(Mischer, Pendleton & Staples, 1969; Lundell & Svensson, 1974; Lundell, Nilsson & Svensson, 1976) and that histamine releases catecholamines from the adrenal medulla in the rat; an effect which is blocked by H_1-receptor antagonists (Yoshizaki, 1973). It is therefore possible that the stimulation of H_1-receptors causes release of catecholamines which in turn inhibit acid secretion through the interaction with β-adrenoceptors.

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REFERENCES

BLACK, J. W., DUNCAN, W. A. M., DURANT, G. J., GANELLIN, C. R. & PARSONS, M. E. (1972). *Nature, Lond.*, **236**, 385–390.
CARTER, D. C. & GROSSMAN, M. I. (1977). *Gastroenterology*, **72**, A13/1036.
DURANT, G. J., GANELLIN, C. R. & PARSONS, M. E. (1975). *J. medl Chem.*, **18**, 905–909.
DURANT, G. J., GANELLIN, C. R. & PARSONS, M. E. (1977). *Agents and Actions*, **7**, 39–43.
HIRSCHOWITZ, B. I. & HUTCHISON, G. (1977). *Gastroenterology*, **72**, A45/1069.
IMPICCIATORE, M., MORINI, G. & BERTACCINI, G. (1978). *Eur. J. Pharmac.*, in the press.
LANE, A., IVY, A. C. & IVY, E. K. (1957). *Am. J. Physiol.*, **190**, 221–228.
LUNDELL, L., NILSSON, G. & SVENSSON, S. E. (1976). *Br. J. Pharmac.*, **58**, 17–25.
LUNDELL, L. & SVENSSON, S. E. (1974). *Ibid.*, **52**, 69–75.
MAIN, I. H. M. & WHITTLE, B. J. R. (1976). *J. Physiol., Lond.*, **257**, 407–418.
MISCHER, A., PENDLETON, R. G. & STAPLES, R. (1969). *Gastroenterology*, **57**, 294–299.
PARSONS, M. E., OWEN, D. A. A., GANELLIN, C. R. & DURANT, G. J. (1977). *Agents and Actions*, **7**, 31–37.
SCHOLES, P., COOPER, A., JONES, D., MAJOR, J., WALTERS, M. & WILDE, C. (1976). *Ibid.*, **6**, 677–682.
YOSHIZAKI, T. (1973). *Jap. J. Pharmac.*, **23**, 695–699.

Reversal of antibiotic-induced muscle paralysis by 3,4-diaminopyridine

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Certain antibiotics can induce respiratory depression during surgery when used in conjunction with some anaesthetics and muscle relaxants (Pittinger & Adamson, 1972). Antibiotics that have been implicated include the aminoglycosides, tetracyclines, polymixins, lincomycin and clindamycin. Reversibility of the antibiotic-induced muscle paralysis by either anticholinesterases or calcium ions is often unpredictable.

Some aminopyridines have powerful facilitatory actions on neuromuscular transmission and can also enhance muscle contractility (Harvey & Marshall, 1977) and we have previously shown that neuromuscular blockade produced by the aminoglycoside antibiotics amikacin and neomycin is reversed by either 4-aminopyridine or 3,4-diaminopyridine (Singh, Marshall & Harvey, 1978b). We have now tested the reversing actions of 3,4-diaminopyridine against muscle paralysis induced by tetracyclines, polymixins, lincomycin and clindamycin.

Experiments were performed on the isolated phrenic nerve-hemidiaphragm preparation of the mouse, mounted in Krebs-Henseleit solution containing 2 g $litre^{-1}$ dextrose, maintained at 32° and gassed with 5% CO_2 in oxygen. Nerve stimulation (rectangular pulses of 0·2 ms duration) at a frequency of 0·05 Hz was alternated with direct muscle stimulation (rectangular pulses of 1 ms duration) at a frequency of 0·05 Hz. Stimulation strength was adjusted to produce maximal twitches. Tissues were exposed to antibiotics in concentrations that produced 80–90% block of indirectly-elicited twitches in 20–60 min. 3,4-Diaminopyridine (0·1 mM) was then added to the tissue bath in the continued presence of the antibiotics and the degree of reversal (expressed as recovery to a percentage of control twitch height) was measured either after 10 min or at the point of maximum recovery. Recovery values are expressed as mean ± standard error of 4–6 experiments.

Polymixin B reduces responses to nerve stimulation whereas responses to direct stimulation are little affected; the neuromuscular block is unaffected by neostigmine and only reversed by high concentrations (10mM) of calcium (Singh, Harvey & Marshall, 1978a). However, we found that 3,4-diaminopyridine restored twitch height to 72 ± 9% in preparations blocked by 0·1 mM polymixin B (Fig. 1a).

Although lincomycin and clindamycin are chemically closely related and both reduce responses to nerve stimulation, clindamycin also reduces responses to direct muscle stimulation (Singh, & others, 1978a). The neuromuscular blocking activity of lincomycin (9·4 ± 0·6 mM) was readily reversible (to 108 ± 7% control) by 3,4-diaminopyridine (Fig. 1b). Clindamycin (2 mM) reduced responses to both nerve and direct stimulation to approximately the same degree, and 3,4-

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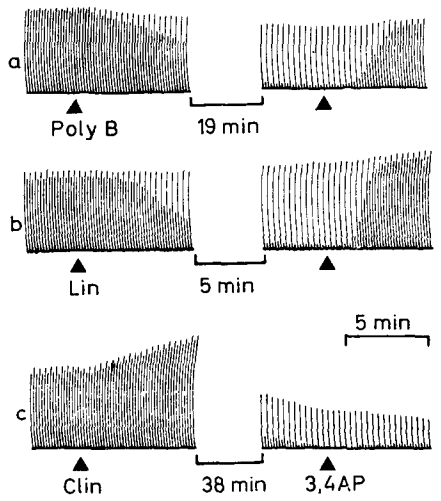

FIG. 1. The effects of (a) polymixin B (0·1 mM) (b) lincomycin (10·5 mM) and (c) clindamycin (2 mM) on alternate responses of the mouse hemidiaphragm to indirect (smaller twitches) and direct stimulation, and the effects of 10^{-4} M 3,4-diaminopyridine (3,4 AP). Poly B: polymixin B; Lin: Lincomycin; Clin: clindamycin.

diaminopyridine was ineffective as a reversal agent (Fig. 1c). When added at a concentration of 1 mM, clindamycin selectively blocked responses to indirect stimulation and the resultant neuromuscular block was reversed to 59 ± 7% control by 3,4-diaminopyridine.

Tetracycline (18·7 mM) and oxytetracycline (11·9 ±1·2 mM) both selectively blocked responses to nerve stimulation. The neuromuscular block produced by tetracycline was not reversed by 3,4-diaminopyridine but the block produced by oxytetracycline was completely reversed by 3,4-diaminopyridine. However, the reversal was only temporary, complete neuromuscular block being restored within 20–25 min in the continued presence of 3,4-diaminopyridine. In contrast, the aminopyridine-induced reversals of blockade induced by polymixin B, lincomycin and clindamycin, were well maintained. Additionally, after washout of polymixin B, lincomycin and clindamycin, concentrations of the antibiotics that had previously abolished twitches were only weakly effective, indicating that the aminopyridine has a prolonged action.

The aminopyridines prolong action potentials and the resultant increased influx of calcium into nerve terminals produces an increase in acetylcholine release (Lundh, Leander & Thesleff, 1977). It is probable that reversal of antibiotic-induced paralysis is caused by such an increase in transmitter output. That both calcium (Singh & others, 1978a) and 3,4-diaminopyridine reverse the action of oxytetracycline to some extent whereas both agents are ineffective against tetracycline is additional evidence that the action of 3,4-diaminopyridine involves calcium ions.

High concentrations of clindamycin act powerfully to reduce muscle contractility and this effect is not reversed by 3,4-diaminopyridine. However, lower concentrations of clindamycin were reversed. Additionally, a combination of clindamycin (1 mM) and a subeffective concentration of tubocurarine (10^{-7} M) was reversible (to 113 ± 5% control). As antibiotic muscle paralysis is usually associated with the concomitant administration of antibiotics and muscle relaxants, aminopyridines may prove useful reversing agents for such paralysis.

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REFERENCES

HARVEY, A. L. & MARSHALL, I. G. (1977). *Comp. Physiol. Biochem.*, 58c, 161–165.
LUNDH, H., LEANDER, S. & THESLEFF, S. (1977). *J. Neurol. Sci.*, **32**, 29–43.
PITTINGER, C. & ADAMSON, R. (1972). *Ann. Rev. Pharmac.*, **12**, 169–184.
SINGH, Y. N., HARVEY, A. L. & MARSHALL, I. G. (1978a). *Anesthesiology*, in the press.
SINGH, Y. N., MARSHALL, I. G. & HARVEY, A. L. (1978b). *Br. J. Anaesth.*, **50**, 109–117.