Causes of Increased Plasma Creatine Kinase Activity after Surgery

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To determine whether drug reactions might play a role in postoperatively increased plasma enzyme activity, we measured creatine kinase (CK), and ornithine carbamoyl transferase (OCT) activities immediately before and on the 1st, 4th, and 8th day after 343 elective surgical procedures performed on 327 patients who had received various drugs preoperatively. We saw no overt clinical evidence of muscle damage, but plasma CK activity was significantly increased on the first postoperative day. Plasma OCT activity was not significantly altered. We found no relationship between prior drug exposure and increased CK activity, but the administration of general rather than regional anesthesia and the duration of anesthesia during surgery were closely related to increased CK activity. Halothane or succinylcholine administration during operation was also associated with a significant increase in CK activity in subjects whose pre-operative CK activity was normal. In contrast, subjects with increased pre-operative CK activities did not show this response to halothane or succinylcholine.

Additional Keyphrases: diagnostic aid • malignant hyperthermia syndrome • ornithine carbamoyl transferase • effects of anesthesia

An increased activity of creatine kinase (CK; EC 2.7.3.2) in the plasma or serum after surgery is a well-known phenomenon (1, 2). Because CK is most active in cardiac and skeletal muscle tissue, muscle trauma incident to operation has been suggested as the probable source of increased activity of circulating enzyme. However, no statistically significant relationship has been shown between either the type of operative procedure (1) or the estimated amount of muscle trauma (2) and the extent of the postoperative increase in CK activity. Certain drugs, administered orally or parenterally, affect circulating CK (3). If given before or during surgery, drugs could be responsible for the postoperative alterations that have been attributed to muscle trauma, and could confound attempts to correlate altered activity with surgically induced muscle trauma.

To test the hypothesis that drug reactions might play a role in the development of postoperative enzyme changes, we measured plasma CK before and after elective surgical procedures requiring regional or general anesthesia with or without neuromuscular blockade. For comparison, the activity in plasma of ornithine carbamoyl transferase (OCT; EC 2.1.3.3), an enzyme derived mainly from hepatic tissue, was similarly measured before and after surgery. Patients exposed before anesthesia to various therapeutic agents and to ethanol were compared to patients not so exposed. The design of the study allowed us to assess the influence of specific anesthetic and neuromuscular blocking agents, and duration of anesthesia-surgery, and the type and site of surgery on plasma CK activity. In addition, we examined whether the presence of supranormal CK activity before surgery predisposes to a greater release of enzyme into the circulation after surgery.

Materials and Methods

During six months, we studied 327 patients who received anesthesia for 343 elective surgical procedures. We selected for study those patients entering the operating suite before 1:00 p.m. on Monday, Wednesday, or Thursday of each week. These days and the time limitation were chosen to permit initial and follow-up specimens to be assayed on the day of collection.

A blood sample was first obtained in the operating room before the patient was anesthetized. Blood was subsequently sampled on the 1st, 4th and 8th postoperative days. The number of specimens obtained decreased progressively as a result of early hospital discharge. Plasma CK and OCT activities were measured, in duplicate, by accepted spectrophotometric-kinetic methods (4).

Before surgery, we recorded data on therapeutic agents such as sedatives, tranquilizers, and analge-
Table 1. Mean Plasma Enzyme Activities before and after Surgery

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Pre-operative</th>
<th>First day</th>
<th>Fourth day</th>
<th>Eighth day</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK</td>
<td>10.5 ± 19.9(341)*</td>
<td>40.9 ± 45.4(327)*</td>
<td>15.0 ± 19.9(250)</td>
<td>7.8 ± 9.9(192)</td>
</tr>
<tr>
<td>OCT</td>
<td>0.86 ± 1.0(328)</td>
<td>0.82 ± 0.98(320)</td>
<td>1.03 ± 1.13(244)</td>
<td>0.98 ± 1.25(190)</td>
</tr>
</tbody>
</table>

* Values are means ± SD. Numbers in parentheses: n. plasma specimens.

Results

A statistically significant increase in plasma CK activity was found only on the first postoperative day (Table 1). Plasma OCT activities were not significantly different for pre- and postoperative specimens. We found no statistically significant relationship between analgesics, sedatives, tranquilizers, or alcohol administered before surgery and postoperative plasma CK activity; no specific anesthetic agents (halothane, cyclopropane, or nitrous oxide) could be implicated in the observed changes. However, the mean increase in plasma CK activity in the pre-operative specimen as compared with that found on the first postoperative day was significantly greater in patients who had received succinylcholine than in subjects who had not. Increased CK activity significantly correlated with duration of anesthesia-surgery, but neither with the type nor site of the surgical procedure. In no instance did we see overt clinical evidence of important muscle (or hepatic) injury.

As shown in Table 2, administration of halothane or succinylcholine to patients with initially normal CK activity was associated with statistically significant increases in plasma CK activity when compared to the changes observed in patients who did not receive these agents. In contrast, although postoperative CK activities were greater in the patients who had an abnormally high resting CK activity, neither halothane nor succinylcholine effected further increases postoperatively in plasma CK activity in these patients.

Discussion

The pattern of CK change we observed, with a peak on the first postoperative day and return to nearly normal values on the fourth postoperative day, is similar to that seen in acute myocardial infarction (5), and might present some difficulties in the differential diagnosis of that condition. Other workers have noted CK elevations in patients undergoing cardiac, thoracic, or abdominal surgery (I); but we could not correlate the CK alterations with specific types or sites of surgery. A role of skeletal muscle trauma in the pathogenesis of this phenomenon, as previously suggested (I, 2) seems likely because duration of anesthesia-surgery and elevated CK activity on the first postoperative day were closely correlated. Presumably, the amount of tissue trauma is correlated with the duration of anesthesia and surgery. Pre-anesthetic drug administration evidently was not implicated in the CK alterations observed.

In some individuals, who appear to be genetically susceptible, muscle injury, manifested by increased CK activity in plasma, has been observed in the malignant hyperthermia syndrome during anesthesia with halogenated agents, or after the administration

Table 2. Effect of Halothane and Succinylcholine on Plasma CK 24 h after Surgery in Patients with Normal or Elevated Pre-Operative Plasma CK Activity

<table>
<thead>
<tr>
<th>Pre-operative CK</th>
<th>Drug</th>
<th>No.</th>
<th>CK normal no. (%)</th>
<th>CK elevated no. (%)</th>
<th>CK mean</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (0-20)</td>
<td>+ halothane</td>
<td>172</td>
<td>60 (34.9%)</td>
<td>112 (65.1%)</td>
<td>42.1</td>
<td>0.022</td>
</tr>
<tr>
<td></td>
<td>— halothane</td>
<td>117</td>
<td>49 (41.9%)</td>
<td>68 (58.1%)</td>
<td>50.3</td>
<td>N.S.</td>
</tr>
<tr>
<td></td>
<td>+ succinylcholine</td>
<td>168</td>
<td>52 (31.0%)</td>
<td>116 (69.0%)</td>
<td>62.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>— succinylcholine</td>
<td>121</td>
<td>57 (47.1%)</td>
<td>64 (52.9%)</td>
<td>52.5</td>
<td>N.S.</td>
</tr>
<tr>
<td>Elevated (20)</td>
<td>+ halothane</td>
<td>17</td>
<td>3 (17.6%)</td>
<td>14 (82.4%)</td>
<td>66.3</td>
<td>N.S.</td>
</tr>
<tr>
<td></td>
<td>— halothane</td>
<td>17</td>
<td>2 (11.8%)</td>
<td>15 (88.2%)</td>
<td>78.9</td>
<td>N.S.</td>
</tr>
<tr>
<td></td>
<td>+ succinylcholine</td>
<td>23</td>
<td>3 (13.0%)</td>
<td>20 (87.0%)</td>
<td>70.6</td>
<td>N.S.</td>
</tr>
<tr>
<td></td>
<td>— succinylcholine</td>
<td>11</td>
<td>2 (18.2%)</td>
<td>9 (81.8%)</td>
<td>76.6</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

N.S.: not significant.
of depolarizing neuromuscular blockers, or both (6). Abnormal resting CK values have been observed in some susceptible patients (7). As a result, there has been much interest in the potential value of pre-operative CK determination as a screening test for susceptibility to the malignant hyperthermia syndrome (8, 9). Elevated CK activity in pre-operative plasma specimens of 9% of our patients did not presage the development of significant muscle damage or the malignant hyperthermia syndrome in these patients. Strenuous exercise, alcoholic myopathy, cardiovascular disease, hypothyroidism, and schizophrenia have been associated with increased plasma CK activity (3), but these could not be implicated in this series of patients. Although unexplained elevations of plasma CK are found in some healthy children and adults, muscle trauma with release of enzyme after the administration of drugs by intramuscular injection has been described. Both the traumatic effects of the hypodermic needle and muscle injury associated with the specific drug administered may contribute to this phenomenon (10). Increased CK values have also been attributed to oral administration of other therapeutic agents (3). In the present study, we saw no evidence of pre-anesthesia drug-induced CK elevation.

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References


