At our mother’s knee – an occasional review

Serum creatine kinase after intramuscular injections

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Summary: Serum creatine kinase (CK) activity was measured after intramuscular injections in 44 patients hospitalized for non-cardiac reasons. The drugs injected were: diazepam, dipyrone, metoclopramide, meperidine, pentazocine and procaine penicillin. Only 3 out of 44 patients (7%) demonstrated significant elevation of CK levels following the intramuscular injections. In these 3 patients the elevation was mainly due to a rise of the MM-isoenzyme fraction with MB levels increased in one patient. These findings do not justify the common clinical notion of regarding intramuscular injections as a frequent cause of serum CK elevation. It is concluded that high CK serum values in a patient with chest pain should always be considered with utmost suspicion, disregarding the possible effects of a previous intramuscular injection.

Introduction

It is an accepted fact that a significant rise of serum creatine kinase (CK) activity may follow intramuscular (i.m.) injections (Braunwald & Alpert, 1983; Hurst, 1982; Nevins et al., 1973). This can lead to the erroneous diagnosis of myocardial infarction in a patient who has been given an i.m. injection for chest pain of non-cardiac origin.

Although various drugs have been reported to cause an increase in serum CK there is not enough information available to predict when and in what pattern a given i.m. injection will result in CK elevation (Cohen, 1972; Meltzer et al., 1970; Nevins et al., 1973). This study was undertaken to investigate the frequency and kinetics of serum CK elevation following intramuscular administration of drugs commonly used in patients admitted for chest pain. Our observations indicate that significant elevation of serum CK after i.m. injections in a common clinical setting is rare.

Materials and methods

Forty-four adult patients (23 male and 21 female, age 40–75 y) who were hospitalized in a medical ward for non-cardiac reasons, were selected for the study. Only patients who had baseline CK values within the normal range (males <137 IU/l, females <118 IU/l), as measured less than 24 h before the injection, were included. All patients who were excluded because of high baseline values were found to have an obvious cause for the elevated CK activity (other than i.m. injections). An informed consent was obtained from all participants. Each patient received a single i.m. injection of one of the following drugs in a gluteal muscle: diazepam (Valium®), dipyrone (Optalgin®), metoclopramide (Pramine®), pethidine, pentazocine (Talwin®) and procaine penicillin. These drugs were chosen because of their frequent intramuscular use in patients complaining of chest discomfort – not necessarily of cardiac origin. The doses and volumes of the injections are shown in Table 1. The injections were

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>5 mg</td>
<td>1</td>
</tr>
<tr>
<td>Dipyrone</td>
<td>1 g</td>
<td>2</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>10 mg</td>
<td>2</td>
</tr>
<tr>
<td>Pethidine</td>
<td>75 mg</td>
<td>1.5</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>30 mg</td>
<td>2</td>
</tr>
<tr>
<td>Procaine penicillin</td>
<td>$1.2 \times 10^4$U</td>
<td>4.5</td>
</tr>
</tbody>
</table>

Table 1 Intramuscular injections given

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administered with a 21-gauge needle by an experienced nurse. No subsequent i.m. injections were given to the subjects for at least 3 days. Simultaneous myocardial injury was excluded in all patients by a daily clinical and electrocardiographic evaluation.

Serum CK activity was measured at 1, 6, 12, 24, 48, and 72 h after the injection. A u.v.-method was used employing a glutathione activated BMC-kit (‘CPK-activated No. 124184’) with creatine phosphate as substrate (Forster et al., 1974). The measurements were done using a Gemssecentrifugal analyser (Electronucleonics) at 37°C. Daily quality control was maintained using BMC Precinorm and Precipath assayed controls. For serum samples (stored at −18°C) with elevated CK activity an electrophoretic measurement of CK-isoenzymes was subsequently performed (on cellulose acetate), applying the Helena CK isoenzyme electrophoresis procedure based on the method reported by Trainer & Gruenig (1968).

Results

The incidence of increased CK activity after the injections is shown in Table II. Only 3 out of the 44 patients had elevation of serum CK above normal during the follow-up period of 72 h. These subjects had received diazepam, dipyrone or penicillin. Table III summarizes the total CK and CK-isoenzymes for these patients. The serum CK activities for all other patients are shown in Table IV.

In all instances the increase of CK activity was primarily due to elevation of the MM-isoenzyme fraction, although one patient (after dipyrone) who had the highest total CK activity also had a rise of the MB-fraction above normal (<151 IU/l). No elevation of the BB-fraction was observed.

The injections that did raise CK were not found to have any specific common denominator, such as pH, osmolality, volume or a particular solvent.

Discussion

Previous studies have documented elevation of serum CK activity following i.m. injections (Knirsch & Gralla, 1970; Meltzer et al., 1970; Sidell et al., 1974). The incidence of this association has been reported to be 45% or more after drugs that included chlorpromazine, barbiturates, atropine, diazepam, chlor-diazepoxide, pralidoxime chloride, digoxin, frusemide, ampicillin, carbenicillin, morphine, pethidine, dexamethasone, nandrolone decanoate and normal saline (Greenblatt et al., 1973; Nevins et al., 1973; Ma et al., 1981; Meltzer et al., 1970). These reports have led authors of textbooks on internal medicine (Braunwald & Alpert, 1983), cardiology (Hurst, 1982) and others (Cacace, 1972) to conclude that i.m. injections are an important cause of serum CK elevation. The aim of this study was to evaluate prospectively the incidence and pattern of CK elevation following i.m. injections.

Table II  Number of patients with elevated CK following i.m. injections

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of patients</th>
<th>No. with elevated CK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Dipyrone</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Pethidine/pentazocine</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Penicillin</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>44</td>
<td>3</td>
</tr>
</tbody>
</table>

Table III  Sequential results of 3 patients with elevated total CK values

<table>
<thead>
<tr>
<th>Drug</th>
<th>Baseline</th>
<th>1 h</th>
<th>6 h</th>
<th>12 h</th>
<th>24 h</th>
<th>48 h</th>
<th>72 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dipyrene (BB, MB, MM)</td>
<td>66* (-9,58)†</td>
<td>88 (-14,74)</td>
<td>209 (-21,188)</td>
<td>236 (-28,208)</td>
<td>179 (-39,140)</td>
<td>112 (-17,95)</td>
<td>66 (-9,57)</td>
</tr>
<tr>
<td>Diazepam (BB, MB, MM)</td>
<td>36* (-36)†</td>
<td>72 (-72)</td>
<td>167 (-167)</td>
<td>n.p.</td>
<td>139 (-13,126)</td>
<td>127 (-127)</td>
<td>81 (-5,66)</td>
</tr>
<tr>
<td>Penicillin (BB, MB, MM)</td>
<td>52* (-6,46)†</td>
<td>103 (-12,91)</td>
<td>115 (-15,100)</td>
<td>148 (-13,135)</td>
<td>104 (-104)</td>
<td>74 (-7,67)</td>
<td>54 (-10,44)</td>
</tr>
</tbody>
</table>

*Total CK (normal: males < 137, females < 118).
†Total CK (normal: BB = 0, MB < 15, MM < 137).
All values are in international units (IU/l).

n.p.: not performed.
in a common clinical setting. We observed increased serum CK activity in only 3 out of 44 patients, each of whom received a different drug.

Most previous investigations have involved young healthy volunteers or laboratory animals (Sidell et al., 1974; Klein et al., 1973). We studied patients hospitalized in a medical ward with ages ranging from 40 to 75 y for whom the prompt and correct diagnosis of myocardial injury is of major clinical importance. The older age and the smaller muscle mass in this age group may explain why the incidence and amount of CK elevation was found to be significantly lower in our study. There are also other variables that could account for the differing results, such as the chemical composition, dose, volume and concentration of the drugs injected (Sidell et al., 1974). However, we tried to solve the common diagnostic problem of a patient in a medical ward with chest pain who has received an i.m. injection on admission or before the correct diagnosis has been made. This study involves an adult patient population with drugs and doses common to everyday clinical practice, leading us to conclude that elevation of CK following i.m. injection in these specific circumstances, which are of clinical interest, is rare.

The increased CK activity in our 3 subjects was primarily caused by a rise of the MM-isoenzyme fraction. However, in one subject a significant associated rise of the MB-fraction was seen. This observation is consistent with reports from previous studies (Ma et al., 1981), and with increased serum CK-MB activity reported in other situations compatible with skeletal muscle injury, such as marathon running (Apple et al., 1984). Although ours is a small sample, the observation indicates that measurement of CK isoenzymes to differentiate between myocardial or skeletal origin in the above circumstances may be of limited practical value. This is a point which calls for further investigation.

It is concluded that elevated serum CK values in a patient with chest pain should always be considered with utmost suspicion, disregarding the possible effects of a previous i.m. injection.

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References

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