THE EFFECT OF BUTHALITONE SODIUM (TRANSITHAL®) ON LIVER AND KIDNEY FUNCTION IN MAN

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BUTHALITONE SODIUM** is one of the latest additions of ultra short-acting barbiturates for anaesthetic purposes. Although it was first described in 1936 (1) investigation of its pharmacological properties was not begun until 1954 (2)

CHEMISTRY AND PHARMACOLOGY

Buthalitone sodium is the sodium salt of 5-allyl-5-iso-butyl thiobarbituric acid and has the following structural formula:

The base has a molecular weight of 240.3. In its commercial form 6 parts by weight of anhydrous sodium carbonate are added to 100 parts of the parent substance to enhance stability of the aqueous solution to atmospheric carbon dioxide. Buthalitone sodium is a yellowish powder, not dissimilar to sodium thiopental and is dissolved in water prior to use. The 10 per cent solution has a pH of approximately 10.5.

Weese and Koss (2) studied the pharmacology of buthalitone sodium mainly in dogs and rabbits. They found that 25 mg/kg. body weight produced very light anaesthesia, 50 mg/kg produced deep narcosis with loss of all reflexes which changed to light anaesthesia after 30 minutes with return to full activity 60 minutes after the injection. A dose of 100 mg/kg. caused deep anaesthesia lasting for 95 minutes and requiring artificial respiration, these animals required 24 hours for complete recovery. A dose of 110 mg/kg caused immediate death. The authors found in their experiments that induction and recovery were both smooth and they commented on the short recovery phase as compared with hexobarbital sodium. Strangely the more rapid recovery was not observed in puppies, which showed a marked tendency to post-anaesthetic sleep. They noted that the drug produced only very slight and transient effects on respiration when injected slowly, excessive respiratory depression was one of the first signs of overdose. Heart action and blood volume were not significantly affected in dogs.

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but there was a slight and transient reduction in blood pressure. The daily administration to rabbits for 13 successive days at 50–60 mg./kg. did not affect the blood picture and urinary tests, and revealed no changes in the parenchymatous organs of sacrificed animals. The same investigators further showed that buthalitone sodium is rapidly detoxified in the liver. Less than 1/20 of a full anaesthetic dose was detectable in the urine of dogs. They found elimination in the rabbit to be so fast that it was possible to give eight intravenous injections of 40 mg./kg. in one day and only after the sixth injection was a slight prolongation of the recovery phase noted.

Rivett (3) found that buthalitone sodium was one-third to one-half as toxic in mice as thiopental sodium and was one-third to one-half as potent as thiopental. They therefore concluded that the therapeutic indices in mice are similar for the two substances.

Anderson (3) also studied buthalitone sodium in dogs and concluded that the substance was approximately half as potent as thiopental sodium in the production of surgical anaesthesia. Anaesthesia lasted about 13 minutes on the average and the recovery phase 45 minutes, but he noted marked individual variation in this. He confirmed the observations of Weese and Koss as to the longer recovery time in puppies and the slight depression of respiration caused by the drug.

CLINICAL STUDIES

Trials of buthalitone sodium in clinical anaesthesia have been described by Weese and Koss (2), Nobes (4, 5), Ruddell (6), Young (3), McColl (7) and Davidson, Love and Kocay (3). These authors describe their use of buthalitone in both in-patients and out-patients for induction of general anaesthesia as required in general surgery, obstetrics and gynaecology, dentistry, and electroshock therapy. All investigators stressed the rapidity of recovery of consciousness. Nobes furthermore comments on the absence of postoperative somnolence and confusion. Many investigators therefore stress the value of the agent in out-patient practice. Side effects reported include nausea and vomiting, hiccoughs, marked hypotension and postoperative headache. Post-anaesthetic amnesia has also been reported. Coughing, sneezing, and retching occurred if the drug was injected too rapidly.

PRESENT STUDY

Before submitting patients to anaesthesia with buthalitone sodium, it was decided to study the effect of the agent on liver and kidney functions of healthy volunteers.

The following standardized laboratory tests were carried out on the day preceding anaesthesia and again 24 hours after anaesthesia.

1. Liver function

- (1) Serum protein albumin, globulin, and total
- (2) Serum bilirubin direct, indirect, and total
- (3) Prothrombin level
- (4) Bromsulphalein retention test: readings after 5 and 30 minutes

- (5) Alkaline phosphatase
- (6) Cephalin cholesterol flocculation
- (7) Thymol turbidity
- (8) Thymol flocculation
- (9) Zinc sulphate turbidity

2. Kidney function

(a) Urine

- (1) Specific gravity
- (2) Bile (Bilirubin); Franklin's modification of Harrison's Test
- (3) Urobilinogen, Watson's method

(b) Phenolsulphonephthalein test: readings after 15, 30 and 60 minutes

The subjects were young, healthy, male volunteers. No preoperative medication was administered. Six volunteers were anaesthetized with double the sleep dose, and one received the sleep dose only. A 2.5 per cent solution of buthalitone sodium was used. The injection was carried out through a #20 gauge needle at the rate of 1 ml. (25 mg.) in approximately 1.5 seconds until the individual closed his eyes, whereupon the sleep dose was repeated rapidly after a short pause. The total injection was usually completed within 70 seconds and in all cases within 90 seconds. Arterial and venous blood pressures, pulse rate, pulmonary ventilation, and cardiac output were recorded during the experiment and will be the subject of a further report.

The duration of sleep was noted, response to verbal command being established as the end-point of the experiment. Respiration was not assisted when it became depressed in order to test the effect of the agent on parenchymatous function under the least favourable conditions.

RESULTS

The patient's age, height, weight, sleep dose, total dose, and total duration of injection are listed in Table I. Results of liver and kidney functions are tabulated in Tables II and III. From these tables it will be noted that irrespective of the amount of buthalitone sodium administered, values for all tests were within normal limits both before and after the drug. Differences between the two readings were not clinically significant and did not indicate impairment of liver or kidney function.

TABLE I

Subject	Age	Wt	Ht	Sleep dose	Inj time	Double sleep dose	Total dose per sq metre body surface	Total inj.time
(1)	22	150	68	500 mg	20 sec.	1000 mg	555 5 mg	70 sec
(2)	25	175	71	500 mg	35 sec.	1000 mg	507 6 mg.	70 sec.
(3)	23	162	68	500 mg	30 sec	1000 mg	537 6 mg.	55 sec
(4)	23	195	71	500 mg	26 sec	1000 mg	480 7 mg.	70 sec
(5)	31	158	73	900 mg.	50 sec	1800 mg	932.6 mg.	90 sec
(6)	23	145	71	700 mg.	38 sec	1400 mg	765 0 mg.	55 sec
(7)	23	225	74	1000 mg	75 sec	Sleep dose only		

Subject	Time	Serum protein (Grams per 100 ml serum)			Serum bilirubin (Mg per 100 ml serum)			Prothrombin level (Seconds)			Bromsulphalein retention test (% dye retention)		Alkaline phosphatase (Bodansky units per 100 ml serum)	Cephalin cholesterol flocculation	Thymol turbidity (Units per 100 ml serum)	Thymol flocculation	Zinc sulphate turbidity
		Total	Albumin	Globulin	Direct	Indirect	Total	Control	Patient	% of Normal	5 minutes	30 minutes					
(1)	Before	7.4	4.5	2.9	16	36	52	13	14	86	50	3	4.0	negative	1.4	0	6.6
	After	6.9	4.4	2.5	08	16	24	13	14	87	71	1	5.2	negative	3.0	0	5.8
(2)	Before	7.6	4.2	3.4	35	55	90	13	13	100	70	0	2.5	negative	2.2	0	7.2
	After	7.6	4.2	3.4	35	55	90	14	15	91	70	0	2.5	negative	2.2	0	7.2
(3)	Before	5.8	3.3	2.5	15	00	15	13	14	87	71	2	2.9	1+ heavy trace	3.4	0	6.0
	After	6.6	3.9	2.5	16	20	36	12	14	75	65	0	3.3	heavy trace	2.2	0	3.4
(4)	Before	6.8	3.9	2.9	05	15	20	14	14	100	67	6	3.0	negative	1.8	0	5.2
	After	6.6	3.3	3.3	10	50	60	13	14	88	60	2	3.0	1+	2.4	0	7.2
(5)	Before	6.7	3.7	3.0	15	30	45	13	14	88	53	1	5.8	negative	1.8	0	7.2
	After	6.9	3.7	3.2	16	08	24	13	13	100	60	6	4.6	negative	2.2	0	6.8
(6)	Before	6.8	4.1	2.7	20	45	65	12	14	75	38	0	2.9	negative	1.3	0	2.4
	After	7.1	4.0	3.1	16	40	56	13	14	85	56	5	2.2	negative	1.6	0	6.0
(7)	Before	7.2	4.1	3.1	20	36	56	13	14	87	93	2	4.0	1+	1.8	0	5.8
	After	6.5	4.1	2.4	10	50	60	14	14	100	77	4	3.5	negative	1.4	0	4.7

TABLE III
KIDNEY FUNCTION TESTS

Subject	Time	Urine			Phenosulphone-phthalein test % dye excreted		
		Specific gravity	Bile	Urobilinogen (mg %)	15 min.	30 min.	60 min.
(1)	Before	1 031	0	26	56		90
	After	1 021	0	23	57		69
(2)	Before	1 020	0	24	46	81	108
	After	1 022	0	24	46	81	108
(3)	Before	1 026	0	32	42	63	79
	After	1 026	0	27	42	60	73
(4)	Before	1 010	0	15	59	86	104
	After	1 020	0	24	24	71	—
(5)	Before	1 008	0	04	39	58	76
	After	1 023	0	13	37	56	72
(6)	Before	1 015	0	18	38	68	88
	After	1 015	0	40	23	49	68
(7)	Before	1 019	0	20	33	51	65
	After	1 023	0	26	37	58	81

DISCUSSION

From the results here presented it would appear that buthalitone sodium administered in clinical doses to healthy individuals has no deleterious effects upon liver and kidney function, even in the absence of assisted respiration. It may now be submitted safely to study under clinical conditions.

Clinical studies now must determine the usefulness of the agent. They should establish whether this new drug is superior to those already available and if so what its specific indications are. The authors have submitted this agent to a comparative pharmacological test in volunteers, and will report their findings in due course. Meanwhile it is the task of extensive clinical trials to tell us whether this new agent has a place in anaesthetic procedures. It still remains to be assessed how pre-anaesthetic medication, the addition of other agents, and the impact of the operation may modify the basic pharmacological properties of buthalitone sodium.

SUMMARY

Double the sleep dose of buthalitone sodium was administered to six young healthy male volunteers and a single sleep dose to one volunteer. Liver and kidney functions of these individuals were tested both before and after the administration of the agent.

No deleterious effects on these two vital parenchymatous functions were demonstrated in any of our tests.

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RÉSUMÉ

Le buthalitone de sodium est une des plus récentes additions à la liste des barbituriques à action ultra-courte pour fin d'anesthésie. Bien qu'il ait été décrit pour la première fois en 1936 (1), ce n'est qu'en 1954 qu'on a commencé à étudier les propriétés pharmacologiques de ce produit.

Le buthalitone, chez les souris et les chiens, s'est avéré la moitié moins toxique et la moitié moins puissant que le thiopental. Au cours d'études cliniques, on a observé un retour rapide à la conscience et l'absence de somnolence et de confusion post-opératoires. On a également observé une amnésie post-anesthésique.

Au cours de l'étude actuelle sur le buthalitone de sodium, on a administré à six volontaires mâles en santé une dose double de celle suffisante pour produire le sommeil et, à un autre, une dose somnifère. Avant et après l'administration du médicament, on a évalué les fonctions hépatiques et rénales des individus. Aucun des résultats n'a permis de dépister des atteintes de ces deux fonctions vitales.

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