A STUDY OF DIAZEPAM (VALIUM®) FOR INDUCTION OF ANAESTHESIA*

GORDON M. WYANT, C.D., F.R.C.P.(C), F.F.A.R.C.S., AND LAVERN J. STUDNEY, M.D.†

DIAZEPAM (Valium®) is one of the most interesting drugs to have been introduced for a long time. It has been used widely for the treatment of anxiety, muscle spasm, and as a tranquillizing-sedative agent. Its anticonvulsant properties have been found valuable in status epilepticus, and anaesthetists have found the sedation it produces useful in the course of regional anaesthesia. Some antiarrhythmic properties also have been ascribed to the agent,[1] and these, together with its hypnotic and analgesic effects, had led to increasing use of the drug in cardioversion.

In 1966 McClish[2] reported on the use of diazepam as an induction agent in place of intravenous barbiturates, and shortly after our study had been started, Fox, Wynands, and Bhambhami[3] compared diazepam with thiopental for induction. Quite recently another paper on the subject has been published by Baker.[4] The present study was undertaken in an attempt to elucidate the usefulness of the drug for that purpose in standard operative procedures on a homogeneous group of patients, using a standard anaesthetic technique for maintenance of anaesthesia.

METHOD

Two hundred patients undergoing gynaecological procedures by the vaginal approach, such as examination under anaesthesia, D & C with or without biopsy of cervix, cone biopsy of cervix, hysterosalpingogram, insertion of Shirodkar suture, and the like were used for the study. Only patients in physical status 1 or 2 or their emergency equivalent were accepted. They were brought to the operating room unpremedicated. Premedication was administered intravenously on the operating table a few minutes before induction of anaesthesia. The patients were divided into four groups of fifty each, selection being entirely randomized. Groups were as follows:

Group 1 – atropine 0.6 mg i.v. + thiopental (2.5%) 2.5 mg/kg
Group 2 – atropine 0.6 mg i.v. + diazepam .3 mg/kg
Group 3 – atropine 0.6 mg i.v. + diazepam .45 mg/kg
Group 4 – diazepam .1 mg/kg i.v. + diazepam .3 mg/kg

Following induction, anaesthesia was maintained with nitrous oxide (8:2 L) supplemented with halothane administered by a Fluotec vaporizer set at 0.5

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†From the Department of Anaesthesia, University of Saskatchewan, and University Hospital, Saskatoon, Saskatchewan.

per cent and using a semiclosed Magill circuit without soda lime absorber. If full surgical anaesthesia could not be achieved or maintained satisfactorily in this standard fashion, sufficient increments were administered to render the anaesthetic adequate, and these adjustments were recorded.

Records were also kept and analysed of the usual vital signs as well as any other manifestations thought to be worth recording. In the postoperative recovery room the time of reaction to verbal stimuli and that to full orientation as to time and space were noted. Also recorded were any untoward effects which might have been attributable to the anaesthetic.

Results

Before results can be compared properly it is necessary to establish the fact that the four groups indeed are comparable in terms of *baseline data.* Review of Tables I and II proves that this is so. The data relating to age, height, and weight listed in Table I were submitted to statistical analysis, and differences in all instances were not significant. The calculated mean body surface area is listed in Table II, as is the distribution of physical status of the patients studied in each group. It is obvious from these figures, without further statistical analysis, that the four groups are comparable in these respects also.

TABLE I

Group	1	2	3	4
Age (yrs)	36.90 ± 3.45	36.18 ± 4.00	36.20 ± 4.23	36.46 ± 3.46
range	18–65	16–68	12–65	21–60
Height (ins)	63.79 ± 0.62	63.325± 0.94	63.445± 1.19	63.365± 0.82
range	58.50–67.50	57.25–68.25	58.00–67.50	57.25–69.50
Weight (lbs)	132.045± 5.16	129.80 ± 5.72	132.295± 6.05	130.88 ± 4.91
range	78.00–176.00	98.00–175.00	94.00–185.00	103.25–165.00

Analysis of variance: age – F = 0.0320, not significant; height – F = 0.4220, not significant; weight – F = 0.004, not significant.

TABLE II

Group		1	2	3	4
Mean BSA (m^2)		1.62	1.60	1.64	1.64
Physical status	1	15	17	14	18
	2	28	24	28	27
	5	7	9	8	5

The *duration* of anaesthesia and of operation, and the time from induction of anaesthesia to start of operation, are listed in Table III. The time from induction of anaesthesia to start of operation has been included in order to determine whether the choice of premedication, induction agent, or dosage variations may have so affected the anaesthetic as to cause possible delay in starting the operation. Again statistical analysis has failed to reveal any differences for the four groups, so that it may be concluded that the type of premedication and

TABLE III

Group	1	2	3	4
Duration of anaesthesia	22.98±2.94	23.84±3.46	25.14±4.11	24.82±2.56
range	9–63	6–66	10–95	9–48
Duration of operation	12.44±2.59	13.50±3.05	15.46±3.66	14.54±2.20
range	4–50	2–53	3–78	3–37
Time for induction of anaesthesia to start of operation	10.54±0.94	10.34±0.88	9.68±0.78	10.28±0.80
range	4–19	4–17	3–17	3–17

All times are in minutes.
Analysis of variance: duration of anaesthesia – F = 0.3594, not significant; duration of operation – F = 0.8049, not significant; time from induction of anaesthesia to start of operation – F = 2.1527, not significant.

TABLE IV

Group	1	2	3	4
Time reacting from end of anaesthesia	7.92±1.43	13.78±2.28	19.26±3.78	13.14±2.05
range	1–25	3–33	3–53	3–30
Time awake from end of anaesthesia	11.08±2.56	18.64±3.15	23.54±3.14	20.62±3.22
range	3–45	3–67	5–50	5–65

All times are in minutes.
Analysis of variance: time reacting – F = 13.6764, $p = 0.01$. Time awake – F = 19.84, $p = 0.01$.

induction used in this study did not exert any effect one way or the other in these regards.

Table IV lists the *time of reaction and awakening* from end of anaesthesia. Reacting time is defined for the purpose of this study as the time at which the patient reacted to simple verbal commands, whereas awakening time is the time to full orientation as to time and space. Both reacting and awakening in the three diazepam groups were significantly longer than in those who had received thiopental for induction of anaesthesia. This difference is statistically significant at the $p = .01$ level. Amongst the diazepam groups the longest mean times occurred in group 3. Patients in this group received the largest amount of diazepam in one single injection, whereas there seemed to be little difference between groups 2 and 4, which differed in the premedication but not in the amount of diazepam used for induction of anaesthesia. This finding is particularly interesting since the total dose of diazepam in group 4 came close to the single dose administered to patients in group 3. It must be concluded that when the dose of diazepam is divided into premedication and induction, the impact of the drug was somewhat blunted as far as its effect on awakening is concerned.

However, if one examines the *quality of anaesthesia* (Table V), it is evident that groups 2 and 4 differ decidedly, and it must be assumed that in this respect the premedication indeed was significant. Induction doses in groups 1 and 2 were left small deliberately, and the consequences of this are quite evident. Inadequate anaesthesia in this connection is defined as one in which either

TABLE V

PEROPERATIVE COMPLICATIONS

Group	1	2	3	4
Inadequate anaesthesia				
number	11	13	3	3
per cent of total	22	26	6	6
Moaning	3	3	2	1
Coughing	6	5	1	1
Moving	8	3		1
Hiccough				2
Incomplete relaxation	2			
Cyanosis (resp. depres.)				1
Prolonged induction	1			

TABLE VI

POSTINDUCTION CHANGES IN CIRCULATORY PARAMETERS

Group	1	2	3	4
Hypotension	11	10	6	9
Tachycardia	4		1	
Bradycardia	2	2		

an additional amount of thiopental was required to obtain adequate induction (group 1) or the concentration of halothane had to be increased beyond 0.5 per cent early in the course of maintenance to obtain satisfactory operating conditions. Three of the eleven patients in group 1 required more thiopental; in all others the concentration of halothane was increased. Complications during the operation were associated most commonly with inadequate depth of anaesthesia and were, therefore, significant, particularly in groups 1 and 2.

Post-induction changes in circulatory parameters are listed in Table VI. Such changes were considered to exist if the systolic blood pressure or pulse rate underwent a change of 20 per cent or more from preinduction values. While the differences in the three groups are not excessive, group 1 had the highest incidence of hypotension and tachycardia. This is significant, particularly in view of the very small dose of thiopental used. On the other hand, diazepam, at least in groups 2 and 4, also presented a significant incidence of hypotension, although this was not associated with tachycardia. It is interesting that in both groups 1 and 2 bradycardia occurred in two instances each.

Patients not infrequently became verbally uninhibited upon induction, especially in group 3 where the total dose of diazepam was quite substantial. Many expressed a feeling of elation and general well-being in a somewhat slurred fashion before losing full consciousness. *Postoperative complications* were few and on the whole insignificant. They are listed in Table VII. In addition to these we found in the first few months when we used veins on the dorsum of the hand or the forearm for injection that virtually every patient who received diazepam complained of burning on injection and later many of them developed thrombosis, which was not only painful but persisted for quite a long time. Once this

TABLE VII
POSTOPERATIVE COMPLICATIONS

Group	1	2	3	4
Dizziness	1			
Drowsiness		1		
Nausea and vomiting				1
Vomiting			1	
Headache			1	
Remembers mask	1			

complication was fully understood, a change was made to the veins in the antecubital fossa and thereafter no patient complained of burning on injection nor was thrombosis encountered.

SUMMARY AND CONCLUSIONS

Different dose ranges of diazepam have been studied in women as to their suitability or otherwise for the purpose of induction of general anaesthesia, and they have been compared with thiopental under standardized conditions. On the basis of our findings it would appear that diazepam is indeed a satisfactory induction agent and because of the minimal effects which it exerts on circulation might be recommended in patients in whom it is advisable to avoid the circulatory depression and tachycardia which so often follows the injection of thiopental, or in those who in the past have demonstrated sensitivity to or intolerance of barbiturates. The state produced by diazepam cannot be compared with thiopental narcosis in that it comes on somewhat more gradually and induces a state of quiescence, unresponsiveness, and amnesia in which the subsequent inhalation agents are accepted readily. Indeed this state of stupor is frequently preceded by a feeling of elation, and general well-being, and by slurring of speech and loquaciousness; these are not seen with thiopental. The only major complication attributable to diazepam itself was the high incidence of burning on injection and of venous thrombosis which followed injection of the drug into the smaller peripheral veins of the upper extremity. However, this complication can be prevented entirely by selecting larger veins such as those in the antecubital fossa.

RÉSUMÉ

Cette étude a pour but d'évaluer le diazépam comme agent d'induction à l'anesthésie générale. On l'a comparé à doses variables avec le thiopentone chez 200 femmes soumises à des interventions gynécologiques vaginales. On les a partagées en quatre groupes de 50 chacun. Le premier groupe a reçu comme prémédication 0.6 mg d'atropine par voie intraveineuse et pour l'induction 2.5 mg/kg de thiopentane à 2.5 pour cent. Le deuxième groupe à reçu la même prémédication mais pour l'induction on a utilisé 0.3 mg/kg de diazépam. Pour le troisième groupe, même prémédication mais la dose de diazépam a été augmentée à 0.45 mg/kg. Quant au quatrième groupe, il a reçu en prémédication 0.1 mg/kg de diazépam

par voie intraveineuse suivi de 0.3 mg/kg aussi de diazépam pour l'induction. On a continué l'anesthésie au protoxyde d'azote–halothane à 0.5 pour cent en autant que cette dose a été suffisante. Les résultats ont été soumis à une analyse statistique.

Il a été établi que les quatre groupes étaient comparables du point de vue age, taille, poids, surface corporelle et état physique. La durée de l'anesthésie et de l'opération de même que le temps écoulé de l'induction de l'anesthésie au début de l'opération n'ont pas été influencés par le genre ou la dose de la prémédication ou de l'agent d'induction. Cependant si l'on analyse le temps écoulé à partir de la fin de l'anesthésie jusqu'au moment des premières réactions et du réveil, il devient évident que ce temps est plus long, et de façon notable, chez des malades ayant reçu atropine et diazépam à 0.45 mg/kg.

A cause des faibles doses de thiopentone dans le groupe 1 et de diazépam dans le groupe 2, ces deux groupes ont présenté le plus grand nombre d'anesthésies insuffisantes nécessitant les plus fréquentes administrations d'halothane au-delà de 0.5 pour cent. Le groupe ayant reçu du thiopentone a présenté le plus fréquemment, malgré les faibles doses utilisés, de l'hypotension et de la tachycardie après l'induction, mais en aucun cas les troubles circulatoires n'ont été sérieux. Il y eut peu de complications postopératoires sauf des thromboses veineuses lorsque l'injection était pratiquée dans une veine dorsale de la main.

En conclusion, le diazépam est un agent convenable pour l'induction de l'anesthésie, mais il est utile surtout lorsque le thiopentone est contre indiqué pour une raison ou pour une autre.

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