Influence of General Anesthesia on Acute Experimental Poisoning of Cats with the Organophosphorus Pesticide Anthio

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UDC 615.285.7.099].015.2.076.7

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 117, № 6, pp. 587-590, June, 1994
Original article submitted December 29, 1993

It is shown that general anesthesia strongly influences the resistance of animals to poisoning with organophosphorus compounds (OPC) such as Anthio, weakens compensatory/adaptive responses, and possibly acts synergistically with OPC in impairing tissue respiration. One to three days after peroral administration of Anthio, reduced oxygen tension in arterial blood and increased heart and respiratory rates were recorded in cats, although the arterial blood pressure tended to drop markedly. Anthio poisoning led to profound changes in the autonomic regulation of functions, which was manifested in sharply decreased parasympathetic influences. The function of the brain's GABA-ergic system did not change appreciably.

Key Words: *cats; anesthesia; organophosphorus compounds; acute poisoning; Anthio pesticide*

We found previously that almost all cats die 2-3 h after their acute experimental poisoning in the pentobarbital-anesthetized state with the organophosphorus pesticide Anthio given *per os* in a dose equal to 20% of its LD_{50} value [15]. Such an effect of Anthio is not consistent with what is known about the systemic toxicity displayed by it at this dose level and raises the question of the role pentobarbital anesthesia might play in aggravating the adverse effects of acute experimental poisoning.

The present study was designed to examine the impact of pentobarbital anesthesia on major parameters of respiration and systemic circulation several days after peroral administration of Anthio to alert cats in the dose indicated above. In such cats we also evaluated the effect of atropine, which is usually employed in cases of poisoning with cholinesterase blockers, as well as the effect from the activation of the GABA-ergic system, which is closely associated with the cholinergic system [12].

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MATERIALS AND METHODS

The experiments were conducted on 7 random-bred adult cats of both sexes weighing 2.2-2.8 kg. Under mild ether anesthesia, the animals were administered intragastrically, via a catheter, the organophosphorus pesticide Anthio (Formothion, Sandoz) in the form of an emulsion in a dose of 1/5 of the LD_{50}, after which the ether supply was discontinued. Several days later, the cats were anesthetized with sodium pentobarbital (40 mg/kg intraperitoneally) and prepared for examination. Details of this preparation and of the procedures used to measure parameters of respiration, systemic hemodynamics, and arterial blood are described in our previous article [15]. Five cats were injected intravenously with atropine (0.5 mg/kg) and with

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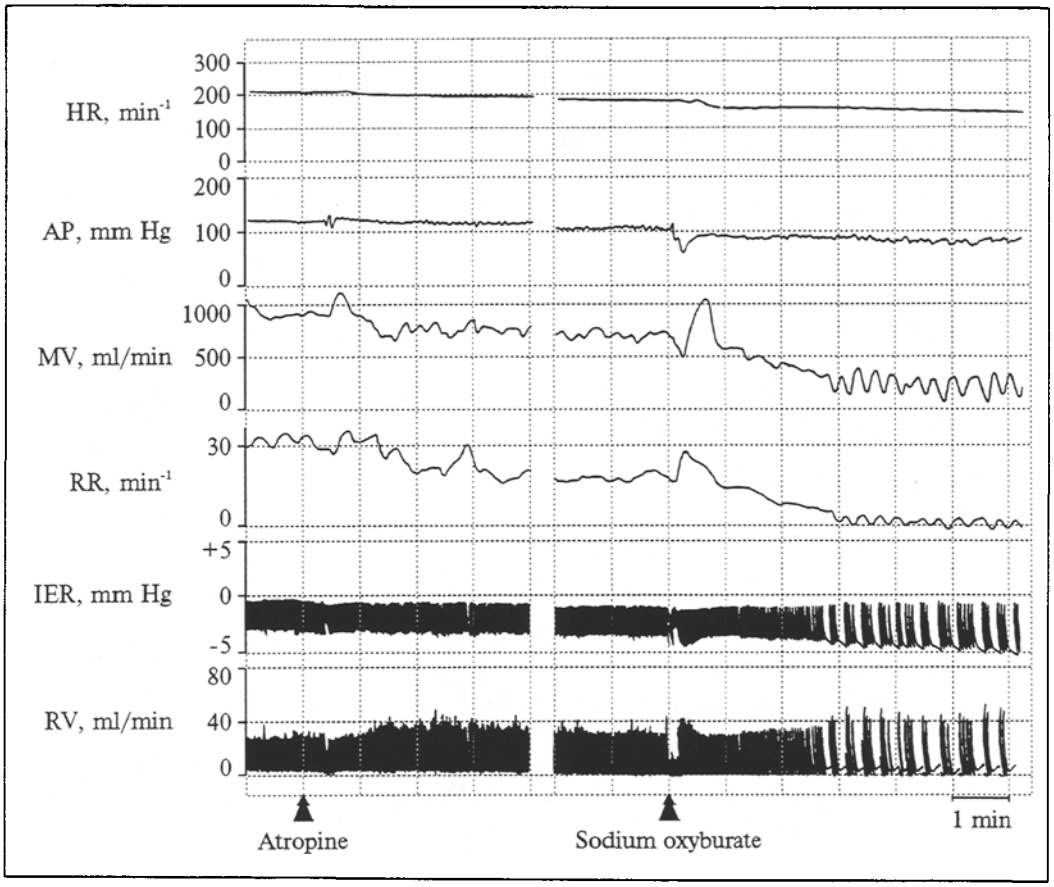

Fig. 1. Effects of intravenously injected atropine and sodium oxybutyrate on parameters of systemic hemodynamics and external respiration in a cat poisoned with Anthio. The times of injection are indicated by arrows. *HR*: heart rate; *AP*: mean arterial pressure in the greater circulation; *MV*: minute volume; *RR*: respiratory rate; *IEP*: intraesophageal pressure; *RV*: respiratory volume.

sodium oxybutyrate (200 mg/kg) 40-60 min after atropine. The results were treated statistically using Student's t test. Differences between the groups were considered to be significant at $p<0.05$.

RESULTS

First of all, it should be noted that the mode of Anthio administration we used did not result in massive mortality of the animals [15], so that one of the cats could be observed up to day 7 after the poisoning. It was also found that as early as on day 4 after Anthio poisoning, respiratory and circulatory parameters in the test cats virtually did not differ from those in the control group (the latter comprised pentobarbital-anesthetized cats from our previous acute toxicity study before their dosing with Anthio). For this reason, the various parameters were recorded in the test group 1 to 3 days after Anthio administration (Table 1). The nonanesthetized cats tolerated the acute poisoning relatively well, so that most of the parameters approached their control values after a few days. This may be interpreted as evidence that the Anthio-induced disturbances of the respiratory and cardiovascular systems were successfully compensated in the alert animals. Our studies indicate that pentobarbital anesthesia inhibits the development of compensatory/adaptive responses in animals exposed to Anthio (and possibly also in those exposed to other organophosphorus compounds) and/or acts synergistically with the pesticide in promoting impairment of tissue respiration [3,13,16].

It can be seen in Table 1 that the parameters of respiration, greater circulation, and arterial blood measured in cats 1 to 3 days after their dosing with Anthio were close to the control values, with a few exceptions. Thus, the heart and respiratory rates were increased, but the mean arterial pressure was markedly lowered ($0.1<p<0.05$). Of considerable importance, in our view, was the finding that oxygen tension in the arterial blood (pO_2) was significantly lower than in the control group, while carbon dioxide tension (pCO_2) was very close to the control value. This may be interpreted as a sign of slowed oxygen diffusion from the lungs to the arterial blood as a consequence of the somewhat decreased permeability of the blood-gas barrier. As the diffusion capacity of carbon dioxide is much greater than that of oxygen, a moderately slowed diffusion of gases through pulmonary tissues should affect primarily the pO_2. We believe also that the moderate impairment of pulmonary function we observed in cats exposed to

Anthio in the wakeful state and the resulting arterial hypoxemia are factors contributing to the development of a persistent and difficult-to-treat pneumonia in persons poisoned with OPC [1,2,5, 6,8,9,11]. It is logical to suppose that the reduction in pO_2 following Anthio poisoning will exert on the body a long-term stimulatory influence which may result in increased frequencies of respiratory movements and cardiac contractions, as was observed in our experiments with cats.

As seen in the table, the control and test groups of cats differed significantly in the values of Querdot's autonomic index (QAI) [4]. It is of interest to note that the change in this index recorded in anesthetized cats several hours after Anthio poisoning [15] was the opposite of that registered in "chronic" cats 1 to 3 days after poisoning with the pesticide (this study). The decrease in QAI several days after dosing with Anthio (in chronic experiments) may be regarded as a sign of increased parasympathetic influences on cardiac activity, which, however, is at odds with the increased heart rate in these animals and with the failure of their heart rate to respond to atropine (see below). This discrepancy may be explained by the reduced stroke volume recorded in cats exposed to Anthio in the wakeful state [10], which could be a consequence of energy-related disturbances in myocardial activity, since OPC are capable of disrupting mitochondrial respiration [3,13].

Measurements of the activity of respiratory muscles (diaphragm, intercostal muscles, and abdominal muscles) showed that as early as 24 h after Anthio administration the electromyographic activity of expiratory muscles was fairly well marked (as compared to that in Anthio-exposed anesthetized cats [15]), and that the overall activity of the main respiratory muscles closely resembled that in the control animals. Hence, no disturbances of the pattern of electrical activity were found one day after the administration of Anthio to alert animals.

To evaluate the state of the cholinergic system in Anthio-intoxicated cats as well as of their GABA-ergic system, which is closely linked with the cholinergic system functionally [12], we used atropine and sodium oxybutyrate, respectively, which were both injected by vein. Atropine and other cholinolytics are frequently used in cases of OPC poisoning to relieve the load on cholinergic synapses under conditions of inhibited cholinesterase activity. Sodium oxybutyrate is an effective agent acting upon the brain's GABA-ergic system, which plays an important role in the functioning of the respiratory center. The results of this part of our study, shown in Table 1 and Fig. 1, indicate that atropine did not affect the heart rate in cats that had received Anthio 1-3 days before in the wakeful state. This suggests a virtual absence of the parasympathetic tonus. The only parameter that was altered significantly by atropine was the respiratory volume, which increased, but the increase was counteracted by the tendency toward a reduced respiratory rate. These findings are indicative of profound changes in the autonomic nervous system in Anthio poisoning, but it is difficult to

TABLE 1. Parameters of Respiration, Systemic Circulation, and Arterial Blood in Cats Exposed to Anthio and to Anthio and Atropine ($M \pm m$)

Parameter	Control (n=13)	Anthio (n=5)	Atropine, 5 min after Anthio (n=5)
MV, ml/min	759±84	811±76	813±92
RV, ml	23.8±1.6	21.4±0.7	31.2±3.1^{+}
RR, cycles/min	27.0±2.1	38.4±2.7**	30.2±3.9
HR, cycles/min	236.7±7.1	260.4±6.8*	260.8±6.6
AP, mm Hg	125.9±5.8	113.0±3.0*	112.6±1.7
QAI	53.1±1.8	37.7±1.7***	–
pHa	7.288±0.023	7.325±0.028	–
$PaCO_2$, mm Hg	29.4±1.2	29.2±0.8	–
PaO_2, mm Hg	86.2±2.3	76.8±1.1***	–
SaO_2, %	94.7±0.4	93.7±0.7	–
SBB, mmol/liter	−11.5±0.9	−9.5±1.3	–

Note. The asterisks denote differences between group 1 (control) and group 2 (Anthio): $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.002$, $^{****}p<0.001$; the cross denotes a significant difference between group 2 and group 3 (Anthio + atropine) ($p<0.02$). *MV*: minute volume; *RV*: respiratory volume; *RF*: respiratory frequency; *HR*: heart rate; *AP*: mean arterial pressure in the greater circulation; *QAI*: Querdot's autonomic index; *pHa*: reaction of arterial blood; pCO_2 and pO_2: carbon dioxide and oxygen tensions in arterial blood; SaO_2: saturation of arterial blood hemoglobin with oxygen; *SBB*: shift of buffer bases.

ascertain whether such changes are pathological or compensatory/adaptive.

The state of the GABA-ergic system was evaluated in qualitative terms - by comparing changes in the respiratory pattern and concomitant alterations in systemic hemodynamics in the test cats with those respiratory and circulatory changes which we had studied in detail in our laboratory on animal models of pathological types of respiration [7,14]. This comparison showed that the activation of the GABA-ergic system that occurred in the cats 1 to 3 days after their dosing with Anthio caused respiratory and circulatory changes similar in character to those observed in normal animals, such as the appearance of apneic respiration with prolonged breath holding at inspiration [7]. Such a similarity indicates that Anthio poisoning does not appreciably affect the function of the brain's GABA-ergic system in cats.

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