DOUBLE-BLIND EVALUATION OF DOXEPIN HYDROCHLORIDE (SINEQUAN®) FOR PREANAESTHETIC MEDICATION

ALLEN B. DOBKIN, M.D. AND ARUNA A. DESAI, M.B.*

DOXEPIN HYDROCHLORIDE is a dibenzoxepin derivative which differs structurally from amitriptyline only by the introduction of one oxygen into the central assymetric ring (Figure 1). It has depressant and antidepressant properties characteristic of other tricyclic compounds used to treat anxiety such as amitryptyline (Elavil®), desipramine (Norpramin®), impramine (Tofranil®), nortripyline (Aventyl®) and protriptyline (Vivactil®). The drug has been marketed mainly for patients with psychoneurotic anxiety; for mixed symptoms of anxiety and depression which may be associated with organic disease; and for alcoholic patients with anxiety and depressive psychic disorders.

Previous clinical trials have indicated that doxepin is well tolerated even in elderly patients and does not appear to cause euphoria or dependence during prolonged therapy. It is compatible with monamine oxidase inhibitors. The effect of alcohol and other sedatives is augmented. It has anticholinergic properties resembling those of scopolamine, causing drowsiness, dry mouth, blurred vision and urinary retention.

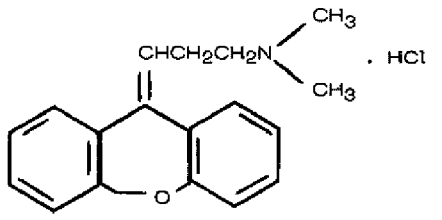
Animals tested with doxepin showed a strong tranquilizing activity as measured by suppression of conditioned avoidance behaviour in rodents; antidepressant effects are shown by augmenting amphetamine stimulation and antagonism to reserpine depression in dogs. Slowing of the EEG occurs in monkeys. There are only slight vasodilator properties as measured by pulse rate and femoral blood flow in the dog. Doxepin relieves smooth muscle spasm induced by histamine, serotonin, barium chloride, and acetylcholine.[1]

Following approval of the Committee on Human Experimentation of the Medical Faculty, this study was performed using a double-blind technique on 442 consenting adults to determine the safety and efficacy of doxepin hydrochloride as a preanaesthetic medicant for patients scheduled to undergo major elective operations under general anaesthesia.

METHOD

The procedures followed were the same as in several previous such studies.[2-4] Identical capsules containing one of 25 mg doxepin, 10 mg diazepam, 100 mg secobarbital or an inert placebo (lactose) were prepared for administration as oral medication the evening before operation. Ampoules were prepared containing the same drugs, in the same dosage, in solution for intramuscular administration. A random-number table was used to assign the four compounds to a list of 475 consecutive numbers (33 doses were discarded because of ampoule breakage). The

*From the Department of Anesthesiology, State University Hospital, State University of New York, Upstate Medical Center, Syracuse, New York, 13210, U.S.A.



DOXEPIN HYDROCHLORIDE
(SINEQUAN[R])

FIGURE 1
Structural formula of Doxepin hydrochloride (Sinequan®).

code was concealed until the study was concluded and the data tabulated on the 442 case studies.

After preanaesthetic rounds, consenting adult patients, who were scheduled for an 8 am. operation in most instances, were assigned premedication by the consecutive numbers. The capsule was administered by the medication nurse at 9 pm. In each case, orders were written to administer a single 100 mg capsule of secobarbital orally if the patient was not asleep within two hours after the coded medication was taken.

One hour before the scheduled operation, a solution of the same compound as had been given the night before was injected intramuscularly along with 0.3 or 0.4 mg scopolamine from a separate syringe.

A questionnaire which included an abstract of vital data from each patient's chart, review of the physician's preanaesthetic assessment, interview of the patient immediately before induction of anaesthesia, and interview of the anaesthetist following induction of anaesthesia, was completed for each patient by a specially trained nurse. Further pertinent information was recorded in the recovery room. The patient was again interviewed the day after the operation, and further information related to the postanaesthetic follow-up was obtained from the chart. The questionnaire was then checked to ensure that all required information was present.

When the study was completed, all data on the questionnaires were transferred to IBM cards and analysed statistically, employing the chi-square test and p values.[5]

RESULTS AND DISCUSSION

Approximately 10 per cent of the patients had difficulty sleeping after the initial night-time medication. The majority of these slept after supplementary medication was given, including those who were in the placebo group. The mean time for administration of medication before induction of anaesthesia was 72 ± 32 minutes.

No untoward effects occurred with any of the drugs during this study. Although several patients complained of stinging at the site of the intramuscular injection, it was not due to any one agent, i.e., it occurred with scopolamine as well as with each of the sedatives and the placebo. Recovery from anaesthesia was marked by a brief

period of bizarre behaviour in six patients of whom two each received the placebo, secobarbital and doxepin. This response probably was unrelated to the premedication although it can occur with scopolamine. One of the two patients in the doxepin group who reacted in this manner was discovered to be an amphetamine addict in the withdrawal stage.

Tables I and II show that the distribution of the case studies was statistically similar according to sex, age, physical state, maintenance agents and supplementary medication, which indicated a satisfactory randomization occurred.

Table II also shows that, although a few more patients required a supplementary dose of secobarbital to induce "sleep" in the placebo group, the difference from the treated groups was not statistically significant. There is no evidence that the amount of thiopentone to induce "sleep" was influenced by the premedication, although the administration of scopolamine may well have masked a difference.

Preinduction answers by the patients (Table III)

Fewer patients were sleepy and more were nauseated in the placebo group than those in the other three groups, and both secobarbital and doxepin appeared to reduce gastrointestinal symptoms. Otherwise there was no statistical difference in the four groups.

Preinduction answers by the patients (Table III)

In the opinion of the anaesthetist, diazepam and doxepin appeared to reduce tension and talkativeness more than did the placebo and secobarbital. Doxepin was thought to induce sleepiness in *fewer* patients than the other sedatives. Otherwise the differences were insignificant. A drug effect, in addition to the action of scopolamine, was not evident more often in the drug-treated groups.

Judgment of the over-all effect of medication (Tables V and VI)

In the judgment of the anaesthetist, analysed statistically, diazepam- and doxepin-treated patients were *not* found to have adequate sedation more often than the placebo- and secobarbital-treated groups. Considering only the patients judged *inadequately sedated*, a difference between groups appears likely. Furthermore, if the assumption is made that the supplementary dose of secobarbital given the previous evening affected the results (see Table VI), there was a contrast between the treated and untreated groups indicating, perhaps, that those who received active drugs appeared to be better sedated than those that received the placebo. However, again, *the difference was not significant statistically.*

Preoperative and postoperative vital data (Tables VII and VIII)

There was no clinical evidence of depression of vital signs due to the drugs tested. The groups were comparable on the basis of past history of thyroid dysfunction, assessment of psychic state, and the character of induction of anaesthesia. Hypotension occurred more often in the postoperative period in the placebo-treated group. This probably was not related to treatment, although some of these patients may have been carried at a deeper level of anaesthesia. Amnesia for the induction period occurred less often in the placebo group, but the difference was not statisti-

TABLE I

DISTRIBUTION OF PATIENTS IN THE STUDY

	Placebo (112 patients)	Secobarbital (116 patients)	Diazepam (114 patients)	Doxepin (100 patients)	Statistical analysis chi-square	significance
Sex						
male	39	41	39	24	4.15	NS
female	73	75	75	76	(3 *df*)	
Age						
<50	59	57	62	54	0.78	NS
>50	53	59	52	46	(3 *df*)	
mean ± SD (yrs)	47.5 ± 16.3	49.5 ± 15.7	49.4 ± 16.9	46.9 ± 16.5		
Physical state (ASA)						
I	24	20	27	21		
II	73	80	63	72		
III	15	15	23	7	12.60	NS
IV	0	1	1	0	(9 *df*)	
Primary maintenance agents						
N_2O + methoxyflurane	40	41	34	34		
N_2O + enflurane	28	29	38	30		
N_2O + "balanced"	18	11	16	11		
N_2O + halothane	20	25	22	19	8.13	NS
N_2O + Forane	6	10	4	6	(12 *df*)	

TABLE II

USE OF SUPPLEMENTARY MEDICATION

	Placebo (112 patients)	Secobarbital (116 patients)	Diazepam (114 patients)	Doxepin (100 patients)	Statistical Analysis chi-square	significance
Secobarbital	17	11	11	11	2.8	NS
Scopolamine	112	116	114	100		NS
Thiopental(induction)	285 mg.	295	280	285		NS
SD	±112	±100	±115	±130		

TABLE III

ANSWERS TO DIRECT QUESTIONS

	Placebo (112 patients) per cent	Secobarbital (116 patients) per cent	Diazepam (114 patients) per cent	Doxepin (100 patients) per cent	Statistical Analysis chi-square (3 *df*)*	significance
Uncomfortable	10	10	7	5	4.50	NS
Worried	45	41	39	36	3.54	NS
Tense	34	28	27	28	2.28	NS
Euphoric	14	6	11	11	2.91	NS
Sleepy	36	43	47	68	10.08	<0.025
Nauseated	12	3	10	4	9.02	<0.050
Vomited	2	0	1	0	3.69	NS
Tired	56	55	51	57	0.80	NS
Diplopia	4	2	6	4	1.48	NS
Dysphoria	16	10	10	9	3.51	NS

*df = degrees of freedom.

TABLE IV

ANAESTHETISTS' IMPRESSIONS OF PATIENTS' STATE

	Placebo (112 patients) per cent	Secobarbital (116 patients) per cent	Diazepam (114 patients) per cent	Doxepin (100 patients) per cent	Statistical Analysis chi-square	significance
Discomfort	12	12	4	9	5.90	NS
Worry	30	28	25	20	3.32	NS
Tenseness	17	21	10	9	9.27	<0.050
Euphoria	8	12	3	7	7.16	NS
Sleepiness	52	44	49	25	19.32	<0.005
Nausea	6	2	3	2	3.33	NS
Talkativeness	18	20	9	10	8.73	<0.050
Lid lag	0	1	1	3	4.55	NS
Weakness	1	1	2	5	5.99	NS

TABLE V

OVER-ALL EFFECT ESTIMATED BY ANAESTHETIST

	Placebo (112 patients) per cent	Secobarbital (116 patients) per cent	Diazepam (114 patients) per cent	Doxepin (100 patients) per cent	Statistical Analysis chi-square	significance
Adequate	73	70	77	82	4.6	NS
Inadequate	25	25	20	9	10.8	$< .01$
Excessive	2	5	3	9	7.8	NS
Supplemental required	16	9	11	11	2.8	NS

TABLE VI

OVER-ALL EFFECT ASSUMING THAT SUPPLEMENTAL SECOBARBITAL HAD NOT BEEN GIVEN

	Placebo (112 patients) per cent	Secobarbital (116 patients) per cent	Diazepam (114 patients) per cent	Doxepin (100 patients) per cent	Statistical Analysis chi-square	significance
Adequate	57	61	66	71	4.8	NS
Inadequate	43	39	34	29	(3 *df*)	

TABLE VII

PREOPERATIVE VITAL DATA

	Placebo (112 patients)	Secobarbital (116 patients)	Diazepam (114 patients)	Doxepin (100 patients)	Statistical Analysis chi-square	significance
Admission						
mean BP mm Hg	134/80	138/81	131/77	133/80		
mean PR/min	83	84	85	84		
Presedation						
mean BP mm Hg	131/78	133/79	126/75	128/78		
mean PR/min	82	82	81	82		
Preinduction						
mean BP mm Hg	133/79	134/80	131/80	130/77		
mean PR/min	79	79	80	81		
Thyroid history	13	8	9	8		NS
Presedative assessment						
stable	84	84	82	75		
nervous	8	10	7	10	3.5	NS
very nervous	20	22	25	15	(6 *df*)	
Induction						
smooth	107	113	113	95		
slow-smooth	4	2	1	3	4.8	NS
difficult	1	1	0	2	(6 *df*)	

TABLE VIII

POSTOPERATIVE VITAL DATA

	Placebo (112 patients)	Secobarbital (116 patients)	Diazepam (114 patients)	Doxepin (100 patients)	Statistical Analysis chi-square	significance
Hypotension						
>20% after induction	8	15	9	6	4.0	NS
>20% postoperative	11	6	7	1	7.8	.05
Amnesia for induction	26	37	29	34	4.2	NS
Shivering after anaesthesia	8	10	13	8	1.4	NS
Nasogastric suction during & after	24	22	28	20	1.2	NS
Nausea and/or vomiting, first 24 hrs	45	32	34	28	5.5	NS
Urine retention						
Yes	9	10	10	7		
No	57	52	55	50	2.0	NS
Urinary catheter used during & after	46	54	49	43	(6 *df*)	
Delay in awakening after surgery, mean in minutes	16	23	20	19		NS

cally significant. Undoubtedly amnesia was due in some measure to the effect of scopolamine.[4] Other differences also lacked statistical significance although there was a higher incidence of nausea and/or vomiting postoperatively in the placebo-treated group. There was no evidence of a greater incidence of urinary retention in the doxepin-treated patients, and the mean time delay in awakening after anaesthesia was similar in the four groups.

Summary and Conclusions

A double-blind evaluation of randomly-assigned placebo, secobarbital (100 mg), diazepam (10 mg) and doxepin (25 mg) was carried out in 442 consenting, adult patients who were scheduled for elective major operations under general anaesthesia. A capsule of the test compound was given orally the night before to aid induction of sleep with provision for supplementary medication with secobarbital if sleep did not occur within two hours. About one hour before induction of anaesthesia, scopolamine (0.3 or 0.4 mg) and one of the test compounds were injected intramuscularly from separate syringes. Data were collected by a specially trained nurse from the patients' records and interviews of patients and anaesthetists. Upon completion of the study, all pertient information was punched on IBM cards and tabulated. The code was then revealed to allow statistical analysis by the chi-square test.

The data were found to be comparable in the four treatment groups, as to sex, age, physical state, and anaesthetic agent used. Vital signs were not affected by the medication and no adverse reactions were observed, although patients appeared to be heavily sedated in some instances. Although the over-all effects of the sedative drugs on the patients were not significantly different from those that received placebo, there were more patients with inadequate sedation in the placebo group. There was no striking difference in the effect of diazepam and doxepin, which appeared to be marginally better than secobarbital and the placebo.

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Résumé

Chez 442 adultes volontaires qui devaient subir une opération élective sous anesthésie générale, nous avons fait une étude à double-inconnu du placebo, du sécobarbital (100 mg), du diazépam (10 mg) et du doxepin (25 mg) médicaments donnés au hazard. La veille de l'opération, nous avons donné par la bouche une capsule du médicament à étudier pour aider l'induction du sommeil et, si, en deça

de deux heures, le sommeil ne survenait pas, nous donnions une médication supplémentaire avec du secobarbital. Une heure avant le début de l'anesthésie, nous avons donné par voie intramusculaire, avec des seringues séparées, de la scopolamine (0.3 ou 0.4 mg) et un des médicaments à étudier. La cueillette des renseignements a été faite par les anesthésistes et des infirmières bien préparées à cette fin et cela d'après le dossier des malades et par des questions aux malades. A la fin de l'étude, tous les renseignements ont été poinçonnés sur des cartes IBM et disposés en tableaux. Alors le code a été décelé pour permettre une analyse statistique par le système "chi-square."

Les données étaient comparables dans les quatre groupes traités en ce qui concerne le sexe, l'âge, l'état physique et l'agent anesthésique employé. Les signes vitaux n'ont pas été influencés par les médicaments et aucune réaction indésirable n'a été observée bien que, en certaines circonstances, les malades semblaient très affaissés. Même si les effets en général des sédatifs sur les malades ne variaient pas beaucoup de ceux produits par le placebo, un plus grand nombre de malades ont eu une sédation inadéquate dans le groupe de ceux qui ont reçu du placebo. Nous n'avons pas observé d'effet très différent entre le diazepam et le doxepin; toutefois, ces deux produits ont semblé légèrement supérieurs au secobarbital et au placebo.

REFERENCES

1. AMA Drug Evaluations. First Edition, American Medical Association, Chicago (1971).
2. DOBKIN, A.B.; ISRAEL, J.S.; & BYLES, P.H. Double-Blind Study of Methotrimeprazine, Morphine and Meperdine for Preanesthetic Medication. Anesth. & Analg., *44*: 510 (1965).
3. DOBKIN, A.B.; MALIK, K.; & ISRAEL, J.S. Double-Blind Study of Hydroxyzine, Promethazine, Secobarbital and a Placebo for Preanaesthetic Medication. Canad. Anaesth. Soc. J., *12*: 499 (1965).
4. DOBKIN, A.B.; ISRAEL, J.S.; EVERS, W.; & BISSET, C.M. Double-Blind Evaluation of Diazepam for Premedication. Canad. Anaesth. Soc. J., *17*: 52 (1970).
5. SOKAL, R.R. & ROHLF, F.J. Biometry: the principles and practice of statistics in biological research (chapter 7, pps. 127–174). W.H. Freeman & Co., San Francisco (1969).