Following a 1-year period of erythropoietin therapy in these children (supported by CILAG Company), there was a 4-week break in the erythropoietin supply as a consequence of a delay in the permission from the national insurance company for this treatment to be continued at government expense. During this period, the Hb level decreased below 5 mmol/L, and the haematocrit (htc) below 23%. Vitamin E was introduced 2 weeks following the restart of erythropoietin therapy, at a dose of 15 mg/kg/day orally. The results were compared with the data obtained earlier when the same patients were treated with erythropoietin alone at the same dosage. As compared with the initial level, the Hb concentration was already significantly higher 2 weeks after the introduction of vitamin E; a significantly elevated Hb level was observed only in the eighth week when the patients were treated with erythropoietin alone. Erythropoietin plus vitamin E resulted in a more rapid increase in the htc also, which was significant in the third week (1 week after the start of vitamin E), whereas the increase was significant only in the fifth week with erythropoietin alone. The explanation for these encouraging results is the antioxidant effect of vitamin E which prevents oxidative haemolysis [4].

Acknowledgement. These studies were supported by OTKA 025010 and ETT 673/1996-06 grants.

Chronic renal failure: behaviour of the polymorphonuclear leukocyte membrane fluidity at baseline and after chemotactic activation

Sir,

Previously [1–4] we examined the behaviour of the erythrocyte membrane dynamic properties, expressed as microviscosity, fluidity, transverse fluidity gradient and protein lateral mobility, in subjects with mild and clinically stable chronic renal failure (CRF), demonstrating a significant alteration of all these properties.

Now, in this clinical condition we evaluated the trend of the polymorphonuclear leukocyte (PMN) membrane fluidity in children (n=9) with chronic glomerulonephritis (n=3), cystic kidney disease (n=9) and chronic glomerulonephritis (n=3).

The PMN membrane fluidity was obtained marking intact PMN cells with fluorescent probe 1-[4-(trimethylamino)-phenyl]-6-phenyl-1,3,5-hexatriene (TMA-DPH) and considering the fluorescence polarization degree [5,6]. In a subgroup of patients this fluorescence parameter was also obtained after activation (prolonged for 5 and 15 min) with two chemotactic agents: 4-phorbol 12-myristate 13-acetate (PMA) and N-formyl-methionyl-leucyl-phenylalanine (fMLP).

From the obtained data it is evident that, at baseline, PMN membrane fluidity does not differentiate normal from CRF subjects (N=0.334 ± 0.026, CRF=0.343 ± 0.024). In normals, after PMN activation with PMA (baseline: 0.334 ± 0.026; 5 min: 0.339 ± 0.023; 15 min: 0.341 ± 0.031) and fMLP (baseline: 0.334 ± 0.026; 5 min: 0.334 ± 0.025; 15 min: 0.338 ± 0.031) no significant variation was observed in PMN membrane fluidity, whilst in CRF, after activation with PMA (baseline: 0.335 ± 0.019; 5 min: 0.347 ± 0.016*; 15 min: 0.347 ± 0.016*; *P < 0.001 vs baseline) and fMLP (baseline: 0.335 ± 0.019; 5 min: 0.354 ± 0.011*; 15 min: 0.342 ± 0.018#; #P < 0.001, #P < 0.01 vs baseline) a constant and significant decrease in PMN membrane fluidity was present. This behaviour might be the expression of a specific metabolic pattern of the PMNs observed in CRF subjects and revealed after in vitro activation only. As is known, there are several data that specify the metabolic and functional abnormalities present in PMN cells under chronic renal failure [7–11]. This datum, that underlines the PMN dysfunction present in this clinical condition, assumes major interest considering that all these CRF subjects were in conservative treatment.

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Methadone is poorly removed by haemodialysis

Sir,

Methadone is a narcotic analgesic which is a common form of treatment for opiate dependence. Its pharmacokinetics are highly variable with plasma half-lives ranging from 19 to 75 h, and bioavailability from 36 to 100%. The total body clearance is about 2 ml/min/kg (1–3.2 ml/min/kg) [1]. Elimination of methadone occurs mainly by metabolism. The major metabolite in human is EDDP (1,5-dimethyl-3,3-diphenyl-2-ethyldiene- pyrrolidine) which is pharmacologically inactive. Elimination through the kidney is also observed. However, there is evidence for pronounced inter-individual differences in the proportion between renal excretion of the metabolite and the parent drug [1,2]. It is well-known that methadone is difficult to use, because the response to change in dose is slow and because there are wide inter-patient variations in methadone clearance [3]. Consequently, major effects of haemodialysis on methadone clearance would have important consequences necessitating dosage adjustment. Presently, the effect of haemodialysis on methadone disposition is unknown. Results obtained in one patient are reported.

A HIV-positive addicted patient on methadone (60 mg per day) was treated by haemodialysis for end-stage renal failure. On the day of the study, methadone was administered 6 h before starting haemodialysis. The haemodialysis was performed for 3 h, using a double needle access to an arteriovenous fistula, polyamide 170 membrane dialyser (Gambro) and a single pass dialysate delivery system, with a constant dialysate (Bicarbonate fluid) flow rate of 500 ml/min: the blood flow entering the dialyser was approximately 300 ml/min and ultrafiltration rate was 460 ml/h. Venous blood samples were drawn before methadone intake, 3 h after methadone administration and hourly during dialysis. Arterial and venous blood entering and leaving the dialyser was sampled simultaneously in mid-dialysis. Methadone and EDDP serum concentrations were assayed by HPLC according to a method previously described [4]. The dialyser extraction ratio \( E \) was calculated from \( C_a \) and \( C_v \), which are respectively the plasma concentrations entering (‘arterial’) and leaving (‘venous’) the dialyser: \( E = (C_a - C_v)/C_a \).

The 3-h haemodialysis clearance \( C_{HD} \) was calculated by the following formula [5]:

\[
C_{HD} = \frac{Q_c C_a - (Q_b - Q_{UF}) C_v}{C_a}
\]

where \( Q_p \) is the plasma flow entering the dialyser derived from the blood flow \( Q_b \) and the haematocrit \( H_t \): \( Q_p = Q_b (1 - H_t) \); \( Q_{UF} \) is the ultrafiltration rate displayed on the dialyser.

At the beginning of dialysis, methadone and EDDP concentrations were 494 ng/ml and 130 ng/ml respectively. At the end of the 3 h dialysis session, methadone and EDDP concentrations were 318 ng/ml and 44 ng/ml respectively. At mid-dialysis, the extraction coefficients and clearance were 18% and 53.5 ml/min and 55% and 17 ml/min for methadone and EDDP, respectively. Those parameters indicate that methadone is poorly removed during a 3-h haemodialysis session despite the use of a high permeability dialyser membrane.

The pharmacological conditions of opiate addicts may be stabilized by methadone maintenance therapy [6]. Clinical success in maintenance treatment requires maintenance of methadone plasma trough level in the therapeutic range and the patient did not report withdrawal symptoms. The observed dialysis clearance and extraction ratios of methadone were low which is in agreement with methadone pharmacokinetic properties: large volume of distribution ranging from 4.1 to 6.7 l/kg and plasma protein binding mainly on alpha-acid-glycoprotein ranging 60–90% [1,9,10]. Consequently, the haemodialysis index [11] defined as the ratio of unbound fraction to volume of distribution was 0.1 which is <20 in the range of poorly removed drugs. The metabolite, EDDP which is more hydrosoluble than methadone is extracted during haemodialysis without clinical consequences due to its inefficacy. In addition, used membrane dialyser has a high permeability.

In conclusion, poor removal of methadone during a haemodialysis session indicates that supplemental methadone dose need not be routinely given to patients following haemodialysis. However, patient-to-patient variability could occur, hence further data should be collected before definitive dosage recommendation could be proposed.

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