Treatment of myxoedema coma - factors associated with fatal outcome

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Abstract. Treatment of myxoedema coma has been associated with a high mortality. The causes of death were analysed in this paper by retrospective study of the records of 11 myxoedema coma patients. The serum thyroxine (T4) and triiodothyronine (T3) levels were estimated retrospectively from the amounts of hormone given to the patients by a two-compartment model. Seven patients died and 4 survived. The patients who died were significantly older (78.9 ± 2.2 years, mean ± SEM) than those who survived (66.8 ± 3.7 years). The initial heart rate was lower in the deceased group, but both groups had increased their heart rate on treatment. The surviving patients showed an increase in body temperature during the first 3 days of treatment, in contrast to the patients who eventually died. The deceased patients had received larger amounts of thyroid hormone and had calculated levels of T3 that were nearly twice as high as those of the surviving patients. Old age and a high serum level of T3 are determinants for the fatal outcome of myxoedema coma. Our analysis underscores the importance of using a cautious replacement regimen in myxoedema coma patients.

Myxoedema coma is uncommon and relatively few patients have been described in the literature since the first report (Ord 1879). The incidence of myxoedema coma is not known. A report summarizing data on patients published between 1911–1961 included 76 myxoedema coma patients (Forester 1963). Thereafter only a few case reports have appeared (Khaleeli 1978; Nielsen & Ranlov 1964; Valiquette et al. 1974; Bergdahl & Karlberg 1970; Woods & Holmes 1977; Copperman 1968; Bacon & Gent 1964; Domm & Vassallo 1973; Lindberger 1975; Hylander et al. 1980; Gramham & Harding 1977; Boström et al. 1972; Leon-Sotomayor & Bowers 1964; Dow & Lerman 1965).

The prognosis for myxoedema coma patients was markedly improved by the introduction of a high dose iv thyroxine (T4) treatment (Holvey et al. 1964). Previously, patients were treated with large doses of triiodothyronine (T3) and mortality ranged between 50 to 80%. A frequent cause of death was circulatory derangement (Forester 1963; Catz & Russell 1961; Nickerson et al. 1960).

When T4 is used for replacement it has to be converted to T3 before it can exert most of its effects (Ingbar & Braverman 1975; Oppenheimer et al. 1972; Surks et al. 1973). The conversion rate of T4 to T3 is reduced in the hypothyroid state and during fasting and starvation, whereas the conversion to the biologically inactive form reversed T3 (rT3) is increased (Burger et al. 1976; Chopra et al. 1975).

In previous studies we have demonstrated that some organ responses to T4 replacement do not proceed in parallel but can occur sequentially (Hylander & Rosenqvist 1983). There was a rapid response in heart rate to orthostatic stimulation, whereas the capacity to perform maximal work recovered more slowly during treatment. The fatal effect of intense replacement therapy might therefore be due to a rapid increase in susceptibility of the heart, whereas the capacity of the myocardium to cope with such an enhanced responsiveness would lag behind. Treatment of myxoedema coma patients with T4 instead of T3 might result in a slow release of T3 which could give the organs enough
time to recover in a coordinated way. This might explain the success of the iv T4 treatment regime.

The aim of the present study was to analyse retrospectively factors which might be of importance for the recovery of myxoedema coma patients.

Materials and Methods

Eleven myxoedema coma patients were found by searching hospital records, indicating computerized registers of hospitalized patients, and by contacting all departments of Medicine and Endocrinology in Sweden. All these patients had been registered under ICD code 240.00. All patient records were retrieved and the validity of the diagnosis was assessed by the following criteria: the patients had to be comatose, hypothermic, and to have depressed levels of thyroid hormone and/or an increased level of thyrotrophin (TSH). Clinical and laboratory data on the patients are given in Table 1.

The patients were treated with thyroid hormone as shown in Tables 1 and 2. In addition, all patients had been given cortisone acetate 100–200 mg/day during the first days. Since the patients had received different doses of either T4, T3 or a combination of the two hormones by the iv or the oral route it was necessary to transform this information in such a way that the different treatment regimes could be compared. Two methods were used. First we estimated the serum T4 and T3 levels using a two compartment model inserting the amounts of hormones given to the patients (Marriott 1966).

\[ T_{4n} = T_{40} \cdot e^{-0.046 \cdot t} \]
\[ T_{3n} = T_{30} \cdot e^{-0.80 \cdot t} + C \cdot \frac{(T_{40} \cdot 0.046) - 0.08}{0.08 - 0.046} \cdot e^{-0.046 \cdot t} \]

\( t \) = time after the initial dose; \( n \) = days of hormone treatment; \( C \) = the percentage of T4 converted to T3.

The initial concentration of T4 was assumed to be 6 nmol/l and that of T3 0.4 nmol/l. The distribution volume for T4 was taken to be 101 and that of T3 to be 381 for a person weighing 70 kg (Pittman 1979). The volumes were then adjusted according to the body weight of the patient. The percentage of T4 converted to T3 (C) was taken to be 15% (Miralles-Garcia et al. 1981). The fractional rate of T4 elimination was set to 0.046 day\(^{-1}\) and that of T3 to 0.80 day\(^{-1}\) (Pittman 1979). The concentration of T3 was averaged for the first 10 days or the numbers of days that the patients were alive. This average serum concentration of T3 was used as an estimate of the total replacement dose during the period.

In the second type of calculation we estimated the hormone dose in T4 equivalents by taking the iv dose as stated and by multiplying the oral T4 dose by 0.5 and the T3 dose by 3 (Pittman 1979). From the sum of T4 and T3 doses a mean daily dose of T4 equivalents was calculated.

The significance of differences between means was tested by Student’s t-test (Armitage 1974).

Results

The clinical and laboratory findings in the 11 patients with myxoedema coma are shown in Table 1. Nine of the 11 patients were admitted between November and March. Four of the patients recovered and 7 died. The 7 patients who died were women. Of the 4 survivors, 3 were males. One patient died of myocardial infarction, 3 of circulatory failure and 3 from cerebral haemorrhage. The time of death varied between 3 and 31 days after initiation of therapy (Table 1). The mean age of the surviving patients was 66.8 ± 3.7 years (mean ± SEM) which differed significantly \((P < 0.05)\) from the mean age of the group of patients who died 78.9 ± 2.2 years.

The mean initial body temperature was 34.1 ± 1.0°C in the group that survived and 32.0 ± 1.0°C in the group that died. The difference in temperature was not significant. Nor was there any significant difference between the results of the initial laboratory tests in the two groups. All patients had increased levels of muscle or liver enzymes ASAT = aspartate-aminotransferase, ALAT = alanine-aminotransferase and low haemoglobin concentrations on admission. Nine of the patients had increased levels of serum creatinine and 2 had normal values. Eight patients were initially hypotraemic. In 5 patients the creatinine phosphokinase concentration (CK) had been analysed. Only one patient had a normal value whereas 4 had increased values. Seven of the patients had low platelet counts. The coagulation factor VIII was measured in 1 patient (No. 4) and was found to be decreased. Serum cholesterol was measured in 2 patients (Nos. 2, 6). The cholesterol value was increased in 1 patient (No. 2) and normal in the other (No. 6). Five patients had a low voltage ECG on admission (Nos. 1, 3, 6, 9, 10), two had hypoglycaemia (Nos. 2, 8) and two developed seizures (No. 10, 11).

The replacement therapy and routes of administration are shown in Table 2. The mean hormone
Table 1.
Clinical and laboratory findings in 11 myxoedema coma patients. Nos. 1–7 deceased patients, Nos. 8–11 survivors.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age years</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Initial body temperature °C</th>
<th>Thyroid hormones analyses</th>
<th>Treatment</th>
<th>Assisted ventilation</th>
<th>Complications</th>
<th>Outcome days of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>86</td>
<td>F</td>
<td>3</td>
<td>33.8</td>
<td>TSH 24.5, T4 17, T3 0.3</td>
<td>+</td>
<td>+</td>
<td>Pneumonia</td>
<td>Circulatory failure, + day 3</td>
</tr>
<tr>
<td>2</td>
<td>85</td>
<td>F</td>
<td>1</td>
<td>35.2</td>
<td>PBI 1.1 µg %</td>
<td>+</td>
<td>+</td>
<td>CO₂ retention</td>
<td>Cerebral haemorrhagia, + day 5</td>
</tr>
<tr>
<td>3</td>
<td>83</td>
<td>F</td>
<td>1</td>
<td>32.0</td>
<td>TSH 51.0, T4 22, T3 0.5</td>
<td>+</td>
<td>+</td>
<td>Asystole</td>
<td>Myocardial infarction + day 14</td>
</tr>
<tr>
<td>4</td>
<td>77</td>
<td>F</td>
<td>1</td>
<td>28.5</td>
<td>TSH 33, T4 18</td>
<td>+</td>
<td>+</td>
<td>Pneumonia</td>
<td>Cerebral haemorrhagia, + day 4</td>
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<tr>
<td>5</td>
<td>76</td>
<td>F</td>
<td>1</td>
<td>32.5</td>
<td>PBI 0.18 µg %</td>
<td>+</td>
<td>–</td>
<td>Atrial flutter</td>
<td>Cerebral haemorrhagia, + day 31</td>
</tr>
<tr>
<td>6</td>
<td>74</td>
<td>F</td>
<td>1</td>
<td>34.5</td>
<td>PBI 1.7 µg %</td>
<td>+</td>
<td>–</td>
<td>Ventricular</td>
<td>Circulatory failure, + day 12</td>
</tr>
<tr>
<td>7</td>
<td>71</td>
<td>F</td>
<td>1</td>
<td>27.9</td>
<td>PBI 0.7 µg %</td>
<td>+</td>
<td>–</td>
<td>Respiratory</td>
<td>Circulatory failure, + day 3</td>
</tr>
<tr>
<td>8</td>
<td>73</td>
<td>F</td>
<td>2</td>
<td>35.0</td>
<td>T4 &lt; 10, T3 &lt; 0.6</td>
<td>+</td>
<td>+</td>
<td>Angina pectoris, atrial flutter</td>
<td>Alive</td>
</tr>
<tr>
<td>9</td>
<td>72</td>
<td>M</td>
<td>4</td>
<td>35.0</td>
<td>TSH 1, T4 &lt; 25, T4 &lt; 0.5</td>
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<td>–</td>
<td>Angina pectoris pneumonia</td>
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<tr>
<td>10</td>
<td>65</td>
<td>M</td>
<td>1</td>
<td>35.2</td>
<td>TSH 145, T4 &lt; 25, T3 &lt; 0.5</td>
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<td>+</td>
<td>Respiratory insufficiency</td>
<td>Alive</td>
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<tr>
<td>11</td>
<td>57</td>
<td>M</td>
<td>1</td>
<td>31.3</td>
<td>TSH 355, T4 6, T3 &lt; 0.45</td>
<td>–</td>
<td>+</td>
<td>Pneumonia</td>
<td>Alive</td>
</tr>
</tbody>
</table>


2 Reference values: highest reference value used for TSH < 7.2 arbU/l.
Lowest reference values used for T3 1.1 nmol, T4 45 nmol/l, PBI 4 µg %.

The dose per day expressed in T4 equivalents was 244.0 ± 19.2 µg (mean ± SEM) in the deceased group and 156.3 ± 55.9 µg in the group that survived. The difference was not significant (P > 0.05). The deceased group had been given 1.56 times as many T4 equivalents per day as the group that survived.

The mean estimated levels of T3 are shown in Table 3. The mean level of T3 was 1.9 times higher in the deceased group. The difference was significant (P < 0.05).

Both survivors and deceased patients developed different medical complications during the treatment. Four patients had pneumonia, 4 arrhythmias and 3 patients developed angina pectoris (Table 1).

The number of patients treated with assisted ventilations was 1 out of 4 in the surviving group and 4 out of 7 among those who died.

The body temperature increase during the initial 3 days of treatment was greater in the surviving patients (Fig. 1).
Table 2.
Replacement therapy (µg) during the first 10 days in 11 myxoedema coma patients. Intravenous treatment is in italics.
Nos. 1–7 deceased patients, Nos. 8–11 survivors.

<table>
<thead>
<tr>
<th>Day No.</th>
<th>Patient No.</th>
<th>Hormone</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
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<th>11</th>
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<tbody>
<tr>
<td></td>
<td>T₄</td>
<td>T₃</td>
<td>T₄</td>
<td>T₃</td>
<td>T₄</td>
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<td>Sum</td>
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<td>88</td>
<td>600</td>
<td>400</td>
<td>250</td>
<td>690</td>
<td>25</td>
<td>308</td>
<td>1030</td>
<td>770</td>
<td>160</td>
<td>950</td>
<td>460</td>
</tr>
</tbody>
</table>

Mean daily
T₄ equivalents 254.7  300.0  219.5  234.1  309.0  231.0  160.0  185.5  72.5  302  65.0
Average $T_3$ concentration estimated by the two compartment mathematical model from the administered thyroid hormone dose to myxoedema coma patients (mean ± SEM).

<table>
<thead>
<tr>
<th>Deceased patients</th>
<th></th>
<th>Surviving patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient No.</td>
<td>Age years</td>
<td>$T_3$ nmol/l</td>
<td>Patient No.</td>
</tr>
<tr>
<td>1</td>
<td>86</td>
<td>3.3 ± 0.5</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>85</td>
<td>3.2 ± 0.9</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>83</td>
<td>2.9 ± 0.2</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>77</td>
<td>2.6 ± 0.4</td>
<td>11</td>
</tr>
<tr>
<td>5</td>
<td>76</td>
<td>5.0 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>74</td>
<td>4.1 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>71</td>
<td>2.0 ± 0.6</td>
<td></td>
</tr>
</tbody>
</table>

$\bar{x} ± SEM$ 3.3 ± 0.4* 1.7 ± 0.6

$N = $ 7 4

The increase in heart rate during the initial 10 days of treatment was comparable in survivors and deceased patients (Fig. 2). The surviving patients started at a mean heart rate of 50 ± 4 beats/min and those who died at 43 ± 4 beats/min ($P > 0.05$).

**Discussion**

The treatment of myxoedema coma has often been discussed in the literature because of the high mortality of this serious condition (Forester 1963; Holvey et al. 1964; Catz & Russell 1961; Nickerson et al. 1960). Since the disease is very uncommon, a systematic evaluation of possible treatment strategies had been difficult. Mortality could be lowered by treating the patients with a large bolus injection of $T_4$ instead of using $T_3$ (Valiquette et al. 1974). The present study of 11 myxoedema coma patients has shown that the use of $T_4$ instead of $T_3$ leads to lower serum levels of $T_3$, which are probably less stressful for the patients.
Many factors might influence the outcome of the myxoedema coma treatment (Green 1968; Nicoloff 1976; Blum 1972), including the age of the patient, the initial body temperature and the circulatory state of the patient prior to coma. A large proportion of the patients who succumbed, died because of circulatory failure (Catz & Russell 1961; Nickerson et al. 1960).

Our previous studies on the normalization of hypothyroid patients have shown that different organ functions recover within different time intervals (Hylander & Rosenqvist 1983). Thus, e.g. the circulatory system regained its adrenergic susceptibility to stimulation before the capacity to perform maximal work was restored. When patients received rapid substitution therapy, this discrepancy in restoration could lead to an overstimulation of the circulatory system (Hylander et al. 1983). Our previous findings prompted us to explore the possibility that the fatal outcome of myxoedema coma treatment could be attributed to such an overstimulation of the circulatory system. Our analyses confirmed previous observations that myxoedema coma patients can die of circulatory failure. In addition, 3 patients died because of cerebral haemorrhage. The patients who died were significantly older and had a lower heart rate before treatment than the survivors. The heart rate increased in both groups with therapy. In the deceased group the increase occurred in spite of the fact that the body temperature remained low during the initial 3 days of treatment. This could signal a toxic effect of T3 and/or a too rapid normalization of the adrenergic susceptibility of the heart in those patients. In support of this we found that the deceased patients had received more hormone and that their estimated serum T3 level was almost twice as high as in the survivors. The high level of T3 might well have contributed to the development of circulatory failure in these patients and a more cautious therapy seems to be advisable.

Cerebral haemorrhages in 3 of our patients might have been due to a deficiency of the coagulation system as previously described in hypothyroid patients (Egeberg 1963; Edson et al. 1975; Orr & Edin 1962). The one patient, who died of haemorrhage had a low level of factor VIII. This test was not performed in the other patients. Whether the haemorrhages could have been prevented by a lower replacement dose is presently unknown.

In conclusion, the factors associated with a fatal outcome of myxoedema coma treatment identified in this paper were age, initial heart rate and type and dose of replacement therapy as well as the ensuing level of T3. The T3 level was estimated to be in the toxic range for several of the patients who died. The results would imply that excessive hormone doses of T3 should be avoided in the treatment of myxoedema coma.

Acknowledgments

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