Study on Pharmacological Action of Carzinophilin

by

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Introductory

Among the latest cncostatic preparations there are known Thio-TEPA¹, ², ³, ⁴ and nitromin of nitrogen mustard preparation. TAMURA⁵ of the Department of Pharmacology, Nihon University School of Dentistry has already reported on the pharmacological actions of carzinophilin on the respiratory system and blood pressure.

Though there have been a few researches, ⁶, ⁷, ⁸ on carzinophilin in the light of biological approaches the present study was undertaken in connection with its actions in terms of the ocular fundus bleeding and electrocardiogram.

Experimental Techniques and Materials

a. Experiment on the blood pressure and respiratory movement

Two (2) domesticated rabbits, each weighing around 2kg, were used for the experimental purpose. As for one, its A. carotis communis are connected with the mercury manometer and as for the other, its trachea was cut open and was connected with Marey's tambour. The carzinophilin solution was injected into their V. auricularis at a fixed rate and the changes in the blood pressure and respiratory movement as results were entered on the kymograph. Carzinophilin used is of Kyowa Fermentation Industry Co., Tokyo, Japan (Lot No. CA-101).

b. Determination of the ocular fundus pressure

The electrocardiogram used is the electronic sphygmo-tornometer manufactured by Japan Electronic Co., Tokyo, with the specimens placed in the non-pressure state anesthetized through the use of urethane.

Experimental Results

a. Action of Carzinophilin 3333.3 U/kg

Immediately following the injection of carzinophilin, a temporary excitation took place in the respiratory movement but it gradually subsided afterwards. The pressure in A. carotis communis showed a little descending curve later to be replaced with a rising tendency. However, these changes are thought negligible. The letters on the cymograph correspond to those on the registering paper, A indicating pre-administration of the drug and the injection was effected between B and C. The upper row shows the ocular fundus bleeding and the lower the electrocardiograph. The feeding speed per second was set at 6 cm.

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The black place on the graph indicates an abnormal rise in the pressure whereas the spotted place shows an abnormal decrease from the normal.

Immediately after the injection (at the point of B), though the cardiograph did not register it, there was observed a shortening or RR from time to time and at the point of C a large movement took place in the curve indicating the pressure in the A. carotis communis. Before and simultaneously with this occurrence an increase of irregular magnitude presented itself in the cardiographic curves. Numerals 1, 2 and 3 on D indicate these curve increments. Although they disappeared at the point of E, they reappeared at F after an interval of about four minutes following the injection (Fig 1).
b. Action of Carzinophilin 5333.3 U/kg

An excitation of temporary nature took place in the respiratory movement immediately after the injection but it came to be inhibited soon afterward. The injection of this amount started a constant rise in the pressure in the A. carotis communis. It is generally acknowledged that it is difficult to read an electrocardiograph taken of rabbits with attendant individual differences. Fig. 2 gives an instance of a rise in P (Fig. 2, P2).
Immediately after the injection a rise took place in R and when the curve of A. carotis communis pressure became more or less stable, the electrocardiograph was brought back to normalcy. Measurements were taken of the ocular fundus bleedings at certain stages of D and E but the changes were strikingly slight. Among these findings what is the most pronounced has been the rise of R which has effects upon the heart. This means that this amount of carzinophilin excites the cardiac movement (Fig. 2).

c. Action of Carzinophilin 6666.6 U/kg

The temporary excitation in respiration took place immediately after the injection of the drug. However, its inhibitory action was not so well noticed as in other cases. But, with reference to the pressure of A. carotis, the only change observed was in the downward direction. The fact that a decrease in the blood pressure already takes place at the point B is attributed to effects that are usually seen when a human hand touches the ears of a rabbit.

Although no changes were observed in the electrocardiogram, pronounced effects came to be seen from the points G to H at the time of A. carotis blood pressure determination (Fig. 3). The breakdown of these effects is as follows:

![Figure 3](image-url)
Former half of 1-P Rise
Latter half of 1-P Decrease
Former half of 2-T Decrease
Latter half of 3-P Decrease
Former half of 4-1 Rise
Latter half of 4-1 Decrease
Immediately before 5-Q Rise
Former half of 6-T Rise
Latter half of 6-T Decrease
Former half of S2 Rised
Latter half of S2 Decrease
At the point of S3 Decrease
Former half of 9-U Rise
Latter half of P-U Decrease
At the point of 14-Q Abnormal curve

Abnormal curves

Reference is made to Fig. 4. On Figs. 3 and 4 the identical changes were seen in common to 5 and 12, 7 and 15, 8, 10 and 11, and 9 and 13. The numerals on Fig. 3 give the order of changes appearing in G. Of them, the most frequent occurrences are between the points G and H.

<table>
<thead>
<tr>
<th>Points</th>
<th>Frequencies</th>
</tr>
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<tbody>
<tr>
<td>9.13</td>
<td>8 times</td>
</tr>
<tr>
<td>5.12</td>
<td>6 times</td>
</tr>
<tr>
<td>2</td>
<td>4 times</td>
</tr>
<tr>
<td>8.10</td>
<td>3 times</td>
</tr>
<tr>
<td>8.11</td>
<td>3 times</td>
</tr>
<tr>
<td>1, 3, 4 &amp; 7</td>
<td>2 times</td>
</tr>
<tr>
<td>6 &amp; 14</td>
<td>1 time</td>
</tr>
</tbody>
</table>

Fig. 4
Reference is made to Fig. 5.

As with the *A. carotis*, no practically pronounced changes have been observed in curves indicating the ocular fundus bleeding.

**Conclusions**

When injected into the rabbits anesthetized under urethane, carzinophilin did not show any effects in terms of the electrocardiography, *A. carotis* blood pressure, ocular fundus bleeding and respiratory movement anywhere from 3000–5000 U/kg. It was only at 6666 U/kg when the effects on the electrocardiogram became apparent. With reference to these effects, what was the most pronounced was at the point *U*. This may be due to the solution used for carzinophilin which contains bicarbonate natrium (0.02 g solution of this drug per 2 cc distilled water is used for 5000 units of carzinophilin). The reason for this is that *U* waves are greatly influenced by the ionic fluctuation of natrium. However, we still lack any conclusive means of determining whether it is due to bicarbonate natrium or carzinophilin itself, as the natrium is the only means known so far to dissolve carzinophilin with. What is used clinically is one with the alkaline solution and therefore it makes no sense when we consider about this matter isolating alkalinity from the rest. In addition to *U*, other minor changes have been observed at the points of *P, Q, S* and *T*. They mean that administration of any large amount of carzinophilin gives rise to some effects in certain parts of heart.

**References**

4) Koyama, K. et al.: Chemotherapy 4 (1956)