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From the Norwegian Radium Hospital and the Municipal Hospital, Oslo, Norway

## **Comparison of Diallyl-nor-Toxiferine and d-Tubocurarine in Humans**

### **Influence of the Induction Agent**

J. STOVNER, R. ENDRESEN, and I. LUND

The great species variation which is characteristic for all muscle relaxants [1] is also present when one compares the two non-depolarizing relaxants, d-tubocurarine and diallyl-nor-toxiferine (Alloferin, Ro 4-3816). WASER [2] reports that in mice Alloferin is about equally potent to d-tubocurarine, while in rabbits and cats, Alloferin is 7 and 9 times respectively more potent than d-tubocurarine. We therefore have attempted to determine the potency, cumulative action and reversibility of Alloferin in relation to d-tubocurarine in clinical practice, using partly a blind technique [3, 4].

### *Experiments*

Figure 1 shows the grip strength curve of 10 conscious human volunteers, using the method of UNNA et al. [5]. During the first minute is given an injection of 55  $\mu\text{g}/\text{kg}$  body weight of either Alloferin or d-tubocurarine (D-TC). The grip strength tested with a dynamometer is plotted on the vertical axis in per cent of control grip strength. It is seen that this dose of Alloferin (Ro 4-3816) depresses the grip strength about 75% of normal, while the same dose of d-tubocurarine only depresses grip strength 50%. Recovery is seen to occur only slightly faster with Alloferin than with d-tubocurarine.

Figure 2 shows the fall in respiratory minute volume (RMV) of patients lightly anaesthetized with thiopentone, after injection of 200  $\mu\text{g}/\text{kg}$  body weight of either Alloferin (Ro 4-3816) or d-tubocurarine (D-TC). The respiratory minute volume in per cent of normal is plotted against time in minutes. Again it is seen that Alloferin and d-tubocurarine in equal doses depress the respiratory minute volume 75% and 50% respectively. Each tracing represents the mean values of 20 patients. The recovery time seems equal with the two compounds.

In other words, equal doses of the two drugs gave for Alloferin a 75% depression-response and for d-tubocurarine a 50% depression-response.

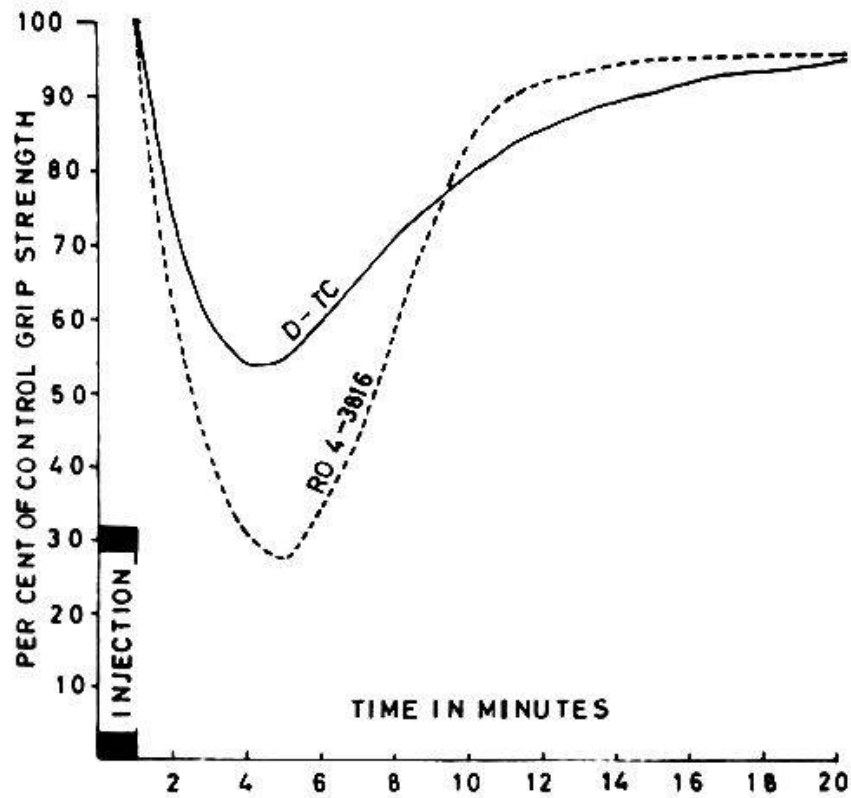


Fig. 1. Grip strength of volunteers after 55  $\mu\text{g}/\text{kg}$  of Alloferin or d-tubocurarine.

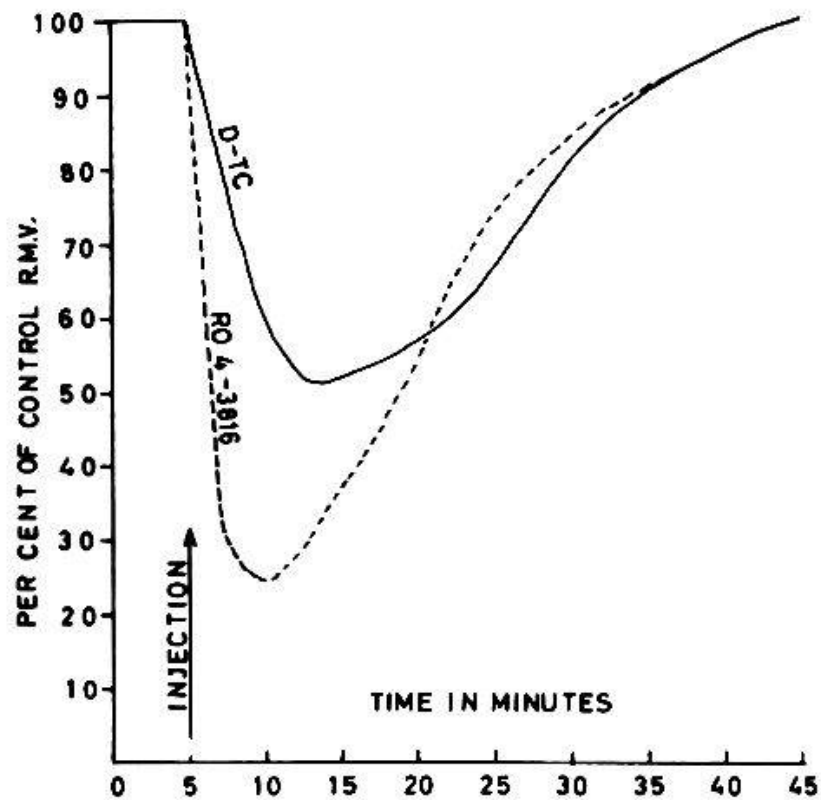


Fig. 2. Respiratory minute volume of anaesthetized patients after 200  $\mu\text{g}/\text{kg}$  of Alloferin or d-tubocurarine.

Table 1  
Classification of intubation (arbitrary scores)

Score 3: Excellent	Well separated vocal cords, not moving. No "bucking" on the tube
Score 2: Satisfactory	Slight movements of the cords when touched. Only slight "bucking" for brief period after insertion of the tube
Score 1: Fair	Conditions less favourable than in the two previous categories, but permitting intubation

This makes the relative potency:

$$\frac{\text{Alloferin}}{\text{d-tubocurarine}} = \frac{75\% \text{ response}}{50\% \text{ response}} = 1.5$$

We concluded therefore that Alloferin was about 1.5 times more potent than d-tubocurarine on grip strength and respiration.

### *Tracheal intubation*

To avoid bias on the part of the anaesthetists, coded solutions of Alloferin and d-tubocurarine were used in comparing the two drugs for tracheal intubation and abdominal relaxation.

Assuming from the above experiments that Alloferin was 1.5 times more potent, the coded solutions were adjusted to a concentration that was thought to be equipotent per unit volume. 1 ml of the coded solutions contained namely either 3 mg d-tubocurarine or 2 mg Alloferin which presumably would give equipotent solutions.

After usual premedication and induction with thiopentone, a single injection of one of the coded relaxants were given and the patients ventilated with pure oxygen by bag and mask for 3 min. Direct laryngoscopy was then performed, the cords were sprayed with 4% Xylocaine and an endotracheal tube inserted. The conditions for intubation and the reactions on the tube were observed and recorded.

We felt that the conditions for intubation was a rather sensitive criterion for determining the potency of a relaxant. During intubation it is, for example, quite possible to decide whether a difficulty is due to anatomical factors or to poor relaxation. We therefore graded the conditions for intubation and gave them arbitrary scores as follows (Table 1).

Intubation was performed on altogether 400 patients divided in 8 groups receiving 4 different doses of each of the coded relaxants. On opening the codes and adding the scores it appeared that the group receiving 375  $\mu\text{g}/\text{kg}$  body weight of d-tubocurarine came out with practically the same score (namely 60% of the highest obtainable) as the group receiving 200  $\mu\text{g}/\text{kg}$  body weight of Alloferin. This gives a relative potency of Alloferin to d-tubocurarine as  $\frac{375}{200} = 1.87$ .

Table 2  
Upper abdominal laparotomies (mean requirements,  $\mu\text{g}/\text{kg}$  body weight)

	d-tubo- curarine	Ro 4-3816	d-tubocurarine Ro 4-3816
Accumulated dose at end of 1st hour	473	273	1.73
Supplementary dose during 2nd hour	96	49	
Accumulated dose at end of 2nd hour	569	322	1.76
Supplementary dose during 3rd hour	68	33	
Accumulated dose at end of 3rd hour	637	355	1.78

As seen this is a somewhat higher potency for Alloferin than found in the experiments.

#### *Abdominal relaxation*

Of practical clinical importance is abdominal relaxation during laparotomies, and we tried to determine the relative potency under these conditions. The requirements of the two coded relaxants in 1100 laparotomies were determined. Anaesthesia was standardized to  $\text{N}_2\text{O}/\text{O}_2$  (3:1) supplemented by i.v. pethidine 25–50 mg and controlled ventilation with a nonbreathing technique (8–10 l ventilation/min).

In the following table is shown the mean requirements of the two relaxants during the 1st, 2nd and 3rd hours of upper abdominal laparotomies, as well as the accumulated doses of the two drugs at the end of each hour. It is seen that the ratio between the accumulated doses of the two relaxants is remarkably constant, namely 1.7 after each hour. This constant ratio can only mean that two compounds are accumulated to the same extent in the body (Table 2).

Our criteria for the presence of residual curarization at the end of operation was the patient's inability to lift the head from the pillow.

Provided the patients were sufficiently awake we found this both a practical and surprisingly clear-cut sign indicating the need for Prostigmin. Prostigmin was given in increments of 0.5 mg until the patients were able to lift the head from the pillow. The dose of Prostigmin required for the different patients postoperatively varied from 0 to 3 mg. On calculating the mean requirement of Prostigmin, no significant difference was found between the Alloferin group and the d-tubocurarine group. The mean requirement was somewhat lower in the Alloferin group, but the difference was too small to be statistically significant.

#### *Effect of the induction agent*

Recently we have started to induce sleep in our patients by intravenous injection of diazepam comparing it with the time-honoured thiopentone for

Table 3  
Muscle relaxant requirement with diazepam or thiopentone induction  
(radical hysterectomies, 100 cases)

Drug used for induction	Alloferin used during 1st hour of operation $\mu\text{g}/\text{kg}$ body weight			d-tubocurarine used during 1st hour of operation $\mu\text{g}/\text{kg}$ body weight		
	Mean	Max.	Min.	Mean	Max.	Min.
Diazepam 50 ♀	239	304	150	401	560	270
Thiopentone 50 ♀	270	310	190	431	510	210

this purpose [6]. Diazepam is known to be a powerful central nervous relaxant causing rapid relaxation in conditions like tetanus [7].

We have tried to determine the requirements of Alloferin and d-tubocurarine in a series of standard gynecological laparotomies, using thiopentone or diazepam as induction agents. The induction doses were 200–300 mg thiopentone or 15–25 mg diazepam. The results are shown in Table 3.

It is seen from the table that the mean requirements of the muscle relaxants were about 10% lower when diazepam was used for induction compared to thiopentone. This finding proved to be statistically significant. It is in good agreement with the finding of JÖRGENSEN [8] who in a similar series of cholecystectomies found a 10% reduction in the requirement of succinylcholine when 20 mg diazepam were given intramuscularly before the operation.

During the 2nd hour of our gynecological laparotomies no significant differences were found in the requirements of muscle relaxants between the thiopentone and the diazepam induced patients.

### *Summary*

1. When giving the same dose of Alloferin and d-tubocurarine to humans, we obtained a 50% stronger response after Alloferin than after d-tubocurarine on the grip strength and the respiratory minute volume.

2. Using a blind technique, Alloferin was 1.8 times more potent for tracheal intubation and 1.7 times more potent for abdominal relaxation than d-tubocurarine. Other characteristics such as duration of action, degree of accumulation and reversibility by Prostigmin were essentially the same for the two compounds.

3. Using diazepam as an induction agent instead of thiopentone reduced the requirements for both Alloferin and d-tubocurarine during the 1st hour of a gynecological laparotomy. During the 2nd hour no significant difference was found in the diazepam and thiopentone series.

### *Zusammenfassung*

1. Wenn wir unseren Patienten Alloferin und d-Tubocurarin in gleich großen Dosen verabreichten, so erhielten wir beim Alloferin eine 50% stärkere Wirkung als beim d-Tubocurarin, und zwar sowohl in bezug auf die Muskelkraft beim Händedruck, als auch in bezug auf das Atemminutenvolumen.

2. Im Blindversuch fanden wir heraus, daß die Wirkung von Alloferin bei trachealer Intubation 1,8mal und für die abdominale Entspannung 1,7mal stärker war als diejenige von d-Tubocurarin. Andere Gegebenheiten, wie z. B. die Wirkungsdauer, der Kumulativeffekt und die Reversibilität durch Prostigmin, waren im wesentlichen bei beiden Präparaten gleichwertig.

3. Wandten wir Diazepam an Stelle von Thiopenton als Induktionsagens an, so konnte während der ersten Stunde einer gynäkologischen Laparotomie die Verabreichung von Alloferin und d-Tubocurarin eingeschränkt werden. Während der zweiten Stunde zeigte sich keine bedeutungsvolle Differenz zwischen Diazepam- und Thiopentofällen.

### *Résumé*

1. Après la même dose d'Alloferine et de d-tubocurarine administrée à des hommes, nous avons obtenu une réponse 50% plus forte après l'Alloferine qu'après la d-tubocurarine sur la force de «la poignée de main» et le débit respiratoire.

2. Il a été noté, à l'aide d'une technique «aveugle», que l'Alloferine était 1,8 fois plus puissante que la d-tubocurarine pour l'intubation trachéale et 1,7 fois plus puissante sur la relaxation abdominale. D'autres caractéristiques telles que la durée d'action, l'effet cumulatif et la réversibilité par la Prostigmine étaient essentiellement les mêmes pour les deux composés.

3. L'utilisation de diazépam, comme agent inducteur à la place du thiopental, réduisait les exigences et en Alloferine et en d-tubocurarine durant la première heure d'une laparotomie gynécologique. Pendant la seconde heure, aucune différence significative n'a été trouvée entre les séries diazépam et thiopental.

### *Riassunto*

1. Somministrando a degli uomini la stessa dose d'Alloferina e di tubocurarina, abbiamo ottenuto con l'Alloferina una risposta del 50% più forte che con la d-tubocurarina; questo per quel che riguarda la forza di «una stretta di mano» e l'attività respiratoria.

2. Servendosi di una tecnica cosiddetta «cieca» si poté dimostrare che l'Alloferina nell'intubazione tracheale era 1,8 volte più potente che la d-tubocurarina e nel caso del rilasciamento addominale 1,7 volte più forte. Altre caratteristiche quali durata d'azione, effetto cumulativo e reversibilità dopo somministrazione di Prostigmina erano essenzialmente le stesse per le due sostanze.

3. Utilizzando come agente induttore il diazepam al posto del tiopental, si ebbe come effetto di diminuire le quantità necessarie di Alloferina e di d-tubocurarina durante la prima ora di una laparotomia ginecologica. Durante la seconda ora non si constatò nessuna differenza essenziale fra la serie con il diazepam e quella con il tiopental.

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