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# 一水合二甲基一氢代-2-(1,3-二磺酸单钠硫代丙基)铵的神经肌肉阻遏和呼吸抑制作用

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## Neuromuscular blocking and respiratory depressing actions of sodium ammonium dimethyl-2-(propano-1,3-dithiosulfate) monohydrate

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**ABSTRACT** The neuromuscular blocking and respiratory depressing actions of the new insecticide sodium ammonium dimethyl-2-(propano-1,3-dithiosulfate) monohydrate (SCD) were investigated. In peroneal-tibialis anterior nerve-muscle preparations of urethane anesthetized rabbit, SCD 6.5 mg/kg iv completely depressed the indirectly elicited twitch tension but not the directly elicited one. This compound also caused initial potentiation of the indirectly elicited twitch tension. In the partially paralyzed preparations, potentiation of contractions occurred following a brief period of indirectly tetanic stimulation. Nereistoxin but not SCD blocked the indirectly elicited twitch tension of isolated rat diaphragm. The neuromuscular blockade induced by SCD and nereistoxin was antagonized by neostigmine and 4-aminopyridine. SCD and nereistoxin had little or no effect on arterial blood pressure and phrenic nerve discharge of rabbits. The results indicated that SCD-poisoned rabbits died of respiratory paralysis following the neuromuscular blockade.

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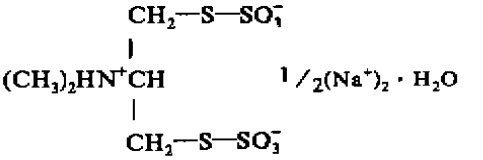
**KEY WORDS** insecticides; sodium ammonium dimethyl-2-(propano-1,3-dithiosulfate) monohydrate; neuromuscular blocking agents; peroneal nerve; phrenic nerve

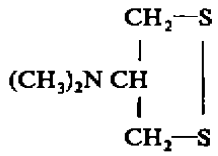
**提要** 麻醉兔 iv 一水合二甲基一氢代-2-(1,3-二磺酸单钠硫代丙基)铵 (SCD) 6.5 mg/kg 后, 间接刺激激发的胫前肌收缩反应短时轻度增加后逐渐变小, 最后消失; 呼吸幅度变小, 最后停止; 血压无明显变化. SCD 对兔膈神经放电无明显影响. 外周呼吸抑制是 SCD 致兔死亡的主要原因. SCD 对离体大鼠膈肌收缩反应没有影响.

**关键词** 杀虫剂; 一水合二甲基一氢代-2-(1,3-二磺酸单钠硫代丙基)铵; 神经肌肉阻滞剂; 腓神经; 膈神经

杀虫单(SCD)化学名为一水合二甲基一氢代-2-(1,3-二磺酸单钠硫代丙基)铵[sodium ammonium dimethyl-2-(propano-1,3-dithiosulfate) monohydrate], 是沙蚕毒素 (nereistoxin, NTX; Fig 1) 类我国创制的新杀虫



**Sodium ammonium dimethyl-2-(propano-1, 3-dithiosulfate) monohydrate (SCD)**



Nereistoxin (NTX)

剂[1,2]. NTX 具有神经肌肉阻遏作用[3]. 本文分析了 SCD 对神经肌肉接头传递的影响及其致兔死亡的原因. 并与 NTX 进行比较.

## MATERIALS

SCD 系温州农药研究所提供，纯度 97.8%. NTX (草酸盐)系南开大学元素有机化学研究所提供，纯度 99%. 4-氨基吡啶 (4-aminopyridine)为美国 Aldrich 产品. 以上药品临用前溶于蒸馏水.

杂种兔，体重 2.3 ± SD 0.3 kg, Wistar 大鼠，体重 206 ± 20 g, 均♀♂不拘. 由本院动物室提供.

## METHODS AND RESULTS

**SCD 和 NTX 对兔神经肌肉接头传递，呼吸和血压的影响** 兔 10 只，随机匀分 2 组. iv 20% 乌拉坦 1 g/kg 麻醉后气管插管，左颈总动脉插管，分离左侧腓总神经和胫前肌，按前文[4]方法记录刺激神经或肌肉激发的胫前肌收缩反应，呼吸运动和血压.农药由耳缘 iv，自主呼吸停止后维持人工呼吸.

在预试验中观察到 SCD 和 NTX 致兔完全神经肌肉阻遏的最小有效剂量分别为 6.5 和 2 mg/kg. iv SCD 6.5 mg/kg, NTX 2 mg/kg 后兔间接刺激激发的胫前肌收缩反应，呼吸和血压的变化见 Fig 1, 2. 二药均先使间接刺激激发的肌收缩反应短时轻度增加，达到给药前的 110 %左右，持续 0.5-1 min. 肌收缩反应随后变小，最后消失；呼吸幅度相应变小，最后停止. SCD 使肌收缩反应发生变化和呼吸停止的时间较 NTX 长，尽管前者使用的剂量较后者大得多.

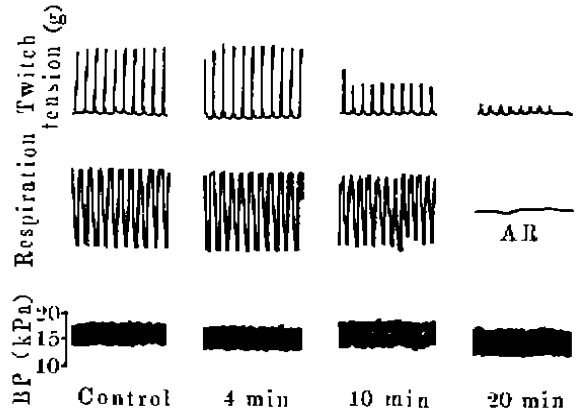



**Fig 1. Indirectly elicited twitch tension of tibialis anterior muscle, respiration and carotid blood pressure in a rabbit ( 2 kg, urethane anesthesia) after iv SCD 6.5 mg / kg. AR = artificial respiration.**

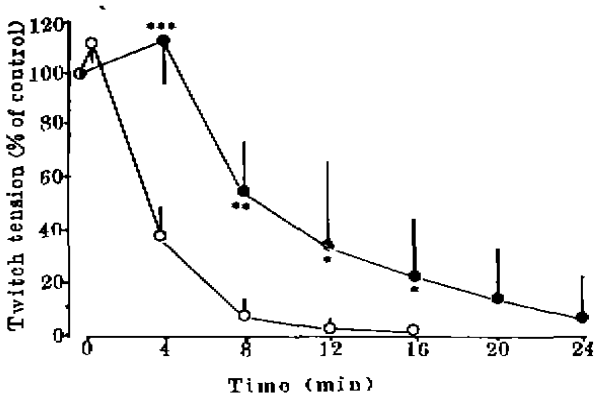



**Fig 2. Effects of iv SCD 6.5 mg / kg and nereistoxin 2 mg / kg on indirectly elicited twitch tension of tibialis anterior muscle of urethane anesthetized rabbits. Nereistoxin (O), SCD (●). $n=5$, $\bar{x}$ ± SD, $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* nereistoxin.**

在刺激神经激发的肌收缩反应变小后，两组兔刺激肌肉激发的肌收缩反应无变化；强直刺激( 64 Hz)腓总神经 10 s 可使肌肉产生一次不能持续的强直收缩,并呈现强直后增加 (post-tetanic potentiation)；甲基硫酸新斯的明 0.2 mg / kg iv 可使肌收缩反应恢复至给药前的 30-50%，但增加剂量亦未见完全恢复；iv 4-氨基吡啶 1 mg / kg (SCD 组) 或 2

mg / kg (NTX 组)可使肌收缩反应完全恢复.

iv SCD 前后兔血压无明显变化 ($P>0.05$). iv NTX 后 15 s 左右兔出现一过性血压下降, 最大下降 6.7 kPa, 持续 20 s 左右, 随后又回复至给药前水平.

**离体大鼠膈肌实验** 按文献[5]方法制备大鼠膈神经膈肌标本, 置于含 37℃ Krebs-Henseleit 溶液肌槽内, 通入 95% $O_2$+ 5% $CO_2$. 由 XWT-204 型台式自动平衡记录仪记录刺激神经激发的膈肌收缩反应. 刺激参数: 频率 0.1 Hz, 波宽 0.2 ms,电压 10 V 的方波. NTX 3 mol / L 19 ± 2.6 min 使膈肌收缩反应完全消失 ($n=5$); 膈肌收缩反应变小以前亦有短时轻度增加. SCD 3, 6 mol / L 对膈肌收缩反应没有影响($n=3$).

**兔膈神经放电实验** 兔 6 只, 匀分 2 组, iv 20 % 乌拉坦 1 g / kg 麻醉, 切口处加用 1.3 %普鲁卡因浸润. 分离颈部左侧膈神经, 置于双极银丝电极上; 同时切断颈部双侧迷走神经干[6]. 记录 iv SCD 6.5 mg / kg 和 NTX 2 mg / kg 前后膈神经发放脉冲, 经 AVB-JA 输入盒和 VC-9 示波器放大、显示, 以 SB-408 示波照相机摄影记录. 兔给药前、后(呼吸接近停止时)膈神经放电频率 SCD 组分别为 40 ± 14 和 42.7 ± 13.6 cpm; NTX 组兔分别为 40 ± 15.7 和 52 ± 8 cpm, 给药后膈神经放电幅度有所增大 (Fig 3).

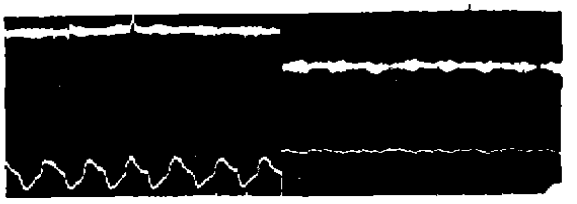


**Fig 3. Effects of iv SCD 6.5 mg / kg on the discharge of phrenic nerve and respiration of an anesthetized rabbit. Upper tracing: discharge of phrenic nerve; Lower tracing: respiratory movement. Left control; Right: 15 min after SCD**

## DISCUSSION

本文结果表明:SCD 和 NTX 一样, 对肌肉收缩过程本身没有影响; 在预试验中曾观察到此二药对兔神经干传导没有影响. 因此, SCD 和 NTX 使刺激神经激发的肌收缩反应变小以至消失,其作用部位在神经肌肉接头处.

SCD 和 NTX 对神经肌肉接头传递的影响具有一些非去极化型肌松剂的特征, 如强直后增加, 可为胆碱酯酶抑制剂新斯的明部分拮抗, 可为 4-氨基吡啶完全拮抗等, 但也有不同之处, 即开始时使间接刺激激发的肌收缩反应短时轻度增加.据报道, NTX 并不影响接头前乙酰胆碱的储存和释放过程, 但可使接头区膜电位先去极 10-20 mV, 然后再复极至给药前水平; 此外, NTX 虽抑制激动剂氨甲酰胆碱激活的 $^{22}Na$ 内流, 但也能轻度激后受体诱导的 $^{22}Na$ 内流, 具有 $N_2$ 受体部分激动剂的特征[7]. SCD 可能也属于这种情形.

SCD 的作用与 NTX 有一些差异. SCD 对兔在体标本的作用较 NTX 弱且慢, 这与下列现象相符: 临床上,杀虫双( SCD 双钠盐)中毒患者只要服毒量较少(如小于 20 ml), 大多中毒症状较轻[8]. SCD 对离体大鼠膈肌收缩反应没有影响, 这一点与 NTX 也不一样. 上述现象提示 SCD 本身没有神经肌肉阻遏作用, 而是在体内转化为有肌松作用的活性物质, 这与开特普(cartap)等其它 NTX 开链衍生物[3]类似. 至于 SCD 是象开特普一样在生物体内转变为 NTX[9]或是其它产物以及影响这种转化的因素尚不清楚. 抑制 SCD 在机体内的转化或可成为寻找其解毒药的途径之一.

SCD 对兔血压无明显影响, 其致麻醉兔死亡的主要原因是呼吸衰竭, 这与 NTX [10] 类似. iv SCD 后兔膈神经放电频率无明显变化, 说明至少在本实验所用剂量下 SCD 对兔呼吸中枢没有抑制作用. 神经肌肉阻遏后的外周呼吸抑制是 SCD 中毒兔死亡的主要原因.

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# 豚鼠气管和血管平滑肌以及心脏传导系统对异丙肾上腺素耐受性的差异

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## Difference of tolerances to isoprenaline between tracheal and vascular smooth muscles and cardiac conduction system in guinea pigs

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**ABSTRACT** Pretreatment to guinea pigs with sc isoprenaline (Iso) 10 μg / kg tid × 7 d reduced the effect of Iso on protecting histamine-induced asthma and decreased its $pD_2$ values in relaxing isolated tracheal strip. This treatment did not change the asthmatic effect induced by histamine and the effect of Iso on positive chronotropic action, but elevated the blood pressure. These results suggest that it is easier to develop the tolerance of $\beta_2$-adrenoceptors of respiratory smooth muscles than that of $\beta_1$-adrenoceptors of heart. Radioligand binding assay showed that the treatment decreased the number of binding sites of β-adrenoceptors on lungs of guinea pigs but did not change the binding affinity.

**KEY WORDS** *beta*-adrenergic receptors; isoproterenol; drug tolerance; trachea; vascular smooth muscle; blood pressure; radioligand assay; asthma

**提要** 豚鼠，反复应用异丙肾上腺素(Iso sc, 10 μg / kg, tid × 7 d)可使该药的抗组胺性哮喘作用减弱，舒张离体气管条作用的 $pD_2$ 值下降，但对心脏的正性频率作用无明显变化. 耐受后，豚鼠的基础血压升高. 放射性配位体测定结果表明，Iso 慢性耐受性

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