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THE PROTECTIVE ACTION OF PICROTOXIN IN PROLONGED SURGICAL ANESTHESIA WITH EVIPAL*

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EVIPAL soluble, the sodium salt of *n*-methyl-cyclohexenyl-methyl malonyl urea, is one of the newer barbiturates characterized by a powerful hypnotic and anesthetic index associated with a remarkably rapid rate of destruction in the system when administered parenterally. This latter characteristic accounts for its rather low toxicity as compared with other short acting barbiturates like nembutal, pernocton and phanodorn.

With respect to its therapeutic index Killian¹ reported a toxic-narcotic ratio of 100:24-27 in rabbits; Weese² a toxic-narcotic ratio of 100:25 in cats and 100:30 in dogs; Kennedy³ a toxic-anesthetic ratio of 100:25-32 intraperitoneally in mice and rats; Maloney and Hertz⁴ a toxic-anesthetic-hypnotic ratio of 100:36:18 in rats and approximately 100:24:20 in rabbits, both intraperitoneally; Gwathmey⁵ a toxic-anesthetic ratio of 100:33, intraperitoneally, in dogs, and Storm⁶ a toxic-narcotic ratio of 100:15, intraperitoneally, in monkeys.

With respect to its destruction Killian¹ has found that the rabbit detoxifies twice the minimal narcotic dose in thirteen minutes, while Halberkann⁷ has indicated that evipal, in contradistinction to other barbiturates, is almost wholly destroyed (97 per cent) in the organism. He was able to recover only 2.8 per cent (average) in the urine of dogs. In the rapidity with which it is disposed by the body evipal bears close resemblance to the gaseous anesthetics, state Coryllos and Bass.⁸ In the speed of its dynamic effects it surpasses them.

Here is an anesthetic agent exhibiting a remarkable pharmacodynamic activity

which is so quickly detoxified by the defense mechanisms of the body that, with due care as to the rate of injection, several doses far in excess of the safety expectancy of a single injection may be successfully employed. In a previous report on this study Maloney and Hertz⁴ recorded this pertinent observation:

The hazard of toxicity is inherent not in the drug per se but rather in its absorption constant in the system in any unit of time. The detoxifying mechanism can cope adequately with a vast quantity of the compound spread over a relatively long period of time whereas it may easily be overwhelmed by a mere fraction of that same amount if absorbed in a moment. . . . Safety and therapeutic efficiency are consequently functions of rate and degree of absorption.

Having had considerable laboratory experience with picrotoxin administered before, combined with, and following the administration of lethal doses of other barbiturates, we treated a case of respiratory embarrassment which occurred early in the course of our animal experimentation with evipal in prolonged anesthesia. The counteracting action of picrotoxin in this case was so effective that it suggested the feasibility of the employment of picrotoxin as a routine prophylactic measure.⁹ Using this technique in numerous laboratory experiments the fact was established that whereas picrotoxin has no inhibitory or retarding effect on the anesthetic action of evipal it effectively prevents the possibility of respiratory paralysis. Since the danger in the intravenous administration of evipal for purposes of anesthesia lies in its possible assault on the respiratory center it follows

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logically that the antecedent protection of this center against such impending assault is good pharmacological procedure. Picrotoxin provides this protection. Consequently all our clinical cases on whom evipal is used for prolonged anesthesia receive routinely a prophylactic dose of picrotoxin.

TECHNIQUE

Selection of Patient. Since evipal is detoxified principally, if not entirely, by the liver we consider functional impairment of this organ the major contraindication. Accordingly, a negative Fouchet test is done routinely before evipal is selected as the anesthetizing agent. In the series of cases here reported (Table 1) no other condition presented itself either as a contraindication or complication following its use. Mention of other possibilities will be made in the discussion.

Preparation of Patient. The patient is prepared in the usual manner. When necessary psychic or nervous stabilization on the night preceding the operation is obtained by the use of morphine-scopolamine, but under no circumstances is preanesthetic medication allowed. Preliminary sedation both complicates the general picture and prevents a correct estimation of the effective anesthetizing dose of evipal. On this matter we are in accord with Heard¹⁰ and Killian.¹ Heard says that preoperative sedatives should be used with caution; and Killian says that their use with evipal is not recommended since their depressant action combines with the action of evipal and impairs respiration.

Induction. Upon signal of readiness from the surgeon 2 c.c. of a 0.3 per cent solution of picrotoxin is injected intramuscularly, the deltoideus being the site usually selected. This is followed by an immediate enhancement of the rate and (or) depth of respiration. The patient is then asked to count audibly as soon as the needle delivering the evipal solution has been inserted into the vein and the injection has begun. The injection is made fairly

rapidly until the patient's voice fades away. An additional one-third of the dose already delivered is then given and the injection is stopped, the needle being held in the vein. The signal is now given the surgeon to begin. Using the same calibre syringe and needle at all times the technician quickly learns to gauge the optimal rate of injection. Individual variations become a negligible factor with the rapidly acquired experience. Because of the relative length of the systemic circulation in man as compared with small laboratory animals the rate of injection in man has to be correspondingly increased in order to produce anesthesia, so rapidly is the drug detoxified. Undue slowness of injection rate serves to retard the induction time as well as boost the initial amount of the anesthetic. The average induction time is twenty to thirty seconds. The presence of picrotoxin in the system acts as a virtual buffer against untoward embarrassment. Respiratory accidents are reduced to the vanishing point with the employment of this technique.

ANALYSIS OF CASES

Blood Pressure. The blood pressure is recorded prior to the administration of picrotoxin. Whenever possible the sphygmomanometer is kept on the arm in which event the pressure is recorded at intervals of five minutes throughout the operation. In every case the pulse and respiration rates are taken at five minute intervals. There is usually an insignificant initial fall of pressure, but this tends to right itself. In our cases the drop was merely 2 to 10 mm. In 2 instances an actual rise in the systolic pressure occurred (150 to 170 and 126 to 130). Two cases exhibiting hypertension showed marked drops (240 to 200 and 160 to 88). In one patient, twenty-five years of age, a pressure of 138 dropped to 92. The average systolic pressures at the beginning and end of the operation for the series were 133 mm. and 118 mm. respectively, constituting an average fall of approximately 15 mm. We have taken a

fall of 30 mm. in an initially normal pressure reading as one indication for a supportive dose of picrotoxin.

Pulse. As a rule the pulse rate tends to increase during the course of the operation. Ten cases in our series manifested slight decreases comparing the rates at the end with those at the beginning. The average pulse rates per minute at the beginning and end were 105 and 116 (10 per cent). Changes in the rate are of minor significance as compared with associated changes in the quality of the pulse. Any sign of threadiness or weakening in the course of an operation is construed as another indication for a supportive dose of picrotoxin.

Respiration. The rate of respiration also tends to increase but like the pulse the increase is not marked. Five showed slight decreases (26-24, 24-18, 36-25, 40-32, 48-40). Three showed considerable increases at the end over the initial rate (22-56, 20-68, 22-68). The majority (78 per cent) showed slight increases. The average increase was 8 per minute, from 29 at the beginning to 37 at the end of operation.

Under evipal anesthesia the respiration closely simulates physiological sleep usually exhibiting a gentle stertor with a definite rhythmicity and depth. We take the quality of the respiration as our cardinal sign, either withholding the evipal administration or gauging the fractional doses according to the minutest detectable changes of rhythm or depth. In this way a smooth course of anesthesia is maintained. Our fractional doses, therefore, are characterized more by smallness and frequency than by quantity. In this connection it is pertinent to state that impairment of rhythm and depth may result from obstruction of the air passage. Unless it causes gagging the mechanical Cornell airway is used routinely. We have had no cases in which apnea, hyperpnea, asphyxia or shock was observed, or anxiety exhibited by surgeon or anesthetist. In no case did any untoward condition arise remotely suggesting an emergency calling for the use of

oxygen-carbon dioxide or any other respiratory stimulant.

Quality of Anesthesia and Relaxation. Care was taken after each operation to have the surgeon express in writing his impressions regarding the quality of the anesthesia and the nature of the relaxation of skeletal muscle and abdominal viscera. These impressions are recorded in the table.

Postoperative Notations. The records reveal one case developing "pleuritic pains" on the fourth postoperative day and one a "hypostatic or bronchial pneumonia" on the second day. Both cases cleared following digitalis medication. The anesthetic, in our opinion, had no causal connection with either condition. There have been no instances of postoperative gastric distress, intestinal distention or malaise. The strict withholding of fermentable or gas-producing foods and drinks may probably have played a beneficial role. The most clamant postoperative disturbance in our records is what is variously described as restlessness, irritability, hyperexcitability, and tremors. For the first case where restlessness was observed postoperatively 180 mgm. of nembutal was ordered, as we felt that the restlessness was probably due to some residue of picrotoxin in the system. However, with notices in the literature (*c.f.* Heard,¹⁰ Coryllos and Bass,⁸ et al.) of such a condition obtaining in which no analeptic was administered it was suspected that the anesthetic agent might play some role in the production of this hypersensitiveness. We tried morphine with unvaryingly good results. A single dose of morphine, 10 or 15 mgm., with or without atropine has always given the desired sedation; (see also Heard¹⁰).

Of the 40 cases presented in this report 26 or 65 per cent lasted fifty minutes or more from the time of incision to the making of the last suture. Of these 26, 18 occupied sixty minutes or more and of the 18, 3 lasted 133, 125 and 125 minutes respectively; the average duration for the series was 58.85 minutes. The average dose per person of evipal used throughout the

No.	Patient			Operation	Duration Minutes	*Total Evipal Grams	Blood Pressure		Picrotoxin during Operation	Respiration			Pulse		Surgeon's Comments	Postoperative Observations of the Internes
	Sex	Age	Weight				Start	End		Start	End	Quality	Start	End		
March, 1936																
1	F	27	165	Cesarean; sterilization; Wassermann 4+	64	2 ¹⁰	240/148	200/140	6 mgm.	40	48	regular	96	132	"Gut is just as relaxed as in spinal anesthe- sia" J. W. Ross	Restless—nembutal 180 mgm.; uneventful re- covery
2	F	21	115	Cesarean section with sterilization	50	2.6 ⁸	120/80	112/80	None	32	40	regular	110	144	"Anesthesia and relax- ation good" J. W. Ross	500 c.c. 5 per cent glu- cose during operation, 1000 c.c. 10 per cent glucose after opera- tion; good recovery; discharged sixteenth postoperative day
3	F	40	210	Cesarean section; steri- lization; para 11, pla- centa previa	60	2 ⁷	130/80	120/80	12 mgm.	44	..	regular	120	120	"Good relaxation" J. W. Ross	Restless on awakening; morphine 15 mgm.; uneventful recovery
4	F	21	138	Cesarean section	50	2.6 ¹⁰	114/66	None	"Silent abdomen" J. W. Ross	Uneventful recovery
5	F	40	165	Sterilization—para 13, glomerulonephritis	40	1.6 ⁶	180/100	166/94	None	22	56	jerky—regular	84	112	"Gut as silent as with spinal anesthesia" J. W. Ross	Slight restlessness; un- eventful recovery
6	F	23	135	Cesarean section	47	2 ¹¹	140/90	130/90	None	30	30	regular	120	108	"Anesthesia excellent" J. W. Ross	Very restless; morphine 15 mgm., recovery un- eventful
7	F	20	124	Excision of hip joint, tuberculosis of hip	63	1.6 ⁸	118/60	116/68	None	20	28	regular	148	114	"Quality perfect; re- laxation fair" P. T. Johnson	Recovery uneventful
April, 1936																
8	F	53	145	Open reduction of frac- ture of humerus	69	1.5 ⁶	Not taken	None	26	24	regular	120	125	"Quality and relaxa- tion good" P. T. Johnson	Quiet; uneventful
9	F	24	115	Cesarean section with sterilization	91	2.4 ¹⁴	130/80	100/70	None	45	48	regular	100	120	"Anesthesia gave good relaxation of intes- tines and abdominal muscles" J. W. Ross	Very restless 7 hours postoperatively; mor- phine 15 mgm. with atropine 0.5 mgm.
10	M	39	165	Open reduction right tibia; intramedullary graft	87	2.1 ⁹	130/80	116/78	6 mgm.	36	25	regular	120	72	"Relaxation good; quality good" P. T. Johnson	Quiet; uneventful re- covery
11	M	26	160	Comminuted intercon- dylar fracture of right humerus	67	2.1 ¹⁰	128/80	None	30	30	regular	84	72	"Relaxation very good" P. T. Johnson	Quiet; uneventful re- covery
12	F	43	120	Appendectomy	28	1 ¹	130/80	120/75	None	22	24	regular	116	94	"Complete relaxation of abdominal wall; intestines very quiet. The anesthesia was perfect" H. R. Burwell	Pleuritic pains on fourth day; cleared up with digitalis. Recovery complete, uneventful

13	F	38	150	Appendectomy; multiple myomectomy; right salpingectomy; left plastic	133	4.7 ¹⁰	130/76	104/66	None	20	40	regular	112	120	"Relaxation good; smooth anesthesia throughout" J. W. Ross	Respiration shallow; heart rate 107; weak; sleep profound. Picrotoxin 6 mgm. Restless after fifth hour. Morphine 15 mgm. Recovery complete
14	M	20	175	Appendectomy	43	1.6 ⁵	110/64	100/66	3 mgm.	18	28	regular	112	128	"Relaxation very good" W. M. Lane	No postoperative distention; no excitement
15	F	14	112	Appendectomy	39	1 ⁵	116/80	110/70	None	28	38	fairly regular	120	136	"Relaxation immediate; best towards last part of operation" W. M. Lane	No postoperative disturbance. Recovery uneventful
16	F	34	112	Right mastoidectomy	24	1 ⁵	115/80	110/70	None	24	18	regular	116	120	"Anesthesia very good; no sign of shock" H. W. Barnes	No postoperative ill effects; no irritability
17	F	25	114	Appendectomy, ovarian cyst, right	32	1.1 ³	138/60	92/62	3 mgm.	20	20	regular	82	120	"Relaxation complete six minutes after the beginning of anesthesia" W. H. Welch	No sign of irritability; no postoperative discomfort
18	F	47	180	Herniorrhaphy	60	1.4 ⁷	164/100	154/100	None	18	20	regular	60	84	"The gut is just as flat as in spinal anesthesia" A. M. Curtis	Developed hypostatic or bronchial pneumonia second day postoperative. Digitalis and morphine cleared it up in three days. Good healing
19	M	20	165	Appendectomy	50	1.6 ⁷	130/76	120/70	None	20	20	regular	78	84	"In the first part of operation intestines were pushed out because of impaired respiration. Tongue had occluded the respiratory passage. After tongue was pulled out relaxation was complete" W. M. Lane	Postoperatively patient is in excellent condition
20	F	16	115	Laparotomy; exploratory	42	1.3 ⁵	123/80	98/60	None	44	40	regular	96	108	"Relaxation good; quality of anesthesia good" H. R. Burwell	Very restless; morphine 15 mgm. atropine 1 mg. No vomiting; no distention; no complications
21	F	18	136	Appendectomy	55	1.8 ¹¹	78/58	68/50	None	40	48	regular	118	120	"Excellent anesthesia" H. R. Burwell	Somewhat irritable; no vomiting; good postoperative condition
22	F	28	118	Laparotomy	70	1.5 ⁵	160/100	88/72	3 mgm.	30	30	regular	84	60	"Good relaxation throughout; very good anesthesia" H. R. Burwell	No postoperative disturbances. Recovery complete
23	F	34	125	Dilatation of rectal stricture; lymphogranuloma inguinale	30	1.3 ⁶	138/90	110/74	None	32	32	regular	120	120	"Relaxation splendid; quality of anesthesia excellent" F. Jones	No postoperative disturbance. Good condition throughout convalescence

* Small figure represents number of fractional injections.

April, 1936

No.	Patient			Operation	Duration Minutes	*Total Evipal Grams	Blood Pressure		Picrotoxin during Operation	Respiration			Pulse		Surgeon's Comments	Postoperative Observations of the Internes
	Sex	Age	Weight				Start	End		Start	End	Quality	Start	End		
24	F	39	180	Appendectomy; der- moid cyst in abdomi- nal cavity	60	1.7 ⁵	150/90	102/50	None	44	48	regular	112	128	"Anesthesia most satis- factory" H. R. Burwell	Hyperexcitable; mor- phine and atropine; abdominal distention for two days but no other complication

May, 1936

25	F	25	180	Appendectomy, right salpingo-oophorectomy, left partial salpingo- oophorectomy	71	1.9 ⁶	148/68	130/68	None	24	40	regular	96	136	"Relaxation good" H. R. Burwell	Slightly restless. Re- covery uneventful
26	F	20	110	Appendectomy	39	2 ⁸	112/78	98/72	None	36	36	regular	160	108	"Anesthesia entirely satisfactory; relaxa- tion perfect" W. H. Welch	No postoperative dis- comfort
27	F	20	120	Decompression; frac- ture of left temporal region	45	2.2 ⁷	110/68	110/70	None	26	40	regular	120	150	"This anesthetic seems to be ideal for this type of operation" A. M. Curtis	Condition good; recov- ery uneventful
28	F	28	118	Appendectomy, bilat- eral oophorectomy	60	2 ⁴	130/83	108/78	None	40	40	regular	150	140	"Good relaxation" W. H. Welch	No postoperative dis- comfort, rapid con- valescence
29	F	24	120	Lymphogranuloma inguinale	17	1.3 ³	150/100	170/110	None	48	40	regular	108	164	"Relaxation, good for 15 minutes" H. R. Burwell	Patient comfortable. No postoperative dis- turbance
30	F	23	138	Bilateral salpingec- tomy; appendectomy; freeing adhesions	50	2.1 ⁶	110/90	100/78	None	22	30	regular	84	120	"Anesthesia fine" W. H. Welch	No postoperative dis- turbance. Condition satisfactory during convalescence
31	F	33	180	Cesarean section with sterilization	78	1.8 ⁹	126/80	130/110	None	24	40	Apneic to begin, later regular	88	120	"Relaxation adequate" J. W. Ross	Came out of anesthesia without restlessness; was unable to void urine eighteen hours postoperative; cath- eterized; recovery un- eventful
32	M	37	160	Amputation of penis by electrocautery	28	1.8 ⁵	162/92	150/100	None	40	32	regular	84	120	"Good relaxation; good anesthesia" R. F. Jones	No signs of irritability; no vomiting, gradual convalescing unevent- ful recovery

June, 1936

33	F	42	100	Appendectomy; supra- vaginal hysterectomy; bilateral salpingo- oophorectomy	53	1.6 ⁶	160/110	140/110	3 mgm.	20	68	irregular, jerky and shallow	120	140	"Abdominal wall and intestines well relaxed. Anesthesia very satis- factory. (R. L. Jack- son Provident Hospi- tal, Baltimore, Md.)"	Patient awoke perfectly quiet. Recovery un- eventful
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34	F	29	130	Appendectomy; bilateral salpingectomy; bilateral partial oophorectomy, myomectomy	125	3.0 ¹³	122/98	120/80	None	44	58	regular	124	116	"Very good relaxation" J. W. Ross	Postanesthetic recovery was good. Restless four hours later. From this point postoperative course was uneventful
35	F	47	...	Appendectomy; bilateral oophorectomy; hysterectomy	125	3.0 ¹⁰	138/88	120/180	None	22	68	regular	90	100	"Excellent relaxation smooth anesthesia throughout" J. W. Ross	Postanesthetic recovery good. No restlessness. Uneventful recovery

July, 1936

36	M	32	150	Appendectomy	44	1.2 ³	120/70	112/74	None	16	32	regular	80	120	"Relaxation good" W. H. Welch	Hyperexcitable; morphine; patient states anesthesia was very good, prefers it to ether
37	F	27	147	Dilatation of rectal stricture	95	1.3 ⁴	120/80	112/76	None	16	28	regular	84	120	"Anesthesia good; relaxation excellent" H. R. Burwell	Patient improved progressively. No adverse signs

August, 1936

38	F	29	108	Appendectomy, cervical dilatation curettage; left salpingectomy	50	2.8 ⁸	106/62	104/54	None	44	60	regular	90	110	"Perfect relaxation was gotten from anesthesia" (Mercy Hospital, Philadelphia, Pa.) Dr. Fortune	Postoperative excitement was observed. Quieted with morphine 15 mgm. Recovery uneventful
39	M	11	86	Gastrectomy	55	1.0 ³	108/75	108/72	None	16	36	regular	80	120	"Excellent relaxation" E. Howes	Patient has not experienced vomiting nor a turn for the worse since operation

September, 1936

40	F	34	135	Repair of vesicovaginal fistula	65	2.6 ⁶	140/80	112/64	None	28	28	regular	120	100	"Anesthesia all to be desired" J. W. Ross	Slightly restless; morphine 10 mgm.; made uneventful recovery
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* Small figure represents number of fractional injections.

series was 1.875 gm. The largest dose used in a single case was 4.7 gm. distributed over ten fractional injections, the initial induction dose being 1 gm. Reference to the table will show the variety of operations performed.

DISCUSSION

Because of its rapid destruction in the system the adaptability of evipal for anesthetics of long duration making use of the technique of fractional injections p.r.n. was soon discovered and adopted.

Rogotzky¹¹ states that it is apparently harmless and especially valuable in general anesthesia of long duration. Sailer¹² and Kohlhaage¹³ while especially advocating its use both as a basal anesthetic and as a general anesthetic for short operations also state that it may be used for prolonged major operations. Sailer warns of the danger of the facile overdose and insists that expert induction is as necessary as in the case of inhalation anesthesia. Garrey and Cohn¹⁴ advise the restriction of its use to good surgical risks until it has been more widely used and better understood. Cousineau¹⁵ urges that the dosage and the rate of injections should be carefully watched. Kaminiker and Rintelen¹⁶ report that while it is employed at the Graz Clinic for certain major operations calling for fractional injections, its employment for orthopedic operations was not approved because of the frequent occurrence of motor unrest. Beck¹⁷ and Baetzner¹⁸ encountered some trembling and twitching. The former attributed this to rapidity of injections, the latter to high basal metabolism which destroyed the substance so rapidly that inadequate dosage probably evoked excitation rather than sleep. He employed supportive amounts of ether or ethyl chloride in those cases. Burkle de la Camp¹⁹ used it for basal, short and long anesthetics without any immediate deleterious results or sequela. Ernst²⁰ reports that prolonged anesthesia was obtained by fractional doses but advises against this because of frequent

changes in the depth of narcosis which is a disadvantage alike to surgeon and patient.

By the prophylactic employment of picrotoxin, the incidence of respiratory embarrassment is effectively offset and by the frequency of administration of minute fractional doses the desired depth and smoothness of anesthesia is easily maintained.

Following the recommendation set forth by the manufacturers of evipal that the dosage should be gauged on the basis of 0.06 c.c. of a 10 per cent solution per pound of body weight with a maximum of 10 c.c. (1 gm.) per person, the earlier investigators tried to establish a dosimetric scale for general use. Heard¹⁰ states that the sleep inducing dose should be one-half the full estimated weight dose. Garrey and Cohn¹⁴ inject 3 to 4 c.c. at the rate of 1 c.c. per fifteen seconds leaving the needle in the vein for subsequent injections p.r.n. To produce anesthesia Sailer¹² injects 7 to 10 c.c. delivering the first 4 c.c. in one minute. To prolong anesthesia two-third to one-half of the initial anesthetizing dose is given. These rules are, however, only of suggestive value. Questions of idiosyncrasies, age, nutritional state, nervous set are always obtrusive. Gorodner²¹ advises that nervous patients require larger and debilitated patients relatively smaller doses. Cousineau¹⁵ reports one death occurring two minutes after the injection of 7 c.c. Morl²² reports a case of death in three minutes of a man seventy-five years of age who received 8 c.c. and Kaminiker and Rintelen¹⁶ report 2 cases of women, seventy years old, who manifested severe respiratory and circulatory disturbances following the injection of 7 c.c. each. Both died; one within nine hours and the other three days. Morl used his observation to stress the warning that schematic dosage according to body weight may result in overdosage. Kaminiker and Rintelen believe that their deaths were not due directly to the narcotic. Harms²³ advises that the calculated weight dosage should be checked by observation of objective symptoms during injection so as

to control factors of possible idiosyncrasies. Westerborn²⁴ states that young patients often needed twice as much as patients between sixty and eighty years of age and robust patients generally required more than anemic or debilitated ones. In our experience the method of individualizing our patients, using the abolition of speech as guide, has proved quite satisfactory. Its utter simplicity commends it. We are not in position to say whether or not this simple method would work satisfactorily without the prophylactic use of picrotoxin.

On the question of contraindications to the use of evipal there is a unanimity of opinion amongst investigators that hepatic dysfunction definitely contraindicates the employment of this agent. Either by way of elucidation or addition, mention has been made of marked sepsis by Merritt;²⁵ peritonitis by Kohlhaage;¹³ bronchial asthma by Boden;²⁶ cachexia, dehydration and certain nose and throat operations by Suraci;²⁷ impaired respiration and suburemic states, by Killian.¹ Early bronchiectasis, diabetes, hypertension, endocarditis and advanced carcinoma are mentioned by Heard¹⁰ as complicating factors. Coryllos and Bass⁸ present a comprehensive statement on contraindications with which we are in complete accord. They state: "It is (therefore) obvious that morbid conditions causing impairment of hepatic functions constitute formal contraindications to the use of evipal. Such conditions are jaundice—whatever the cause, acute toxemias and bacteremias, or chronic and prolonged suppurations."

SUMMARY

The adaptability of evipal soluble by fractional injections for use in prolonged clinical surgical anesthesia because of its rapidity of action and detoxification is discussed.

The efficacy of picrotoxin as a prophylactic measure to protect the respiratory center from untoward or undue assault by the barbiturate is advanced.

The technique employed in the production and maintenance of good clinical surgical anesthesia is described.

Analysis is made, and a table presented, of 40 operations performed under prolonged evipal anesthesia by the employment of this technique.

A brief discussion of the literature pertinent to the subject is presented (a) on the experiences and impressions of investigators (b) on the problem of schematic dosage and gradation of fractional doses and (c) on the question of contraindications to the use of evipal.

We wish to acknowledge with thanks our deep appreciation of the kindness of the following: The Research Department of the Winthrop Chemical Company for generously providing the evipal soluble used in this study; the surgeons whose names appear in the table for faith in our judgment; and the internes, Doctors J. C. Oliver, U. I. Carrington and T. C. Simmons for invaluable aid in the course of administering the anesthetic and for keeping the postoperative records on the condition and progress of the patients.

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