

REFERENCES

- 1 Xiao SH, Yang YQ, Guo HF, Zhang CW, Jiao PY, You JQ. Effects of mebendazole, albendazole and albendazole sulfoxide on glycogen contents of *Echinococcus granulosus* cysts in infected mice. *Acta Pharmacol Sin* 1990; 11 : 546-9.
- 2 Xiao SH, You JQ, Guo HF, Feng JJ, Jiao PY, Sun HL *et al*. Effects of mebendazole on glucose uptake of *Echinococcus granulosus* cysts. *Acta Pharmacol Sin* 1992; 13 : 473-7.
- 3 Huang TY, Chu CH. *In vitro* studies on glycolysis of *Schistosoma japonicum*. *Acta Biochim Sin* 1959; 2 : 102-10.
- 4 Everse J, Kaplan NO. Lactate dehydrogenase: Structure and function. In: Meister A, editor. *Advances in Enzymology*; vol 37. NY: Wiley, 1973 : 61-133.
- 5 Bradford MM. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. *Anal Biochem* 1976; 72 : 248-54.

45-49
BIBLID: ISSN 0253-9756 中国药理学报 *Acta Pharmacologica Sinica* 1993 Jan; 14 (1) : 45-49 (8)

二氢石蒜碱的降压作用

陈必义、杜佐华¹、曾繁典¹、胡崇家¹、马广恩²、洪山海²
(昆明医学院药理教研室, 昆明 650031, 中国)

R 972.4

Hypotensive effect of dihydrolycorine

CHEN Bi-Yi, DU Zuo-Hua¹, ZENG Fan-Dian¹, HU Chong-Jia¹, MA Guang-En², HONG Shan-Hai² (*Department of Pharmacology, Kunming Medical College, Kunming 650031, China*)

ABSTRACT Dihydrolycorine-HCl(DL) is a derivative of lycorine, an alkaloid isolated from *Lycoris radiata* Herb. DL iv 20, 40, and 80 mg · kg⁻¹ lowered the mean arterial pressure in pentobarbitone-anesthetized normotensive rats, cats, and conscious rats either normotensive or renovascular hypertensive. In pithed rats DL depressed the hypertensive effect of reaction to electric stimulation to the T₇₋₉ segments of spinal cord. DL also depressed the hypertensive effect of phenylephrine. In rabbit aorta ring and rat anococcygeus muscle, DL antagonized the contractile effect of methoxamine, with pA₂ values of 5.93 and 6.35, respectively.

These results suggest that DL can block α₁-adrenoceptors.

KEY WORDS dihydrolycorine; blood pressure; renovascular hypertension; thoracic aorta

摘要 二氢石蒜碱盐酸盐(DL) 20, 40, 80 mg · kg⁻¹ iv 能降低麻醉及清醒正常血压大鼠、麻醉猫和清醒肾血管性高血压大鼠的血压, 并抑制电刺激大鼠脊髓 T₇₋₉ 节段引起的升压反应, DL 抑制苯福林增高毁脊髓大鼠血压的作用。在兔主动脉和大鼠肛尾肌, DL 拮抗甲氧明 pA₂ 值分别为 5.93 和 6.35。结果提示 DL 能选择性阻断 α₁-肾上腺素受体。

关键词 二氢石蒜碱; 血压; 肾血管性高血压; 胸主动脉

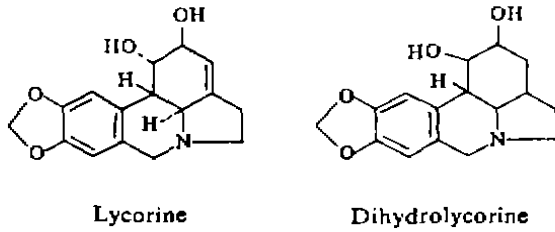
石蒜科石蒜属植物石蒜中所得石蒜碱(lycorine)经接触氢化而成二氢石蒜碱(dihydrolycorine), 为吡咯哌啡里啉(pyrrophenanthridine)衍生物。石蒜碱有降压作用⁽¹⁾, 但是二氢石蒜碱有无降压作用则未见报道。本文研究其对不同生理和病理状态的动物血压的影响及降压机制。

Received 1990-11-26

Accepted 1992-06-10

¹ Tongji Medical University, Wuhan 430030, China

² Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 200031, China



MATERIALS AND METHODS

二氢石蒜碱盐酸盐(DL)由中国科学院上海药物研究所植化室提供, 白色结晶, 易溶于水, 以蒸馏水新鲜配制使用. 普萘洛尔(propranolol, Pro, 北京制药厂), 利血平(reserpine, Res, 广州制药厂), 筒箭毒碱(tubocurarine, Tub, 上海第十制药厂), 育亨宾(yohimbine, Yoh, Sigma), 哌唑嗪(prazosin, Pra, 北京制药工业研究所), 阿托品(atropine, Atr), 甲氧明(methoxamine, Met)和苯福林(phenylephrine, Phe, 武汉制药厂), B-HT₉₂₀ (2-amino-6-allyl-5,6,7,8-tetrahydro-4H-thiazolo-[4,5d]-azepine, Thomae). 大鼠和猫用♂, 由同济医科大学实验动物中心提供.

麻醉大鼠降压试验 大鼠 30 只, 体重 $200 \pm s 20$ g, 戊巴比妥钠 $50 \text{ mg} \cdot \text{kg}^{-1}$ ip 麻醉, 气管插管, 用 DH-1 型人工呼吸机作正压呼吸, 通气量 $250 \text{ ml} \cdot \text{min}^{-1}$. 右侧颈外静脉插管, 注入肝素 $500 \text{ IU} \cdot \text{kg}^{-1}$ 抗凝, 同侧颈总动脉插管, 接压力传感器和 LMS-2B 二道生理记录仪, 记录收缩动脉压(SAP), 舒张动脉压(DAP), 按 $\text{DAP} + (\text{SAP} - \text{DAP}) / 3$ 算平均动脉压(MAP), 以 $50 \text{ mm} \cdot \text{s}^{-1}$ 描记的动脉搏动波计算心率(HR). 待 BP 和 HR 稳定后, 从颈外静脉注入 DL, 共分 4 组, 其中 3 组分别给予 DL 20, 40, $80 \text{ mg} \cdot \text{kg}^{-1}$, 一组于 24 h 前 Res $1 \text{ mg} \cdot \text{kg}^{-1}$ ip 后, 给 DL $40 \text{ mg} \cdot \text{kg}^{-1}$.

麻醉猫降压试验 猫 18 只, 体重 $2.6 \pm s 0.5$ kg, ip 戊巴比妥钠 $30 \text{ mg} \cdot \text{kg}^{-1}$ 麻醉, 颈外静脉和颈总动脉插管, 记录 MAP 和给药. 其中一组于 15 min

前 Pro $0.5 \text{ mg} \cdot \text{kg}^{-1}$ iv.

清醒大鼠降压试验⁽²⁾ 大鼠体重 $265 \pm s 25$ g, 乙醚浅麻醉, 右侧颈外静脉和颈总动脉插管后, 将管的另一端从颈后部引出, 管内充盈肝素 $1000 \text{ IU} \cdot \text{ml}^{-1}$, 术后 5-6 h, 大鼠活动自如, 记录 AMP 和给药.

清醒肾血管性高血压大鼠降压试验^(2,3) 大鼠体重 $172 \pm s 20$ g, 经手术将大鼠左肾动脉嵌入不锈钢夹(内径 0.2 mm)内, 使其狭窄. 术后 3 wk 形成高血压, 余步骤同清醒大鼠降压试验.

毁脊髓大鼠试验^(4,5)

1 电刺激毁脊髓大鼠试验⁽⁶⁾ 大鼠体重 $230 \pm s 21$ g, 乙醚浅麻醉, 从右侧眼眶内侧插入一直径 1.5 mm 的不锈钢针, 经枕骨大孔直下脊髓腔, 捣毁脊髓. 在脊髓腔内置一电极, 除相当于 T₇₋₉ 节段处裸露外, 余全部涂以绝缘漆, 另在相应皮下置一电极作为参考电极. 记录 BP, 用 YSD-4 型生理药理多用仪刺激脊髓 T₇₋₉ 节段, 刺激参数 50 V, 10 ms 方波, 持续 10 s. 在两轮刺激之间给药.

2 毁脊髓大鼠血压试验 大鼠体重 $220 \pm s 15$ g, 共分 5 组, 其中 2 组先分别给予不同剂量 Phe, B-HT₉₂₀. 余三组先给 DL, 15 min 后再给 Phe 和 B-HT₉₂₀.

兔胸主动脉环和肛尾肌试验⁽⁷⁾ 兔 $2.2 \pm s 0.2$ kg, ♀♂ 兼用, 击头致昏, 取胸主动脉, 制成宽 4 mm 的环. 大鼠体重 $230 \pm s 18$ g, ♂, 放血后取肛尾肌, 置于 10 ml Krebs 液中, $37 \pm 0.5^\circ\text{C}$, 通 95% O₂+5% CO₂, pH 7.3-7.4. 肌肉收缩经肌张力传感器(JH-1A-20)与 LMS-2B 二道生理记录仪记录. 静息张力和平衡时间, 主动脉环 2 g, 2 h, 肛尾肌 0.5 g, 1 h, 实验前 15 min 加 Pro $1 \mu\text{mol} \cdot \text{L}^{-1}$. 以 $1 \text{ g} \cdot \text{mol} \cdot \text{L}^{-1}$ 的 1/2 递增作 Met 累积给药的量-效曲线. 以此为对照, 冲洗, 张力恢复后, 加入受试药, 15 min 后重作 Met 量-效曲线. 求拮抗剂 pA₂ 值⁽⁸⁾, 另一个试验于主动脉环浴槽中加入 KCl $40 \text{ mmol} \cdot \text{L}^{-1}$, 标本收缩达稳定后, 每 10 min 以 $1 \text{ g} \cdot \text{mol} \cdot \text{L}^{-1}$ 的 1/2 累积剂量加受试药. 空白试验($n=6$)表明, KCl $40 \text{ mmol} \cdot \text{L}^{-1}$ 引起的主动脉收缩能维持 2 h 以上.

RESULTS

DL 的降压作用 给麻醉大鼠、猫，清醒正常血压大鼠、肾血管性高血压大鼠 iv DL 后 MAP 立即下降，1-3 min 达最大值，以后回升。HR 随 MAP 降低而减慢，但恢复较 MAP 快(Fig 1)。

降压作用分析

1 利血平试验 24 h 前 ip Res 处理的大鼠和 15 min 前 iv Pro 处理的猫，DL 的降压作用显著减弱($P < 0.01$)。

2 毁脊髓大鼠 BP 试验

2.1 大鼠毁脊髓后，DAP 为 4.8 ± 0.8

kPa，DL 显著抑制电刺激脊髓 T₇₋₉ 节段的升压反应，Pro 减弱 DL 的抑制作用，Res 也抑制升压反应，并与 DL 有协同作用(Fig 2)。电刺激大鼠脊髓 T₇₋₉ 节段，主要引起升压反应，对心率影响小。

2.2 毁脊髓大鼠分别给 Phe、B-HT₉₂₀ 增高 DAP 的作用及 DL 对其影响(Fig 3)。

Phe 增高 DAP 的最大值(16.9 kPa)较 B-HT₉₂₀ (9.5 kPa)高，且曲线斜率 Phe 比 B-HT₉₂₀ 大(分别为 5.61 和 2.95)，这是大鼠血管平滑肌突触后 α_1 和 α_2 肾上腺素受体介导的升压反应特征⁽⁹⁾。DL 抑制 Phe 增高 DAP 的作用，最大反应无明显压低($P > 0.05$)，对

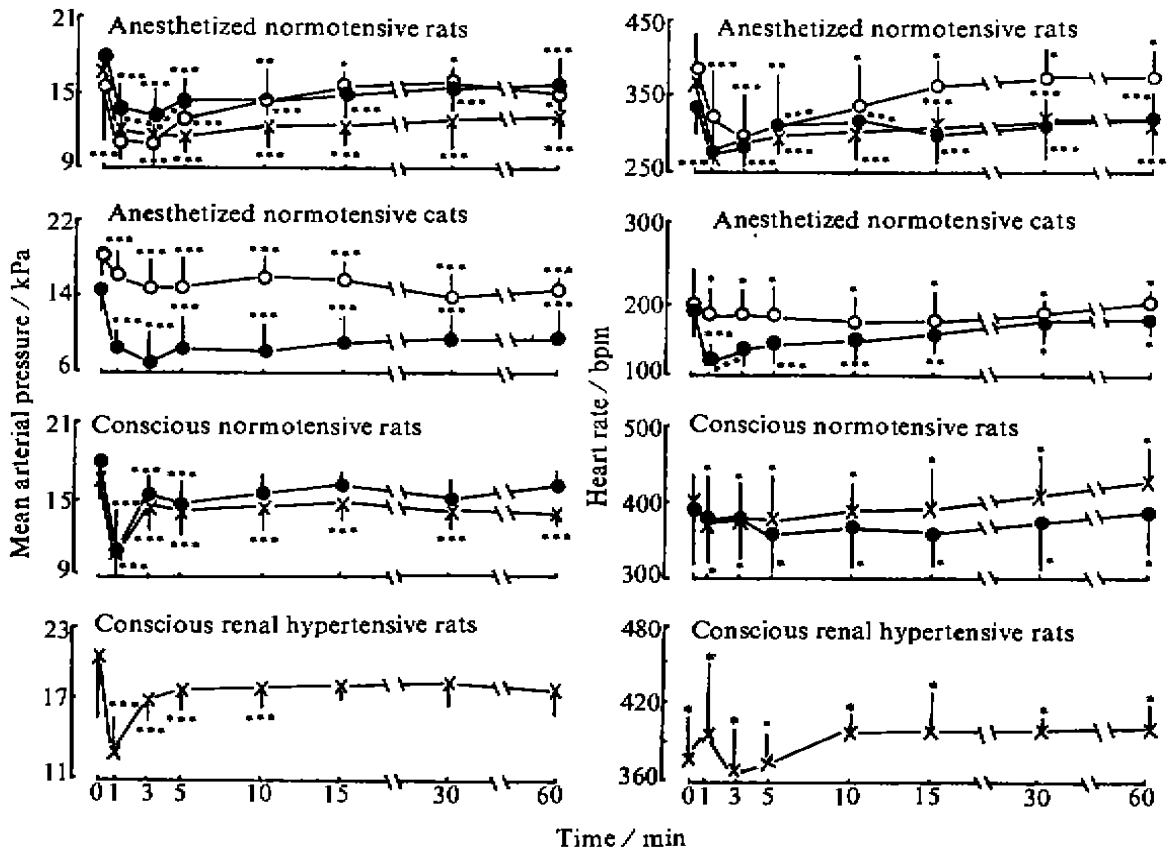


Fig 1. Effects of iv dihydrolycorine-HCl 20 (○), 40 (●), and 80 (×) mg·kg⁻¹ on mean arterial pressure and heart rate of anesthetized normotensive rats (n=5-7) and renovascular hypertensive rats (n=5). $\bar{x} \pm s$. * $P > 0.05$, ** $P < 0.05$, *** $P < 0.01$ vs control.

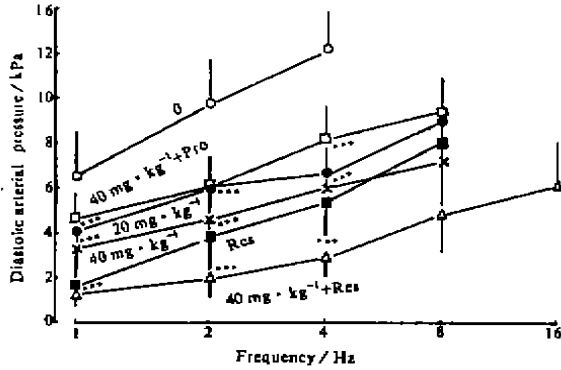


Fig 2. Effects of iv dihydrolycorine-HCl (DL) or combination with propranolol (Pro) or reserpine (Res) on pressor effects of pithed rats induced by electric stimulation (Frequency 1-16 Hz, 50 V, 10 ms, 10 s), $n = 5-7, \bar{x} \pm s$. * $P > 0.05$, ** $P < 0.05$, *** $P < 0.01$ vs 0.

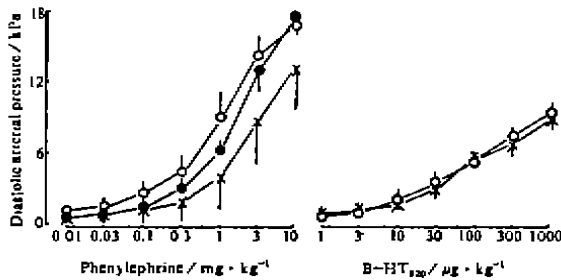


Fig 3. Effects of iv dihydrolycorine-HCl (DL) on phenylephrine and B-HT₉₂₀ to increase DAP of pithed rats. Control (○), DL 20 (●), and 40 (×) $\text{mg} \cdot \text{kg}^{-1}$, $n = 5-7, \bar{x} \pm s$.

B-HT₉₂₀ 增高 DAP 的作用则无明显影响, 也不压低最大反应。

3 DL 和 Pra 对 Met 收缩肛尾肌和主动脉环的影响(Fig 4), DL 抑制 Met 收缩肛尾肌和主动脉环的作用, 最大反应变化不大 ($P > 0.05$), 求得 DL 在肛尾肌、胸主动脉环上拮抗 Met 的 pA_2 值分别为 6.35 和 5.93, Pra 为 8.24 和 8.00。

DL 对高钾引起的胸主动脉环收缩无松弛

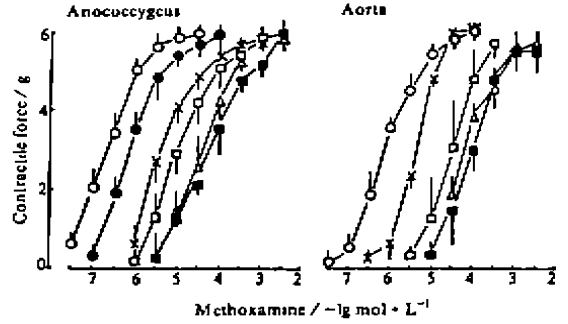


Fig 4. Effects of methoxamine in the absence (○) or presence of DL 3 (●), 10 (×), 30 (□), 100 (▣) $\mu\text{mol} \cdot \text{L}^{-1}$ and prazosin 1 $\mu\text{mol} \cdot \text{L}^{-1}$ (▤) on rat anococcygeus and rabbit aorta ($n = 5-7, \bar{x} \pm s$).

作用, DL 对大鼠肛尾肌和兔主动脉环无直接作用。

DISCUSSION

实验表明, DL 对麻醉大鼠、猫, 清醒正常 BP 大鼠和清醒肾血管性高血压大鼠均有迅速显著的剂量依赖性降压作用, 降压同时 HR 减慢, 以及 DL 对大鼠肛尾肌和兔主动脉环无直接作用。提示 DL 的降压作用机制可能与直接扩血管药不同, 即不是直接松弛血管平滑肌而降压。Res 和 Pro 减弱 DL 的降压作用, 以及电刺激毁脊髓大鼠试验 DL 抑制升压反应, Pro 减弱之, 与利血平有协同作用, 提示 DL 的降压作用机制可能与交感神经系统以及 α -肾上腺素受体有关。

毁脊髓大鼠 BP 实验提示 DL 可能有选择性阻断大鼠血管平滑肌 α -肾上腺素受体作用, 兔主动脉环和大鼠肛尾肌实验进一步提示 DL 有 α -肾上腺素受体阻断作用。B-HT₉₂₀ 通过激活血管突触后 α_2 -肾上腺素受体升高 BP, 这种血管收缩反应需要细胞外钙内流, 许多经典钙拮抗剂如维拉帕米尔均能抑制 B-HT₉₂₀ 激活大鼠突触后 α_2 -肾上腺素受体的升压反应, 显著压低最大反应⁽¹⁰⁾, DL 没有这种作用, 提示

DL 既无 α_2 -肾上腺素受体阻断作用, 也无钙拮抗作用。高钾去极化时, 细胞外钙内流引起血管平滑肌收缩⁽¹⁾, DL 对这种收缩无松弛作用, 进一步提示 DL 无钙拮抗作用。

综上所述, DL 的降压作用可能与选择性阻断突触后 α_1 -肾上腺素受体有关, 对 α_2 -受体和钙通道无阻滞作用。另外也可能与对 β -肾上腺素受体和交感神经末梢的影响有关。

REFERENCES

1 Shimamoto K, Isozaki T. Contribution to the emetic action of lycorine hydrochloride. *Folia Pharmacol Japon* 1958; 54 : 21-32.
 2 Qian JQ, Thoolen MJMC, van Meel JCA, Timmermans PBMWM, van Zwieten PA. Hypotensive activity of tetrandrine in rats: Investigation into its mode of action. *Pharmacology* 1983; 26 : 187-97.
 3 Dahl LK, Heine M, Thompson K. Genetic influence of the kidneys on blood pressure. Evidence from chronic renal homografts in rats with opposite predispositions to hypertension. *Circ Res* 1974; 40 : 94-101.
 4 Gillespie JS, Maclaren A, Pollock D. A method of stimulating different segments of the autonomic outflow from the spinal column to various organs in the pithed cat and rat. *Br J Pharmacol* 1970; 40 : 257-67.

5 Gillespie JS, Muir TC. A method of stimulating the complete sympathetic outflow from the spinal cord to blood vessels in the pithed rat. *Br J Pharmacol Chemother* 1967; 30 : 78-87.
 6 Hashimoto T, Kondo K, Shiina A, Toyo-Oka T, Kawasaki K-i, Kimura K-i, et al. The partial agonist activity of xamoterol (ICI 118, 587) studied by heart rate response in pithed rats. *Jpn Circ J* 1988; 52 : 60-5.
 7 Gillespie JS. The rat anococcygeus muscle and its response to nerve stimulation and to some drugs. *Br J Pharmacol* 1972; 45 : 404-16.
 8 Van Rossum JM, Hurkmans JATM, Wolters CJJ. Cumulative dose-response curves II. Technique for the making of dose-response curves in isolated organs and the evaluation of drug parameters (1). *Arch Int Pharmacodyn Ther* 1963; 143 : 299-330.
 9 Van Meel JCA, de Jonge A, Timmermans PBMWM, van Zwieten PA. Selectivity of some alpha adrenoceptor agonists for peripheral alpha-1 and alpha-2 adrenoceptors in the normotensive rat. *J Pharmacol Exp Ther* 1981; 219 : 760-7.
 10 Scarborough NL, Carrier GO. Nifedipine and alpha adrenoceptors in rat aorta. I. role of extracellular calcium in alpha-1 and alpha-2 adrenoceptor mediated contraction. *J Pharmacol Exp Ther* 1984; 231 : 597-602.
 11 Walter U, Waldmann R, Nieberding M. Intracellular mechanism of action of vasodilators. *Eur Heart J* 1988; 9 Suppl H : 1-6.

49-51 哮喘 雌二醇 卵白蛋白 组胺 (9)
 BIBLID: ISSN 0253-9756 中国药理学报 Acta Pharmacologica Sinica 1993 Jan; 14 (1) : 49-51

雌二醇对豚鼠卵白蛋白致敏过程的影响¹

万有², 翁世艾 (河南医科大学药理教研室, 郑州 450052, 中国)

R 974.3

Effect of estradiol on the course of ovalbumin sensitization in guinea pigs¹

WAN You², WENG Shi-Ai
 (Department of Pharmacology, He-nan Medical University, Zhengzhou 450052, China)

Received 1990-12-12 Accepted 1992-07-01

¹ This paper was awarded the Excellent Thesis of Young Pharmacologist at the 3rd National Symposium of Biochemical Pharmacology in Penglai, 1990-06-09.

² Now in Department of Pathophysiology, Tongji Medical University, Wuhan 430030, China.

ABSTRACT The latent period of ovalbumin (Ova)-induced asthma in Ova-sensitized guinea pigs was shorter in the ovariectomized animals with sc estradiol (E_2) 400 or 50 $\mu\text{g} \cdot \text{d}^{-1} \times 14 \text{ d}$ and in animals with intact ovary (84 ± 35 , 82 ± 33 , and $100 \pm 32 \text{ s}$, respectively) than in the ovariectomized animals ($140 \pm 29 \text{ s}$) ($P < 0.05$). The histamine (His) content of the lungs and His released from lungs under Ova challenge *in vitro* increased in the group of ovariectomy with sc E_2 50 $\mu\text{g} \cdot \text{d}^{-1} \times 14 \text{ d}$ as compared with those without sc E_2 (56 ± 9 and $47 \pm 11 \text{ ng/g wet weight vs } 44$