Diagnostic aspects of T1 measurements in blood serum with increased level of paramagnetic ions

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Abstract: In some diseases, for example, Wilson's disease, hemosyderosis, and chronic lymphomic leukemia (CLL), there is an elevated level of paramagnetic ions (Cu^{+2}, Fe^{+3}, Zn^{+2}) in blood serum. It is well known that the existence of these ions shortens T_1 and T_2 relaxation times of the water protons. When specific chelating agents are added to the blood serum from patients with one of these diseases, longer relaxation times are observed. In this communication we show some examples of such enhancement as an alternative method of estimation and monitoring of Cu^{+2} and Fe^{+3} levels in the blood serum.

Synopsis: In Wilson's disease, hemosyderosis, chronic lymphomic leukaemia (CLL) and others, an elevated level of paramagnetic ions (Cu^{+2}, Fe^{+3}, Zn^{+2}) in blood serum has been observed. It is well known that the presence of these ions shortens water protons relaxation times T_1, $T_{1\rho}$ (relaxation time in rotating frame) and T_2. Specific chelating agents added to solution may cancel the metal ion effect. .In this communication we show several examples of such paramagnetic relaxation time enhancement as an alternative method of estimation and monitoring of Cu^{+2}, Fe^{+3} and Zn^{+2} ions levels in the blood serum.

Materials and Methods: The following model solutions have been studied: 1) $CuSO_4$ and $CuCl_2$, 2) $ZnSO_4$, 3) $FeCl_3$ in water and rabbit blood serum and in the presence of chelating agents (d-penicillamine, TETA, desferrioxamine). We also examined human blood serum samples from patients suspected of having Wilson's disease, from patients suffering from hemosyderosis and leukaemia and from healthy volunteers.

Proton NMR relaxation studies were performed with a 60 MHz Bruker Minispec system using the Inversion Recovery (IR) sequence for measurements of spin-lattice relaxation times T_1, the CPMG echo sequence for spin-spin relaxation times T_2 and the standard method for $T_{1\rho}$.

Results: Figure 1 shows the results from copper-concentration dependent T_1 measurements of water, serum, and chelator solutions. Figure 2 shows the influence of a chelator on T_1 in human blood serum across a range of copper concentrations. We observed similar T_1 behaviour in the iron and zinc solutions. Measurements of T_2 and $T_{1\rho}$were made only for human serum samples.

Discussion: We observed a strong influence of iron and copper ions (in concentration 1 - 1×10^{-5} mol/l and 5×10^{-5} – 1 mol/l respectively), and much smaller influence of zinc ions (concentration from 10^{-5} to 6 mol/l) on relaxation time T_1 and T_2 in water and serum aqueous solutions. An addition of suitable complexing ligand significantly narrowed the range of change of T_1. The results presented in the figures support the idea of using values of relaxation times for indirect determination of the presence of paramagnetic ions in blood serum. Relaxation measurements should be carried out in serum samples before and after addition of chelator and compared. For healthy patients both measurements should give equal relaxation times, whereas if high levels of paramagnetic ions are present, significant differences should be observed.

Conclusions: Therefore, measured differences in relaxation times in human serum before and after complexation (chelation) can be used as a diagnostic tool. This blood serum test is a fast and inexpensive diagnostic. It would be particularly helpful, for example, in the case of identification of Wilson's disease patients, because there is high probability that other members of family will have the disease.

References

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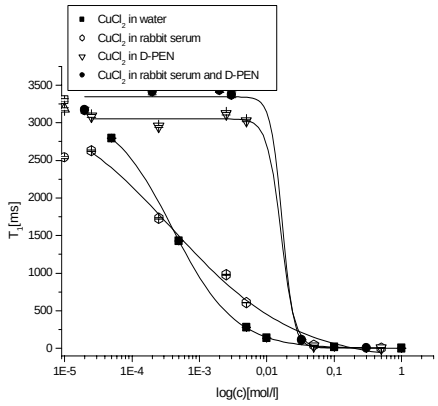

Figure 1: Copper concentration dependencies of T_1 in water $CuCl_2$ and blood serum (rabbit) solutions before and after chelation (20mg/ml)

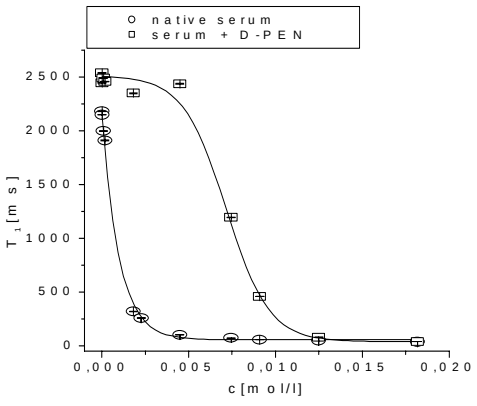

Figure 2: Copper concentration dependence of T_1 in $CuCl_2$ solutions in human blood serum before and after chelation