Ineffectiveness of Phenytoin Treatment on IgA-Containing Circulating Immune Complexes in IgA Nephropathy

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Dear Sir,

After the first report [1] indicating that in patients affected with IgA nephropathy, phenytoin selectively decreases serum IgA – especially polymeric IgA – levels, leading to a reduction in the number of episodes of macroscopic hematuria and in some cases a decrease in the amount of IgA deposits, a recent trial reported by Clarkson et al. [2] failed to find any significant influence of this treatment on the clinical and histological course of this nephropathy.

Since immunological studies from our group [3] and others [4] in agreement with recent experimental models [5, 6] suggest a primary role for IgA-containing circulating immune complexes (IgAIC) in Berger’s and Henoch-Schönlein’s glomerulonephritis (GN), we would like to comment the data we obtained by monitoring IgAIC detected by a modified conglutinin solid-phase assay [3], in two groups of patients: one (3 Berger’s GN and 2 Henoch-Schönlein’s GN) treated with phenytoin (300 mg/day for 8–14 months), and the other (3 Berger’s GN and 2 Henoch-Schönlein’s GN) without any treatment (control group).

In the group of patients treated with phenytoin, we observed (table I), as early as 3 months after treatment was started, a significant reduction in mean serum IgA levels (p < 0.05). The IgA concentration decreased by 24.8% after 3 months and by 31.4% at the end of the follow-up. No significant fluctuations were observed in the control group.

A slight reduction in mean polymeric IgA values -detected by the reduction-alkylation test [7] – was observed from the beginning to the end of the follow-up (p < 0.1), and was particularly evident in 3 of 5 cases who initially showed high values of polymeric IgA.

The IgA-containing immune complex levels showed a slight, although not significant (p > 0.1), decrease from the beginning to the end of the follow-up in both groups of patients, with and without treatment (table I). No correlation was found between IgA levels and IgAIC values (r=0.17, p > 0.1).

Fig. 1. G.B. ♂ 23 year old, affected with Berger’s GN ( ). After 3 months of phenytoin treatment, total IgA and polymeric IgA decreased, whereas IgAIC increased concomitantly with the appearance of gross hematuria.

Z.V. ♂ 19 year old, affected with Henoch-Schönlein’s GN ( ). During phenytoin treatment, IgAIC initially decreased, but rose again concomitantly with gross hematuria even though a decrease in total IgA and polymeric IgA had been obtained.

In 2 cases on phenytoin (1 Berger’s GN and 1 Henoch-Schönlein’s GN) gross hematuria was observed: the IgAIC levels were very high, albeit a decrease in total IgA and polymeric IgA was
obtained (fig. 1). A correlation between high levels of IgAIC and increase in hematuria was observed also in the control group, as well as in other previously studied cases [3].

Table I. Laboratory data before (0), at 3 months (3), and at completion (end) of phenytoin treatment (5 patients) and control (5 patients) groups. Results are expressed as mean ± standard deviation

No significant change in serum creatinine, IgG and C3d levels was observed in either group (table I). Urinary protein loss was mildly, though not significantly (p > 0.1), decreased at the end of the treatment. A slight decrease of serum IgM was observed (p < 0.1) after several months on phenytoin.

In conclusion, our data add further support to the hypothesis that phenytoin can decrease serum IgA levels and possibly normalize polymeric IgA; nevertheless these effects were dissociated from any decrease in circulating IgAIC which is thought to play the most important pathogenetic role in IgA nephropathy. In fact, IgAIC increased during episodes of macroscopic hematuria and this was not prevented by phenytoin treatment, even when a decrease in total and polymeric IgA had been obtained.

These findings might account for the ineffectiveness of phenytoin treatment observed in a controlled trial on IgA nephropathy [2].


