# SODIUM 5-ALLYL-5-(1-METHYLBUTYL)-2-THIOBARBITURATE, A SHORT ACTING ANÆSTHETIC

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Swanson and Page[1], in animals, and later Zerfas, McCallum, Shonle, Swanson, Scott and Clowes[2], in both animals and humans, were the first to report the use of a barbiturate, namely, sodium amytal (sodium *iso*-amyl ethyl barbiturate), as a general anæsthetic. Fitch, Waters, and Tatum[3] also emphasised the importance of employing short acting members for surgical procedures. Thus, thiopentone sodium, a thiobarbiturate, is now being extensively used clinically as a short acting anæsthetic.

Among the many thiobarbituric acid derivatives synthesised by Shonle and his associates[4], the sodium salt of 5-allyl-5-(1-methylbutyl)-2-thio-

TABLE I

Comparison of anæsthetic dose, duration of action, and lethal dose of sodium 5-allyl-5-(1-methylbutyl)-2-thiobarbiturate and thiopentone sodium, administered intravenously

| Species of animals | Number used | Compound | M.A.D. mg./kg. | Average duration of observed M.A.D. minutes | Average duration of action of symptoms of M.A.D. minutes | AD50±S.E. mg./kg. | LD50±S.E. mg./kg. |
|---|---|---|---|---|---|---|---|
| Rats ... ... | 40 | Sodium 5-allyl-5-(1-methylbutyl)-2-thiobarbiturate | 33·0 | 11 | 248 ... ... ... ... ... ... ... | 31·5 ± 0·80 | 65·0 ± 3·20 |
| Rabbits... ... | 31 | | 20·0 | 5 | 48 ... ... ... ... ... ... ... | 18·1 ± 1·23 | 26·9 ± 1·38 |
| Dogs ... ... | 26 | | 15·0 | 15 | 113 ... ... ... ... ... ... ... | 13·3 ± 0·83 | 36·3 ± 1·35 |
| Monkeys ... | 8 | | 15·0 | 8 | 75 ... ... ... ... ... ... ... | 12·5 ± 1·00 | — |
| Rats ... ... | 50 | Thiopentone sodium | 35·0 | 10 | 275 ... ... ... ... ... ... ... | 32·3 ± 1·39 | 63·1 ± 4·54 |
| Rabbits... ... | 25 | | 25·0 | 5 | 47 ... ... ... ... ... ... ... | 23·1 ± 1·60 | 31·1 ± 2·21 |
| Dogs ... ... | 25 | | 17·5 | 15 | 142 ... ... ... ... ... ... ... | 16·0 ± 0·97 | 36·4 ± 1·29 |
| Monkeys ... | 10 | | 17·5 | 10 | 87 ... ... ... ... ... ... ... | 16·5 ± 1·01 | — |

barbituric acid appears to have the desired promptness and brevity of action. The same series of compounds have been prepared by Tabern and Volwiler[5], Miller, Munch, Crossley, and Hartung[6], and Gruhzit, Dox, Rowe, and Dodd[7].

In the study of sodium 5-allyl-5-(1-methylbutyl)-2-thiobarbiturate, rats, rabbits, dogs, and monkeys were used. As shown in Table I, the drug, administered intravenously, produced in rats an anæsthetic dose (AD50±S. E.) of 31·5±0·80 mg./kg.; a lethal dose (LD50±S. E.) of 65·0±3·20 mg./kg.; and a duration of action of the observed anæsthetic doses and symptoms of recovery of 11 and 248 minutes, respectively. In rabbits, the AD50±S. E. was 18·1±1·23 mg./kg.; the LD50±S. E., 26·9±1·38 mg./kg.; and the length of anæsthesia, 5 minutes with complete recovery in 48 minutes. In dogs, the AD50±S. E. was 13·3±0·83 mg./kg.; the LD50±S. E., 36·3±1·35 mg./kg., with an anæsthetic period of 15 minutes and complete recovery in 113 minutes.

Also in Table I is given a comparison of the dosage, duration of action, and therapeutic index of sodium 5-allyl-5-(1-methylbutyl)-2-thiobarbiturate and thiopentone sodium. It will be noted that in general the anæsthetic dose is smaller, the duration of action shorter, and the therapeutic index greater with the new thiobarbiturate than with thiopentone sodium.

TABLE II

DURATION OF ACTION OF ANÆSTHETIC DOSES OF SODIUM 5-ALLYL-5-(1-METHYLBUTYL)-2-THIOBARBITURATE GIVEN INTRAVENOUSLY THREE TIMES WEEKLY FOR 4 WEEKS

| Dog Number | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|---|
| Sex | | M | F | M | M | F | M | M | F |
| Body Weight kg. | Initial | 8·2 | 8·0 | 7·3 | 8·8 | 7·6 | 9·1 | 9·3 | 7·5 |
| | Final | 9·5 | 9·4 | 8·6 | 9·4 | 8·3 | 9·9 | 9·4 | 7·0 |
| Dose Number | Dosage mg./ kg. | Duration of Action minutes | | | | | | | |
| 1 | 15 | 120 | 119 | 158 | 342 | 116 | 115 | 143 | 140 |
| 2 | 15 | 128 | 213 | 214 | 365 | 151 | 122 | 359 | 267 |
| 3 | 15 | 176 | 177 | 233 | 360 | 112 | 175 | 449 | 238 |
| 4 | 15 | 125 | 95 | 155 | 305 | 95 | 95 | 275 | 215 |
| 5 | 15 | 240 | 233 | 141 | 234 | 109 | 118 | 288 | 166 |
| 6 | 15 | 231 | 230 | 206 | 235 | 148 | 143 | 289 | 167 |
| 7 | 15 | 242 | 283 | 251 | 285 | 220 | 230 | 258 | 249 |
| 8 | 15 | 79 | 119 | 87 | 127 | 73 | 80 | 297 | 85 |
| 9 | 15 | 117 | 119 | 144 | 210 | 115 | 132 | 230 | 180 |
| 10 | 15 | 138 | 105 | 193 | 200 | 132 | 137 | 190 | 120 |
| 11 | 15 | 164 | 161 | 162 | 223 | 98 | 105 | 217 | 160 |
| 12 | 40 | D | D | S | S | D | S | D | D |

D=Died. S=Survived.

On the average, there was no loss of anæsthesia in 8 dogs injected intravenously with anæsthetic doses of sodium 5-allyl-5-(1-methylbutyl)-2-thiobarbiturate, every other day for 4 weeks (Table II). Furthermore, after

the same length of time, no more than the lethal dose, 40 mg./kg., was required to kill the same animals. Obviously, no tolerance was developed by repeated administration. When injected by vein in anæsthetic doses, this thiobarbiturate did not appear to be excreted in the urine. Like all short acting barbiturates, sodium 5-allyl-5-(1-methylbutyl)-2-thiobarbiturate produced a lowering of blood pressure and a depression of

TABLE III

THE EFFECT OF INTRAVENOUS ANÆSTHETIC DOSES OF SODIUM 5-ALLYL-5-(1-METHYLBUTYL)-2-THIOBARBITURATE ON BODY TEMPERATURE, PULSE AND RESPIRATION

| Dog Number | Compound | Dose mg./kg. | Maximum Change in Rectal Temperature °F. | Average |
|---|---|---|---|---|
| 1 | Sodium 5-allyl-5-(1-methylbutyl)-2-thiobarbiturate | 15 | −0·8 | −0·66 |
| 2 | | | −1·0 | |
| 3 | | | −0·9 | |
| 4 | | | −0·5 | |
| 5 | | | −0·1 | |
| 6 | | 17·5 | 0 | −0·72 |
| 7 | | | −0·8 | |
| 8 | | | −0·6 | |
| 9 | | | −1·3 | |
| 10 | | | −1·2 | |
| 11 | Thiopentone sodium | 17·5 | −0·1 | −0·14 |
| 12 | | | −0·2 | |
| 13 | | | −0·2 | |
| 14 | | | −0·1 | |
| 15 | | | −0·1 | |
| 16 | | 20 | −0·5 | −0·78 |
| 17 | | | −1·2 | |
| 18 | | | −1·1 | |
| 19 | | | −0·5 | |
| 20 | | | −0·6 | |

| Dog Number | Maximum Change in Pulse Rate per minute | Average | Maximum Change in Respiration per minute | Average |
|---|---|---|---|---|
| 1 | +72 | +59·2 | − 7 | − 3 |
| 2 | +64 | | 0 | |
| 3 | +80 | | 0 | |
| 4 | +12 | | − 8 | |
| 5 | +68 | | 0 | |
| 6 | +96 | +50·8 | −24 | −14 |
| 7 | +16 | | − 4 | |
| 8 | +38 | | −17 | |
| 9 | +52 | | −17 | |
| 10 | +52 | | − 8 | |
| 11 | +26 | +36·8 | −12 | − 8 |
| 12 | +40 | | − 8 | |
| 13 | +32 | | − 4 | |
| 14 | +44 | | − 4 | |
| 15 | +42 | | −12 | |
| 16 | +52 | +40·8 | − 8 | −14 |
| 17 | +60 | | −24 | |
| 18 | +68 | | 0 | |
| 19 | +48 | | −13 | |
| 20 | −24 | | −25 | |

respiration, especially when given rapidly by vein. No inhibition of the vagus in dogs followed anæsthetic doses. In this respect, sodium 5-allyl-5-(1-methylbutyl)-2-thiobarbiturate is different from sodium

amytal, but similar to seconal sodium (sodium propylmethyl-carbinyl allyl barbiturate), pentobarbitone sodium, and thiopentone sodium. All dogs that died from lethal dosage and those that survived were sacrificed for pathological study. No pathological lesions were discovered.

TABLE IV

PRE-ANÆSTHETIC MEDICATION VALUE OF SODIUM 5-ALLYL-5-(1-METHYLBUTYL)-2-THIOBARBITURATE IN RATS WITH NITROUS OXIDE-OXYGEN ANÆSTHESIA

| Compound | Rat Number | Weight g. | Dose | |
|---|---|---|---|---|
| | | | mg./kg. | Approximate percentage of Lethal Dose |
| Sodium 5-allyl-5-(1-methylbutyl)-2-thiobarbiturate | 1 | 109 | 22 | 20 |
| | 2 | 123 | 22 | 20 |
| | 3 | 113 | 22 | 20 |
| | 4 | 92 | 22 | 20 |
| | 5 | 100 | 22 | 20 |
| | 6 | 112 | 27·5 | 25 |
| | 7 | 89 | 27·5 | 25 |
| | 8 | 80 | 27·5 | 25 |
| | 9 | 112 | 27·5 | 25 |
| | 10 | 122 | 27·5 | 25 |
| Thiopentone sodium | 11 | 91 | 22 | 20 |
| | 12 | 92 | 22 | 20 |
| | 13 | 119 | 22 | 20 |
| | 14 | 90 | 22 | 20 |
| | 15 | 97 | 22 | 20 |
| | 16 | 121 | 27·5 | 25 |
| | 17 | 109 | 27·5 | 25 |
| | 18 | 100 | 27·5 | 25 |
| | 19 | 81 | 27·5 | 25 |
| | 20 | 91 | 27·5 | 25 |

| Compound | Rat Number | Length of Anæsthesia | | | |
|---|---|---|---|---|---|
| | | Induction | | Total Duration | |
| | | 95—5 | | 85—15 | |
| | | Normal minutes | After Hypnotic minutes | Normal minutes | After Hypnotic minutes |
| Sodium 5-allyl-5-(1-methylbutyl)-2-thiobarbiturate | 1 | 2·30 | 1·20 | 1·50 | 15 |
| | 2 | 2·50 | 1·10 | 1·50 | 20 |
| | 3 | 3·10 | 1·40 | 1·60 | 17 |
| | 4 | 3·40 | 1·50 | 1·50 | 13 |
| | 5 | 3·30 | 1·30 | 1·25 | 15 |
| | 6 | 2·50 | 1·10 | 1·25 | 30+ |
| | 7 | 2·75 | 1·10 | 1·50 | 30+ |
| | 8 | 3·20 | 1·40 | 1·50 | 30+ |
| | 9 | 2·50 | 1·20 | 1·20 | 30+ |
| | 10 | 3·40 | 1·30 | 1·30 | 30+ |
| Thiopentone sodium | 11 | 2·20 | 1·10 | 1·50 | 10 |
| | 12 | 3·70 | 1·20 | 1·20 | 15 |
| | 13 | 2·50 | 1·50 | 1·10 | 12 |
| | 14 | 2·40 | 1·20 | 1·05 | 10 |
| | 15 | 2·60 | 1·30 | 1·20 | 14 |
| | 16 | 2·10 | 1·10 | 1·10 | 30+ |
| | 17 | 3·50 | 1·50 | 1·50 | 30+ |
| | 18 | 3·60 | 1·40 | 1·40 | 30+ |
| | 19 | 3·40 | 1·25 | 1·10 | 30+ |
| | 20 | 3·00 | 1·40 | 1·25 | 30+ |

As shown in Table III, this compound, similar to most barbiturates, when administered intravenously in dogs in anæsthetic doses lowered body temperature, increased pulse rate, and decreased the respiration.

The pre-anæsthetic value of sodium 5-allyl-5-(1-methylbutyl)-2-thio-

barbiturate in rats (Table IV) was found to be 25 per cent. of the lethal dose, according to the method of Barlow and his co-workers[8]. The new thiobarbiturate and thiopentone sodium were given intraperitoneally.

## CONCLUSIONS

Sodium 5-allyl-5-(1-methylbutyl)-2-thiobarbiturate and thiopentone sodium are closely similar in pharmacological action, although the former shows a trend of being shorter in action in rats, dogs and monkeys. By repeated intravenous injection of sodium 5-allyl-5-(1-methylbutyl)-2-thiobarbiturate to dogs, no tolerance develops. The pre-anæsthetic value of sodium 5-allyl-5-(1-methylbutyl)-2-thiobarbiturate appears the same as that of thiopentone sodium.

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