EFFECT OF HAEMODIALYSIS ON THYROID FUNCTION

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Unexplained tachycardias, and rarely, cardiac arrhythmias occur during haemodialysis in a significant number of stable long-term dialysis patients. Recent reports that (1) intravenous heparin causes a marked rise in serum free thyroxine levels (Hollander et al., 1967) and (2) that a significant number of apparently euthyroid patients with paroxysmal atrial tachycardia have elevated serum free thyroxine levels during their attacks (Schatz, 1967) suggested that the use of heparin during haemodialysis might be a causative factor in producing tachycardias and/or arrhythmias.

Twelve euthyroid patients (9 males, 3 females, aged 12–53 years), on long-term, twice weekly, twin coil dialysis were studied. Pre- and postdialysis blood samples were analyzed for (1) total serum thyroxine and protein bound iodine, (2) T3 resin uptake, (3) thyroxine binding globulin and thyroxine binding prealbumin capacity and (4) serum free thyroxine levels.

The findings were as follows: (1) no change in total serum thyroxine or protein bound iodine, (2) an increase in T3 resin uptake in 10 of 11 patients, (3) no consistent changes in thyroxine binding globulin or prealbumin capacity and (4) an increase in serum free thyroxine to 3–8 times control values in 11 of 12 patients, as shown in Figure 1. The average total dose of heparin was approximately 100 mg and protamine was not used.

The usual serum free thyroxine levels seen in symptomatic thyrotoxicosis are between 10 and 25 mmcg/100 ml. The initial levels were all in the normal or just slightly above normal range. At the end of dialysis, 11 of the 12 patients had a quite significant rise and 3 of them had values well in excess of those usually seen in thyrotoxicosis. Of the 2 patients followed postdialysis, one had returned to normal within 14 hours and the other by 24 hours.

A significant increase in pulse rate (greater than 20 beats per minute), in the absence of obvious causative factors such as hypotension, fever, agitation, etc., occurred in only 3 of the 12 patients and bore no relation to either the degree of increase in serum free thyroxine or the total dose of heparin.

The changes in pulse rates in each of these patients during 20 stable dialyses were then reviewed. The same 3 patients almost consistently exhibited an unexplained increase of 20 beats per minute or more, whereas the other 9 rarely did so.

Figure 2 shows the response to intravenous injection of as little as 5 mg of heparin in 5 euthyroid control patients and in one patient with mild hypothyroidism secondary to administration of radioactive iodine. Three of the 5 control patients showed a significant rise and 2 a slight rise in serum free thyroxine within minutes, with values returning to normal within one hour. None of the controls had an increase in pulse rate during this period.

The patient with hypothyroidism showed a rise from 1.5 to 8 mmcg/100 ml with no increase in pulse rate.

Figure 3 shows the result of an initial dose of 10 mg of heparin followed by a 4-hour infusion of 40 mg of heparin, on a patient with severe, untreated, primary myxoedema. The
scale on the left is much reduced and the patient’s initial value was only 0.2 mmcg/100 ml. The serum free thyroxine level rose rapidly to 1.6 mmcg/100 ml, 8 times the initial value and by 4 hours the pulse rate had risen from 64 per minute to 95 per minute with many ventricular premature beats. Both values then gradually returned to normal within 10 hours.

These findings suggest that in a particularly sensitive patient, such as the one just shown, a heparin induced rise in serum free thyroxine has a very significant effect on pulse rate. Whether or not the rise in pulse rate observed in certain patients during dialysis is related to a peculiar sensitivity to changes in serum free thyroxine or to other unknown factors is not as yet clear. The mechanism of this heparin-induced rise in serum free thyroxine remains to be elucidated. The increase in T3 resin uptake and serum free thyroxine, in the absence of changes in total serum thyroxine and protein binding capacity, suggests that decreased protein binding rather than increased production of thyroxine is responsible. Also, the fact that similar changes occur in thyroidectomized patients on replacement therapy rules out an effect on the hypothalamic-pituitary-thyroid axis.

It has been suggested that the well-known effect of heparin in elevating plasma free fatty acid levels, raises serum free thyroxine levels by means of the free fatty acids competing for protein binding sites (Hollander et al., 1967). However, as can be seen in Figure 4, this is

Fig. 1. Change in serum free thyroxine levels in 12 patients during haemodialysis.
Fig. 2. Effect of small doses of heparin on serum free thyroxine levels in 5 euthyroid patients and one patient with hypothyroidism.

Fig. 3. Effect of 4-hour heparin infusion on serum free thyroxine and heart rate in a patient with severe hypothyroidism.

not so. With heparin alone, both the free fatty acid and serum free thyroxine rose significantly. With heparin and a preceding neutralizing dose of protamine, the serum free thyroxine showed the same response but there was no significant increase in free fatty acid levels.
Fig. 4. Effect of heparin and protamine on plasma free fatty acids and serum free thyroxine levels.

Presumably, the heparin molecule itself, or some substance stimulated or changed by it, does compete for the protein binding sites, thus causing an increase in serum free thyroxine. However, the exact mechanism remains obscure.

Summary

Even small doses of heparin cause a marked rise in serum free thyroxine levels. In certain sensitive patients, such as those with hypothyroidism, the effect upon pulse rate and cardiac rhythm may be significant and even potentially dangerous. The same problems may apply to other patients such as those receiving heparin following myocardial infarction or pulmonary embolism. Certain dialysis patients do exhibit unexplained increases in pulse rate. Whether or not these episodes are in any way related to (1) the use of heparin and/or its effect on serum free thyroxine, or (2) a peculiar sensitivity to these changes, is as yet, not clear.

Our preliminary investigations have not shown a clear relationship between them but we feel that this area deserves further study.

REFERENCES
