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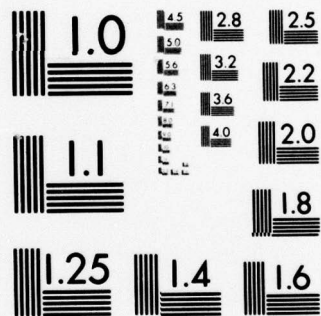
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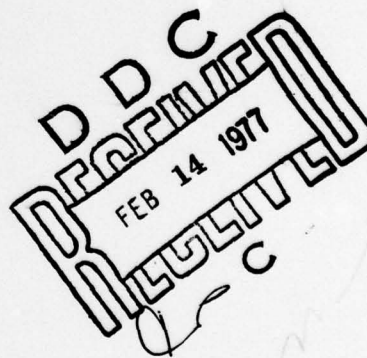


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Resin hemoperfusion: A potential new treatment for thyroid storm*

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Thyroid storm or crisis is a serious condition characterized by very high serum concentrations of triiodothyronine (T3) and thyroxine (T4) and by an exaggeration of the usual manifestations of thyrotoxicosis (Ingbar, 1966; McArthur et al., 1947; Mazzaferri and Skillman, 1969). Presently accepted modes of therapy for thyroid storm include propylthiouracil or methimazole to decrease thyroid hormone synthesis (Ingbar, 1966), iodine to block glandular release (Wartofsky et al., 1970), and propranolol to decrease tissue sensitivity to T3 and T4 (Das and Krieger, 1969). In spite of the effective glandular blockade permitted by the available forms of chemotherapy, the mortality of thyroid crisis remains high (Mazzaferri and Skillman, 1969). This high mortality may be partly related to the fact that following the initiation of inhibition of thyroid hormone synthesis and secretion, several days are required before serum T3 and T4 concentrations decrease significantly. A treatment modality that would directly remove these hormones from the circulation and would decrease their serum concentrations within several hours would be highly desirable. The purpose of the present study was to evaluate the ability of an extracorporeal resin hemoperfusion (RH) system, employing uncharged Amberlite^R XAD-4 resin, to bind thyroid hormone and to rapidly decrease serum T3 and T4 concentrations in thyrotoxic dogs.

MATERIALS AND METHODS

Approximately 650 grams of uncharged Amberlite^R XAD-4 polymeric adsorbent resin manufactured by Rohm and Haas Chemical Company, Philadelphia, Pennsylvania, and supplied through the courtesy of Extracorporeal Medical Specialties, Inc., King of Prussia, Pennsylvania, were placed in a Lexan column (length, 21 cm; diameter, 7 cm; volume, 1049 cm³) which was enclosed at each end by a no. 10 stainless steel mesh filter. Three hundred cm of plastic tubing were employed in the perfusion assembly. A cannula was inserted into the femoral artery or vein of a dog to allow inflow into the resin column; a brachial vein cannula was utilized to return the resin outflow blood. Blood was perfused through the column by a Sarns^R roller pump (Model no. 5500) at the rate of 100 ml/min. Resin inflow and outflow pressures were monitored and maintained at 80-100 mm Hg and 50-70 mm Hg, respectively. Heparin was infused into the resin inflow tubing to maintain clotting times greater than 20 minutes.

Control experiments were performed in the same manner as resin hemoperfusion experiments except that blood was pumped through a Dow hollow fiber artificial kidney (Model no. 4) instead of through a resin filled column. This particular control assembly was chosen because it presumably has no ability to remove T3 and T4 except by non-specific adsorption and because it has a volume of approximately 140 ml, which is similar to the fluid dead space of the experimental assembly. Therefore, the control assembly

* The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or reflecting the views of the Department of the Army or the Department of Defense.

was employed to ascertain the effect of hemodilution alone (by the saline charge in the RH system) on serum T3 and T4 concentrations.

Hemoperfusion was performed on mongrel dogs (25-35 kg) made thyrotoxic by the daily administration of approximately 3 mg T4 i.m. for at least 7 days. During perfusion, blood samples were obtained every 30-60 minutes from the resin inflow cannula for all measurements except those used in the calculation of clearance rates; the latter samples were taken simultaneously from both resin inflow and outflow cannulae.

Hematocrit, white blood count, hemoglobin, platelet count, sodium, potassium, chloride, bicarbonate, pH, calcium, glucose, blood urea nitrogen, uric acid, cholesterol, total protein, albumin, bilirubin, and glutamic oxaloacetic acid transaminase were measured by standard techniques (Henry et al., 1974). Cortisol was determined by radioimmunoassay (Foster and Dunn, 1974) utilizing an antiserum produced in our laboratory by Dr. Joseph Bruton. T3 was measured either at Nichols Institute (San Pedro, California) by radioimmunoassay (Chopra et al., 1972) or in our laboratory by a modification of the same technique utilizing T3 antiserum obtained from Dr. D. Mayes (Endocrine Sciences, Tarzana, California). Free T4 (FT4) was determined at Nichols Institute by equilibrium dialysis (Sterling and Brenner, 1966). T4 was measured either at Nichols Institute by radioimmunoassay (Chopra, 1972) or in our laboratory utilizing the RIA-MATTM Circulating I¹²⁵ T4 Kit (Mallinckrodt Inc., St. Louis, Mo.).

Clearance rates (ml/min) were calculated by the formula:

$$\text{Flow rate (ml/min)} \times \frac{\text{inflow concentration} - \text{outflow concentration}}{\text{inflow concentration}}$$

Clearance rates for the entire 2 hour period were derived from the clearance rates (ml/min) by integration of the area under a curve utilizing Simpson's formula. The logarithmic mean serum T3 or T4 was then multiplied by the 2 hour clearance value to obtain the total amount of T3 and T4 removed. Calculations of clearance rates and total amount removal during the control period and of clearance rates during RH were based upon actual serum concentrations or percentage changes. However, calculations of total hormone removal during RH have been corrected for the effects of hemodilution by subtracting the amount of hormone 'removed' during the 2 hour control period from that removed during 2 hour resin perfusion.

RESULTS

Routine chemistries. None of the routine chemistries demonstrated significant alterations during 2 hours of RH except for the mean ($\pm$ SD) serum albumin concentration which decreased from 2.6 ± 0.5 g/100 ml prior to RH to 2.3 ± 0.5 g/100 ml after TH ($p < .05$), and the mean ($\pm$ SD) serum glucose concentration which increased from 85 ± 16 mg/100 ml to 122 ± 38 mg/100 ml ($p < .05$).

Thyroid function tests. During 2 hour control perfusion, serum T3, T4, and FT4 concentrations decreased by a mean of 20% ($n = 3$), 17% ($n = 5$), and 0% ($n = 2$), respectively. During 2 hour RH, mean ($\pm$ SEM) T3 concentrations ($n = 6$) decreased from 846 ± 233 ng/100 ml to 352 ± 78 ng/100 ml ($p < .05$); mean serum T4 concentrations ($n = 9$) decreased from 34 ± 7 μ g/100 ml, initially, to 20 ± 6 μ g/100 ml following perfusion ($p < .01$); and FT4 levels ($n = 4$) were 97 ± 27 ng/100 ml, initially, and 52 ± 16 ng/100 ml at 2 hours.

During control perfusion experiments the mean percent decreases were derived from the actual serum concentrations observed in each experiment. However, the values given (*vide infra*) for mean percent decrease during RH have been corrected for the decreases observed during the aforementioned control period, which were presumed to represent an effect of hemodilution. During 5 control experiments, the mean decrease in serum T4 concentration averaged 17%. Therefore, to correct for hemodilution, the actual percent decrease of T4 concentration which was achieved during each RH experiment was divided by 0.83 to obtain the theoretical percentage that would have been reached if hemodilu-

tion had not occurred. Similarly, the observed decrease in serum T3 concentration during control experiments averaged 20%, and this value (0.80) was used to correct the changes seen during RH. Free T4 concentrations did not decrease during 2 control experiments. When the values obtained after 2 hour RH were corrected in this manner, mean T4, T3, and FT4 concentrations decreased 35%, 39%, and 46%, respectively.

Clearance rates and total hormonal removal during RH. During the 2 hour control experiment without resin, the 'clearance' rates of T4 ($n = 1$) at time 0 and 2 hours were 18 ml/min and 0 ml/min, respectively. The average 'clearance' rate of T3 ($n = 2$) was 40 ml/min at time 0, and 0 ml/min at 1 and 2 hours. Therefore, 1080 ml of serum were 'cleared' of T4, and 800 ml of serum were 'cleared' of T3, and 194 μ g T4 and 1.86 μ g of T3 were 'removed' during mock perfusion experiments. During RH the mean clearance rate of T4 ($n = 2$) at 0, 1 hour, and 2 hours was 40 ml/min, 54 ml/min, and 24 ml/min, respectively. The mean T3 ($n = 2$) clearance rate was 86 ml/min at time 0, 66 ml/min at 1 hour, and 50 ml/min at 2 hours. As a result, an average of 5600 ml of serum were cleared of T4, and the total amount of T4 and T3 removed during 2 RH experiments was 1990 μ g and 60.4 μ g, respectively, after correction for hemodilution.

DISCUSSION

In the present study, extracorporeal resin hemoperfusion rapidly decreased serum T3, T4, and FT4 concentrations in thyrotoxic dogs. Serum T3 concentration was decreased by 39%, serum T4 was decreased by 35%, and FT4 concentrations were decreased by 46% after 2 hours of RH. Total T3 and T4 removed in 2 hours averaged 60.4 μ g and 1990 μ g, respectively, after correction for hemodilution. Thyrotoxic patients have a distribution space containing approximately 180 μ g T3 and 982 μ g T4 (Nicoloff et al., 1972); therefore it seems that RH may have the capability of removing sufficient quantities of T3 and T4 to be clinically useful in selected patients with severe thyrotoxicosis or thyroid storm. Conceivably, an even greater benefit might accrue from either a more prolonged interval of RH or from intermittent RH therapy. This latter method may allow removal of T4 and T3 which had been sequestered in compartments other than that of serum, and which could have re-equilibrated between treatment periods.

All dogs tolerated RH well, a finding consistent with previous human and animal studies which effectively employed similar resins to remove other substances (e.g. glutethimide, Fiorinal[®], barbiturates, ethchlorvynol and bile salts) (Nealon et al., 1966; Rosenbaum et al., 1971; Rosenbaum, 1972; Vale et al., 1975; Willson et al., 1974). In the present study, with the exception of serum albumin and glucose concentrations, no significant alterations in serum chemistries were observed during resin hemoperfusion. Serum chemistries generally did not change in earlier studies employing resin hemoperfusion; although platelet count or white blood count occasionally decreased, they returned to normal when hemoperfusion was discontinued. The mechanism by which resin beads remove T3 and T4 is unknown but may relate to the extremely large surface area of the beads which allows various types of chemical binding to occur.

In summary, RH of thyrotoxic dogs appears to be a safe, effective means of decreasing serum T3, T4 and FT4 and may hold promise for the treatment of thyroid storm in man.

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) The ability of an extracorporeal hemoperfusion system employing neutral Amerlite resin to bind thyroid hormone and to decrease circulating levels of triiodothyronine (T3), thyroxine (T4), and free thyroxine (FT4) was evaluated in dogs made thyrotoxic by the intramuscular administration of thyroid hormone. Since the resin column and tubing were charged with saline, the effects of hemodilution from this source on serum T3 and T4 was assessed by control perfusion through a column which did not contain any resin. After correction for hemodilution, the mean serum T3, T4 and FT4 decreased during 2 hours of resin hemoperfusion by 39%, 35%		

→ and 46%, respectively. Hormonal clearance rates were calculated in two experiments and the estimated net hormone removed averaged 60.4 ug of T3 and 1990 ug of T4. Hematologic indices and routine chemistries did not change significantly in these dogs during the procedure except for a decrease in mean serum albumin concentration and an increase in mean serum glucose concentration.

Hemoperfusion through this resin system seems to be a safe, effective means of decreasing serum T3, T4, and FT4 in thyrotoxic dogs and warrants evaluation for the treatment of thyroid storm in man.