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High-titre hepatitis B immune globulin

Standard immunoglobulin preparations (gammaglobulin) have proved effective over the years in preventing type A hepatitis in circumstances such as localised outbreaks in institutions and schools and among overseas travellers. We are now, it seems, to have available preparations of immune globulin containing high titres of antibody to the hepatitis B surface antigen (HBsAg) which will be of comparable efficacy for hepatitis B virus infections.[1-3] Clearly it will be important to know about the exact need for such prophylaxis, as well as its limitations, for the decision to use it will nearly always have to be made at a moment's notice and against a highly emotional background. One of the hospital staff may have pricked a finger on a needle contaminated with blood from a patient known to be HBsAg positive; or there may be a patient within the dialysis/transplantation unit whose regular blood check has shown a positive result for the first time, with all the possible implications for the nursing and medical staff.

One of the recent controlled trials, in which immunoglobulin containing high titres of antibody to HBsAg was compared with low titre preparations, was concerned with its value after "needle prick" exposure.[3] At first sight the results seem impressive. Among 251 persons passively immunised with low-titre globulin, hepatitis developed in 17 (6·8%) within six months, as compared with 5 (2·0%) of 253 who received the new specific preparation with anti-HBs in very high titres. This difference was statistically significant: but after a further three-month follow-up 6 more cases had appeared, all in the high-titre group, making the final incidence of hepatitis (4·4%) not significantly different from that in the low-titre group. The explanation for these late onset cases was not clear. One possibility is that the virus may have already been established at the time of the immunoglobulin injection and that the appearance of viral antigens on the surface of infected liver cells was prevented by the circulating antibody. Immune destruction of these cells, with accompanying clinical features of acute hepatitis, would not then occur until antibody levels had fallen to a point at which viral antigens could be expressed. Such a suppression of cell-surface viral determinants by specific antibody has been described in vitro.[4] A second possibility is that the high-titre globulin may have completely prevented the development of active immunity, either because the infection was never acquired or because of feedback suppression of the active immune response by the passively administered antibody. The late cases of hepatitis in this group would then all be due to an inapparent second exposure to the virus at a time when passively acquired circulating anti-HBs had fallen below a protective level. This effect would not be seen in the low-titre group, in which a higher incidence of subclinical infection and permanent immunity might be expected.

Support for this second theory may be found in the previously published Veterans' Administration Cooperative Study,[5] in which the frequency of anti-HBs in those receiving low-titre globulin rose progressively during follow-up and at six months was significantly higher than that in the high-titre group (32% and 7%, respectively). Furthermore, in one case in the high-titre group the virus responsible for the late hepatitis was subtype ayw, while the original exposure had been to the adw subtype; a well-documented second exposure 16 weeks after the first had been to subtype ayw.

It seems, then, that repeated injections of hepatitis B immune globulin will be required if there is a likelihood of further exposure. This must be considered a serious disadvantage, since the long-term hazards of such an approach are unknown. One possibility is that there will be an increase in the incidence of sensitisation reactions. Nevertheless, for protection against a single accidental inoculation hepatitis B immune globulin must be the current treatment of choice, and supplies for this purpose are now obtainable through the directors of the local public health laboratory service.

Undoubtedly, patients with renal failure on dialysis who become positive for HBsAg can be highly infectious, as has been shown by the serious outbreaks of type B hepatitis in units. In considering the use of immunoglobulin the crucial question here is whether exposure is likely to recur. Unless the method of prophylaxis used is one that allows active immunity to develop it must continue to be given for long periods. The multicentre study of hepatitis B immune globulin in prevention of dialysis-associated hepatitis sponsored by the American National Heart Lung Institute[2] showed that 6·9% of staff members receiving high-titre globulin developed hepatitis within eight months, compared with 11·1% in those given low-titre globulin. This difference was not statistically significant, but results obtained in the patients in the same dialysis units were more striking (7·9% as compared with 23·3%), and here the result would have been attained by chance in less than 1 in 100 trials. At 12 months, however, the incidence of hepatitis in the group receiving the high-titre preparation had more than doubled, and probably there was, again, a failure to develop active immunity. In Britain there

has been a remarkable fall in the incidence of type B hepatitis in haemodialysis units since action was taken on the recommendations of the Rosenheim Report.[6] Prophylactic immunoglobulin has not been used: but there has been scrupulous attention to careful hygiene; testing of all patients for HBsAg before admission; and dialysis of HBsAg positive patients in isolation.

Another problem is the protection of a further group at particular risk from hepatitis B virus infection—the spouses of patients with acute type B hepatitis.[1] In the recently reported study[1] the incidence of type B hepatitis in susceptible spouses receiving globulin preparations without detectable anti-HBs was as high as 27% (9 of 33), emphasising the infectivity of patients developing acute type B hepatitis. The corresponding figure in those spouses who received high-titre immune globulin, up to 30 days after recognition of jaundice in the probands, was 4% (1 of 25). The follow-up period analysed was only five months, and whether later cases could occur (as in the other trials) is not known.

In summary, the introduction of hepatitis B immune globulin makes possible effective prophylaxis for hepatitis B virus infection in certain conditions and for a limited period of time. But the development of effective and safe vaccines must continue to remain the priority, particularly for the long-term protection of people who are likely to be exposed repeatedly to potentially infectious material.

[1] Redeker, A G, *et al*, *New England Journal of Medicine*, 1975, **293**, 1055.
[2] Prince, A M, *et al*, *New England Journal of Medicine*, 1975, **293**, 1063.
[3] Grady, G F, and Lee, V A, *New England Journal of Medicine*, 1975, **293**, 1067.
[4] Joseph, B S, and Oldstone, M B A, *Journal of Experimental Medicine*, 1975, **142**, 864.
[5] Seeff, L B, *et al*, *Lancet*, 1975, **2**, 939.
[6] *Report of the Advisory Group on Hepatitis and the Treatment of Chronic Renal Failure 1970-72*. London, DHSS, 1972.

Tryptophan and depression

Several pieces of indirect evidence link brain concentrations of 5-hydroxytryptamine (5-HT) with depression. For instance, 5-hydroxyindole concentrations are lowered in the brains of depressed patients who have committed suicide,[1-3] and the concentration of the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) is lower in the cerebrospinal fluid of depressive patients.[4] Other indirect evidence for the role of 5-HT comes from the action of drugs known to be beneficial in the treatment of affective disorders: Coppen *et al*,[5] for example, have reported that the combination of tryptophan with a monoamine oxidase inhibitor—known to raise brain 5-HT concentration in rats[6]—is more effective in treating depression than a monoamine oxidase inhibitor alone. Other workers have reported similar observations.[7 8]

The explanation seems to be that tryptophan 5-hydroxylase, the first enzyme in the pathway of 5-hydroxytryptamine synthesis, is normally unsaturated with substrate[9 10]; so that when brain L-tryptophan concentrations are raised by administration of this ammino-acid 5-HT synthesis is increased.[6] This should be true of depressed and normal individuals. Whether decreased concentrations of 5-HT in the brain in themselves produce the mood change is still unknown, but this view seems unlikely since the concentration of 5-HIAA in the cerebrospinal fluid remains lowered in patients who have recovered from depression.[11]

To try to assess the usefulness of L-tryptophan in treating depression, either alone or in combination with other drugs, a one-day meeting was recently held at the Royal College of Physicians (organised by Cambrian Pharmaceuticals, who market L-tryptophan (Optimax) in Britain). G Curzon reviewed evidence[12 13] that the plasma free (non-protein bound) tryptophan is an important determinant of 5-HT concentration in the brain and outlined the physiological factors which alter the ratio of free to bound tryptophan in plasma. Such changes need not alter the amount of 5-HT in the brain which is "functionally" active—that is the 5-HT that stimulates postsynaptic receptors. This latter point was expanded by A R Green, who showed that measurements of 5-HT concentration or synthesis (or, indeed, the amounts of 5-hydroxyindole in the cerebrospinal fluid) do not necessarily indicate functional activity. Grahame-Smith[6] has shown that, while tryptophan administration increases the concentration of 5-HT in the rat brain, this change does not increase its activity as a neurotransmitter.[14] The implication is that giving L-tryptophan to patients may not in itself improve depression, since it may not alter the activity of functional 5-HT. Furthermore, tryptophan administration has other effects besides increasing brain 5-HT synthesis; G W Ashcroft and D Eccleston showed that administration of tryptophan and a monoamine oxidase inhibitor increases brain concentrations of tryptamine,[15] another amine with pharmacological activity in the central nervous system.

Hence while tryptophan availability seems important in controlling brain 5-HT concentrations, we do not know whether there are changes in its availability in depressed patients. The evidence is conflicting. Ashcroft and Eccleston did find a lowered concentration of total plasma tryptophan in their patients, but no decrease in the free fraction. In contrast, Coppen described two studies in which patients had lowered free tryptophan but unchanged total tryptophan concentrations compared with normal controls. M Aylward described changes in plasma free tryptophan in women with postmenopausal depression which were very similar to those seen in Coppen's patients. He went on to show a correlation between free plasma tryptophan levels and endogenous plasma oestrogen concentrations. Giving oestrogens to these patients both increased the plasma free tryptophan concentration and improved mood. This action of oestrogen is probably a direct effect, since in vitro oestrogens displace tryptophan from plasma albumin.

Two trials were described in which L-tryptophan had been given to groups of depressed patients. In the first J Dencker enlarged upon his recent brief report[16] of the double-blind multicentre trial carried out in Scandinavia of imipramine versus tryptophan in 42 patients. This trial showed that tryptophan was as effective as imipramine as judged by the total score on the Hamilton rating scale: both groups showed a statistically significant improvement, but there was a lower frequency of side effects with L-tryptophan. The results concerned only the first few weeks of treatment, and a trial is still in progress. A longer-term assessment is clearly necessary before a critical evaluation can be made of this form of treatment, though the results confirm an earlier report.[17]

A second double-blind trial, described by J Walinder, showed that chlorimipramine plus L-tryptophan was more effective in treating depression than the former drug alone. The patients' retardation scores were not improved further by L-tryptophan, suggesting that chlorimipramine (or any other specific inhibitor of 5-HT reuptake) plus L-tryptophan might prove advantageous in cases in which depression of mood is more prominent than retardation. This clinical study was