Anesthesiology
50:218–220, 1979

Interaction of Neuromuscular Blocking Effects of Neomycin and Polymyxin B

Chingmuh Lee, M.D., and A. J. C. de Silva, M.D.†*

Neomycin and polymyxin B produce neuromuscular blocks with distinct features by different mechanisms of action. In eight anesthetized cats the authors studied their interaction by examining the neuromuscular block produced by an equipotent mixture. Values of onset, potency, dose–response relations, duration and reversibility of block, the train-of-four and tetanic responses during block, the frequency–block relationships, and the posttetanic twitch behavior were well approximated by averaging the corresponding values previously reported for each antibiotic. Edrophonium, 0.2 mg/kg, reversed the block by 8 to 35 per cent. 4-Aminopyridine, 0.6 mg/kg, completely reversed the block and caused a long-lasting overshoot of the twitch response. The authors conclude that neomycin and polymyxin B are additive in neuromuscular effects, not only in terms of potency and duration, but also in terms of the characteristics of the blocks produced. (Key words: Antagonists, neuromuscular relaxants: 4-aminopyridine; edrophonium. Antibiotics: neomycin; polymyxin B.)

IN NEUROMUSCULAR PHARMACOLOGY, while interactions between antibiotics and other drugs have been well studied,[1,2] interactions among antibiotics are relatively unclear. Neomycin, the most potent neuromuscular blocking aminoglycoside, and polymyxin B, the most potent polypeptide, block neuromuscular transmission by different mechansisms of action[1,3,4] and produce blocks whose features are different.[5,6] This report describes the interaction of the neuromuscular blocking effects of these two antibiotics.

Method

The method was essentially similar to what we previously used in the study of neomycin and polymyxin B.[5,6] Eight cats weighing 2.4 (±0.4, SD) kg were anesthetized with alpha-chloralose, 60 mg/kg, and pentobarbital, 10 mg/kg, injected intraperitoneally. For each cat a solution that contained, in 1 ml of 0.89 per cent saline solution, neomycin sulfate, 6 mg/kg, and polymyxin B base, 1 mg/kg, was prepared. This was taken as a unit of roughly equipotent mixture.[5,6] Test drugs were injected intravenously.

* Associate Professor.

† Anesthesia Fellow.

Received from the Department of Anesthesiology, UCLA School of Medicine, Los Angeles, California 90024. Accepted for publication June 20, 1978.

Address reprint requests to Dr. Lee.

Results

Neuromuscular block produced by the equipotent mixture was not preceded by fasciculation or a transient increase in twitch response. Full onset of effect required 2–7 min (mean 4.0; ±standard error of mean 0.9). The ED_{50} was 1.9–4.7 units (3.2 ± 0.5). The ED_{95} was 3.5–8.1 units (5.5 ± 0.9). Recovery of block from 75 to 25 per cent required 8–57 min (28 ± 8).

At the point of 50 per cent block of the twitch the characteristics of block were as follows: train-of-four ratio 0.3–1.0 (0.72 ± 0.11), tetanic peak-to-twitch ratio 5.0–18 (9.4 ± 1.5), tetanus faded 0–27 per cent (9 ± 4) in 5 sec, 10-second posttetanic twitch to pretetanic twitch ratio 2.8–6.9 (4.4 ± 0.5). Posttetanic facilitation was initially present in every case. However, this persisted in only two instances, giving way to posttetanic exhaustion in the remaining six (fig. 1). A posttetanic exhaustion sufficient to convert a 50 per cent block to a total block occurred in one of these cats. Overall, the lowest posttetanic twitch was 0–1.4 (0.49 ± 0.18) times as forceful as the pretetanic twitch. In those six instances where posttetanic facilitation gave way to posttetanic exhaustion, the twitch decreased from the augmented level to the pretetanic level in 30 sec–2 min (1.2 ± 0.3 min), reached the lowest point in 3–5 (4.2 ± 0.5) min, and recovered to pretetanic level in 9–22 (16 ± 2.8) min. Even in the two cats whose posttetanic twitch never decreased to below the pretetanic level, a transient dip was observable in the time course of posttetanic facilitation (fig. 1, C).

4-Aminopyridine, 0.6 mg/kg, completely reversed the block in all cats. Time required for an 80 per cent block to be reversed from 20 per cent of control to 100 per cent of control was 5.5–13 (8.3 ± 1.1) min. A long-lasting overshoot of the twitch response followed. The highest twitch tension reached was 102–160 per cent (133 ± 7) of control, observed in 100–254 (143 ± 30) min. Edrophonium chloride, 0.2 mg/kg, given to four cats with an 80 per cent block caused the twitch to increase by 8–35 per cent (21 ± 5) of control within 1 min.

With the onset of neuromuscular block, mean arterial blood pressure decreased 4–50 torr (23 ± 6).

0003-3022/79/0300/0218 $00.65

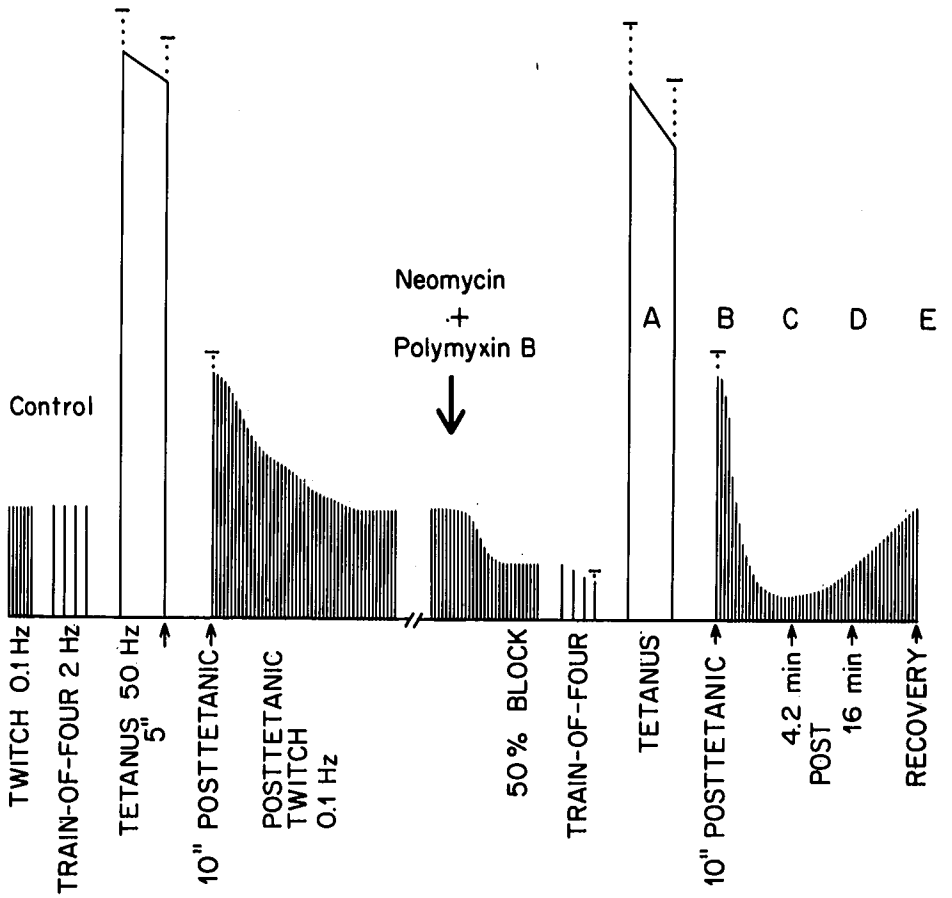

FIG. 1. Neuromuscular variables at control (*left of thick arrow*) and during blockage of transmission by equipotent mixture of neomycin and polymyxin B (*right*). Note relative sparing of tetanus from block (*A*), initial posttetanic augmentation of twitch (*B*), followed by posttetanic exhaustion (*C*), and subsequent recovery from posttetanic exhaustion to pretetanus level (*D*) and to control (*E*). This diagram is based on composite experimental data obtained from eight cats. The height indicates, to scale, the relative force output of muscle. The horizontal distance does not indicate real time to scale. Dotted vertical lines indicate standard errors of mean values.

The decrease averaged 22 per cent of control. After 4-aminopyridine, the mean pressure returned to the control level. ($P > 0.5$, t tests for paired values.)

Discussion

In every aspect examined, the neuromuscular blocking effect of the equipotent mixture was well approximated by averaging the values obtained with each antibiotic (table 1). The dose–response curve roughly paralleled those of the components, as judged by similar ED_{95}:ED_{50} ratios. Posttetanic exhaustion, a unique feature of neomycin-induced neuromuscular block,[5] became less observable but remained demonstrable. This can be explained by

TABLE 1. Neuromuscular Blocking and Hypotensive Effects of Neomycin, Polymyxin B, and an Equipotent Mixture

	Neomycin*	Polymyxin B*	Equipotent Mixture
Onset (min)	2	5–8	4 (2–7)
ED_{50} (mg/kg)	38	6.7	3.2 units*
ED_{95} (mg/kg)	58	10.8	5.5 units*
Recovery time (min)	10–20 (for 80 per cent)	72 (for 50 per cent)	28 (for 50 per cent)
Train-of-four ratio	1	0.42	0.72
Tetanus	Not blocked No fade	Relatively spared Slight fade	Slightly blocked Faded 9 per cent
10-second posttetanic facilitation	+++	+++	+++
Postfacilitation posttetanic exhaustion	+++	0	+
Edrophonium	Partial reversal	0, or enhancement	Partial reversal
4-Aminopyridine	Reversal (with overshoot)	Reversal (with overshoot)	Reversal (with overshoot)
Blood pressure decrease	—	Approximately 30 per cent	Approximately 22 per cent

* Unit stands for neomycin sulfate, 6 mg/kg, + polymyxin B base, 1 mg/kg.

the fact that neomycin contributes to only half the blockade produced by the mixture, and that polymyxin B has an opposite effect, namely posttetanic facilitation. The "tetanus-sparing" characteristic of neomycin-induced block[5,7] and a slight train-of-four and tetanic fade which distinguishes polymyxin B from neomycin also remained demonstrable. One main advantage of 4-aminopyridine is its ability to reverse antibiotic-induced neuromuscular block,[8,9] where anticholinesterase agents and calcium have not proven satisfactory after two decades of trials.[1] This advantage is also preserved in the presence of the mixed block. Therefore, despite differences in their mechanisms of action, the neuromuscular effects of neomycin and polymyxin B appear to interact *in vivo* by a straightforward addition.

The authors are indebted to Elaine Yang, M.D., and Chan Kieu, M.D. for translation of reference 9.

References

1. Pittinger C, Adamson R: Antibiotic blockade of neuromuscular function. Annu Rev Pharmacol 12:169–183, 1972
2. Van Nyhuis LS, Miller RD, Fogdall RP: The interaction between *d*-tubocurarine, pancuronium, polymyxin B, and neostigmine on neuromuscular function. Anesth Analg (Cleve) 55:224–228, 1976
3. Wright JM, Collier B: The effects of neomycin upon transmitter release and action. J Pharmacol Exp Ther 200: 576–587, 1977
4. Wright JM, Collier B: The site of neuromuscular block produced by polymyxin B and rolitetracycline. Can J Physiol Pharmacol 54:926–936, 1976
5. Lee C, Chen D, Barnes A, et al: Neuromuscular block by neomycin in the cat. Canad Anaesth Soc J 23:527–533, 1976
6. Lee C, Chen D, Nagel EL: Neuromuscular block by antibiotics: Polymyxin B. Anesth Analg (Cleve) 56:373–377, 1977
7. Flacke WE: Acute and subchronic effects of neomycin on neuromuscular transmission. V Internat Congr Pharmacol, p. 69, 1972
8. Lee C, de Silva AJC, Katz RL: Antagonism of polymyxin B-induced neuromuscular and cardiovascular depression by 4-aminopyridine. ANESTHESIOLOGY (accepted for publication
9. Sobek V, Lemeignan M, Streichenberger G, et al: 'Etude sur le diaphragme isole' de rat de l'antagonisme entre substances curarisantes et aminopyridines. Arch Int Pharmacodyn 171:356–368 1968