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Potentiation of the Combination of Pancuronium and Metocurine by Halothane and Isoflurane in Humans with and without Renal Failure

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Dose–response relationships for a 1:4 weight ratio–mixture of pancuronium and metocurine were studied during inhalational anesthesia with halothane and isoflurane in patients with and without renal failure. The time for recovery from 10 to 20% of control thumb twitch tension also was determined. In subjects with normal renal function, relaxant doses required for 95% twitch height suppression (ED_{95}) were 50% of those predicted by simple addition of effects when used with a balanced anesthetic technique, 37% of predicted when used with 1.3 MAC halothane, and 25% of predicted when used with 1.3 MAC isoflurane ($P < 0.05$). In subjects with renal failure, ED_{95} values for the combination were 40% of predicted when used with 1.2 MAC halothane and 45% of predicted when used with 1.2 MAC isoflurane (NS). For relaxants used singly in renal failure, pancuronium alone was slightly enhanced by 1.2 MAC halothane (85% of predicted), while 1.1 MAC isoflurane reduced the ED_{95} to 57% of predicted ($P < 0.05$). Similar results were obtained for metocurine alone when used in renal failure (77 and 58% of predicted when used with halothane and isoflurane, respectively) (NS). Predicted values are published results for balanced anesthesia in normals. Recovery times were prolonged twofold in renal failure ($P < 0.05$). Thus, the combination of pancuronium and metocurine is synergistic to the same degree in normals and in renal failure patients, but the total blockade produced by the combination is enhanced by halothane and isoflurane only in normals. (Key words: Anesthetics, volatile: halothane; isoflurane, Interactions (drugs): anesthetics; neuromuscular relaxants. Kidney: failure. Neuromuscular relaxants: metocurine; pancuronium.)

THE READY AVAILABILITY of dialysis has allowed prolonged survival for patients with end-stage renal disease and has led to dramatic increases in the number of such patients requiring surgery. Renal failure leads to significant functional impairment of all of the body's major systems and to alterations in the pharmacology of most drugs. The duration of action of many of the drugs used during anesthesia is prolonged by renal failure. Those drugs used to provide muscle relaxation are of particular concern because prolongation of their action has contributed to postoperative respiratory failure.[1] The plasma clearances of metocurine and pancuronium in anephric patients are one-half[2] and one-third,[3–6] respectively, of the clearance in normals, while serum concentrations of neuromuscular blocking agents required in renal failure are approximately two times higher than those required in normals.[2,4] These agents also have major dose-dependent autonomic side effects, including heart rate, heart rhythm, and blood pressure disturbances.[7] Methods for reducing the required dosage or duration of action of the neuromuscular blocking agents could reduce the risk of these potentially serious complications. Drug interaction effects offer two ways of reducing neuromuscular blocking agents doses: potentiation of the agents by inhaled anesthetics, and synergistic interactions between different neuromuscular blocking agents.

When used in normal subjects, individual nondepolarizing neuromuscular blocking agents are enhanced by inhaled anesthetics in a dose-dependent fashion.[8] For example, pancuronium dose requirements are reduced by a factor of 0.56 by 1.25 MAC of halothane and a factor of 0.32 by 1.25 MAC of isoflurane.[8] Potentiation of metocurine alone has not been investigated, nor has potentiation by inhaled agents been investigated in renal failure.

Certain combinations of nondepolarizing neuromuscular blocking agents are synergistic in their effects at the neuromuscular junction.[9–11] In particular, when pancuronium and metocurine are combined in a weight ratio of 1:4 as part of a balanced anesthetic technique (nitrous oxide, barbiturate, narcotic, relaxant), there is a twofold reduction in the relaxant dose required to reduce muscle twitch tension by 95% relative to the dose predicted by simple addition of effects.[11] Potentiation of combinations of neuromuscular blocking agents by inhaled anesthetics has not been investigated previously, either in normal subjects or in patients with renal failure. Therefore, dosage requirements were determined for the 1:4 combination of pancuronium and metocurine during halothane and isoflurane anesthesia in human subjects with and without renal failure.

Methods

The study population consisted of 56 patients with end-stage renal disease who were undergoing renal transplant, allograft nephrectomy, or vascular access procedures and 46 ASA I–III patients with normal

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TABLE 1. Anesthetic and Neuromuscular Blocking Agents Used in Study Groups

Group	Number of Patients	Age yr (SD)	Anesthetic Agent	MAC(SD)*	Neuromuscular Blocking Agent
Normal renal function					
1	9	36 (11)	Balanced†	—	Panc. + Metoc.‡
2	12	34 (11)	Halothane	1.3 (0.2)	Panc. + Metoc.
3	10	36 (11)	Isoflurane	1.3 (0.2)	Panc. + Metoc.
4	8	29 (11)	Halothane	1.2 (0.2)	Pancuronium
5	7	39 (10)	Isoflurane	1.2 (0.2)	Pancuronium
Renal failure					
6	6	33 (16)	Halothane	1.2 (0.3)	Pancuronium
7	6	36 (13)	Isoflurane	1.1 (0.3)	Pancuronium
8	7	41 (13)	Halothane	1.1 (0.3)	Metocurine
9	6	42 (15)	Isoflurane	1.1 (0.4)	Metocurine
10	7	31 (12)	Halothane	0.6 (0.1)	Panc. + Metoc.
11	8	39 (11)	Halothane	1.2 (0.2)	Panc. + Metoc.
12	8	40 (24)	Isoflurane	0.6 (0.1)	Panc. + Metoc.
13	8	35 (7)	Isoflurane	1.2 (0.2)	Panc. + Metoc.

* Age corrected end-tidal anesthetic values (see text).
† Barbiturate + narcotic + N_2O + relaxant.
‡ 1:4 weight ratio of pancuronium + metocurine.

renal function undergoing elective gynecologic and general surgical procedures. Informed consent was obtained according to a protocol approved by the Human Research Committee of The Oregon Health Sciences University. Patients were randomly assigned to one of the groups shown in table 1. The anesthetic concentrations shown are measured end-tidal values that were converted to MAC equivalents by reference to published values for MAC as a function of age for halothane[12] and isoflurane.[13] Groups 1, 4, and 5 served as controls by comparison with previously published neuromuscular blocking agent dosage requirements.[8,11] Groups 10 and 12 were included to investigate the effects of different inhaled anesthetic concentrations on the combination of pancuronium and metocurine.

TABLE 2. ED_{50} and ED_{95} Values for Pancuronium Alone and the 1:4 Weight Mixture of Pancuronium and Metocurine Used with Barbiturate–Narcotic–N_2O–Relaxant Anesthesia and with Halothane or Isoflurane Anesthesia in Patients with Normal Renal Function

Agent Relaxant	Pancuronium	Pancuronium + Metocurine
ED_{50}		
Balanced*	—	8.5 (0.8) + 34 (3.2)
Halothane	26 (3)	7.0 (0.5) + 28 (2.0)†
Isoflurane	14 (4)†	4.4 (0.6) + 18 (2.4)†
ED_{95}		
Balanced*	—	18 (3) + 72 (12)
Halothane	45 (6)	14 (1.2) + 56 (5)†
Isoflurane	36 (11)†	9 (1.4) + 36 (6)†

Values are expressed as mean (SD) in μg/kg.
* Barbiturate + narcotic + N_2O + relaxant.
† Significant difference at $P < 0.05$.

Premedication, used in 83% of cases, consisted of morphine sulfate 8 mg/70 kg im and/or diazepam 10 mg po given 1 h prior to surgery. Monitoring included continuous mass spectrometric analysis of end-tidal anesthetic and CO_2 concentrations (Perkin–Elmer Corporation, Pomona, California) and continuous measurement of thumb twitch tension (force of evoked thumb adduction) using a Grass® F10 transducer (Grass Instruments Corporation, Quincy, Massachusetts). Supramaximal 0.2 ms bipolar stimuli at a repetition rate of 0.17 Hz from a Grass® stimulus generator were delivered to the ulnar nerve at the wrist using needle electrodes. Anesthesia was induced with sodium thiopental, and ventilation with 60% N_2O was assisted or controlled as required for normocarbia. Temperatures ranged from 35.4° C to 37.8° C. Intubation of the trachea usually was performed without the use of muscle relaxants. However, in five patients, it was necessary to use succinylcholine 1.0 mg/kg. No group contained more than one of these patients. In these five cases, at least 20 min were allowed to elapse before additional neuromuscular blocking agents were given (range 25 to 35 min). Neuromuscular blocking agents were administered in incremental doses until less than 10% of control thumb twitch tension remained. Additional doses were given according to surgical requirements. An index of relative recovery time was obtained by measuring the time required for twitch tension to recover from 10 to 20% of control with stable anesthetic concentration. Reversal at the end of the procedure was by standard techniques and was verified by train-of-four testing[14] and by return of twitch tension to >90% of control.

TABLE 3. Recovery Times from 10 to 20% of Control Twitch Tension for Pancuronium Alone and the 1:4 Weight Mixture of Pancuronium Plus Metocurine Used with Balanced Anesthesia and with Halothane or Isoflurane Anesthesia in Patients with Normal Renal Function

Agent Relaxant	Pancuronium	Pancuronium + Metocurine
Balanced*	—	12 (6)
Halothane	11 (3)	7 (2)†
Isoflurane	20 (12)	11 (6)

Values are expressed as mean (SD) in min.
* Barbiturate + narcotic + N_2O + relaxant.
† Significant difference at $P < 0.05$.

A dose–response graph was constructed for each patient and for each group. The doses required for 50% reduction of twitch tension (ED_{50}) and for 95% reduction of twitch tension (ED_{95}) were determined from a regression on the grouped data expressed in log dose–probability coordinates.[15] Comparisons of dosage results were by one-way analysis of variance with a significance level of 5% (*i.e.*, groups stratified by renal status and anesthetic agent were treated separately).

Results

NORMAL RENAL FUNCTION

Dose–response graphs for pancuronium plus metocurine with balanced anesthesia, halothane 1.3 MAC, and isoflurane 1.3 MAC when used in normal patients are shown in figure 1. The intercepts of the three lines are significantly different ($P < 0.05$), but they are parallel to within expected statistical accuracy. Ninety-five per cent confidence bands of the means are shown for each fit. The ED_{50} and ED_{95} results are summarized in table 2. Doses and standard deviations for the metocurine fraction are defined as exactly four times those for the pancuronium fraction. All dosage differences are significant ($P < 0.05$). Recovery times from 10% of control twitch tension to 20% twitch tension range from 7 to 20 min and are shown in table 3. The values for Group 2 (normals, halothane with pancuronium plus metocurine) are significantly different ($P < 0.05$). However, only six recovery time measurements are available in this group, and they include the two most rapid recovery times observed in the study.

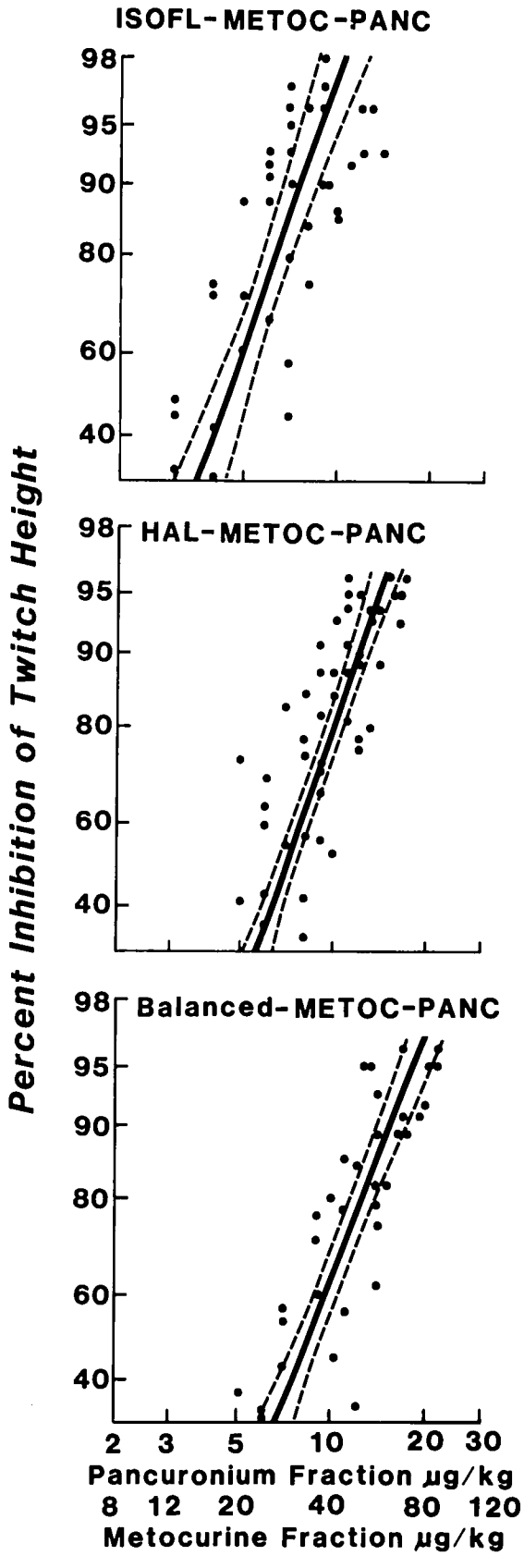

FIG. 1. Dose–response for the 1:4 pancuronium:metocurine combination with N_2O–narcotic–relaxant, halothane, and isoflurane anesthesia. Dashed lines enclose 95% confidence regions.

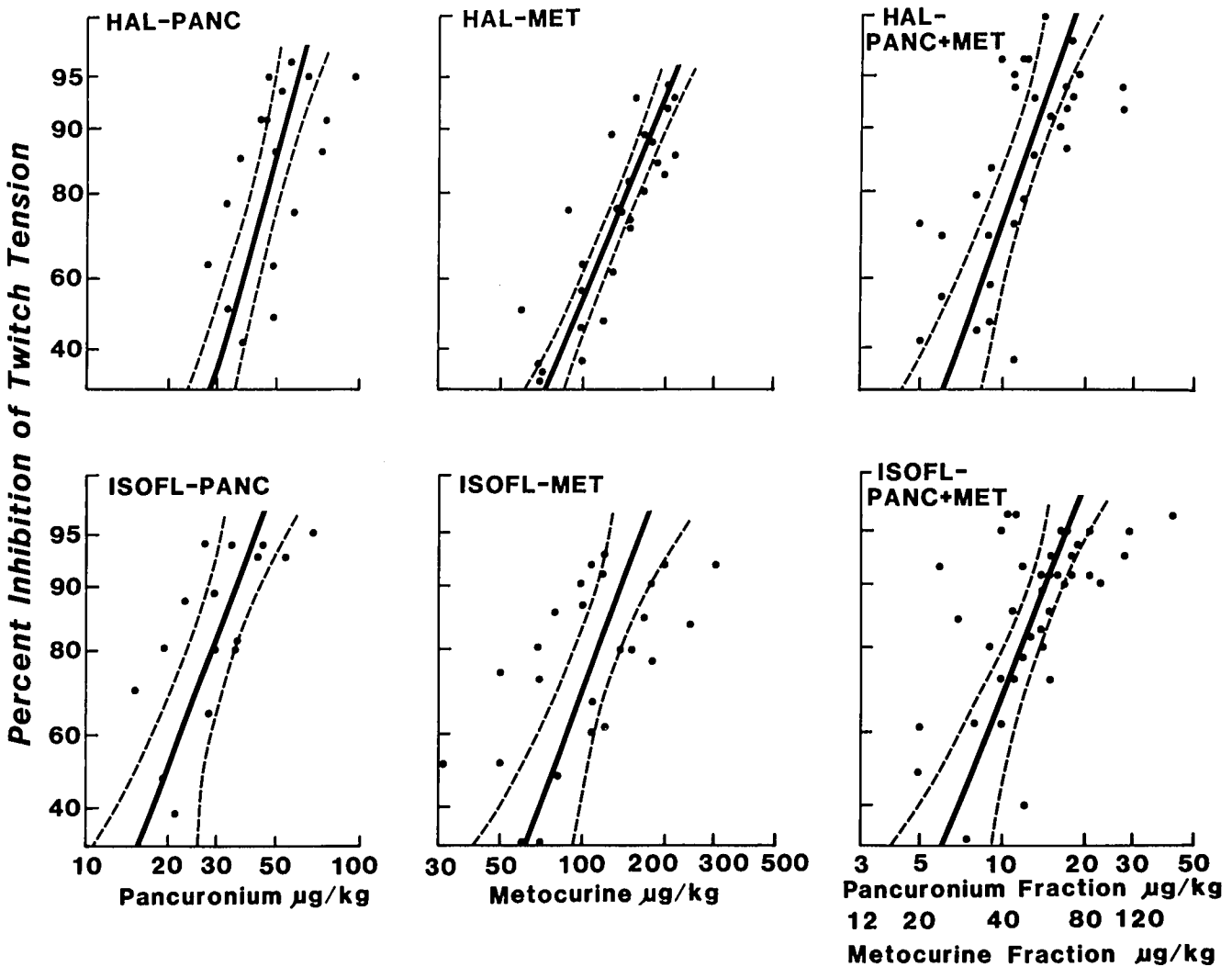

FIG. 2. Dose–response for pancuronium alone, metocurine alone, and the 1:4 weight ratio mixture of pancuronium and metocurine when used in combination with halothane and isoflurane in patients with renal failure. Ninety-five per cent confidence regions are shown.

RENAL FAILURE

Dose–response results from the least-squares analysis for halothane and isoflurane anesthesia with pancuronium, with metocurine, or with the 1:4 mixture of pancuronium and metocurine are shown in figure 2. Ninety-five per cent confidence bands for the means are indicated.

The ED_{50} and ED_{95} results are summarized in table 4. For the combination of metocurine and pancuronium, the differences shown are not significant. Recovery times from 10 to 20% of control twitch tension, shown

TABLE 4. ED_{50} and ED_{95} Values for Pancuronium Alone, Metocurine Alone, and the 1:4 Weight Mixture of Pancuronium and Metocurine Used with Halothane and Isoflurane Anesthesia in Patients with Renal Failure

Agent Relaxant	Pancuronium	Metocurine	Pancuronium + Metocurine*
ED_{50}			
Halothane	35 (6)	98 (10)	7.6 (1.8) + 30 (7)
Isoflurane	20 (6)†	79 (21)	8.0 (2.0) + 32 (8)
ED_{95}			
Halothane	61 (10)	223 (31)	14 (3) + 56 (12)
Isoflurane	41 (12)†	167 (60)	16 (3) + 64 (12)

Values are expressed as mean (SD) in µg/kg.
* 1:4 mixture of pancuronium and metocurine.
† Significant difference ($P < 0.05$).

in table 5, range from 28 min to 42 min and are not significantly different between groups. However, the recovery time difference between grouped normals and renal failure patients is significant (12 *vs.* 26 min, $P < 0.05$).

The results of our investigation of neuromuscular blocking agent dose–response differences between 0.6 MAC and 1.2 MAC halothane and isoflurane are summarized in table 6. Values range from 14 μg/kg pancuronium plus 56 μg/kg metocurine to 20 μg/kg pancuronium plus 80 μg/kg metocurine with no significant differences observed.

TABLE 5. Recovery Times from 10 to 20% of Control Twitch Tension for Pancuronium Alone, Metocurine Alone, and the 1:4 Weight Mixture of Pancuronium and Metocurine Used with Halothane and Isoflurane Anesthesia in Patients with Renal Failure

Relaxant Agent	Pancuronium	Metocurine	Pancuronium + Metocurine*
Halothane	18 (4)	24 (13)	18 (11)
Isoflurane	29 (13)	27 (14)	42 (17)

Values are expressed as mean (SD) in min. There are no significant differences between the groups.
* Barbiturate + narcotic + N_2O + relaxant.

Discussion

Our data confirm the previously published data of Lebowitz *et al.*,[11] on the combination of pancuronium and metocurine with a balanced anesthetic and extends that work by demonstrating that the combination is enhanced by halothane and isoflurane to a similar degree as is pancuronium alone. It is unlikely that these findings are due solely to our particular methods, since our data for pancuronium alone agree closely with that of Miller *et al.*,[8] who measured dose response relationships for pancuronium with halothane and isoflurane at three different anesthetic concentrations for each. Interpolating from their results to 1.2 MAC and converting from mg/m^2 to mg/kg (by assuming 1.75 m^2 to correspond to 70 kg) yields an ED_{50} of 0.021 mg/kg of pancuronium in the presence of 1.2 MAC halothane and 0.012 mg/kg with 1.2 MAC isoflurane. Our results of 0.026 mg/kg and 0.014 mg/kg, respectively, are not significantly different from these.

The 1:4 combination of pancuronium and metocurine is synergistic in patients with renal failure to the same degree as in normal patients. However, in contrast to the situation in normal patients, we find no potentiation of the combination by two different concentrations of halothane and isoflurane in the presence of renal failure. The ratio of the ED_{95} for the combination found in normals with a balanced anesthetic[11] to that found with inhaled anesthetics in subjects with renal failure is 1.3 (95% confidence limits 1.0–1.6) for halothane, while for isoflurane it is 1.1 (95% confidence limits 0.9–1.3). This is consistent with the lack of inhaled agent dose effect on the combination of pancuronium and metocurine when used in renal failure. However, metocurine muscle relaxation is enhanced by halothane and isoflurane in patients with renal failure to the same degree as is relaxation produced by pancuronium alone. Recovery times are prolonged by approximately a factor of two in renal failure, consistent with previous observations.[2–4]

The synergistic interaction between the curare derivatives and pancuronium may be due to a preponderance of prejunctional effects for the curare-like drugs and postjunctional effects for pancuronium.[11]

Ngai[16] has reviewed the effects of inhaled anesthetics in potentiating neuromuscular blockade. Possible mechanisms include the following: central nervous system effects, decreases in the sensitivity of the postjunctional membrane, and action at the muscle membrane, possibly by interference with Ca^{++} coupling.

Numerous manifestations of renal failure may contribute to the differences we found between normal patients and renal failure patients. Renal failure changes both intracellular and extracellular electrolyte concentrations, particularly Na, K, Ca, and Mg. In addition, major changes in protein binding and in neuromuscular transmitter number and function accompany renal failure.

The shorter recovery time for the pancuronium–metocurine combination suggests that the speed of recovery for the combination would be increased by decreasing anesthetic depth, particularly with isoflurane.

We conclude that the 1:4 combination of pancuronium and metocurine, when used in patients with normal renal function, is enhanced by halothane and to a greater degree by isoflurane, allowing very small doses of the combination to be used for clinical muscle relaxation with lesser autonomic side effects, greater ease of reversibility, and, possibly, a shorter duration of action than pancuronium alone. The combination of pancuronium and metocurine can also be used safely in renal failure, but it is not enhanced by either halothane or

TABLE 6. ED_{95} Values for the 1:4 Combination of Pancuronium Plus Metocurine for Different End-tidal Anesthetic Concentrations in Patients with Renal Failure

Agent	MAC	Panc. + Metoc.
Halothane	0.6	18 (4) + 72 (16)
Halothane	1.2	14 (3) + 56 (12)
Isoflurane	0.6	20 (10) + 80 (40)
Isoflurane	1.2	16 (3) + 64 (12)

Doses in μg/kg as mean (SD). The differences are not significant.

isoflurane. In addition, the duration of action of both pancuronium and metocurine used alone and as the combination of pancuronium plus metocurine is prolonged by approximately a factor of two by renal failure.

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