THE EFFECTS OF INHALATION ANAESTHETIC AGENTS ON CONVULSANT (LD-50) DOSES OF LOCAL ANAESTHETICS IN THE RAT

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THE INITIAL STUDIES dealing with attempts to prevent the central nervous system toxicity observed after overdosage of local anaesthetic drugs were done in 1926 by Tatum, Atkinson, and Collins.^{1,2} In dogs, cats, rabbits, and monkeys, they showed that phenobarbital prevented and treated the convulsions produced by cocaine overdose. Although Knoefel³ and Steinhaus⁴ were unable to reproduce these results, the cautious use of barbiturates is still recommended to prevent or control convulsions produced by local anaesthetics in man.⁵

Moore⁶ reported on the usefulness of oxygen as an antidote to prevent this complication. He treated patients with oxygen and the muscle relaxant succinylcholine to obviate seizures once the early signs of confusion, nausea and vomiting, increased respiratory activity, blood pressure rise, and tachycardia occurred. He indicated that because they masked the warning signs and further promoted cardiorespiratory collapse barbiturates were dangerous. On the other hand, Usubiaga *et al.*⁷ illustrated in man that high levels of procaine prolonged the duration of action of succinylcholine in low concentration by freeing it from plasma protein, but in higher concentrations it probably interfered competitively with its hydrolysis by pseudocholinesterase. The same group of investigators observed that succinylcholine did not alter the EEG spikes typical of convulsions, but merely blocked endplate depolarization, thus negating the motor sequelae of CNS activity.⁸ From these conclusions it is inferred that the role of succinylcholine in local anaesthetic toxicity is to facilitate airway procurement during violent seizures, a contention of certain danger if used by the inexperienced.⁵

It appears that ultrashort acting barbiturates may still have a place in symptomatic relief of this type of convulsion in man. Adriani⁹ suggested that under these circumstances such drugs ought to be used with caution when cardiorespiratory depression is present. Remmer¹⁰ proposed that the prior injection of phenobarbital in addition to CNS antagonism promoted the liver microenzyme systems and therefore, by induction of a "procarboxylase" system, it would decrease the duration of toxic symptoms. In another study, barbital and phenobarbital shortened the duration of toxicity produced by lidocaine in mice, while ethionine inhibited these effects.¹¹ These latter two actions may actually play a minor role in the prevention or treatment of drug-induced convulsions.

Previous studies combining inhalation agents with toxic doses of local anaesthetic drugs were discouraging. Wood and Haggart¹² showed in mice and dogs that ether, chloroform, and cyclopropane potentiated the effects of cocaine, pro-

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caine, and lidocaine, apparently reducing the LD-50 significantly by an additive depressive effect on the cardiorespiratory system, while at the same time convulsions were non-apparent. The protecting effect that recently introduced agents might have on the CNS toxicity produced by local anaesthetics has not been investigated. The purpose of this study was to determine whether one or all of these agents might have a protective or detrimental action in the neurological toxicity of overdose of local anaesthetics.

MATERIALS AND METHODS

Male Sprague-Dawley albino rats weighing from 65–90 gm were used. The intraperitoneal LD-50 doses of procaine, lidocaine, and tetracaine were determined using 20 rats per agent. They were found to be 230 mg/kg for procaine, 100 mg/kg for lidocaine, and 30 mg/kg for tetracaine. With these dosages, 80 per cent of the rats convulsed. The two main observations made throughout the study were duration of seizure measured by obvious grand mal activity and time from injection to death as noted by absence of respiratory and cardiac activity. Gases were delivered at constant flows into a chamber containing the rats, as described elsewhere.¹³ The animals were kept in this chamber 30 minutes and then injected and replaced in a different chamber into which the same gases were delivered. The oxygen concentration of both chambers was kept constantly at 21 per cent (P_{O_2} 126) by measuring it at the bottom of the chambers with a Beckman Oximeter. When only oxygen was used, the P_{O_2} in the chamber was 514 mm Hg. A Mayo gas vapour analyser was employed to measure the percentage concentration of halothane, methoxyflurane, and fluoroene.

It was intended to deliver 1.3 MAC to the chamber in the experiments with high concentrations and 0.3 MAC to the chamber in those experiments with low percentages. Twenty-four rats were employed for each of the twelve experiments. Each of four groups of six rats was injected with one of the three local anaesthetic agents or saline. The gases employed in this experiment were air, 100 per cent O_2 , N_2O-O_2 in 4:1 ratio, and halothane, methoxyflurane, and fluoroene vaporized in a mixture of nitrous oxide and oxygen to contain 21 per cent of the latter gas. The room temperature was kept constant at 24° C. The total flow was 5 L/min. in all experiments.

RESULTS

Rats inhaling oxygen and air exhibited no abnormal behaviour. When high concentrations of anaesthetic agents were given, the rats were asleep within 15 minutes. Those animals breathing N_2O-O_2 and low percentages of volatile agents were excited and agitated before injection. After injection of local anaesthetics, they were ataxic and unable to right themselves. Myoclonic activity preceded grand mal seizures, although not all animals who were myoclonic convulsed. Some, but not all, of those injected animals had tachypnoea and hyperpnoea. Apnoea usually preceded death. The results are summarized in Table I.

TABLE I
EFFECTS OF INHALATION ANAESTHETIC AGENTS AND O₂ UPON THE LETHAL AND CONVULSANT PROPERTIES OF LD-50 OF LOCAL ANAESTHETICS

Agent	Concentration (%)	Saline		Procaine		Lidocaine		Tetracaine	
		convulsed*	died*	convulsed*	died*	convulsed*	died*	convulsed*	died*
Air	—	0	0	4	3	5	3	5	3
Oxygen	70	0	0	6	5	6	5	4	3
N ₂ O-O ₂	21	0	0	2	2	4	5	5	6
N ₂ O-O ₂ + halothane	.86	0	0	0	5	0	5	0	3
N ₂ O-O ₂ + halothane	.25	0	0	1	2	0	4	0	2
N ₂ O-O ₂ + fluoroene	3.8	0	0	0	5	0	6	0	4
N ₂ O-O ₂ + fluoroene	1	0	0	0	4	2	5	0	1
N ₂ O-O ₂ + methoxyflurane	.21	0	0	0	3	0	5	0	1
N ₂ O-O ₂ + methoxyflurane	.05	0	0	2	0	3	4	5	1

*Number of animals affected in a group of six.

DISCUSSION

Statistically, in this study, O₂, N₂O-O₂, or the various inhalation agents regardless of concentration did not significantly guard against the lethal complications of local anaesthetic toxicity comparatively observed when air was inhaled by rats. Although high percentages of halothane, methoxyflurane, and fluroxene appeared to reduce the convulsive activity seen, this is a moot point. The results suggested that these agents increase the lethal effects of local anaesthetic agents. With concentrations of 1½ MAC, the results were similar to those of Wood and Haggart,¹² who noted that inhalational agents ablate obvious convulsions, but increase lethal complications by summation effects with local anaesthetic drugs, depressing the cardiorespiratory system. When low concentrations of methoxyflurane were inhaled, the administration of all local anaesthetic agents showed a reduced lethal potential. Specifically, with low percentages of fluroxene and halothane, tetracaine appeared to be less toxic. It could be hypothesized that there is a dual action of these agents depending on concentration; at high percentages, the convulsant effects of toxic levels of local anaesthetic drugs might be antagonized by suppression of the trigger zone of the CNS, located in the amygdalar¹⁴ region of the rhinencephalon, but this suppression also affects the respiratory centre which, combined with the already present suppression produced by local anaesthetic agents, results in apnoea and eventually death. This was further demonstrated in the rats breathing high oxygen concentrations, which showed no protection by this gas alone. Therefore, its alleged beneficial effects shown in other studies^{6,15} might be due to the fact that ventilatory exchange was maintained.

It can only be inferred that at low concentrations the trigger zone is suppressed, while the additive detrimental effect on respiratory and cardiac functions does not reach lethal potency, thus resulting in relative protection from toxicity.

In an analogous situation, Richards *et al.*¹⁶ showed in mice that the protective range of pentobarbital is narrow. The LD-50 of lidocaine was lowered by concentrations of pentobarbital greater than 40 mg/kg. No change was noted with less than 20 mg/kg. However, protection was achieved with dosages between 20 and 40 mg/kg. This dual effect on the LD-50 of lidocaine by pentobarbital can be interpreted as protection against convulsions at intermediate doses, and a combined barbiturate-local anaesthetic depression on cardiorespiratory functions at higher concentrations. Perhaps a more careful titration of anaesthetic agent concentration might better protect against convulsive and lethal effects of local anaesthetics.

SUMMARY

The inhalation of low concentrations of anaesthetic mixtures by rats appeared to provide protection from the obvious convulsions produced by intraperitoneal injections of LD-50 doses of local anaesthetic drugs. However, higher concentrations enhanced the lethal effects of procaine, lidocaine, and tetracaine, probably by a summation of their depressive action on the cardiac and respiratory functions.

RÉSUMÉ

L'inhalation par des rats de faibles concentrations de mélanges gazeux anesthésiques a semblé procurer à ces animaux une protection contre les convulsions évidentes produites par les injections LD-50 intrapéritonéales d'anesthésiques locaux. Cependant, de plus fortes concentrations ont augmenté les effets mortels de la procaine, de la lidocaïne, de la tétracaïne, probablement par l'addition de leur action dépressive sur les fonctions cardiaques et respiratoires.

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