigation 2 h after intake she was cyanotic, respiratory collapse developed followed by seizures and cardiac arrest. Intensive care treatment including forced diuresis with sodium bicarbonate was started, approximately 2 h and 20 min after intake. The patient was conscious 3 h after intake. Thereafter she only experienced malaise and diplopia, symptoms which did not disappear until 30 h after intake. Nothing pathological was otherwise found in her physical status. Repeated blood tests including kidney and liver function tests were normal. A slight proteinuria was present up to 10 h after intake. Pulmonary X-ray was normal. The ECG was initially pathological. The QRS complex was widened and the ST-segment flattened. These changes had disappeared 30 h after intake. The patient recovered fully and was discharged after 3 days but followed for 6 months in the psychiatric open ward. Whole blood concentrations of chloroquine and its metabolites were determined (Bergqvist & Frisk-Holmberg, 1980) in venous samples obtained at admittance during the hospitalization and the follow-up period. Figure 1 shows the blood concentration time curve for chloroquine and its metabolites desethylchloroquine and one at present unknown metabolite. Neither of the metabolites reached the peak chloroquine concentrations. The decline of chloroquine blood concentrations was rapid during the first days but slowed down and after 2 months a marked prolongation was observed. The elimination of both chloroquine and its metabolites followed a tri-exponential decline. The apparent half-life of the terminal exponent of chloroquine was approximately 60 days and seemed still longer for the metabolites.

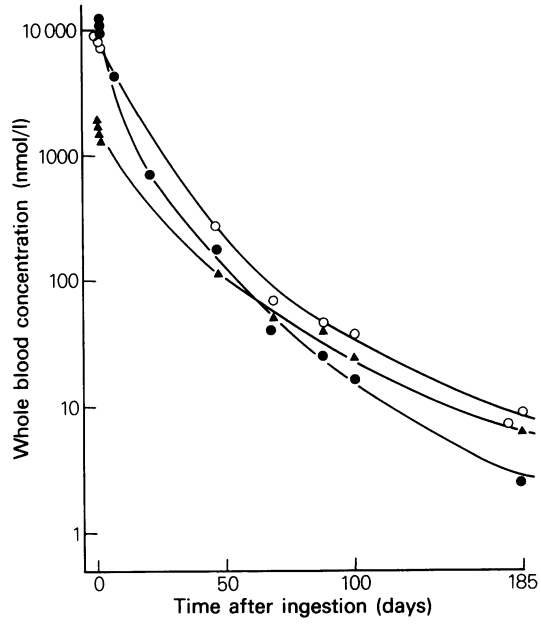

Figure 1 Serial blood concentration determinations of chloroquine (●), desethylchloroquine (○) and an unidentified metabolite (▲) in a patient.

The present case report demonstrates that chloroquine in a dose of 82 mg/kg body weight with blood concentrations of approximately 10 μmol/l can be tolerated. The intoxication picture is similar to that described previously (Bochner *et al.*, 1978; Friberg & Lund, 1982) but the dose is higher. Symptoms were present when blood concentrations were high and disappeared when the blood concentrations fell below 4 μmol/l. This is in agreement with our previous report (Frisk-Holmberg *et al.*, 1979). Above serum concentrations of 2.5 μmol/l 80% of chronically treated patients experienced side effects but below 1.3 μmol/l no side effects were demonstrated. The whole blood concentrations of chloroquine are about 8 times higher than the serum concentrations (Frisk-Holmberg & Bergqvist, 1982).

The elimination of the major metabolite (desethylchloroquine) was slower than that of chloroquine. Chloroquine on the other hand was eliminated at a rate almost six times slower than reported previously (Frisk-Holmberg *et al.*, 1979; McChesney *et al.*, 1967). This could be of practical importance in the handling of chloroquine over-dosages since both

chloroquine and its metabolites have been associated with toxicity. Therefore forced acid diuresis could be recommended to enhance both the elimination of chloroquine and its more water soluble metabolites.

MARIANNE FRISK-HOLMBERG, YNGVE BERGQVIST & ULF ENGLUND

Section of Clinical Pharmacology, Department of Medical Pharmacology, Uppsala University, Box 573, S-751 23 Uppsala and Falu Central Hospital, S-791 00 Falun, Sweden

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TRANSPLACENTAL PASSAGE AND HALF-LIFE OF SODIUM VALPROATE IN INFANTS BORN TO EPILEPTIC MOTHERS

Sodium valproate (VPA), a broad spectrum antiepileptic drug, is now widely used in the treatment of epilepsy. Since VPA produces dose-related teratogenic effects in rodents (Whittle, 1976) and antiepileptic drug therapy must be continued throughout pregnancy, it is important to determine the likelihood of foetal exposure to the antiepileptic drug. In this paper, we report the placental transfer and the half-life of VPA in infants.

The subjects were six pregnant epileptic women and their infants. Their mean ± s.d. age was 26.0 ± 3.6 years, and the mean duration of antiepileptic therapy was 8.6 ± 5.9 years (VPA therapy : 1.6 ± 0.9 years). Maternal blood was sampled from the antecubital vein in the first stage at labour, and umbilical cord blood was collected from the umbilical artery and vein immediately after the delivery of the neonate. In order to determine half-life of VPA in the neonate, sampling (50–100 μl) was carried out at least four times in each case from the neonatal antecubital vein into a 1 ml syringe or from the neonatal heel using a haematocrit tube.

Serum levels of VPA were measured using gas liquid chromatography (Kaneko *et al.*, 1981).

VPA had been administered to the mothers in combination with other antiepileptic drugs except in one case (see Table 1).

A mean concentration of 12.87 ± 5.23 μg/ml of VPA in serum was obtained in the first stage of labour, and umbilical vein and artery samples contained 26.90 ± 16.21, and 31.25 ± 18.21 μg/ml, respectively.

As shown in Figure 1, VPA levels in umbilical cord blood tended to be elevated compared with those in maternal serum. In the case of umbilical artery samples this elevation was statistically significant ($P < 0.05$, Student's t-test).

The serum half-life of VPA was studied in four of the six neonates and the results were shown in Table 1. The gestational ages of these infants were 39 or 40 weeks. The half-life of VPA ranged from 21.5 to 35.0 h with a mean of 28.3 h. There was no significant correlation between VPA concentrations in umbilical cord samples and the half-lives of VPA in the infants.

Brachet-Liermain & Demarques (1977) reported that the cord/maternal serum concentration ratios of VPA were found to be 0.5 and 1.0 in two cases at term. Half-lives of VPA in the infants (between 10 and 70 h) exceeded those obtained in adult epileptics. Alexander (1979) also reported that the con-