# THE RESPONSE OF ANIMALS TO SUXAMETHONIUM (SUCCINYLDICHOLINE) AND SUCCINYLMONOCHOLINE

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## ABSTRACT

The time which elapses before cessation of breathing, and blood pressure and blood gas changes after the intramuscular administration of suxamethonium, or a mixture of suxamethonium and hexamethonium, is compared in immobilised African elephants *(Loxodonta africana)* and buffaloes *(Syncerus caffer)*. In addition, the respiratory responses of elephants and other animals to intravenous administration of suxamethonium and succinylmonocholine are reported on, as are the effects of darting animals with succinylmonocholine. The results show that respiration is affected in a similar fashion in all species investigated. However, the characteristic gradual decrease in respiratory rate seen in elephants during culling, using suxamethonium, resembles the effects observed when succinylmonocholine is administered. It is suggested that elephants are killed by this first breakdown product of suxamethonium during culling and/or that unique acetylcholine receptors may be involved.


Key words: Elephants, *Loxodonta africana*, culling, suxamethonium, succinylmonocholine, stress.

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## INTRODUCTION

The blood biochemical responses of wild animals to suxamethonium during culling have been well documented[5 6]. Although the blood compositional changes found in elephants are similar to those seen in the blood of buffaloes, impalas, rabbits, etc, the elephants take much longer to die than do any of the other species investigated. African elephants collapse on average 2,6 min after being darted with suxamethonium, but often make attempts at voluntary movement and may remain conscious for up to 25 min. All other species studied, show iso-electric electroencephalographic recordings soon after collapse[6] which occurs within 2 to 3 min of darting.

The reason for this apparent insensitivity of the respiratory muscles of elephants to suxamethonium is not clear. In these animals there is a gradual decrease in respiratory rate after the administration of suxamethonium, in contrast to the more dramatic cessation of breathing seen in other species. The exact comparative time taken for the cessation of breathing, cardiac activity, etc. for elephants and buffaloes is reported here. In addition, the responses of animals killed with suxamethonium are compared to those killed with a mixture of suxamethonium and hexamethonium, the latter compound having been introduced in an attempt to decrease the physiological response to culling[7 8]. Furthermore, because suxamethonium (succinyldicholine) is broken down to succinylmonocholine in the body, the effects of the latter compound administered intra-venously and intra-muscularly were investigated. The sample sizes in the present study are small because of the cost of the animals and carcasses could not be used for human consumption due to the presence of drug residues. A series of different experiments were thus conducted (in some cases on single animals) in an effort to better understand the action of suxamethonium on a variety of species.

## MATERIALS AND METHODS

Buffalo (*Syncerus caffer*) (n=15) impala *(Aepyceros melampus melampus)* (n=8), elephants *(Loxodonta africana* (n=11), wildebeest *(Connochaetes taurinus)* (n=10), zebra *(Equus burchelli)* (n=4) and warthog *(Phacochaerus aethiopicus)* (n=5) were darted as described previously, immobilising them with succinylmonocholine[9] or the appropriate dose of carfentanil (Jansen Pharmaceutical, Beerse, Belgium)[5 6 7 8]. The methods used for measuring arterial $PO_2$, $PCO_2$, pH, arterial blood pressure, respiratory rate, haematocrit and osmolality in immobilised animals and the concentration of plasma glucose, total lipid, total protein, lactate, cortisol and total catecholamines have also been described[2 4 6]. After completion of all procedures in immobilised animals, they were allowed to stabilise for about 20 min, control blood samples were taken and they were given an intra-muscular or intra-venous dose of either suxamethonium (Scoline, Glaxo, London, England) or succinylmonocholine[9] with or without physostigmine (Roche, Baste, Switzerland), neostigmine methyl sulphate (Kompani Ultramar, Hamburg, West Germany) or hexamethonium chloride[7 8] (Sigma, United Kingdom). Recordings continued until a zero blood pressure was recorded at which stage a further blood sample was taken in some cases. For the comparison of the effects between suxamethonium only or suxamethonium and hexamethonium, blood samples were taken at 2 min intervals until death. Results are reported as means ± S.D. or as percentage of control value where relevant.

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## RESULTS

### Effects of intra-muscular suxamethonium and a suxamethonium/hexamethonium mixture in animals immobilised with carfentanil.

Regular respiratory movements stopped after 5,3 ± 2,4 min in buffaloes (n=3) and after 2,1 ± 0,1 min in impalas (n=3) killed with suxamethonium and after 3,4 ± 0,7 min in buffaloes (n=3) and 1,4 ± 0,5 min in impalas (n=3) killed with the mixture. Respiratory effort ceased after 12,6 ± 4,0 and 8,0 ± 0,7 min in buffaloes and impalas killed with suxamethonium respectively, and after 5,1 ± 1,1 and 3,7 ± 1,0 min respectively in animals killed with the mixture. In all animals killed with suxamethonium. Blood pressure also tended to fall faster in the mixture group and by plotting $PO_2$ versus blood pressure, it was found that in all animals, blood pressure decreased only when arterial $PO_2$ was between 25 and 20 mmHg. The changes in concentrations and values for the blood variables investigated (see above) from the pretreatment control samples to those taken immediately after no blood pressure was recorded, were similar to the ones reported earlier[5 7 8]. The only difference observed between the suxamethonium and suxamethonium/hexamethonium groups was a decreased total catecholamine response in the latter (significant, $P < 0,05$, in impala and buffaloes). Of the 3 elephants which received the mixture, one died quickly (see above) whereas the other 2 showed no effects other than a slight initial decrease in blood pressure. These animals were then given suxamethonium (60 min later) and died in the usual way.

Table 1: **Change with time from control for blood gases and blood pressure in elephants and buffaloes after the administration of suxamethonium (S) and suxamethonium/hexamethonium (S/H). Results are expressed as percentage of control value (means). Drugs were administered intramuscularly at time zero (To)**

| Variable and treatment | | Time (min) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0 | 2 | 4 | 6 | 8 | 10 | 14 | 18 | 22 | 26 | 30 |
| **Buffaloes** | | | | | | | | | | | | |
| $PO_2$ | S(n=3) | 100 | 74 | 35 | 20 | 18 | 18 | - | - | - | - | - |
| | S/H(n=3) | 100 | 68 | 28 | 18 | 18 | 18 | - | - | - | - | - |
| $PCO_2$ | S(n=3) | 100 | 102 | 110 | 130 | - | - | - | - | - | - | - |
| | S/H(n=3) | 100 | 124 | 144 | 158 | - | - | - | - | - | - | - |
| Blood | S(n=3) | 100 | 102 | 104 | 55 | 20 | 0 | - | - | - | - | - |
| pressure | S/H(n=3) | 100 | 102 | 94 | 64 | 33 | 0 | - | - | - | - | - |
| **Elephants** | | | | | | | | | | | | |
| $PO_2$ | S(n=3) | 100 | 94 | 87 | 80 | 75 | 69 | 51 | 35 | 25 | 19 | 18 |
| | S/H(n=1) | 100 | 86 | 70 | 60 | 55 | 49 | 24 | 18 | 18 | 18 | 18 |
| $PCO_2$ | S(n=3) | 100 | 105 | 110 | 116 | 124 | 132 | 185 | 228 | 252 | 260 | 264 |
| | S/H(n=1) | 100 | 125 | 150 | 172 | 195 | 218 | 226 | 242 | 250 | 250 | 250 |
| Blood | S(n=3) | 100 | 104 | 109 | 111 | 111 | 111 | 105 | 70 | 44 | 30 | 0 |
| pressure | S/H(n=1) | 100 | 98 | 96 | 92 | 84 | 76 | 15 | 0 | - | - | - |

### Effects of darting animals with succinylmonocholine

A number of animals from different species were darted with succinylmonocholine. The results are shown in Table 2. In animals that were immobilised and which recovered subsequently, respiration was regular, mucous membranes were pink, muscle fasiculations were observed and a marked hyperaemia of the conjunctival mucous membranes was evident. In one of the buffaloes investigated (No. 3, Table 2), 0,02 mg $kg^{-1}$ physostigmine was administered 32 min after darting and the impression gained was that succinylmonocholine acts as a neuromuscular blocker in a fashion similar to that of suxamethonium (i.e. depolarising), but that the respiratory muscles are affected less.

### Effects of intra-venous suxamethonium and succinylmonocholine in animals immobilised with carfentanil:

The results obtained are shown in Table 3. In all animals investigated, the intra-

elephants, regular respiratory movements continued until a few minutes before blood pressure was zero, with a gradual decrease in rate and depth throughout the time period (n=3 for suxamethonium and n=1 for suxamethonium/hexamethonium). The percentage change in $PO_2$, $PCO_2$ and blood pressure with time was proportionately similar for impala and buffaloes, for both the suxamethonium and mixture groups. For clarity, only the buffalo and elephant results are presented in Table 1. The results show that all responses in elephants are delayed compared to those of buffaloes and that in animals exposed to the mixture, $PO_2$ decreased and $PCO_2$ increased sooner than in

venous administration of either suxamethonium or succinylmonocholine resulted in a change in respiration after a lag period (A in Table 3); cessation of breathing in the case of the former compound and deep breaths (sighs) in the case of the latter. Respiration then usually returned to normal (B in Table 3) with no further effects. In some cases, however, respiration gradually decreased in rate and depth and finally stopped (C in Table 3). The dosages of the 2 substances used, never resulted in quick and complete irreversible cessation of breathing, although it is postulated here that this would occur with greater amounts. Two responses were thus observed with intravenous

suxamethonium, depending on dosage: cessation of breathing, followed by a return to normal and cessation of breathing, followed by a return to normal with subsequent gradual decrease in respiratory rate and depth until all activity ceased. When physostigmine was administered together with suxamethonium, respiration was completely inhibited at a dose level which the animal had previously survived (Table 3). When an elephant was given neostigmine before receiving a low dose of intramuscular suxamethonium, decreased rate and depth of respiration were observed for a short while, followed by a more prolonged inhibition (Table 3). Succinylmonocholine always produced sighs and when given in sufficient amounts, resulted in a gradual inhibition of the rate and depth of respiration.

Table 2: **Effects of darting animals with succinylmonocholine**

| Species | Dose | Time (min) from darting: Time to recumbancy | Time to up | Time to cessation of respiration |
|---|---|---|---|---|
| **Buffalo *(Syncerus caffer)*** | | | | |
| Adult female | 3g | 7,20 | 38,29 | - |
| Adult female | 5g+ | 4,11 | - | 6,30 |
| Adult female | 3g | 8,02 | 55,00 | - |
| Adult female | 5g+ | 5,50 | - | 28,07 |
| Sub adult female | 1,5g | No effect | | |
| Adult male | 5g | 7,40 | 46,30 | |
| Sub adult female | 3g | No effect | | |
| **Impala *(Aepyceros melampus melampus)*** | | | | |
| Adult male | 0,5g | about 15 | 53,30 | - |
| Adult male | 3g | 0,50 | - | 4,15 |
| Adult male | 1g | 3,30 | - | 10,25 |
| Adult male | 0,8g | No effect | | |
| Sub adult male | 0,8g | 7,42 | 38,36 | |
| Adult male | 0,7g | 21,02 | 55,54 | |
| Adult male | 0,6g | No effect after 36 min | | |
| **Wildebeest *(Connochaetes taurinus)*** | | | | |
| Adult male | 1g | No effect after 50 min | | |
| Adult male | 2g | 8,06 | Death due | to regurgitation |
| Adult male | 1,35g | 25,5 | 35,35 | - |
| Adult male | 1,5g | No effect after 40 min | | |
| Adult male | 1,5g | No effect after 40 min | | |
| Adult male | 1,8g | 29,16 | 44,38 | - |
| Sub adult male | 2,0g | No effect after 30 min | | |
| Adult male | 2g | 6,22 | - | 24,55 |
| **Zebra *(Equus burchelli)*** | | | | |
| Adult female | 2,5g | No effect after 30 min | | |
| Adult male | 3,5g | 67 | 9,56 | - |
| Adult male | 3,5g | 7,56 | | 16,34 |
| Adult male | 2,5g | No effect | | |
| **Warthog *(Phaccohaerus aethiopicus)*** | | | | |
| Adult male | 0,6g | No effect | | |
| Adult female | 0,7g | 14,06 | 102 | - |
| Adult female | 0,5g | 7,42 | - | 25,30 |
| Sub adult male | 0,5g | No effect | | |
| Adult male | 0,5g | No effect | | |
| **Elephant *(Loxodonta africana)*** | | | | |
| Adult male | 25g | No effect | | |

## DISCUSSION

*Elephants* showed a different response to intra-muscularly administered suxamethonium during culling compared to buffaloes[5]. Although the blood constituent and cardiovascular changes were similar in both species, the time course was markedly different. Elephants showed a gradual and slow inhibition of respiration. This cannot be explained by differences in dosage, because in this study both species received about 3 mg $kg^{-1}$ suxamethonium. In addition, the same response was observed, irrespective of route of administration, i.e. intra-venous or intra-muscular, although time differences were evident (see also above). These results may indicate a difference in the affinity of the nicotinic acetylcholine receptors of the respiratory muscles of *elephants* for suxamethonium, or a different mode of action of suxamethonium in these animals. A combination of these effects is possible. It is known that hexamethonium has an antagonistic effect at certain skeletal neuromuscular junctions during a competitive blockade[1]. Suxamethonium is a depolarising neuromuscular blocker, but its effect was seemingly antagonised in 2 of the 3 elephants investigated, although not in one of the animals of the other species studied. Furthermore this effect was not seen in any conscious elephants culled with the mixture[8]. The anaesthetic used is not known to have any effects on the action of neuromuscular blockers, but could possibly have influenced the combined action of suxamethonium and hexamethonium in elephants. Collectively, these observations may point to unique acetylcholine receptors in the respiratory muscles of these animals.

Hexamethonium in combination with suxamethonium, when administered to immobilised impalas and buffaloes, resulted in more rapid changes in $PO_2$, $PCO_2$ and blood pressure than when only suxamethonium was used. These effects were also seen in the one elephant which died when the mixture was given. The results indicate that the effects of hexamethonium at autonomic ganglia and other areas where transmission may be blocked (e.g. chemoreceptors), are similar in the different species. It is thus only the action of suxamethonium and the possible antagonistic effect of hexamethonium on the respiratory muscles in elephants which differed from those in other animals investigated. Another possible explanation is that it is not suxamethonium which blocks neuromuscular transmission in the respiratory muscles of elephants, but one of its breakdown products. Succinylmonocholine is one such substance and 25 g was administered to an elephant during the culling operation (Table 3). This dose is in excess of the amount of succinylmonocholine which would result from the breakdown of suxamethonium used during culling. No effects at all were observed, but the experiment was stopped after 14 min. From the results for immobilised animals, it is clear that this

Table 3: **Effects of intravenous suxamethonium and/or succinylmonocholine on immobilised animals. With repeat treatments, the time interval was 20-25 min**

| Species | Drug | Dose | Time *(s) A | B | C |
|---|---|---|---|---|---|
| **Buffalo** | | | | | |
| Adult male | M | 0,5 and lg | No effect | | |
| | M | 2g | 235 | 290 | 366 |
| Adult male | S | 10mg | 50 | 248 | - |
| | S | 20mg | 40 | 136 | 312 |
| **Impala** | | | | | |
| Adult male | M | 0,5g | 26 | 80 | 147 |
| **Wildbeest** | | | | | |
| Adult female | S | 50mg | 15 | 37 | 552 |
| Adult female | S | 10mg | 98 | 120 | 484 |
| **Elephant** (body mass estimated from shoulder height,. National Parks Board tables) | | | | | |
| *1200* kg male | S | 900mg | 76 | 244 | - |
| | S | 1,8g | 52 | 264 | 528 |
| 240kg female | S | 180mg | 60 | 108 | - |
| | S | 360mg | 36 | 84 | - |
| | | 550mg | 52 | 268 | 470 |
| 1650kg female | S | 1,3g | 34 | 60 | 650 |
| 400kg male | S | 300mg | 25 | 76 | - |
| | M | 600mg | 21 | 80 | - |
| | S* | 600 | 95 | very slight respiratory effort up to 2695 | |
| 290 male | S | 200mg | 33 | 48 | - |
| | S | 200mg | 53 | 111 | - |
| | M | 200mg | 34 | 67 | - |
| | M | 400mg | 14 | 23 | - |
| | M | 600mg | 104 | 150 | 1374 |
| 260kg female | S** | 100mg | 102 | 242 | - |
| | S | 100mg i.m. | 248 | 371 | 3112 |

*Time A: From time of injection of drug until a change in respiratory pattern was observed

Time B: From time of injection of drug until respiration returned to normal

Time C: From time of injection of drug until respiration stopped

S = suxamethonium
M = succinylmonocholine
* also received 8,8 mg of physostigmine
** also received 6 mg of physostigmine

substance may block respiration (at sufficient dosage), but that it takes some time. In addition, the results obtained with intra-venously administered suxamethonium, seem to indicate that this substance does cause an initial block from which the animal may recover, but if sufficient amounts are used, this is followed by a gradual inhibition of respiration in a manner similar to the effects of succinylmonocholine. In in vivo cat sciatic-gastrocnemius preparations, succinylmonocholine has been shown to have a definite but weak blocking action[3]. When the dose was repeated after apparent recovery of the endplate transmission, a more intense block was induced. A similar result was obtained after recovery from a prior suxamethonium dose. This suggests that succinylmonocholine may have a low affinity for the nicotinic acetylcholine receptor, but that at a critical dose an effective block is induced. It is therefore possible that cholinesterase activity in elephants (true and/or pseudo) is such that at the dosages used, only succinylmonocholine reaches the motor endplates of respiratory muscles, with the resultant slow inhbition when suxamethonium is used during culling. If this were the case, it would also appear that receptor affinity is less for succinylmonocholine than for suxamethonium. Receptor affinity for these substances and cholinesterase activity therefore require further investigation on a comparative basis.

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