DURATION OF THE ANTICHOLINESTERASE EFFECT OF CERTAIN ORGANIC PHOSPHORUS COMPOUNDS

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It is now believed that organic phosphorus compounds cause irreversible and prolonged cholinesterase inactivation. This theory was formulated after the publication of the data of Mazur and Bodansky [6], showing that it takes 50 days for the cholinesterase activity of brain tissue to be restored 90% after the administration of diisopropyl fluorophosphate (DFP). These data suggest that new enzyme formation is responsible for the restoration of cholinesterase activity. A number of other organic phosphorus compounds were subsequently found to have a prolonged anticholinesterase effect. However, some of the experimental organic phosphorus compounds were found to have an anticholinesterase effect less durable than that of DFP. Kewitz [5], for example, demonstrated that the colinesterase activity of a mouse’s diaphragm is 90% restored the second day following the administration of phosphacol (Mintacol) in the LD₅₀ dose (this is not observed until the fifth day after DFP administration), while the cholinesterase activity of the brain is restored 60% after five days (restored 35% five days after DFP administration). Restoration of cholinesterase activity after the administration of tetraethyl pyrophosphate, parathion [3] Paraoxon [2] and hexaethyl pyrophosphate [1] is much quicker than after DFP administration.

On the basis of these data, Kewitz [5], Friedberg and Erdmann [3] proposed that considerable spontaneous cholinesterase reactivation may occur after the administration of such organic phosphorus compounds as Mintacol, parathion, Paraoxon, etc. and not after the administration of DFP, systox or isosystox.

We compared the duration of the inhibitory effects exerted by armine, phosarbin and DFP on the cholinesterase of the whole blood, brain (and spinal cord) and muscles of white mice.

EXPERIMENTAL METHODS

Experiments were performed on 20-40 male and female white mice of various weights and ages. The experimental preparation was injected subcutaneously in the maximal tolerance dose: 0.4 mg/kg for armine and phosarbin and 3 mg/kg for DFP. Cholinesterase activity was determined after 1, 2, 6 hrs and 1, 2, 3, 4 and more days after the preparation was administered – until the original levels were restored. We used the Plattend–Hestrin method [4], which determines the amount of acetylcholine remaining undestroyed after contact with the colinesterase source (i.e., the experimental tissue), to determine cholinesterase activity. The cholinesterase activity was expressed in the number of milligrams of acetylcholine destroyed after one hour per 1 g of tissue (Q Ch E). The cholinesterase activity of the whole blood, brain, spinal cord and muscles was determined. Since cholinesterase activity fluctuates considerably under normal conditions, we first established the normal level in each different series of experiments.

EXPERIMENTAL RESULTS

The duration of armine’s anticholinesterase effect was studied in three identical series of experiments. The results of these investigations are summed up in Fig. 1. Very acute depression of the enzyme’s activity was observed after the administration of the 0.4 mg/kg dose of armine. Only one day after its administration, however, the cholinesterase activity of the blood was almost completely restored, the original level being reinstated after two days. Although restoration of the cholinesterase activity of the brain and spinal cord tissue began six hours after the injection, it was considerably slower; cholinesterase activity returned to the normal level seven to nine days after the armine injection. In the muscles, cholinesterase activity was less depressed and rapidly restored, the normal enzymatic activity being observed after two or three days.
Only one hour after the phosarbin injection, acute depression of the cholinesterase activity of the experimental tissues was observed; considerable restoration of cholinesterase activity was observed, however, towards the end of the first day in the blood and after two days in the brain and spinal cord. Although individual fluctuations of 7-12 days were observed, complete restoration of the activity usually occurred 12 days after the injection (Fig. 2).

Concurrent experiments were conducted with DFP in order to compare the duration of the effects of armine and phosarbin with the duration of the effect induced by this well-studied preparation. The results obtained (Fig. 3) are in full accord with the data obtained by Mazur and Bodansky in their study of the duration of DFP's anticholinesterase effect on rabbits. The activity of the blood was restored towards the end of the first week after DFP administration. It took one month for the cholinesterase activity of the brain to be restored approximately 80% and two months for the total restoration of this index.

Comparison of the speed with which cholinesterase activity is restored after the injection of armine, phosarbin and DFP showed some differences. After the injection of armine or phosarbin, it took two days for restoration of the original cholinesterase activity of the blood and 7-12 days for that of the brain. DFP-induced cholinesterase inhibition lasted considerably longer: the cholinesterase activity of the blood was restored after a week, while that of the brain did not return to the original level until more than a month after administration of the preparation. One can therefore propose that there are differences in the mechanism of the inhibitory effects exerted by the experimental compounds. If it is true that DFP effects irreversible cholinesterase inhibition with no spontaneous reactivation possible, it is hardly possible for the latter to occur under the influence of armine and phosarbin. Restoration of cholinesterase activity within as short a time as two to seven days can scarcely be ascribed wholly to the forma-