FAILURE OF METHYLPREDNISOLONE TO PROTECT LEAD-SENSITIZED RATS AGAINST ENDOTOXIN

Robert B. Jones, et al

Naval Medical Research Institute
Bethesda, Maryland

27 June 1973
DISCLAIMER NOTICE

THIS DOCUMENT IS BEST QUALITY AVAILABLE. THE COPY FURNISHED TO DTIC CONTAINED A SIGNIFICANT NUMBER OF PAGES WHICH DO NOT REPRODUCE LEGIBLY.
RESEARCH INSTITUTE, W., 2001

Title: METHODS TO PROTECT LEAD-SENSITIZED RATS AGAINST INFECTION

PROGRAM: S. L. Will, and Lutz K. Riesow

PREPARED UNDER

Report No. 1

A. STATEMENT OF THE PROBLEM

B. FOUNDATION STATEMENT

C. CONTRIBUTION NOTES

D. SPONSORING MILITARY ACTIVITY

E. SUMMARY

Doses of lead acetate, in doses that protect normal rats against lead poisoning, were administered to lead-sensitized rats. These rats were then exposed to a lethal dose of virus, and it was found that the protection against the lethal effects was significantly increased when lead acetate was administered in combination with the virus. This result suggests that the lead acetate may be effective in protecting against the toxic effects of lead acetate, even in cases where the lead acetate has previously been administered alone.
<table>
<thead>
<tr>
<th>KEY WORDS</th>
<th>LINK A</th>
<th>LINK B</th>
<th>LINK C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. METHYLPREDNISOLONE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. LEAD-SENSITIZED</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. RATS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. ENDOTOXIN</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Failure of Methylprednisolone to Protect Lead-Sensitized Rats Against Endotoxin

ROBERT B. JONES, JAMES L. WISE, AND LUTZ A. KEOW

Experimental Medicine Division, Naval Medical Research Institute, Bethesda, Maryland 20014

Received for publication 27 June 1974

Methylprednisolone, in doses that protect normal rats against endotoxin, has no effect in lead-sensitized rats.

The administration of lead acetate (PbAc₂) sensitizes both rats (7) and subhuman primates (4) to minute amounts of bacterial endotoxin. The mechanism of this sensitization has not been defined, although it has been suggested that alterations in either the degradation of endotoxin (8), or in carbohydrate metabolism (3, 4), may be important. Glucocorticoids are demonstrably effective in protecting normal animals against endotoxin (1, 5). The purpose of the present investigation was to determine if this was also the case in lead-sensitized animals.

Under light ether anesthesia, femoral cut-downs were performed on male Sprague-Dawley rats weighing 180 to 220 g, and an intravenous injection of 20 mg of PbAc₂ dissolved in 0.5 ml of deionized water given. This was immediately followed by an injection of 0.5 ml of Serratia marcescens endotoxin (Difco Laboratories) suspended in 0.15 M NaCl buffered to pH 7.4 with 0.02 M sodium phosphate (PBS), after which 37,000 times more sensitive to endotoxin, the methylprednisolone was without any effect.

As can be seen from Table 1, methylprednisolone was quite effective in protecting non-lead-treated rats, a single injection causing a fivefold increase in the mean lethal dose. However, in the lead-treated rats, which were approximately 37,000 times more sensitive to endotoxin, the methylprednisolone was without any effect.

This failure of a potent glucocorticoid to protect lead-sensitized rats against endotoxin suggests that lead may produce important qualitative, as well as quantitative, differences in the response of an animal to endotoxin. Furthermore, it would seem to indicate that under certain circumstances the efficacy of steroids in the treatment of septic shock may be a function of other, seemingly unrelated, factors.

We gratefully acknowledge the excellent technical assistance of Stanley Shapiro. This work was supported by the Bureau of Medicine and Surgery, Navy Department Subtask MR011.0001.002.0006.

LITERATURE CITED


TABLE 1. Effect of lead acetate and methylprednisolone on endotoxin lethality in rats

<table>
<thead>
<tr>
<th>Lead acetate (mg/kg)</th>
<th>Methylprednisolone (mg/kg)</th>
<th>No. of animals</th>
<th>Endotoxin LD₅₀* (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>-</td>
<td>65</td>
<td>16.5</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>64</td>
<td>(11.6-23.6)*</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>152</td>
<td>82.7</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>178</td>
<td>(66.4-102.9)</td>
</tr>
</tbody>
</table>

* Body weight.
* Abbreviation: LD₅₀, mean lethal dose.
* Numbers in parenthesis are the 95% confidence limits for each LD₅₀.


