Absorption and Excretion of Pralidoxime in Man after Intramuscular Injection of PAM-2CL and Various Cholinolytics

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Summary. A dose of 1.0 g (10.0—14.0 mg/kg body weight) of pralidoxime mixed with various cholinolytics was given by i.m. injection to 29 healthy male subjects. A concentration of pralidoxime in blood of 4 μg/ml was reached after 5 to 10 min with all the mixtures and was maintained for about 1 to 2 h. The calculated half lives of pralidoxime in three groups of subjects were 62.2, 60.0 and 61.8 min., respectively. — The urinary excretions of pralidoxime during the first 4 h after the injections averaged 75.0, 79.6 and 69.6 per cent, respectively, of the total amount given. — The results are compared with published information about similar oximes.

Key words: Pralidoxime chloride, pharmacokinetics, anticholinesterase poisoning.

The effects of the acute administration of various salts of pralidoxime (iodide, chloride, methylsulphate, methane sulphonate) have been investigated extensively in normal man (Jager and Stagg, 1958; Jager et al., 1958; Sundwall, 1960 and 1962; Barkman et al., 1963; Calesnic et al., 1964 and 1967; Taylor et al., 1965; Kondritzer et al., 1968; Quinby, 1968; Sidell et al., 1969 and 1970; and Holland and White, 1971).

Due to its low solubility in water and the toxicity of the iodide ion — a 1 g dose would be equivalent to about 700 mg of sodium iodide — the iodide compound has been replaced by the corresponding methane sulphonate (Davies and Willey, 1958), and chloride (O’Leary, Kunkel and Jones, 1961). On the basis of its physiological compatibility, excellent water solubility, stability and content of oxime the chloride form should be the therapy of choice in the treatment of human anticholinesterase poisoning (Kondritzer, Ellin and Edberg, 1961).

The investigations of possible therapeutic and “prophylactic” treatments of experimental animal and human anticholinesterase poisoning have established that they are effective only if cholinesterase-reactivating oximes and cholinolytic drugs, usually atropine sulphate, are used (see comprehensive review in Koelle, 1963). In recent years animal experiments have shown that the combination pralidoxime-atropine-benactyzine, given as a single mixed intramuscular injection, is superior in several respects to the combination pralidoxime-atropine as an antidote for organophosphate poisoning (Kreicer, 1967; Jović and Vojvodić, 1971).

The object of the present study was to establish the feasibility of this combined therapy and to observe its effects on the absorption rate, blood concentration and urinary excretion of the oxime.

Methods

The investigations were performed in twenty-nine healthy male volunteers, aged 25 to 45 years. The mean body-weight was 78 ± 8 kg (mean ± SE). All the subjects underwent thorough physical examination and routine blood and urine analyses beforehand. They were told that they would participate in a study of an effective antidote for anticholinesterase poisoning. The test procedures were described to them, including the necessity for multiple venipunctures. They were also informed that they might possibly develop certain symptoms, although these were left unspecified.

The volunteers were divided into three groups:

The first group of twelve subjects received an intramuscular injection of:

- Pralidoxime chloride 1.0 g
- Atropine sulphate 0.002 g
- Benactyzine hydrochloride 0.003 g

The second group of twelve subjects received an intramuscular injection of:

- Pralidoxime chloride 1.0 g
- Benactyzine hydrochloride 0.01 g

The third group of five subjects received an intramuscular injection of:

- Pralidoxime chloride 1.0 g.
All the injections were performed by a "double blind" test procedure.

The pralidoxime chloride used was synthesized by M. Milojević, ITMZ, Belgrade. Atropine and benactyzine were obtained from commercial sources. The different mixtures were autoclaved at 120°C for 30 min, freeze-dried and stored in powder form in sterile rubber capped flasks (Maksimović and Vojvodić, 1972). The content of a flask was dissolved in 2 ml of isotonic saline immediately before use.

Immediately after collection whole blood and urine were analyzed for their oxime content by the method of Creasy and Green (1959) as modified by Maksimović and Vojvodić (1969). For determination of pralidoxime in urine, the subject was asked to empty his bladder completely before drug administration and at 30 min intervals for the next 4 h. Twenty-four hours after the injection an additional urine sample was collected. Before an injection and 60 to 120 min afterwards, each subject drank 100ml of tea to ensure a reasonable urine flow.

Results

A. Blood levels and time course of pralidoxime excretion

The administration of pralidoxime alone (Group 3) and in combination with the cholinolytics (Groups 1 and 2) gave identical results. Fig. 1 can be regarded, therefore, as typical of the dynamics of absorption and elimination of the oxime from blood.

After reaching a maximum the concentration of pralidoxime in blood then fell fairly slowly, and 3 h after the injection the blood level of oxime was still 1—2 µg/ml.

Calculation of the velocity constant (k) characterizing drug-elimination rate from the bloodstream to urine (Martin, 1962) showed for the first group that k was $1.114 \times 10^{-2}$ min$^{-1}$, for the second group $1.154 \times 10^{-2}$ min$^{-1}$, and for the third group $1.120 \times 10^{-2}$ min$^{-1}$, respectively. The corresponding half lives ($t_{1/2}$) were: 62.2, 60.0 and 61.8 min, respectively.

B. Urinary excretion of pralidoxime

There were no significant differences between the three groups in the pattern of urinary excretion of pralidoxime, so Fig. 2, which represents excretion

Table 1. Mean excretion of pralidoxime in the urine in the first four hours after its i.m. injection in different mixtures

<table>
<thead>
<tr>
<th>Group and mixture</th>
<th>Total oxime excreted in 4 h (mg/ml; mean ± SE)</th>
<th>Total volume of urine produced during 4 h (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. PAM-2C1</td>
<td>16.53 ± 4.30</td>
<td>454 ± 56</td>
</tr>
<tr>
<td>Atropine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benactyzine</td>
<td>17.09 ± 4.14</td>
<td>466 ± 83</td>
</tr>
<tr>
<td>II. PAM-2C1</td>
<td>16.35 ± 2.88</td>
<td>426 ± 68</td>
</tr>
<tr>
<td>Benactyzine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III. PAM-2C1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

after pralidoxime alone (Group 3) can be taken as representative of all subjects. The peak urine level of oxime of 2—3 mg/ml, was reached 45 min after injection, and remained at the same level for 2 h in all the groups.

After this time the concentration of oxime fell slowly, and four hours afterwards it was still between 1—2 mg/ml of urine. Pralidoxime chloride