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Isoamylase levels in bone marrow transplant patients are affected by total body irradiation and not by graft-versus-host disease

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Abstract. The mean total serum amylase levels in patients was 3.2 ± 0.5 μkat/l (± SE) before total body irradiation (TBI) prior to bone marrow transplantation of which 50% was due to pancreatic isoamylase and 50% salivary isoamylase. Total serum amylase increased to a maximum of 100.3 ± 12.3 μkat/l on the first day after TBI and most of this increase was due to an increase in salivary isoamylase (90.0 ± 12.1 μkat/l). In association with this, all patients had clinical symptoms of parotitis. An increase in pancreatic isoamylase was found in 27% of the patients; however, none of them had clinical symptoms of pancreatitis. Serum amylase levels returned to normal within 5 days after TBI but then decreased to subnormal values, remaining below the normal range for 3 weeks. Pancreatic isoamylase returned to pre-irradiation levels 1.5 months after TBI, while salivary isoamylase remained low for the rest of the observation time. TBI of 7.5 Gy at 26 cGy/min gave significantly lower salivary amylase at 2 days after TBI compared with 10 Gy at 4 cGy/min: 32 ± 4 versus 76 ± 13 μkat/l ($P < 0.05$). At 2.5 and 6 months after TBI significantly higher total amylase levels were recorded for patients treated with 7.5 Gy of TBI compared with 10 Gy: 2.5 ± 0.4 and 2.7 ± 0.3 versus 2.0 ± 0.5 and 0.8 ± 0.3 μkat/l, respectively ($P < 0.01$, $P < 0.05$, respectively). Acute or chronic GVHD did not affect acinar cells in this investigation.

Key words: Total body irradiation, isoamylase – Graft-versus-host disease, isoamylase – Bone marrow transplantation, isoamylase

Total body irradiation (TBI) induces tissue damage in many organs, including the pancreas and salivary glands, leading to increased serum amylase levels. These levels, however, are found to return to normal within 1 week [1, 8].

Symptoms such as nausea, vomiting and dryness of the mouth are also common in patients after TBI [1, 8, 9] and may persist for up to 6 months. These symptoms may, among other things, reflect damage to the pancreatic and salivary glands. Acute graft-versus-host disease (aGVHD) has been shown to affect exocrine pancreatic ducts but not exocrine or endocrine cells [5]. To our knowledge, serum amylase levels have not been studied with regard to chronic GVHD (cGVHD). We therefore followed the activities of total amylase, salivary and pancreatic isoamylases in serum from 30 bone marrow transplant patients at various time intervals up to 1 year after TBI.

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Materials and methods

Serum amylase, pancreatic and salivary isoamylases were measured before TBI and at various times up to 1 year after TBI in 30 consecutive patients subjected to allogenic bone marrow transplantation. The average age of the patients was 31 years (range 2–58). Nine patients suffered from acute lymphocytic leukaemia: ten had chronic myelocytic leukaemia, six had acute myelocytic leukaemia, two had myeloma, one had a neuroblastoma, one a myelodysplastic syndrome and one myelofibrosis. As conditioning therapy before transplantation, 27 patients received cyclophosphamide (120 mg/kg over 2 days), two patients received melphalan (140 mg/m^2) and one patient busulphan (16 mg/kg). Eight patients receiving T-cell-depleted marrow were given TBI delivered by a linear accelerator at a total of 7.5 Gy, with 7 Gy toward the lungs at a dose rate of 26 cGy/min. The other 22 patients received 10 Gy of TBI, with 9 Gy toward the lungs at a mean dose rate of 4 cGy/min. As prophylaxis against GVHD, 21 patients received cyclosporin A and methotrexate, eight patients received T-cell-depleted bone marrow, and one patient received no prophylaxis since he received bone marrow from his HLA-identical twin brother. A description of the treatment has been published in detail previously [12].

Serum amylase activities were determined using a Phadebas amylase test (reference range 1.5–6 μkat/l). Pancreatic and salivary isoamylase were measured with a Phadebas iso amylase test using salivary inhibitor from wheat (Pharmacia, Uppsala, Sweden, reference range 0.6–3.3 μkat/l for pancreatic isoamylase and 0.4–4.0 μkat/l for salivary isoamylase).

Results

Pre-irradiation samples were available from 20 of the 30 patients. The mean serum amylase was 3.2 ± 0.5 μkat/l (mean ± SE), the mean pancreatic isoamylase was

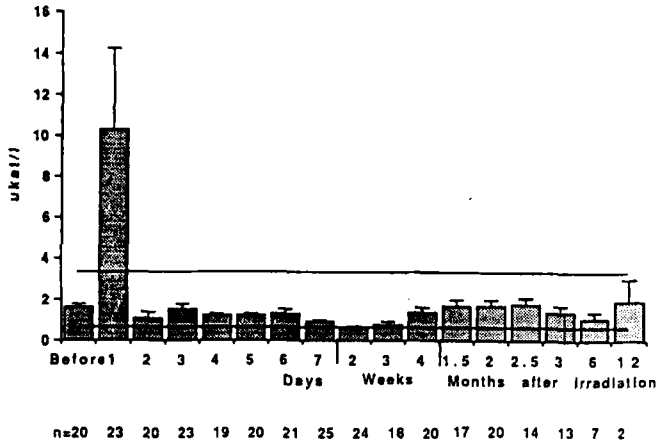

Fig. 1. Pancreatic isoamylase levels in bone marrow transplant patients during the first year following TBI. *Vertical lines* indicate SEM. Reference range is indicated by the two *horizontal lines*

1.6 ± 0.2 µkat/l and salivary isoamylase 1.6 ± 0.4 µkat/l. After TBI the serum amylase increased to a maximum of 100.3 ± 12.3 µkat/l after 1 day ($n = 23$, Figs. 1, 2). Most of this increase was due to an increase in salivary isoamylase (90.0 ± 12.1 µkat/l). An increase in pancreatic isoamylase was seen in eight (27%) of the patients (mean 27.1 ± 8.8 µkat/l).

Serum amylase activities returned to normal within 5 days as did the activities of both isoamylases. The serum amylase activity then continued to fall, reaching subnormal levels 2 weeks after TBI ($n = 24$), and remained below pre-irradiation levels for the rest of the observation time. However, after 3 weeks the reference level was reached and at 1.5 months after TBI the highest serum amylase value post-TBI was reached (2.2 ± 0.4 µkat/l, $n = 17$).

Pancreatic isoamylase remained below pre-irradiation levels for 4 weeks, but then returned to normal 1.5 months after TBI ($n = 17$). The decrease in pancreatic isoamylase during the first month was not more pronounced in the patients who had high pancreatic isoamylase after TBI.

Salivary isoamylase remained below pre-irradiation levels for the rest of the observation time. However, in 13 patients salivary isoamylase increased above the lower boundary of the reference range (0.4 µkat/l) after a mean of 3.3 months.

Patients receiving 7.5 Gy of TBI had significantly lower total and salivary isoamylase levels at day 2 compared to patients receiving 10 Gy of TBI: 32 ± 5 and 31 ± 5 compared with 77 ± 13 and 76 ± 13 ($P < 0.05$, $P < 0.05$, respectively for total and salivary isoamylase). At 2.5 months post-TBI, total amylase levels were significantly higher: 2.5 ± 0.4 for patients given 7.5 Gy of TBI compared with 2 ± 0.5 ($P < 0.01$) for patients treated with 10 Gy of TBI. At 6 months the corresponding figures were 2.7 ± 0.3 and 0.8 ± 0.3 for 7.5 Gy and 10 Gy of TBI, respectively ($P < 0.05$).

All patients had clinical symptoms of parotitis within 12 h after TBI which persisted for 24–48 h. No patients had clinical symptoms of pancreatitis even though 27% of them had increased pancreatic isoamylase. However, intestinal symptoms such as nausea, vomiting and diarrhoea were seen in all patients and necessitated total parenteral nutrition for a mean of 3.8 weeks (range 2–8 weeks). A correlation between the duration of dryness of the mouth and the duration of depressed salivary isoamylase was seen (below reference range 0.4 µkat/l, $r = 74$, $P < 0.001$, $n = 18$). There was also a correlation between the duration of total parenteral nutrition and the duration of depressed pancreatic isoamylase (below reference range 0.6 µkat/l, $r = 0.63$, $P < 0.005$, $n = 20$).

At 3 and 4 weeks during aGVHD there was no difference in patients with or without GVHD. As an example, total amylase at 4 weeks was 2.1 ± 1.2 in 11 patients with aGVHD grade I–II compared with 1.6 ± 0.7 in nine patients with no aGVHD. There were no differences observed between five patients who developed cGVHD and nine patients without cGVHD at 3–12 months. However, patients with cGVHD tended to have higher total amylase levels compared with patients without cGVHD (2.5 ± 0.5 compared with 1.9 ± 0.3, respectively), and the total amylase levels were due to an equal distribution between pancreatic and salivary isoamylase (n.s.). In two patients, one with and one without cGVHD, serum amylase was analysed after 1 year. Total serum amylase was 3.6 and 1.0 µkat/l (pancreatic isoamylase, 2.9 and 0.8 µkat/l; salivary isoamylase, 0.7 and 0.2 µkat/l), the higher values in the patient with cGVHD.

Discussion

The hyperamylasaemia seen in this study most probably reflects an acute TBI-induced damage to the cells of the salivary glands and the exocrine pancreatic tissue. Serum

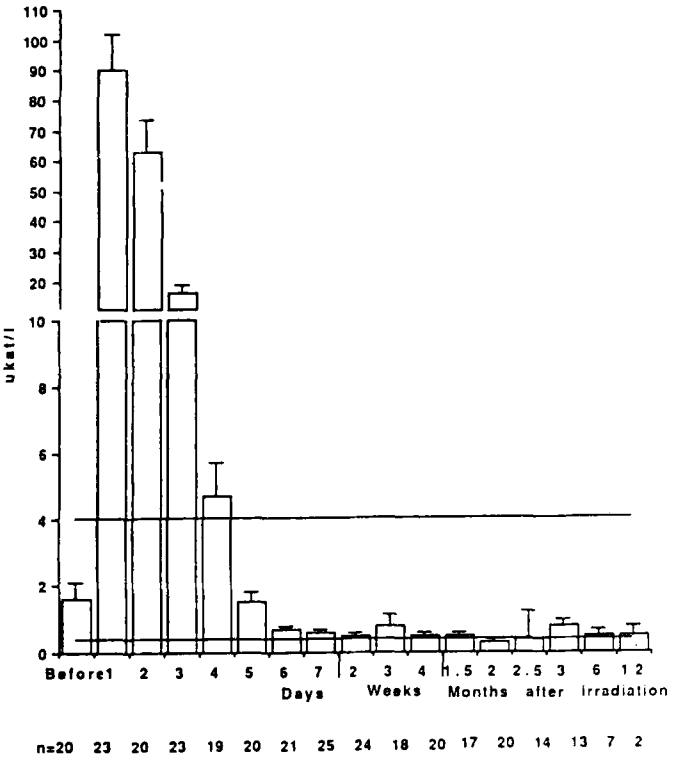

Fig. 2. Salivary isoamylase levels in bone marrow transplant patients during the first year following TBI. *Vertical lines* indicate SEM. Reference range is indicated by the two *horizontal lines*

amylase normalized within 5 days after TBI. Our findings are in agreement with earlier studies by Barrett et al. [1] and Junglee et al. [8]. However, these studies were discontinued after 1 week while in the present study serum amylases were followed for up to 6 months after TBI in most patients. The serum amylase levels continued to decrease and reached subnormal levels and remained low until 4 weeks after TBI. This reduction represents further evidence of long-term tissue damage caused by TBI.

The higher contribution of salivary isoamylase to the acute increase in total serum amylase and the following prolonged depression of the salivary isoamylase after TBI are probably due to more severe radiation damage to the salivary glands than to the pancreas. Our data suggest that the total dose of irradiation is more important than the dose rate. Patients receiving 7.5 Gy at a fast dose rate, 26 cGy/min, compared to 10 Gy at a slow dose rate, 4 cGy/min, have less serious acute damage and faster recovery as measured by salivary and total amylase.

Dryness of the mouth after BMT may be linked to salivary gland insufficiency caused by irradiation [7]. The higher amylase levels in patients with cGVHD compared with patients without GVHD could be explained by an immunological attack with continuous leakage of amylase. Alternatively, these patients may have a low salivary and pancreatic juice production, which might give a relatively higher amount of amylase to the serum.

No clinical symptoms of acute irradiation damage to the pancreas were detected. However, symptoms which may be linked to subsequent pancreatic exocrine insufficiency, such as nausea, vomiting and diarrhoea were seen in all patients. There are several other reasons for these symptoms after BMT, including damage to the gastrointestinal tract by chemotherapy, irradiation, infections and GVHD. However, among our patients a GVHD did not cause any damage to the pancreas as measured by amylase. Foulis et al. have shown that aGVHD induces ductal changes in the human pancreas, which is concordant with our findings [5].

Using the dog as an experimental model, Nacchiero et al. [11] suggested that pancreatic secretory insufficiency after TBI may play a role in the post-irradiation gastrointestinal symptomatology. This was supported by Corring et al. [3] who showed a depressed pancreatic function in dogs after irradiation, and Michel et al. [10] detected marked histological changes and exocrine insufficiency in dogs succumbing to cachexia after irradiation. Our finding that gastrointestinal symptoms persist as long as the depression in pancreatic isoamylase levels, supports these findings. It has been proposed by several investigators that salivary amylase may contribute to the intestinal digestion of starch especially during pancreatic diseases where pancreatic isoamylase levels are diminished [4, 6, 13]. We have previously reported a homeostatic regulation of serum amylase [2] where the salivary isoamylase increased when the pancreatic isoamylase decreased and vice versa. However, after TBI, both salivary and pancreatic isoamylases are depressed and, therefore, no compensatory mechanism can be expected.

A reduction in food intake can also lead to diminished amylase release [14]. This can partly explain the low levels during the first month after TBI when the patients were maintained on total parenteral nutrition. One would therefore expect an increase in both pancreatic and salivary isoamylase levels when oral nutrition was reinstated. This did not happen, however.

To conclude, the correlation between the early gastrointestinal symptoms and depressed pancreatic isoamylase levels makes it possible that the decrease in exocrine pancreatic function is one cause of the symptomatology of the intestinal syndrome after irradiation. Therefore, substitution with digestive enzymes may be of value after TBI in reducing gastrointestinal symptoms.

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