FURTHER STUDIES OF THE INFLUENCE OF CARBON DIOXIDE ON
NEUROMUSCULAR BLOCKING AGENTS IN THE CAT*

BY

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It has been previously established that the activity
of the common neuromuscular blocking agents in
the cat is modified by the administration of
carbon dioxide. It was found that carbon dioxide
opposed the action of suxamethonium, decameth-
onium and gallamine, but enhanced the activity
of tubocurarine (Payne, 1958). This effect has
not been fully explained and it was thought that
the examination of other less common relaxants
under the same circumstances might prove help-
ful in determining the mode of action. Accord-
ingly two drugs once in clinical use, benzoquin-
onium (Mytolon) and laudexium (Laudolissin)
as well as two new tropane derivatives D.F.596
and D.F.648 (Haining et al., 1959), still under-
going trial, were investigated.

METHOD

The sciatic nerve-anterior tibialis muscle prepara-
tion in the intact cat (Brown, 1938) was used to
study the effects of the drugs in the presence of
5 per cent carbon dioxide. A detailed description
of the method employed has been published
previously (Payne, 1958). The drugs were ad-
ministered by the divided dose technique recom-
manded by Paton (personal communication) and
described elsewhere (Payne and Rowe, 1957). In
a series of eleven cats, the effect of benzoquin-
onium was studied in two, while the actions of
laudexium, D.F.596 and D.F.648 were investi-
gated in three each. In the study of the tropane
derivatives soleus muscle activity was also
examined.

RESULTS

Benzoquinonium.

In the two cats studied, the administration of
5 per cent carbon dioxide antagonized the neu-
romuscular blocking properties of benzoquinonium
as shown in figure 1. From the same figure it
can be seen that this antagonism developed des-
pite a 20 per cent reduction in the size of the
muscle twitch during the administration of car-
bondioxide before the drug was injected. It is
also obvious that, although the neuromuscular
block was less effective under the influence of
carbon dioxide, the recovery process was slower.

Laudexium.

The influence of carbon dioxide on laudexium
was investigated in three cats, in none of which
was there any evidence of either antagonism or
enhancement. In one, however, there was a
slight delay in the recovery time of the muscle
twitch during the administration of carbon
dioxide (fig. 2).

D.F.596.

In the three cats given D.F.596 there was
definite evidence of an enhanced effect of the
drug on both the anterior tibialis and soleus
activity in the presence of 5 per cent carbon
dioxide (fig. 3). Again it was noted that when
the drug was used during the administration of
carbon dioxide, the development of neuromus-
cular block was more gradual and the recovery
process slower than during the control period.

D.F.648.

The influence of carbon dioxide on D.F.648
followed closely the pattern established for
D.F.596. In the three animals studied the en-
hanced effect in the presence of carbon dioxide
was unequivocal (fig. 4).

When the tropane derivatives were used to
obtain neuromuscular block, the anterior tibialis
was considerably more sensitive to their action
than was soleus (figs. 3 and 4).

*Work done in the Pharmacological Department,
Royal College of Surgeons of England.
Sciatic nerve—tibialis anterior muscle preparation in the intact cat. The tracings show the development of resistance to the action of benzoquinonium on exposure to carbon dioxide with subsequent return of the normal response when carbon dioxide is withdrawn. Note (a) the reduction in size of the muscle twitch and (b) the more prolonged recovery time during exposure to carbon dioxide.

**DISCUSSION**

The weak action of benzoquinonium in the presence of carbon dioxide supports the earlier impression that most relaxants are antagonized by this gas, but the demonstration of an increase in the neuromuscular blocking activity of the tropane derivatives when carbon dioxide is inhaled has only added to the difficulties of interpretation. Two other drugs, mecamylamine and d-tubocurarine chloride, the myoneural blocking actions of which are enhanced by carbon dioxide (Payne and Rowe, 1957; Payne, 1958), both have pK values within the physiological range and are therefore liable to alteration in their degree of dissociation with changes in blood pH (Albert, 1952). Originally this was thought to explain the response obtained with these two drugs in the presence of carbon dioxide (Payne,
POTENTIATION OF D.F.596 BY CO2

CONTROL 5% CO2 RECOVERY

Sciatic nerve—tibialis anterior and soleus muscle preparations in the intact cat; blood pressure. The action of D.F.596 is enhanced in the presence of carbon dioxide. Note the hypotensive effect of each intravenous injection.

1959), but doubt was thrown on the adequacy of the explanation by the demonstration that if the blood pH was lowered by the intravenous infusion of acid the action of tubocurarine was weakened (Payne, 1960). The demonstration here that both tropane derivatives are enhanced in the presence of carbon dioxide is further proof that changes in drug ionization are unnecessary for the development of this effect, as it is unlikely that exposure to carbon dioxide can influence the dissociation of those substances (Haining, personal communication).

The failure to demonstrate any change in the activity of laudexium when exposed to carbon dioxide probably should not be accepted as conclusive. Only three animals were studied and the concentration of carbon dioxide employed was never raised above 5 per cent. Possibly had a higher concentration been used some change might have been obtained.

The more gradual onset of neuromuscular block and the slower recovery process during exposure to carbon dioxide could be related to the reduction in limb blood flow associated with the accumulation of carbon dioxide (Holmdahl, 1956) but this explanation is difficult to reconcile with the conflicting action of carbon dioxide on different relaxant drugs.

SUMMARY

The influence of carbon dioxide on the neuromuscular blocking properties of benzoquinonium, laudexium and two tropane derivatives has been studied.

The action of benzoquinonium is antagonized by carbon dioxide; the effect of tropane deri-
POTENTIATION OF D.F.648 BY CO₂

CONTROL  5% CO₂  RECOVERY

ANT. TIB.  SOLEUS

B.P.

Sciatic nerve—tibialis anterior and soleus muscle preparations in the intact cat; blood pressure. The action of D.F.648 is enhanced in the presence of carbon dioxide. Note the slight hypertensive effect of each intravenous injection.

Potentiation of D.F.648 by CO₂

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REFERENCES


